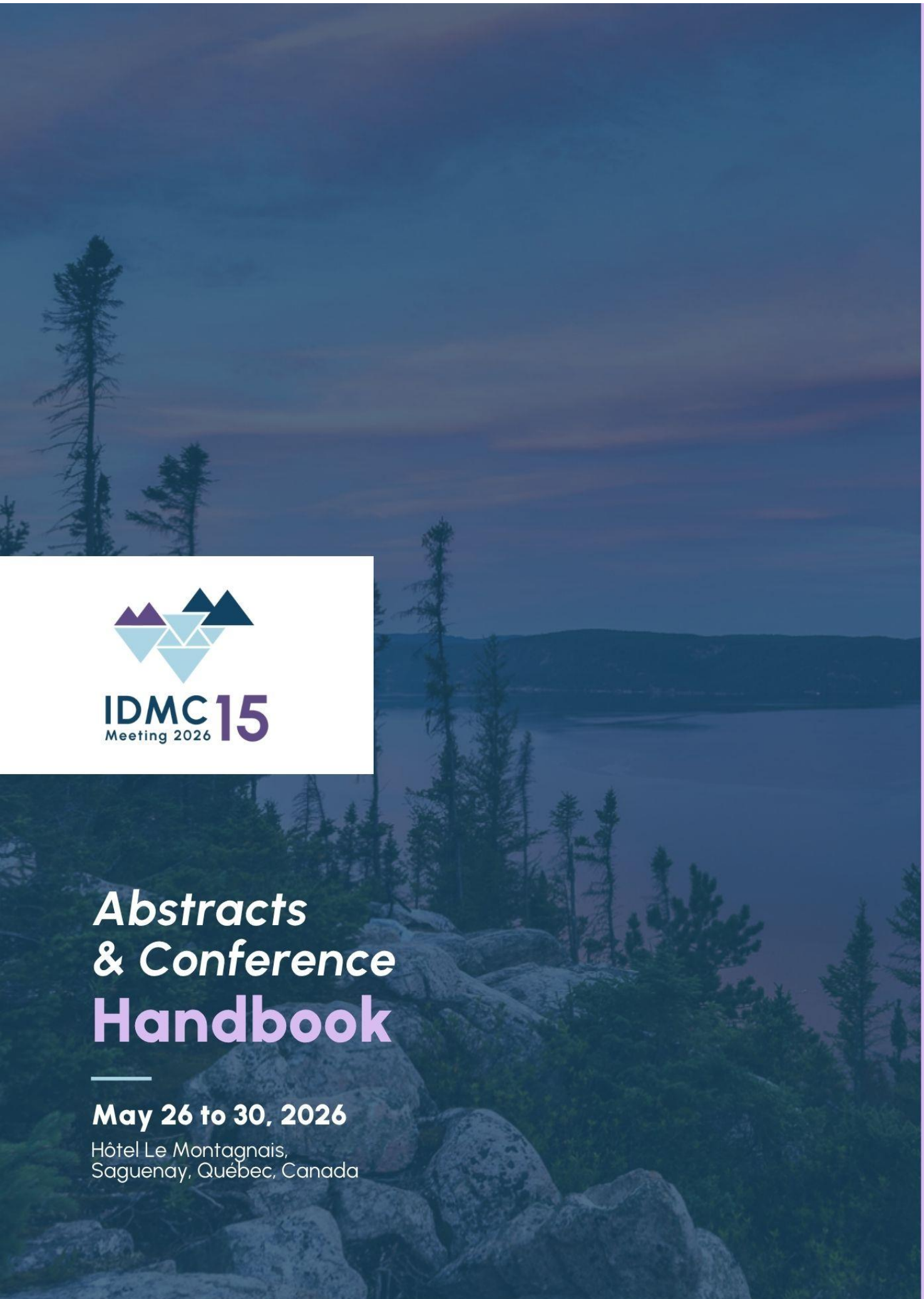


IDMC 15
Meeting 2026

Abstracts & Conference Handbook

May 26 to 30, 2026

Hôtel Le Montagnais,
Saguenay, Québec, Canada

Welcome message

We are delighted to welcome you to the upcoming edition of our meeting, taking place in the beautiful Saguenay–Lac-Saint-Jean region of Quebec, Canada.

This unique region is internationally recognized for having the highest prevalence of myotonic dystrophy type 1 (DM1) in the world and has played a pivotal role in advancing DM research and clinical care since the early 1980s. It is home to the Groupe de recherche interdisciplinaire sur les maladies neuromusculaires (GRIMN) and the site where one of the world's longest-running natural history studies in DM1 was initiated in 2002.

Beyond its scientific significance, Saguenay–Lac-Saint-Jean is renowned for its breathtaking landscapes, rich culture, and warm hospitality. The region offers an exceptional setting for both scientific exchange and meaningful human connections. Thanks to the longstanding engagement of the local DM1 community, patients and patient-partners will also contribute directly to the meeting, sharing their experiences and perspectives throughout the conference.

This event will provide a unique opportunity to discover recent advances, exchange ideas, and strengthen collaborations among all members of the myotonic dystrophy community — including researchers, clinicians, patients, patient-partners, advocacy organizations, and representatives from the pharmaceutical sectors.

IDMC-15 promises to be an unforgettable experience featuring cutting-edge scientific presentations, interdisciplinary discussions, and inspiring interactions. It will also offer a rare opportunity to experience the place where much of the history of DM1 research and care in Quebec was shaped, and to meet some of the individuals who played a defining role in increasing awareness of the disease and advancing evidence-based care for affected individuals and families.

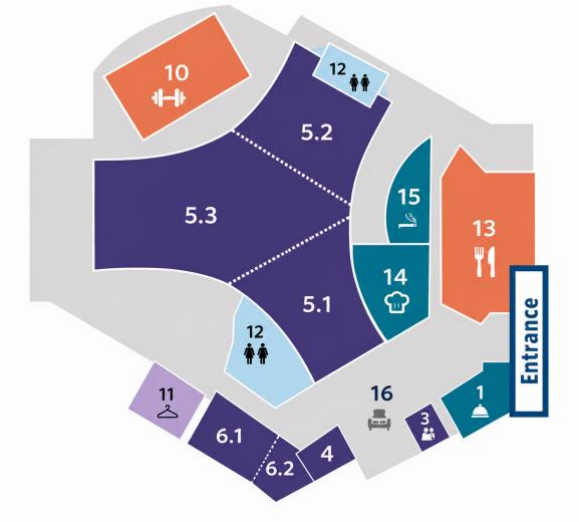
Summary

Venue

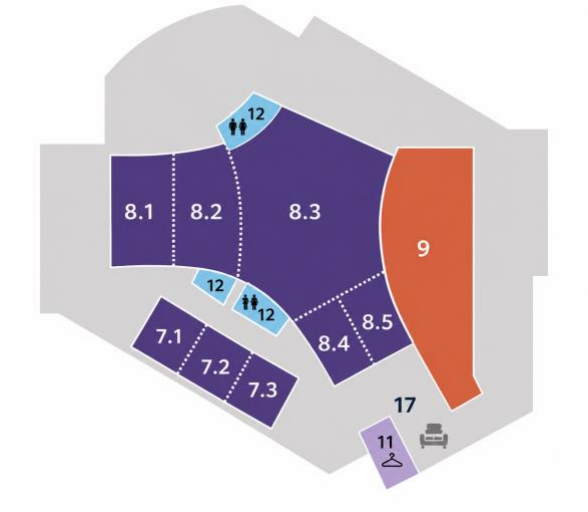
Hôtel Le Montagnais
1080, Boul. Talbot, Chicoutimi
(Québec) G7H 4B6
418-543-152 | 1-800-463-9160

Map of the Montagnais

First Floor



Ground Floor



Rooms

1. Front desk
3. Salon des affaires
4. Yvonne Néron
5. Montagnaise (5.1 – 5.3)
6.1. Armand Couture
6.2. Robert Gravel
7.1. Wigwam
7.2. Tente
7.3. Tipi
8.1 Totem Sud
8.2. Totem Nord
8.3. Réserve centre
8.4. Réserve Sud
8.5. Réserve Nord
9. Bar
10. Amenities
11. Wardrobe
12. Restrooms
13. Restaurant
14. Chef's course
15. Convenience store
16. Reception Hall

Room Allocation

Ground floor

Totem Nord et Réserve Centre: Breakfast and Lunch breaks

Tipi-Tente-Wigwam & Réserve Sud-Nord: Poster sessions

First floor

La Montagnaise: Main congress room and Gala evening

Reception Hall: Registration desk and participant welcome

Internet/Wi-Fi

Free Wi-Fi is available on site: Le-Montagnais

No password required.

Accommodations

Le Montagnais (Congress Venue)

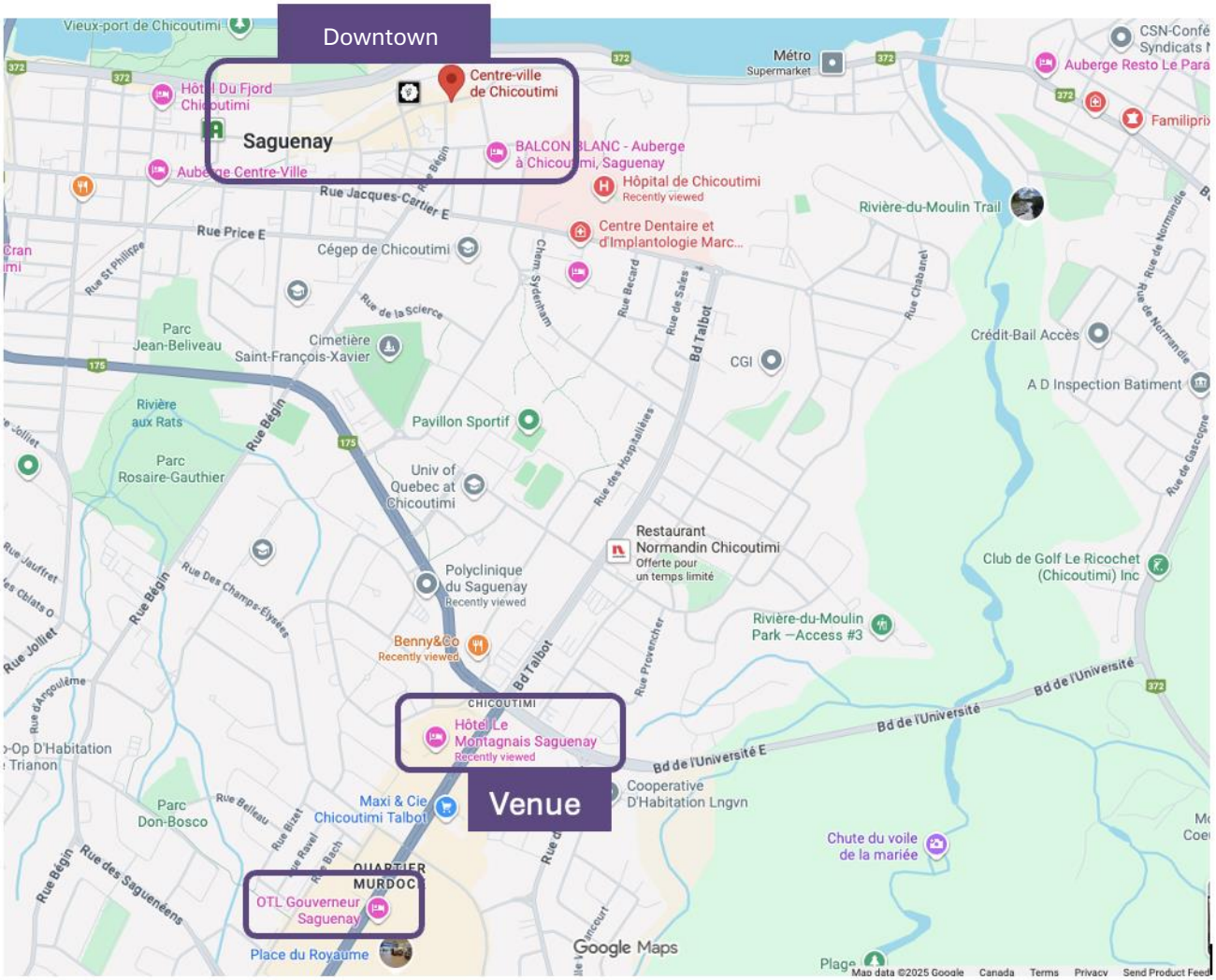
https://lemontagnais.qc.ca/en/

OTL Gouverneur Saguenay

750 m from the venue

https://www.otlhotelsaguenay.ca/en/

Map of Saguenay



Google map

Public transportation

Bus

In-City bus line

- For more information and bus line: https://sts.saguenay.ca
- 4$ CAD (Cash only)

Car rent

- Enterprise | 418-698-8755 | enterprise.com
- Location Sauvageau | 418-698-5411 / 418-548-2115 / 418-544-7655 | sauvageau.qc.ca
- National Car Rental | 418-549-3888 / 418-547-7486 / 418-677-2061 | nationalcar.ca

Taxi

TAXI-UNIS: 418-543-3868 | 418-545-3868 | taxis-unis.com

More about Saguenay

If you would like more information about Saguenay–Lac-Saint-Jean, click on the following link: https://promotion.saguenay.ca/en

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Nicolas Dumont, PhD, Université de Montréal, Montréal, Québec, Canada
Benjamin Gallais, PhD, Université du Québec à Chicoutimi, ÉCOBES, Saguenay, Canada
Luc Laberge, PhD, ECOBES, Saguenay, Canada

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Junior Chair

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Maryse Gagne, M.Sc. CORAMH, Saguenay, Canada
Cynthia Gagnon, PhD. GRIMN & Université de Sherbrooke, Saguenay, Canada
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Marc-Olivier Dugas, M.Sc. GRIMN, Saguenay, Canada

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Université de Montréal

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant
Université de Montréal

Invited speakers

The early history of the description of regional founder diseases in Quebec

Dr. Bernard Brais, M.D.C.M., M.Phil., Ph.D., FRCP(C)

Neurogeneticist, Professor of Neurology and Human Genetics, Clinical Chief of the Rare Neurological Disease Group of the Montreal Neurological Institute, Faculty of Medicine, McGill University

Dr Bernard Brais is a neurogeneticist and historian of medicine, Professor of Neurology and Human Genetics at McGill University and Clinical chief of the Rare Neurological Diseases group of the Montreal Neurological Institute. His research has been centered on the study of the genetic basis of rare neuromuscular disorders and ataxias with founder effects in the French-Canadian population of Quebec. He played a leading role in the identification of the first pathogenic variants in different genes responsible for hereditary conditions more common in Quebec. His major gene cloning work has been focused on uncovering the genes for late-onset neurological diseases such as Oculopharyngeal Muscular Dystrophy (OPMD) and Spinocerebellar ataxia type 27B (SCA27B).

Reducing diagnostic wandering using AI-based tools: the AIDY project

Pr. Roman Hossein Khonsari, MD, PhD

Pr. Roman Hossein Rhonsari is a consultant craniofacial surgeon at Necker-Enfants malades Hospital (AP-HP) and professor at Université Paris Cité, specialising in the clinical management of syndromic craniosynostoses. He heads the Craniofacial Growth and Form laboratory at the Imagine Institute in Paris and is medical director of PRIM3D, the central 3D design and printing platform for the Paris university hospitals. He chairs the Scientific Committee of ERN CRANIO and previously served as Chief Medical Officer of the Health Data Hub, France's national health data platform.

He trained in general surgery and maxillofacial surgery in Paris and Nantes, completed a craniofacial surgery fellowship at Great Ormond Street Hospital, London, and earned a PhD in craniofacial development from King's College London. He is an alumnus of the *École normale supérieure*. He was visiting professor in biomechanical engineering at University College London from 2021 to 2024 and has been visiting professor in craniofacial surgery at Erasmus Medical Center, Rotterdam, since 2026. His recent work includes the development of AIDY, a diagnostic application trained on more than one million clinical facial photographs. In 2024, he received the Ig Nobel Prize in Anatomy for research on geographic morphogenesis.

Tracking Economic Outcomes of Myotonic Dystrophy Patients - Planning Ahead Before It's Too Late

Dr. Jason Robert Guertin, PhD

Dr. Jason Robert Guertin is an Associate professor in Economic Evaluation of Health Technologies at Université Laval, Director of the short master-level program in Economic Evaluation of Health Technologies and a Researcher at the CHU de Québec-Université Laval research center and Université Laval's Tissue Engineering Laboratory (LOEX). His research program, supported via an FRQS Chercheur-boursier Junior 2 award (2023-2027), aims to support the economic evaluation of various regenerative medicine technologies using real-world cost-effectiveness analyses.

In addition to his academic appointment, in 2025, he became a member of the Health Economics Methods Advisory (HEMA) Working Group, an initiative created by Canada's Drug Agency (CDA-AMC), the National Institute for Health and Care Excellence (NICE) and the Institute for Clinical and Economic Review (ICER).

Art and 30 Years of IDMC; creative practice emerging from two artists living alongside and with myotonic dystrophy

Dr Jacqueline Donachie

Baxter Fellow | Associate Dean, Enterprise & Economic Transformation, Duncan of Jordanstone College of Art & Design, University of Dundee

Dr Jacqueline Donachie is Baxter Fellow at Duncan of Jordanstone College of Art and Design at the University of Dundee. Following graduation from Glasgow School of Art Donachie won a Fulbright Award for MFA at Hunter College in New York in the late 1990's, and has established an award-winning career as an artist working across socially engaged, interdisciplinary art practice.

Early collaborations, notably the artist book DM (2002) and the Wellcome Trust funded Tomorrow Belongs to Me (2006) with Professor of Human Genetics Darren Monckton (University of Glasgow) have been internationally cited for their contribution to the significant progress made in connecting families affected by inherited disability with the scientific researchers who study their genetic inheritance.

Her AHRC funded doctoral study Illuminating Loss, The Capacity for Artworks to Shape Research and Care in the Field of Genetics (Northumbria, 2016) was interdisciplinary, practice led and involved a high level of filmed participant interview with a range of women affected by myotonic dystrophy, recruited in collaboration with the UK Patient Registry. The work continued a long collaborative engagement with biomedical researchers in Newcastle and Glasgow, and the resultant moving image work Hazel won AHRC Best Doctoral Film prize in 2015. These films have been premiered at IDMC conferences, then exhibited in forums from small family support group meetings to international exhibition venues including the Gallery of Modern Art in Glasgow and the Tate in Liverpool, and are included in both Scottish and National art collections.

Scientific Program

Tuesday, 26 May 2026

09:00 - 14:00	Pharma Day with Euro-DyMA and MDF
09:00 - 16:00	Registration

Wednesday, 27 May 2026

08:00 - 16:00	Registration
8h15-8h30	Introduction
08:30 - 09:00	Invited Speaker – Past IDMC organizers
09:00 - 10:00	**Session: Pathogenic Mechanisms I**
	Single-Molecule Analysis Reveals Asymmetric CpG Methylation at the DM1 Locus Driven by Somatic Instability – Thomas D. Hoekman
	Alternative Splicing of SORBS1 Affects Neuromuscular Junction Integrity in Myotonic Dystrophy Type 1 - Morgan Gazzola
	Tissue-Specific Regulation of Full-Length MBNL1 via Alternative Transcriptional Termination - Katarzyna Taylor
	Profibrotic Factors and Extracellular Matrix Remodeling Associated with Muscle Fibrosis in Myotonic Dystrophy Type 1- Preeti Kumari
10:00 - 10:30	**Speed Dating**
10:30 - 12:15	**Poster Session with Coffee Break**
12:15 - 13:15	Lunch
13:15 - 13:30	**Flash Talk**
	Investigating the basis of sleep dysregulation in myotonic dystrophy type 1 - Belinda Pinto
	A cross-sectional study exploring the alignment between patient-reported and biomechanical dysphagia outcomes in myotonic dystrophy type1 (DM1) - Jodi Allen
	Growth, development, and social participation in congenital and childhood-onset myotonic dystrophy type 1: A nationwide survey in Japan - Yuzuha Ichimura
	DM1 RAN Proteins Accumulate in Autopsy Brain Regions with Degenerative and Neuroinflammatory Changes and Promote Tau Aggregation in Neuronal Cells – Monica Banez-Coronel
	Advancing motor function assessment across childhood in congenital and childhood-onset DM1 - Michael Kiefer
13:30 - 14:15	**Patient Engagement in Research**
14:15 - 15:00	**Session: Children with DM**
	Natural history of oropharyngeal dysphagia in children with congenital and childhood myotonic dystrophy type 1: a 3-year longitudinal cohort study - Saskia Scholten
	On the Move: Longitudinal Insights Advancing the Understanding of Motor Function in Paediatric Myotonic Dystrophy Type 1 - Lynn Orriëns
	Cognitive and Behavioral Impairment in Congenital and Childhood-Onset Myotonic Dystrophy Type 1: A Longitudinal Analysis - Anna Falco

Thursday, 28 May 2026

08:00 - 16:00	Registration
	Introduction
08:30 - 09:00	Invited Speaker: Roman Khonsari, MD, PhD
09:00 - 10:15	**Session: Development of Biomarkers and Clinical Outcome Assessments I**
	Clinical Validation of Socially Assistive Robot-Administered Physical Tests in Myotonic Dystrophy Type 1 - Killian Lachaux
	Multi-omic profiling stratified by the Splicing Index enables circulating biomarker discovery in myotonic dystrophy type 1 - Melissa Hale
	DM1-Hub registry: building a nationwide infrastructure to define the natural history of myotonic dystrophy type 1 - Gisela Nogales-Gadea
	Cerebrospinal fluid multi-omic biomarkers of myotonic dystrophy type 1 - Preeti Kumari
	Disease progression in Myotonic Dystrophy Type 2 -Johanna Hamel
10:15 - 10:45	Coffee Break
10:45 - 11:30	**Session: Clinical Manifestations, Activity and Participation I**
	Cognitive and Social cognition functioning in adults with childhood myotonic dystrophy type 1 - Simon-Pierre Gagnon
	A Multidimensional Profile of Dysphagia in Myotonic Dystrophy Type 1 (SwallowDM1) - Jodi Allen
	Preimplantation Genetic Testing in Myotonic Dystrophy Type 1: Clinical Outcomes and Insights - Johanna Bruijnes
11:30 - 12:45	**Session: Cell and Animal Models for DM**
	A repressible CUG repeat RNA mouse model to study the neurological manifestations and their reversibility in myotonic dystrophy type 1 - Larissa Nitschke
	Bioengineered 3D Muscle Tissues Identify an MBNL1-Independent Mechanism of Calcitriol-Mediated Myotonia Rescue - Juan M. Fernández-Costa
	Transcriptomic and molecular characterization of a neuronal mouse model for myotonic dystrophy type 1 (DM1) - Juan D. Arboleda
	Consequences of congenital myotonic dystrophy during neuromuscular development - Caroline Hermitte
	RNA and RAN Protein Gain-of-Function Effects in a Novel DM2 BAC Transgenic Mouse Model - Hannah Golliher
12:45 - 13:45	Lunch
13:45 - 15:00	**Session: Pathogenic Mechanisms II**
	Evidence of nuclear DMPK transcript degradation and cytoplasmic export in DM1 cells using dSTORM Super Resolution Microscopy - Petter Hamilton-Stanley
	Axon initial segment disruption and impaired vesicle transport reveal neuron-intrinsic mechanisms of brain dysfunction in DM1 - Louison Daussy
	Toxic CUG RNA repeats disrupt developmentally regulated splicing in oligodendrocytes causing transient hypomyelination in a mouse model of myotonic dystrophy - Gabriele Ordazzo

	Converging mechanisms of DMPK and TCF4 CTG repeat expansions underpin Fuchs endothelial corneal dystrophy - Christina Zarouchlioti
	Autism-related traits in myotonic dystrophy type 1 - Łukasz Sznajder
15:00 - 15:15	**Flash Talk**
	Methylation of CCG variant repeats is associated with heterogeneous methylation of CpG sites surrounding DMPK expansion in DM1 patients - Jovan Pesovic
	Development and Expert Evaluation of a Clinical Checklist for Adult Myotonic Dystrophy Type 1 Care – Charles Kassardjian
	Apathy as a Distinct Executive Phenotype in Adult Myotonic Dystrophy Type 1 - Melissa M. Dixon
	Proteogenomic Discovery of Splice-Junction Peptides as Novel Biomarkers in Cerebrospinal Fluid of Myotonic Dystrophy Type 1 (DM1) - Marwa Zafarullah
15:15 - 16:15	Late-Breaking session
16:15 - 19:00	**Poster and Networking Session**
Friday, 29 May 2026	
08:15 - 08:30	Introduction
08:30 - 09:00	Invited Speaker: Jason Robert Guertin, PhD
09:00 - 10:00	**Session: Development of Biomarkers and Clinical Outcome Assessments II**
	Developing digital endpoints to assess ambulation in DM1: analytical validation and feasibility of using a wearable sensor in daily living - Stéphane Motola
	Beyond balance: exploring cerebellar cognition in Myotonic Dystrophy Type 1 - Carola Rita Ferrari Aggradi
	Cross-sectional and 3-year longitudinal analysis of RNA mis-splicing in vastus lateralis muscle in a DM1 cohort - Cécilia Légaré
	Multicenter Multimodal Imaging Reveals System-Level CNS Disruption in Pediatric Myotonic Dystrophy Type 1 - Tahereh Kamali
10:00 - 10:30	Coffee Break
10:30 - 11:30	**Session: Clinical Manifestations, Activity and Participation II**
	Frailty in DM1: Prevalence and Associations with Disease-Specific Factors - Irati Larrañaga
	Everyday Cognitive Failures in Myotonic Dystrophy Type 1 (DM1): A Longitudinal Study – Stefan Winblad
	Vitamin D Deficiency and Respiratory Muscle Dysfunction in Myotonic Dystrophy Type 1 - Daniel Jaraj
	Identifying an Appropriate Patient-Reported Outcome Measure for Oropharyngeal Dysphagia in Myotonic Dystrophy Type 1 - Claudia Côté
11:30 - 12:30	**Session: Clinical Management, Rehabilitation and Quality of Life Improvement**
	Energy Expenditure and the Accuracy of Predictive Equations in Myotonic Dystrophy Type 1 - Isis B.T. Joosten
	Feasibility, acceptability and effects of a telerehabilitation-based Respiratory Training Program in Myotonic Dystrophy Type 1 - Elie Fiogbé
	The Current Landscape of Perinatal Information Provision and Genetic Counseling in Congenital Myotonic Dystrophy Type 1 in Japan - Ayumi Yonei
	Impact of assisted reproductive technologies on reproductive outcomes in women with myotonic dystrophy: a retrospective study - Patricia Garay-Albízuri
12:30 - 13:30	Lunch

13:30 - 14:45	**Session 5: Preclinical and Clinical Drug Development**
	Multiscale imaging uncovers xenogeneic regenerative capacity of human pericytes as a cell therapeutic vehicle - Renée H.L. Raaijmakers
	Scaling therapeutic discovery in DM1: A validated high-throughput platform combining in vitro screening and machine learning - Virginia Arechavala-Gomeza
	Tricyclo-DNA antisense oligonucleotide compounds to tackle toxic CUGexp-RNA in a mouse model of Myotonic Dystrophy type 1 - Julie Fagioli
	Sensor-Regulated Decoy Gene Therapy for Myotonic Dystrophy Type 1 - Ludovic Arandel
	Interventionally Contracting Somatic CTG Repeat Expansions as a Disease-Modifying Strategy for Myotonic Dystrophy Type 1 - Shuqian Tang

Session's topics overview

Session 1: Pathogenic Mechanisms I

- Darren Monckton
- Aymeric Ravel Chapuis

This session focuses on the underlying biological and molecular mechanisms driving disease progression. Topics may include genetic mutations, RNA toxicity, protein dysfunction, genome stability, and cellular pathways involved in disease pathogenesis.

Session 2a: Development of Biomarkers and Clinical Outcome Assessments I:

- Valeria Sansone
- Elie Fiogbe

This session highlights research on biomarkers that aid in diagnosis, disease monitoring, and prognosis, as well as the development and validation of clinical outcome assessments for evaluating disease progression and treatment response.

Session 3a: Clinical Manifestations, Activity and Participation I:

- Karin Faber
- Joana Garmendias

This session covers the diverse clinical symptoms associated with the disease and their impact on daily life. Presentations may address functional impairments, activity limitations, and participation restrictions, integrating both clinical and patient-reported outcomes.

Session 4: Cell and Animal Models for DM:

- Eric Wang
- Pauline Garcia

This session focuses on the generation and use of cellular and animal models to study disease mechanisms and test therapeutic interventions. It includes advancements in transgenic models, stem cell research, and novel methodologies for model optimization.

Session 5: Preclinical and Clinical Drug Development:

- Andy Berglund
- Cécilia Légaré

This session addresses the translation of scientific discoveries into therapeutic strategies. Topics may include drug screening, target identification, gene therapy, preclinical studies, and early-phase clinical trials evaluating the safety and efficacy of potential treatments.

Session 6: Children with DM:

- Anne-Berit Ekström
- Nikoletta Nikolenko

This session explores the specific challenges and research related to pediatric populations affected by DM. Presentations may include early disease manifestations, impact on motor development and functional milestones, pediatric clinical trials, treatments and strategies for early intervention.

Session 7a: Clinical Management, Rehabilitation and Quality of Life Improvement:

- Masanori Takahashi
- Anne Bruijnes

This session focuses on improving patient care through clinical management strategies and rehabilitation approaches. Topics may include multidisciplinary care models, assistive devices, and interventions, such as fatigue management and exercise.

Patient Engagement in Research: This session highlights meaningful partnerships between patients and researchers to enhance the relevance and impact of scientific discovery.

Late-Breaking session: This one-hour session will feature newly generated, unpublished data from researcher, and industry-sponsored clinical trials.

Social program

Tuesday, 26 May 2026

Welcome Reception in La Baie: 4h10 – 10:00 pm

Our opening conference will offer a unique perspective on the connection between the region's original settlement and the high prevalence of myotonic dystrophy type 1. In addition, you will have an unforgettable immersion in the settlement story through the acclaimed production *La Fabuleuse Histoire d'un Royaume*, specially designed for IDMC participants.

This special reception is the perfect opportunity to connect with fellow attendees, experience the warmth of local hospitality, and officially kick off IDMC-15 in a relaxed and welcoming atmosphere. Cocktails and hors d'oeuvres will be served throughout the evening.

Transportation to the venue will start in the following order **for bus 1-2-3**

OTL Le Gouverneur at 4h10 PM

Le Montagnais at 4h20 PM

La Saguenéenne at 4h30 PM

Transportation for the bus 4-5-6

OTL Le Gouverneur at 4h40 PM

Le Montagnais at 4h50 PM

La Saguenéenne at 5h00 PM

Transportation for the bus 7

OTL Le Gouverneur at 5h10 PM

Le Montagnais at 5h20 PM

La Saguenéenne at 5h30 PM

Buses returning from the event will **depart** La Baie between **9:45 PM** and **10:00 PM** and will **provide transportation** back to the congress venue, **the** OTL**,** and La Saguenéenne.

Wednesday, 27 May 2026

Step Back in Time: The Story of Val-Jalbert and Saguenay–Lac-Saint-Jean: 3:30 – 11:00 pm

Step into the past with a visit to the historic village of Val-Jalbert, a living testimony to the roots of the Saguenay-Lac-Saint-Jean region.

Wander through remarkably preserved buildings, walk the streets of a once-thriving industrial community, and gain insight into the social and economic forces that shaped the settlement of the area. This immersive experience offers a unique perspective on the history and heritage of the region where IDMC-15 takes place.

Transportation will depart from the congress venue. Dinner will be served on-site at Val-Jalbert, allowing you to continue the journey into the past while enjoying local hospitality.

Departures will be from the congress venue only. You need to check your bus number and departure time on your ticket (green one).

Departure times will range from 3:30 PM to 4:30 PM. Return transportation will be provided to the congress venue, the OTL, and La Saguenéenne according to your departure time.

Thursday, 28 May 2026

Free diner: 7:00 – 11:00pm

Bites, Sips & Saguenay Vibes: Chicoutimi Downtown

Discover a wide range of dining experiences downtown, where local flavors and international cuisine offer something for every palate. Convenient shuttle service will bring you to the venue from the congress venue only and ensure a comfortable return to congress venue, OTL and La Saguenéenne.

Departure time at 18h30 and 19h00 from the

Return time run from 9h30-10h00 and 11h00.

For the return to the hotels, transportation will depart from Restaurant La Cuisine (387, rue Racine Est, Chicoutimi) and will stop at the congress venue, OTL and La Saguenéenne.

Special Activity for Trainees: CORAMH

For the first time at an IDMC conference, we are excited to host a special event exclusively for trainees. This evening activity, organized by our Student Committee, will be a fun and informal opportunity to connect with fellow trainees.

Registration is mandatory. Dinner will be offered free of charge. The departure time at the congress venue wil be at 18h30 or 19h00.

For the return to the hotels, transportation will depart from CORAMH at 22h00 and 22h30 and will stop at the congress venue, OTL and La Saguenéenne.

Friday, 29 May 2026

Awards and Gala Night: Dine, Dance & Celebrate! Starting at 05:30pm

Step into an elegant evening at the Congress Venue with great company, lively music, and a festive atmosphere that will keep you on your feet all night—featuring Saguenay's local delicacy, poutine, alongside a delicious dining experience.

Oral presentations Wednesday May 27, 2026

Session: Pathogenic Mechanisms I

80 - Single-Molecule Analysis Reveals Asymmetric CpG Methylation at the DM1 Locus Driven by Somatic Instability

Thomas D. Hoekman[1], Lisa Rahm[2], Casper de Visser[1], Yavuz Ariyurek[3], Susan L. Kloet[3], Lotte L.J. Put[4], Hans van Bokhoven[2], Peter A.C. 't Hoen[1], Derick G. Wansink[1]

[1]Department of Medical BioSciences, Radboud University Medical Center, Nijmegen, The Netherlands, [2]Department of Human Genetics, Donders Institute for Brain, Cognition, and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands, [3]Leiden Genome Technology Center, Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands, [4]Department of Neurology, Maastricht University Medical Center, Maastricht, The Netherlands; Mental Health and Neuroscience Research Institute, Maastricht University, Maastricht, The Netherlands

The expanded CTG repeat in the *DMPK* gene is characterized by somatic instability and has been associated with abnormal, local CpG methylation profiles. DNA methylation flanking *DMPK* has been investigated across different tissues, with distinct methylation signatures reported to correlate with either cognitive or

muscular phenotypes. However, it remains unclear how DNA methylation is distributed across the DM1 locus, or how it relates to CTG repeat length and cellular identity. Using genome-wide enzymatic methyl (EM)-sequencing in early-stage iPSC-derived neurons, we identified a strong association between repeat length and DNA methylation, with extensive 5' site methylation in cells carrying large expansions (>2000 CTGs). Although EM-sequencing improves CpG mapping and reduces DNA fragmentation compared to bisulfite-based methods, it provides only bulk measurements and requires independent measurement of CTG repeat length. To overcome these limitations, we applied amplification-free targeted long-read sequencing, enabling single-molecule resolution analysis of repeat length and CpG methylation across the DM1 locus. Oxford Nanopore sequencing of DNA derived from iPSCs and primary myoblasts expressing a wide range of CTG repeat lengths revealed clear repeat length-dependent DNA methylation on both sides of the repeat. The 5' region was largely unmethylated in alleles carrying ~100-400 CTGs but became hypermethylated above ~600 triplets. In contrast, the 3' region (direction of *SIX5*) remained largely unmethylated up to ~900 CTGs and showed pronounced hypermethylation only above ~1200 CTGs, demonstrating asymmetric, repeat length-dependent methylation thresholds. Even within individual samples, heterogeneous repeat lengths showed similar repeat-length dependent methylation thresholds, suggesting ongoing somatic instability shapes DNA methylation. Altogether, our results establish a direct relationship between somatic instability and DNA methylation in DM1. By applying this approach to longitudinal samples from patient tissues and iPSC-derived cells, we are tracking somatic CTG repeat instability over time and relate repeat length dynamics to epigenetic changes at the DM1 locus.

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125 - Alternative Splicing of SORBS1 Affects Neuromuscular Junction Integrity in Myotonic Dystrophy Type 1

Caroline Hermitte[1], Hortense de Calbiac[2], Gilles Moulay[3], Antoine Mérien[1], Jeanne Laine[3], Hélène Polvèche[1], Michel Cailleret[1], Edor Kabashi[2], Stéphane Vassilopoulos[3], Denis Furling[3], Cécile Martinat[1], Morgan Gazzola[1]

[1]Institut des cellules souches pour le traitement et l'étude des maladies monogéniques (I-Stem), Corbeil-Essonnes, [2]Institut Imagine, Hôpital Necker, Paris, [3]Institut de myologie, Hôpital de la pitié Salpêtrière, Paris

Rational: Myotonic dystrophy type 1 (DM1) is a multisystemic neuromuscular disease caused by the expansion of CTG repeats in the 3' untranslated region of the DMPK gene. Expanded CUG-containing DMPK transcripts aberrantly sequester RNA-

binding proteins, notably Muscleblind-like (MBNL) proteins, leading to widespread splicing defects. We previously identified abnormal splicing of SORBS1 exon 25 in DM1 and in MBNL1/2 double-knockout human induced pluripotent stem cell (hiPSC)-derived skeletal muscle cells, suggesting that SORBS1 mis-splicing may contribute to DM1 pathophysiology.

Methods: We investigated SORBS1 exon 25 splicing misregulation in human skeletal muscle biopsies from DM1 patients and healthy controls. To assess the functional consequence of SORBS1 exon 25 exclusion, we used antisense oligonucleotide-mediated exon-skipping strategy in mouse and zebrafish models, as well as in hiPSC-derived skeletal muscle cells.

Results: In fetal skeletal muscle biopsies from congenital DM1 patients, inclusion of SORBS1 exon 25 was reduced by 52.6 ± 10% compared to controls. Consistently, analysis of RNA sequencing data from the DMseq database revealed significant misregulation in tibialis anterior muscle from 40 adult DM1 patients, with a 15.8 ± 3.7% decrease in exon inclusion. In mice, forced exclusion of Sorbs1 exon 25 induced neuromuscular junction (NMJ) defects, including increased denervation (10.5% ± 3.4%) and postsynaptic destabilization (5.7% ± 2.5%). In zebrafish, exon 25 misregulation impaired locomotor performance, reducing trajectory, distance and velocity, while also disrupting acetylcholine receptor cluster (AChR) morphology. Similarly, in hiPSC-derived skeletal muscle cells, enforced SORBS1 exon 25 exclusion reduced the formation of large AChR clusters upon agrin stimulation.

Conclusion: These findings identify SORBS1 exon 25 as a critical MBNL-dependent splicing event required for proper NMJ formation and maintenance. The aberrant SORBS1 splicing in DM1 highlights a novel mechanism by which splicing dysregulation disrupts neuromuscular connectivity, underscoring the importance of RNA processing in NMJ integrity and disease pathogenesis.

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131 - Tissue-Specific Regulation of Full-Length MBNL1 via Alternative Transcriptional Termination

Katarzyna Taylor[1], Marta Jakimowicz[1], Klaudia Kubiak[1], Magdalena M Masłoń[2], Eliza Kopera[1], Anna Baud[1], Lukasz J Sznajder[3], Krzysztof Sobczak[1]

[1]Laboratory of Gene Therapy, Institute of Molecular Biology and Biotechnology, Adam Mickiewicz University in Poznań, Poland, [2]Laboratory of RNA Biology, Malopolska Centre of Biotechnology, Krakow, Poland, [3]Department of Chemistry and Biochemistry, University of Nevada, Las Vegas, NV, USA

Functional loss of the Muscleblind-like (MBNL) family of proteins contributes to a broad spectrum of symptoms in myotonic dystrophy (DM). Deepening our understanding of MBNL gene biology—the focus of this study—may provide insight into DM pathomechanisms, symptom development, and potential therapeutic strategies.

Here, we describe an immune-specific RNA processing event within the MBNL1 locus that modulates the balance between full-length MBNL1 and a truncated alternative isoform, termed altMBNL1.

We show that activation of an intronic polyadenylation (IPA) combined with inclusion of a cryptic exon within the longest MBNL1 intron leads to production of altMBNL1 RNA predominantly in immune cells and secondary lymphoid organs. Notably, cryptic exon inclusion inversely correlates with full-length MBNL1 levels.

DRB-driven analysis of transcription kinetics reveals that rapid transcription across the long MBNL1 intron favours skipping of the weak cryptic splice site, whereas transcriptional slowing—induced by mutant RNA polymerase II—enhances exon inclusion, consistent with the “window of opportunity” model.

We identify a key RNA-binding protein that safeguards transcriptional integrity across the MBNL1 intron. Its depletion in various cell lines activates IPA and cryptic exon inclusion, resulting in reduced full-length MBNL1 expression and altMBNL1 RNA upregulation. Antisense oligonucleotide screening uncovers two cis-regulatory elements controlling cryptic exon splicing, validated by targeted mutagenesis. CRISPR-Cas9 deletion of the cryptic exon promotes MBNL1-dependent splicing programs, supporting functional relevance.

We further show that altMBNL1 is a relatively stable RNA with canonical 3'-end features of messenger RNAs and its sensitivity to deadenylase depletion. altMBNL1 may be translationally engaged, as evidenced by publically Ribo-seq and micropeptide detection from a splicing minigene.

Together, these findings reveal an immune-specific mechanism regulating endogenous full length MBNL1 expression. Given high CNBP and low DMPK expression in immune cells, this pathway may be particularly relevant to immune dysfunctions in DM2.

174 - Profibrotic Factors and Extracellular Matrix Remodeling Associated with Muscle Fibrosis in Myotonic Dystrophy Type 1

Preeti Kumari[1, 2], Zhaozhi Li[1, 2], Greta Tacconi[1, 2], Akhila Gundavelli[1, 2], Rojashree Jayakumar[1, 2], Ningyan Hu[1, 2], Sudeshna Das[1, 2], Thurman Wheeler[1, 2]

[1]Massachusetts General Hospital, [2]Harvard Medical School

Fibro/adipogenic progenitors (FAPs) are stromal cells that differentiate into fibroblasts and adipocytes, and play critical roles in muscle repair and fibrosis. Following acute muscle injury, FAPs transiently expand to support myogenesis and ECM deposition. In aging and senescence, muscle stem cells (MuSCs) can initiate fibrosis through trans-activation of FAPs to acquire a fibrogenic phenotype. In necrotizing myopathies and muscular dystrophies, fibrosis results from repeated rounds of muscle degeneration and regeneration combined with chronic inflammation. DM1 myopathy is non-necrotizing and shows very little evidence of regeneration or cellular inflammation, suggesting that MuSC dysfunction may contribute to fibrosis in DM1. The HSA^LR transgenic and the HSA^LR;Mbnl1-/- (HM) double homozygous mouse models of DM1 express a (CUG)_n repeat expansion, develop progressive myopathy, and share the molecular mechanism of human DM1. Here we test the hypothesis that MuSC dysfunction contributes to fibrosis in DM1. Using enzymatic digestion and fluorescence-activated cell sorting, the total number of MuSCs was 2.5-fold higher and the proportion of MuSCs among sorted cells was 3-fold higher in *HSA^LR* mice compared with *mdx* or WT controls. RNA sequencing analysis identified over 400 differentially expressed genes in HM vs WT MuSCs. Gene Set Enrichment Analysis revealed significant upregulation of pathways related to extracellular matrix organization, collagen degradation, cell cycle regulation, and cellular senescence. Key upregulated genes (*Lgals3*, *Spp1*, *S100a4*, *Mmp13*, *Col13a1*, *Fabp5*) are associated with ECM remodeling and fibrosis, while *Cdk6* and *Hmga2* are senescence related. Droplet digital PCR and immunofluorescence analyses confirmed increased expression of these genes in MuSCs, stromal cells, and muscle tissue of DM1 mouse models, and in human DM1 muscle biopsies. Our data suggests DM1 molecular pathogenesis induces fibrosis by promoting senescence and upregulation of profibrotic mediators in MuSCs and their niche. Expanding knowledge of MuSC-niche interactions will facilitate development of strategies to mitigate fibrosis in DM1 patients.

176 - Myogenic progenitors fuse with mature fibers and give rise to centrally located nuclei in DM1

Vanessa Todorow[1, 2], Xavière Lornage[3], Shinichiro Hayashi[2], Benedikt Schoser[1], Denis Furling[3], Peter Meinke[1], Frédérique Rau[3]

[1]Friedrich-Baur-Institute, Munich, [2]National Center for Neurology and Psychiatry Tokyo, [3]Sorbonne Université, Inserm, Paris

Central nuclei are a prominent and early histopathological feature of skeletal muscle in myotonic dystrophy type 1 (DM1), yet their cellular origin and underlying mechanism remain unclear, as they occur largely in the absence of overt muscle degeneration. Here, we sought to determine whether muscle stem cells (MuSCs) contribute to central nuclei formation in DM1 muscle. We combined an adult, myofibre-specific Mbnl1/2 knockdown mouse model with lineage tracing, MuSC ablation, proliferation assays, and single-nucleus RNA sequencing (snRNA-seq), and complemented these analyses with histological and snRNA-seq profiling of human DM1 muscle biopsies. In adult mouse muscle, myofibre-restricted Mbnl depletion recapitulated key DM1 features, including myotonia, fibre type remodelling, increased myonuclear content, and a marked increase in centrally located nuclei without detectable necrosis. EdU incorporation and Pax7 lineage tracing demonstrated robust MuSC activation, proliferation, and fusion into existing myofibres, while genetic ablation of Pax7+ MuSCs abolished the increase in central nuclei, establishing MuSC fusion as a major source of these nuclei. Mouse snRNA-seq revealed the emergence of distinct myonuclear populations with transcriptional features normally restricted to developmental or stress-associated states. In human DM1 muscle biopsies, we observed increased numbers of central and peripheral myonuclei, elevated PAX7+ and Ki67+ nuclei, including Ki67+ myonuclei, and an expanded myonuclear population with a mixed transcriptional identity sharing features with both MuSCs and mature myofibres. Together, these data demonstrate that a substantial proportion of central nuclei in DM1 muscle arise from MuSC fusion with existing myofibres. Our findings reveal an unexpected MuSC contribution to DM1 muscle homeostasis and highlight that central nuclei in DM1 do not solely reflect classical degeneration-associated regeneration, underscoring the need to reassess their biological significance in this disease.

Flash Talk

8 - Investigating the basis of sleep dysregulation in myotonic dystrophy type 1

Belinda Pinto[1], Emily Davey[1], Juan Arboleda[1], Miguel Gutierrez[1], Charles Thornton[2], Karyn Esser[1], Eric Wang[1]

[1]University of Florida, [2]University of Rochester Medical Center

Myotonic Dystrophy Type 1 (DM1) has profound CNS symptoms, with sleep dysregulation and hypersomnia being particularly debilitating. However, the physiological basis for these symptoms is unknown. Interestingly, actigraphic studies of DM1 patients suffering from hypersomnia show low amplitude sleep-wake rhythms with a ~2 hour delayed sleep phase or non-24-hour sleep wake disorder suggesting that disruption of circadian mechanisms could contribute to sleep dysregulation in DM1. To determine the basis of this phenotype, we have undertaken circadian activity analyses of multiple DM1 mouse models in which MBNL function is perturbed to different degrees: 1) the KI^{480}, which has 480 CTG repeats knocked into the mouse *Dmpk* 3' UTR, representing a mild form of the disease 2) the $Mbnl2^{-/-}$, which lacks the dominant MBNL in the CNS, representing a severe form of the disease and 3) KI^{1700}, with 1700 CTG repeats, and $KI^{480}/KI^{480}; Mbnl2^{+/-}$, representing intermediate symptomology. We find a variety of circadian activity phenotypes ranging from a shorter circadian period in the KI^{480} model to a phase delay of 2-3 hours in the KI^{1700} and $KI^{480}/KI^{480}; Mbnl2^{-/+}$ mice with a loss of rhythmic activity in the $Mbnl2^{-/-}$ mice. Interestingly, the models which display a phase delay reminiscent of DM1 patient symptomology, have a normal circadian period length as determined in the absence of light cues. This suggests that this phenotype may be due to altered photic entrainment. To further determine whether these mice have entrainment defects, we will examine phase response curves and response to phase advances and phase delays. As MBNL2 plays an important role in splicing regulation, we will perform transcriptomic analyses of key tissues involved in entrainment; the SCN and the ipRGCs. Findings from these studies will shed light on how circadian disruption contributes to sleep dysregulation in DM1 and other repeat expansion diseases.

95 - A cross-sectional study exploring the alignment between patient-reported and biomechanical dysphagia outcomes in myotonic dystrophy type1 (DM1)

Jodi Allen[1], Tom Parry[2], Caroline Waszkiewicz[1], Chris Turner[1], Christina Smith[3], Roganie Govender[4], Sue Mallett[2], Stuart Taylor[2]

[1]The National Hospital for Neurology and Neurosurgery, University College NHS Foundations Trust, UK, [2]University College London Centre for Medical Imaging, UK, [3]University College London Division of Psychology & Language Sciences, UK, [4]University College London Division of Surgery & Interventional Science

Studies in myotonic dystrophy type 1 (DM1) consistently demonstrate poor association between patient-reported dysphagia symptoms and instrumental assessment findings. This disconnect, potentially reflecting disease-related anosognosia or reduced symptom awareness, complicates clinical assessment and may lead to underdiagnosis of dysphagia. We investigated relationships between biomechanical dysphagia severity and patient-reported symptoms.

Ninety-four adults with DM1 were recruited from across the UK to a tertiary neuromuscular centre (July 2023 to August 2024). During the same visit, participants completed the Sydney Swallowing Questionnaire (SSQ), and Swallowing Quality of Life Questionnaire (SWAL-QOL), followed by a videofluoroscopic swallowing study using the Modified Barium Swallow Impairment Profile (MBSImP). Participants were stratified into three dysphagia severity groups based on MBSImP oral and pharyngeal sum score tertiles for comparison of symptom scores. Descriptive and graphical analysis was used.

Median age was 45 years (IQR 38, 52); 52 were female. MBSImP oral scores ranged from 3 to 17 (max 22) and pharyngeal scores from 1 to 23 (max 29), with higher scores indicating greater impairment. SSQ scores ranged from 20 to 1096 (max 1700), with higher scores indicating greater symptom burden; scores increased across oral dysphagia tertiles: median 136 (IQR 70, 350; n=27), 224 (84, 426; n=20), and 264 (106, 578; n=45), and pharyngeal dysphagia tertiles: median 152 (57, 270; n=22), 194 (78, 398; n=39), and 350 (183, 663; n=31). SWAL-QOL swallowing symptom scores (range 0-100, with higher scores indicating fewer symptoms) decreased across oral tertiles: median 68 (43, 81), 57 (41, 82), and 46 (34, 66), and pharyngeal tertiles: 68 (46, 86), 65 (38, 86), and 43 (30, 59). Individual questionnaire items will be presented, highlighting those with poor sensitivity for detecting differences in dysphagia severity.

These findings suggest that limitations in measurement sensitivity, rather than anosognosia, may explain previously observed disconnect between patient-reported and instrumental measures.

119 - Growth, development, and social participation in congenital and childhood-onset myotonic dystrophy type 1: A nationwide survey in Japan

Yuzuha Ichimura[1], Yuko Shimizu-Motohashi[2], Minobu Shichiji[3], Rie Honda[1], Michio Kobayashi[4], Tsuyoshi Matsumura[5], Hotake Takizawa[6], Toshio Saito[5], Akinori Nakamura[7], Kazuma Sugie[8], Atsuko Ishii[9], Ayumi Yonei[10], Tomoya Kubota[1], Yasuhiro Takeshima[11], Harumasa Nakamura[6], Midori Senoo[12], Haruo Fujino[9, 13], Hirofumi Komaki[2], Keiko Ishigaki[3], Masanori P. Takahashi[1, 9, 10]

[1]Clinical Neurophysiology, The University of Osaka Graduate School of Medicine, [2]Department of Child Neurology, National Center of Neurology and Psychiatry, [3]Tokyo Women's Medical University School of Medicine, [4]Department of Neurology, NHO Akita National Hospital, [5]Department of Neurology, NHO Osaka Toneyama Medical Center, [6]Department of Neurology, National Center of Neurology and Psychiatry, [7]Department of Neurology, NHO Matsumoto Medical Center, [8]Department of Neurology, Nara Medical University, [9]United Graduate School of Child Development, The University of Osaka, [10]Department of Genetic Counseling, The University of Osaka Hospital, [11]Department of Pediatrics, Hyogo Medical University, [12]Myotonic Dystrophy Patient's Group of Japan (DM-Family), [13]Graduate School of Human Sciences, The University of Osaka

Pediatric-onset myotonic dystrophy type 1 (DM1) differs clinically from adult-onset DM1. Congenital DM1 presents with neonatal hypotonia, respiratory impairment, and intellectual disability, while childhood-onset DM1 is also frequently associated with intellectual disability and autistic traits; these neurodevelopmental features markedly affect schooling, employment, and quality of life (QOL). This study aims to clarify the epidemiology, development, symptoms, and QOL of patients with pediatric-onset DM1 in Japan.

Questionnaires, primarily completed by parents, were mainly distributed through a patient registry (Remudy) with additional distribution via patient groups and neuromuscular centers. Survey items included basic demographics, genetic testing results, growth and development, schooling, employment, and family information. For comparative analyses, patients were classified by age at onset into congenital (CDM; <1 month), childhood-onset (ChDM; <10 years), and juvenile-onset DM1 (JDM; <18 years).

Of approximately 470 questionnaires distributed, 145 were returned, and 119 cases were included (48 CDM, 36 ChDM, 35 JDM). Mean current ages were 14.5, 22.9, and 36.5 years, respectively. In CDM pregnancies, polyhydramnios and massive hemorrhage during delivery occurred in 54.2% and 35.4%. In CDM, achievement

rates for major developmental milestones (head control, sitting, independent walking) remained at 30-40% at ages when these milestones are normally achieved. At two years of age, approximately 20% had achieved single-word speech and 15% two-word sentences. Intellectual disability was twice as frequent in CDM/ChDM as in JDM. Regarding final education attainment (n=70), 92.9% of CDM and 82.6% of ChDM graduated from high school, predominantly from special education schools, whereas 53.3% of JDM patients attained education beyond high school. Employment rates were 64.3% (CDM), 73.9% (ChDM), and 56.3% (JDM); assisted commuting was required by 50.0%, 52.6%, and 33.3%, respectively. Median monthly income was 20,000, 40,000, and 70,000 Japanese yen, respectively.

These findings provide critical insights into growth, development, and social participation for pediatric-onset DM1 in Japan.

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190 - DM1 RAN Proteins Accumulate in Autopsy Brain Regions with Degenerative and Neuroinflammatory Changes and Promote Tau Aggregation in Neuronal Cells

Monica Banez-Coronel[1], Eduardo E. Rijos[1], John D. Cleary[1], Tao Zu[1], Anthony T. Yachnis[1], Laura P.W. Ranum[1]

[1]University of Florida

Repeat-associated non-AUG (RAN) proteins have been reported in 18 repeat-expansion disorders, including DM1 and DM2. In DM2, toxic LPAC and QAGR RAN proteins accumulate in human autopsy brains, with prominent LPAC RAN protein aggregation in regions showing organized necrosis and macrophage/microglia infiltration (Zu et al., Neuron 2017). Less is known about the role of RAN proteins in DM1. Although polyglutamine RAN proteins were reported in cardiomyocytes and leukocytes from DM1 patients and mice, due to the lack of suitable antibodies to detect RAN proteins in the brain, it has remained unclear if DM1 RAN proteins contribute to DM1 brain pathology.

Because the DM1 CTG·CAG expansion is bidirectionally transcribed, we developed and validated novel antibodies recognizing putative polyLeucine and polySerine RAN proteins expressed from sense (CUG reading frame) or antisense (AGC reading frame) expansion transcripts. These antibodies were used for immunohistochemical analyses of DM1 and control postmortem human brain tissue.

Our data show that sense (polyLeu) and antisense (polySer) RAN proteins accumulate in DM1 frontal cortex and hippocampus as large cytoplasmic neuronal aggregates or microaggregates in glial cells and axons (n=9 DM1; n=9 controls). White

matter regions with intense RAN-positive staining show pathological features of disease, including activated microglia, increased GFAP staining and white-matter atrophy. Additionally, regions with prominent RAN protein accumulation also show robust Tau deposition and neurofibrillary tangles. Similar to a report showing polySer domains trigger tau aggregation, we show DM1 polySer RAN proteins promote neuronal p-Tau aggregation in a dose dependent manner.

Together, these results demonstrate that sense and antisense RAN protein aggregates accumulate in DM1 brain regions showing hallmark CNS features including, pTau aggregates, white matter-atrophy and neuroinflammation. Our data identify RAN proteins as contributors to DM1 brain histopathology and highlight the need to fully understand the role of RAN proteins in disease.

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199 - Advancing motor function assessment across childhood in congenital and childhood-onset DM1

Michael Kiefer[1], Julia Hartman[1], Kiera Berggren[1], Amanda Butler[1], Aileen Jones[1], Melissa McIntyre[2], Man Hung[3], Samuel Carrell[1], Melissa Hale[1], Craig Campbell[4], Valeria Sansone[5], Nicholas Johnson[1]

[1]Center for Inherited Myology Research, Department of Neurology, Virginia Commonwealth University, Richmond, Virginia, USA, [2]Department of Pediatric Neurology, University of Utah, Salt Lake City, Utah, USA, [3]Roseman University, Salt Lake City, Utah, USA, [4]Department of Pediatrics, London Children's Hospital, University of Western Ontario, London, Ontario, Canada, [5]The NEuroMuscular Omnicentre (NEMO) Clinical Center, Milan, Italy

Therapeutic development in myotonic dystrophy has advanced rapidly, yet pediatric trials remain limited by the lack of feasible, sensitive, and clinically meaningful endpoints. Capturing motor function across a wide range of ages and abilities is essential to detect treatment effects and inform trial design.

Secondary analysis of previous natural history study of 138 observations from 42 children aged 3-15 years with CDM showed delayed walking in congenital myotonic dystrophy (CDM), with a median age of independent walking of 24 months (IQR 18-27). Age at independent walking was strongly correlated with [MBNL]inferred, a biomarker of splicing dysregulation (rho = −0.708, p = 0.001), and predicted later motor performance, including 10-meter walk/run velocity (R^2 = 0.31, β = 0.2, p = 0.003). These results highlight the need for endpoints that capture motor function in young children who have not achieved independent walking and demonstrate the value of early quantitative motor assessment to inform trial design across childhood.

Building on these insights, the TREAT-EXT and ASPIRE natural history studies were designed to establish feasible and sensitive outcome assessments in congenital and childhood-onset DM1. Data collection is ongoing and includes evaluation of the Gross Motor Function Measure (GMFM). The GMFM is validated in multiple neuromuscular conditions and captures motor abilities from infancy through adolescence. Interim analysis of five children aged 9-16 years with CDM demonstrated feasibility, with only 2.9% of items scored as "Not Tested." Item difficulty was consistent across GMFM-88 and the Rasch-derived GMFM-66, with lower scores in higher-level domains. GMFM-88 and GMFM-66 scores were strongly correlated (r = 0.95), supporting use of GMFM-66 in DM1. Scores ranged from 20.8-99.2 (GMFM-88) and 35.2-89.7 (GMFM-66).

Overall, these findings support the feasibility of GMFM to quantify motor function in pediatric DM1 and guide clinical trial design.

Session: Children with DM

40 - Natural history of oropharyngeal dysphagia in children with congenital and childhood myotonic dystrophy type 1: a 3-year longitudinal cohort study

Saskia Scholten[1], Marloes Lagarde[1], Lynn Orriëns[2], Corrie Erasmus[2], Saskia Houwen - van Opstal[1], Simone Knuijt[3], Jan Groothuis[3], Hilde Braakman[2]

[1]Department of Rehabilitation, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, Amalia Children's Hospital, Nijmegen, The Netherlands, [2]Department of Paediatric Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical centre, Nijmegen, Amalia Children's Hospital, The Netherlands, [3]Department of Rehabilitation, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, The Netherlands

In myotonic dystrophy type 1 (DM1), weakness of oropharyngeal musculature may cause difficulties with mastication and swallowing (oropharyngeal dysphagia, OD). Although clinical features of OD in children with DM1 have been described, knowledge of long-term progression remains limited. This study aims to investigate the prevalence and progression of OD, the functional oral intake and patient or caregiver-reported complaints related to OD in children with DM1, distinguishing between congenital and childhood-onset DM1.

We retrospectively analyzed data collected over a 3-year period, from children with DM1 (0-18 years). Data were obtained from speech language therapy (SLT) reports, in

which OD severity was graded using the Australian Therapy Outcome Measures (AusTOMs) swallowing scale and functional oral intake using the Child Eating and Drinking Ability Scale (CEDAS); both scales were based on history taking, observation, and clinical measurements. Patient or parent-reported complaints were derived from SLT history taking.

We present repeated measurements from 141 visits of 56 children (28 congenital-onset DM1, 28 childhood-onset DM1), with 1-4 assessments per child. Preliminary results from the index visit show that 91% of the children exhibit OD, 54% have a limited functional intake, and 69% report complaints. Across all visits, children with congenital DM1 show slightly more severe OD and relatively greater limitations in functional oral intake compared to children with childhood DM1. OD severity and functional oral intake are plotted against age for congenital DM1, childhood DM1, and the total group.

Both children with congenital and childhood-onset DM1 frequently present with OD, and functional limitations in oral intake are also common. OD tends to be slightly more severe in congenital DM1. Since OD occurs more frequently than reported complaints, regular SLT consultation is recommended.

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89 - On the Move: Longitudinal Insights Advancing the Understanding of Motor Function in Paediatric Myotonic Dystrophy Type 1

Renske van der Heijden[1], Wietske van Dortmont[1], Lieze Hoogveld[2], Maaike Pelsma[2], Lisa Suppers[2], Saskia Houwen[2], Lynn Orriëns[1], Hilde Braakman[1]

[1]Department of Pediatric Neurology, Amalia Children's Hospital, Radboud University Medical Centre, Nijmegen, the Netherlands, [2]Department of Rehabilitation, Amalia Children's Hospital, Radboud University Medical Centre, Nijmegen, the Netherlands

Children with myotonic dystrophy type 1 (DM1) present with a clinical profile that differs from adults, yet the natural history of paediatric DM1 remains poorly characterized. A clearer understanding of disease progression is essential for guiding clinical care and informing the selection of appropriate outcome measures for future therapeutic trials.

This retrospective cohort study evaluated longitudinal changes in motor function, muscle strength, and endurance in children (aged 0-18 years) with DM1 over the course of 1 to 4 years, with the dual aim of describing the disease course and evaluating the suitability of currently used outcome measures. Assessments were conducted during routine clinical care by physical and occupational therapists at the

Amalia Children's Hospital, Radboudumc, in Nijmegen, the Netherlands. Outcome measures included the Motor Function Measure (MFM), goniometry, grip strength, isometric muscle strength, the Childhood Myositis Assessment Scale (CMAS; endurance items), timed function tests, the 6-Minute Walk Test (6MWT), and the Nine-Hole Peg Test (NHPT).

Fifty-eight children with DM1 (29 congenital DM1, 29 childhood DM1, median age 12;5 years) were included. At the index visit, the most prominent challenges involved distal motor function, head lift, walking distance, and grip strength. Preliminary one-year analyses showed no significant changes in MFM domain scores, isometric muscle strength, 6MWT, or NHPT. Full longitudinal trajectories across all visits will be presented, including comparisons between children with congenital and childhood-onset DM1.

This study provides new insights into motor function patterns and their changes over time in children with DM1. These findings support more targeted identification of emerging challenges, tailored supportive interventions, and improved monitoring in clinical practice. Consensus on a core set of responsive, norm-referenced outcome measures is needed to adequately capture the impact of DM1 on motor function throughout childhood in future prospective studies.

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168 - Cognitive and Behavioral Impairment in Congenital and Childhood-Onset Myotonic Dystrophy Type 1: A Longitudinal Analysis

Anna Falco[1], Susanna Pozzi[2], Federica Martinazzo[2], Emilio Albamonte[2], Andrea Lizio[2], Irene Giacompolli[2], Valentina Franchino[2], Marika Pane[1], Kiera Berggren[3], Nuran Dilek[4], Nicholas Johnson[3], Chad Heatwole[4], Valeria Ada Sansone[2]

[1]The NeMO Center in Rome, U.O.C. Neuropsichiatria Infantile, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy., [2]The NEMO Center in Milan, Neurorehabilitation Unit, University of Milan, ASST Niguarda Hospital, Milan, Italy, [3]Virginia Commonwealth University, Neurology Department, Richmond, Virgina, USA, [4]Center for Health and Technology, University of Rochester, Rochester, NY, USA

Central nervous system involvement represents the main cause of disability in pediatric Myotonic Dystrophy type 1 (DM1), including cognitive impairment as well as behavioral, mood, and sleep disorders. However, longitudinal trajectories of neuropsychological functioning in this population remain poorly characterized.

We aimed to characterize the neuropsychological profile of patients with congenital (CDM) and childhood-onset (ChDM) DM1 at baseline and over time, and to assess

whether cognitive impairment affects the feasibility of motor performance assessments.

Thirty-two patients (18 CDM and 14 ChDM) underwent a comprehensive assessment including cognitive, behavioral, adaptive, and psycho-affective measures, with an average of four annual follow-up evaluations per patient. Associations between cognitive-behavioral functioning and the feasibility of motor performance assessments were examined.

Cognitive and behavioral involvement was observed in pediatric DM1 patients. Moreover, CDM patients showed greater cognitive impairment than ChDM patients, with significantly lower median FSIQ (40.0 [40.0 - 45.0] vs 83.5 [80.0 - 95.0], p=0.011), as well as poorer adaptive functioning and higher autistic traits, although these differences were not statistically significant. The longitudinal analysis revealed a significant overall improvement in emotional regulation (-0.54 points/months, SE:0.10; p=0.0008) and decline in social-communication abilities (-0.25 points/months, SE:0.10; p=0.0205), alongside a trend toward cognitive deterioration in both groups. Finally, autistic features and emotional dysregulation were associated with reduced feasibility across all motor assessments, whereas cognitive impairment had a greater impact on the Iowa Oral Performance Instrument.

Cognitive-behavioral impairment is a feature of pediatric DM1, particularly pronounced in CDM patients. Despite differences in their neuropsychological profiles, both groups showed similar longitudinal trends, with emotional regulation improving over time, and social-communication and cognitive functions remaining areas of vulnerability. Given their impact on motor assessment feasibility and quality of life, cognitive-behavioral profiles should be routinely assessed in pediatric DM1, both in clinical practice and in clinical trials.

Oral presentation Thursday May 28, 2026

Session: Development of Biomarkers and Clinical Outcome Assessments I

31 - Clinical Validation of Socially Assistive Robot-Administered Physical Tests in Myotonic Dystrophy Type 1

Killian LACHAUX[1], Elodie GAGNON[2], Florentin THULLIER[1], Julien MAÎTRE[1], Kevin BOUCHARD[1], Cynthia GAGNON[3, 4, 5], Élise DUCHESNE[5, 6, 7, 8], Sébastien GABOURY[1]

[1]Département d'Informatique et Mathématique, Université du Québec à Chicoutimi, Chicoutimi, Québec, Canada., [2]Département des Sciences de la Santé, Université du

Québec à Chicoutimi, Chicoutimi, Québec, Canada, [3]Faculté de médecine et des sciences de la santé, Université de Sherbrooke, Sherbrooke, Québec, Canada, [4]Centre de recherche et d'innovation du Centre intégré universitaire du Saguenay-Lac-St-Jean, Clinique des maladies neuromusculaires, Hôpital de Jonquière, Jonquière, Québec, Canada, [5]Groupe de recherche interdisciplinaire sur les maladies neuromusculaires (GRIMN), Saguenay-Lac-St-Jean Integrated University Health and Social Services Center, Saguenay, Quebec, Canada, [6]Center for Interdisciplinary Research in Rehabilitation and Social Integration (Cirris), Capitale-National Integrated University Health and Social Services Center, Quebec City, Quebec, Canada, [7]CHU de Québec-Université Laval Research Center, Quebec City, Quebec, Canada, [8]School of Rehabilitation Sciences, Faculty of Medicine, Université Laval, Quebec City, Quebec, Canada

Standardized physical assessments (particularly the 30-Second Chair Stand Test (30sCST), 10-Meter Walk Test (10mWT), and Grip Strength Test (GST)) are essential for monitoring functional capacity in neuromuscular diseases. However, these assessments are time-intensive, susceptible to inter-rater variability, and place considerable burden on clinicians facing increasing workloads. While Socially Assistive Robots (SARs) have shown promise in rehabilitation settings, their deployment for standardized clinical assessments remains limited. Few studies have validated SAR-based systems in real-world clinical environments or evaluated their accuracy against clinician-obtained measurements, particularly for populations with neuromuscular conditions such as myotonic dystrophy type 1 (DM1).

To develop and validate a SAR-based system for automated administration of standardized physical assessments matching therapist accuracy.

A clinical study used the TEMI robot integrated with artificial intelligence capabilities. 12 healthy and 3 DM1 affected individuals completed three standardized tests under passive clinician supervision. The system employed computer vision AI algorithms and a locally hosted Vision Language Model (VLM) for automated data extraction. SAR-generated metrics were compared with clinician measurements for reliability validation.

The SAR system closely matched clinician measurements overall. After protocol refinement, automated 30sCST repetition counts reached 100% accuracy. For the 10mWT, robot timing strongly correlated with clinician timing (Pearson r=0.991) and produced a 0.252-second mean absolute error. The VLM-based GST module extracted dynamometer grip values with 87.65% accuracy. Following clinician check-

in confirming safe transfers and ambulation, the robot autonomously administered the battery, freeing clinicians for other tasks without sacrificing measurement quality.

This study demonstrates the feasibility and reliability of SAR-based physical assessments in real-world clinical practice. The system provides standardized, repeatable measurements comparable to expert clinicians while reducing assessment burden and supporting scalability. The integration of locally hosted AI, particularly for automated data extraction from medical devices, offers a privacy-compliant solution adaptable to diverse clinical tools.

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118 - Multi-omic profiling stratified by the Splicing Index enables circulating biomarker discovery in myotonic dystrophy type 1

Dove Enicks[1], Claire Wells[1], Marina Provenzano[1], Christopher Crumbaugh[1], Lesly Turcios-Hernandez[1], Nicholas Johnson[1], Melissa Hale[1]

[1]Center for Inherited Myology Research, Department of Neurology, Virginia Commonwealth University, USA

The Splicing Index (SI) is a sensitive measure of disease-associated RNA mis-splicing and strongly correlates with muscle strength and function in DM1. However, its reliance on muscle biopsies limits scalability and repeat assessment, posing challenges in an increasingly diverse therapeutic landscape. Development of minimally invasive circulating biomarkers that mirror validated muscle biomarkers would enable less invasive and more dynamic monitoring of disease state, functional decline, and/or therapeutic response. Prior blood-based DM1 biomarker discovery efforts have achieved limited resolution due to the use of weak phenotypic correlates such as CTG repeat length to select biospecimens for study inclusion. To overcome these challenges, we leveraged timepoint-matched muscle biopsy and blood biospecimens from a deeply phenotyped cohort of DM1 participants (NCT03981575 and HELP-DM1) (n = 159). Using SI-based stratification to ensure sampling across the disease spectrum, we applied an unbiased multi-omic discovery approach to identify candidate circulating RNA and protein biomarkers associated with muscle disease severity. We integrated total muscle RNA sequencing (n = 95), blood total RNA sequencing (n = 36), and SomaScan 11K plasma proteomic profiling (n = 40) to explore cross-tissue associations. Consistent with prior studies, RNA splicing and gene expression changes in blood were limited and did not correlate with RNA splicing severity in skeletal muscle. Plasma proteomic profiling identified multiple proteins whose relative abundance demonstrated moderate and significant

correlations with the SI (n = 227, Spearman |r| ≥ 0.5, p < 0.05). Several candidate proteins exhibited concordant RNA expression changes in skeletal muscle (*SPX, EDA2R)*, supporting cross-tissue biological relevance. Together, these early analyses support the feasibility of an SI-anchored framework to identify candidate circulating biomarkers reflective of muscle disease in DM1. Ongoing analyses are exploring associations of top proteomic candidates with clinical measures of muscle performance and disease burden in other affected organ systems, including the CNS.

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156 - DM1-Hub registry: building a nationwide infrastructure to define the natural history of myotonic dystrophy type 1

Gisela Nogales-Gadea[1], Alvaro S. Larran[1], Marc Corral-Juan[1], Alba Herrero-Gómez[1], Anna Revert Barberà[2], Clara Moliner Diaz[1], Usua Laresgoiti Garay[3], Eva Coll Liesa[1], Alicia López-Martín[1], Raquel Pérez Gómez[4], Luis Orduña Rubio[4], Gerardo Gutiérrez-Gutiérrez[5], Ana Lara Pelayo[6], Andone Sistiaga[7], Macarena Cabrera[8], Jorge Alonso-Pérez[9], Daniel M. Borràs[1], Sebastián Figueroa-Bonaparte[2], Virginia Arechavala-Gomeza[3], Arturo López-Castel[4]

[1]Badalona Neuromuscular Research Group (GRENBA), Germans Trias i Pujol Research Institute (IGTP), Badalona, Catalonia, Spain, [2]Neuromuscular Pathology Unit, Neurology Service, Neuroscience Department, Germans Trias i Pujol University Hospital, Badalona, Spain, [3]Nucleic Acid Therapeutics for Rare Disorders (NAT RD), Biobizkaia Health Research Institute (IIS Biobizkaia), Barakaldo, Spain, [4]INCLIVA Biomedical Research Institute (INCLIVA), Valencia, Spain. Human Translational Genomics Group, University Research Institute for Biotechnology and Biomedicine (BIOTECMED), University of Valencia, Burjassot, Spain, [5]Neurology Department, Infanta Sofía University Hospital, Madrid, Spain, [6]Service of Neurology, Marqués de Valdecilla University Hospital, Santander, Spain, [7]Department of Clinical and Health Psychology and Research Methodology, Faculty of Psychology, University of the Basque Country (UPV/EHU), Donostia-San Sebastián, Gipuzkoa, Spain, [8]Neurology Department & Instituto de Biomedicina de Sevilla (IBiS), Virgen del Rocío University Hospital, Seville, Spain, [9]Neuromuscular Diseases Unit, Neurology Department, University Hospital of Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Tenerife, Spain

Myotonic Dystrophy Type 1 (DM1) is a rare, multisystemic disorder with highly variable clinical expression and no approved disease-modifying therapies. Understanding its natural history is critical to improve patient care and accelerate therapeutic development. We present DM1-Hub, a nationwide registry and collaborative network

in Spain designed to systematically collect harmonized, multidimensional data from individuals with DM1 and controls. The initiative integrates 50 hospitals across eight regions, involving over 100 trained professionals and more than 20 dedicated staff, including managers, researchers, nurses and neuropsychologists. The registry was built through a structured process encompassing site selection, standardized training, and continuous quality monitoring to ensure uniform data collection. A centralized REDCap platform enables real-time data entry and harmonization across all sites, while governance protocols ensure adherence to international standards and regulations, and interoperability with global DM1 initiatives. This infrastructure supports longitudinal data collection and fosters multidisciplinary engagement, creating a robust foundation for defining the natural history of DM1, identifying prognostic markers, and improving trial readiness. By connecting clinicians, researchers, and patient associations, DM1-Hub aims to accelerate knowledge generation and optimize care pathways. Our experience demonstrates that building a large-scale, decentralized registry is feasible and scalable when supported by structured coordination, harmonized protocols, and continuous training, and this model can serve as a blueprint for similar initiatives in other rare neuromuscular disorders.

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187 - Cerebrospinal fluid multi-omic biomarkers of myotonic dystrophy type 1

Preeti Kumari[1], Nadine Jarrar[1], Tamkin Sahraki[1], Akhlila Gundavelli[1], Hugo Huang[1], Sudeshna Das[1], Thurman Wheeler[1]

[1]Massachusetts General Hospital, Harvard Medical School

Alternative splicing is mis-regulated in DM1 central nervous system (CNS) tissue. Metabolic disturbance in cerebral white matter is evident by magnetic resonance spectroscopy and correlates with visualspatial deficits in DM1. Here we test the hypothesis that cerebrospinal fluid (CSF) provides a source of convenient molecular indicators of CNS involvement in DM1. Individuals with DM1 and unaffected (UA) controls underwent brain MRI scans, cognitive testing, and lumbar puncture. Brain MRI scans were analyzed using FreeSurfer software. We isolated extracellular vesicles (EVs) from cell-free CSF by ultracentrifuge and quantified alternative splicing by droplet digital PCR. In a subset of CSF samples, we measured metabolites by methanol extraction, lyophilization, liquid chromatography/mass spectrometry, and MetaboAnalyst software. *GOLGA4* splicing in EVs correlates strongly with volume of cerebral white matter, cerebral cortex, and ventral diencephalon (r = -0.90 - 0.96). We found 59 metabolites with differential abundance in DM1 individuals as compared to

UA controls. Principal component analysis of these metabolites separated the DM1 and UA groups, with receiver operating characteristic curve-area under the curve value of 1.0. Metabolite Set Enrichment Analysis revealed increased abundance of metabolites involved in glutathione, nicotinamide, and sphingolipid metabolism, and reduced abundance of metabolites associated with gluconeogenesis, carbohydrate, and amino acid metabolism. CSF methylsuccinic acid, which we previously found elevated in DM1 urine samples, correlates strongly with the Trail A and Trail B tests (r = 0.94 and 0.90), alternative splicing of transcripts *GOLGA4* and *NCOR2* in CSF EVs (r = 0.90 and 0.92), and cerebellum white matter volume (r = -0.87). Our data suggest that metabolic disturbance evident in DM1 blood and urine samples also involves the CSF and support a multi-center study to identify and validate CSF multi-omic biomarkers of CNS involvement in DM1. The Food and Drug Administration, Myotonic Dystrophy Foundation, Sanofi, and Muscular Dystrophy Association provided support.

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207 - Disease progression in Myotonic Dystrophy Type 2

Johanna Hamel[1], Katy Eichinger[1], Jeanne Dekdebrun[1], James Hilbert[1], Lindsay Baker[1], Nicole Koopman[1], Chad Heatwole[1], Michael P. McDermott[1], Charles A. Thornton[1]

[1]University of Rochester Medical Center

Myotonic dystrophy type 2 (DM2) results in progressive muscle weakness and, variably, in multi-systemic disease. Understanding disease progression will inform outcome measure development and trial design.

We completed an observational study evaluating individuals with DM2 at 0, 12, and 36 months. Assessments included manual (MMT) and quantitative muscle strength testing (QMT, in percent predicted), 6-minute walk test (6MWT), 30 feet walk/run (30FWR, feet/sec), ascend and descend 4 stairs (steps/sec), sit to stand (s), Individualized Neuromuscular Quality of Life (INQoL), 36-Item Short Form Health Survey (SF-36), DM functional rating scale, and upper and lower extremity function scales. Associations between baseline strength and function measures and patient-reported outcomes were assessed using Spearman correlation analysis. Changes from baseline at 12 and 36 months were assessed using paired t-tests.

Thirty-nine participants with DM2 enrolled (mean age 55 years, mean age at symptom onset 39 years, 59% female). Follow-up was available in 35 at 12 months and in 30 at 36 months. No significant changes were seen at 12 months except for SF-36 Role-Physical subscale (mean change -7.7 p, 0.03). At 36 months, a decline in function

(mean change) was noted in 30FWR (-0.8, p=<.0001), ascend (-0.15, p=0.039) and descend (-0.17, p=0.04) 4 stairs, DM functional rating scale (-1.9, p=0.002), Lower extremity function scale (-5.4, p=0.008), SF-36 Role-physical subscale (-17.5, p=0.0002), INQoL- independence (11.5, p=0.001) and INQoL total (4.9, p=0.04). Lower body strength (MMT, QMT respectively) and functional measures showed moderate to strong correlations at baseline: Sit to stand (MMT, r=0.80, p=<.0001, QMT r=0.81, p=<.0001), ascend stairs (MMT&QMT r=0.72, p<.0001), and 30FWR (MMT r=0.75, p<.0001, QMT 0.74, p<.0001). The SF-36 physical function subscale correlated strongly with average MMT (0.81, p<.0001) and QMT (0.70, p<.0001).

DM2 disease progression is slow but can be measured with functional assessments. Self-perception of the disease correlates with functional measures.

Session: Clinical Manifestations, Activity and Participation I

56 - Cognitive and Social cognition functioning in adults with childhood myotonic dystrophy type 1

Simon-Pierre Gagnon[1, 2], Cynthia Gagnon[1, 2], Louis Richer[3], Justine Dolbec[1], Benjamin Gallais[3, 4]

[1]Groupe de Recherche Interdisciplinaire sur les Maladies Neuromusculaires (GRIMN), [2]Faculté de médecine et des sciences de la santé, Université de Sherbrooke (UdS), [3]Département des sciences de la santé, Université du Québec à Chicoutimi (UQAC), [4]Centre d'Étude des conditions de vie et des besoins de la population (ÉCOBES)

Background: Myotonic dystrophy type 1 (DM1) is an autosomal dominant disorder characterized by multisystemic involvement and is classified into five phenotypes based on age of onset and CTG expansion. Current empirical evidence on how cognitive and social cognition deficits reported in childhood DM1 (ChDM1) evolve in adulthood remains limited. These impairments may contribute to poorer education and reduced social participation. However, social cognition is still rarely assessed in adults with ChDM1, with most studies focusing on children and adolescents.

Objective: To document the cognitive profile and social cognitive functioning of adults with ChDM1 and to examine potential associations between cognitive and social cognitive performance.

Methods: Fifty participants from Quebec and France were included in the sample. All underwent a neuropsychological battery assessing intellectual, and visuospatial

abilities, as well as executive control. Social cognition was assessed through emotion recognition, Theory of Mind (ToM), and faux-pas recognition. Descriptive statistics, correlational analyses, and hierarchical multiple regression were performed.

Results: Mean intellectual functioning fell within the borderline intelligence range. 58% to 90% of participants had results one SD or more below normative expectations of cognitive abilities. Social cognition was impaired in more than 40% of the sample. On the TOM-15, 34% scored two SD below norms for the total score. 43% of the sample had impaired emotion recognition, especially regarding anger, disgust, and fear recognition. Hierarchical multiple regression showed that cognitive abilities explained more variance in social cognition tests than disease-related clinical variables (e.g., number of CTG repeats, years of education).

Discussion/Conclusion: Adults with ChDM1 exhibit impairments in intellectual functioning, visuospatial abilities, and social cognition, with substantial ToM deficits, coherent with previous findings. These findings suggest a distinct sociocognitive impairment profile in ChDM1, contributing to an enhanced understanding of the long-term neurocognitive profile in ChDM1.

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100 - A Multidimensional Profile of Dysphagia in Myotonic Dystrophy Type 1 (SwallowDM1)

Jodi Allen[1], Tom Parry[2], Chris Turner[1], Ronan Astin[1], Christina Smith[3], Roganie Govender[4], Sue Mallett[2], Stuart Taylor[2]

[1]The National Hospital for Neurology & Neurosurgery, University College London NHS Foundation Trust, UK, [2]University College London Centre for Medical Imaging, UK, [3]University College London Division of Psychology & Language Sciences, UK, [4]University College London Division of Surgery & Interventional Science, UK

Dysphagia in myotonic dystrophy type 1 (DM1) increases risk of respiratory failure, pneumonia, malnutrition, dehydration, and choking-related death. We aimed to characterise the multidimensional profile of dysphagia in DM1 by investigating morphometric changes in swallowing-related muscles and their associations with biomechanical function, strength, and symptoms. We examined relationships with quality of life, physical function, and respiratory function to inform prevention of these life-threatening outcomes.

We recruited 94 adults with genetically confirmed DM1, with and without dysphagia, across the UK (July 2023 to August 2024), alongside caregivers, based on an a priori

sample size calculation. During a single visit to a tertiary neuromuscular care centre, participants underwent fifteen assessments including: swallowing assessments—quantitative muscle ultrasound, videofluoroscopic swallowing study, isometric tongue and bite force, tests of swallowing and chewing efficiency (TWST, TOMASS), and patient-reported questionnaires (SSQ, SWAL-QOL); and non-swallowing assessments—Muscle Impairment Rating Scale (MIRS), DM1 Activity and Participation Scale (DM1-Activ), Myotonia Behaviour Scale (MBS), hand-opening time, spirometry with respiratory muscle strength testing, and a speech comprehensibility assessment. Caregivers completed the Scale of Quality of Life of Caregivers (CARES). For analysis, participants were stratified into three dysphagia severity groups using tertiles derived from MBSImP oral and pharyngeal sum scores.

Both oral and pharyngeal dysphagia severity were linearly associated with jaw and tongue strength, patient-reported symptoms, swallowing-related quality of life (QoL), physical activity, and MBS scores. Pharyngeal severity showed additional associations with TOMASS measures (time per swallow, time per bite, masticatory swallows per bite), dietary adaptation, respiratory function, speech comprehensibility, hand-opening time, and caregiver QoL. Despite group-level associations, individual profiles varied considerably, reflecting the known phenotypic heterogeneity of DM1.

Key findings from this large, comprehensive dataset will be presented, with discussion of evidence-based recommendations for targeted assessment and individualised treatment of dysphagia in DM1.

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126 - Preimplantation Genetic Testing in Myotonic Dystrophy Type 1: Clinical Outcomes and Insights

Johanna Bruijnes[1], Fauve van Veen[2], Malou Heijligers[3], Ronald van Golde[4], Marianne van Buul[5], Alwin Derijck[6], Nicole Corsten-Janssen[7], Catharina Faber[1], Els Vanhoutte[3], Isis Joosten[1]

[1]Department of Neurology and MHeNS School for Mental Health and Neuroscience, Maastricht University Medical Centre+, Maastricht, The Netherlands, [2]Department of Dermatology and GROW School for Oncology and Reproduction, Maastricht University Medical Centre+, Maastricht, the Netherlands, [3]Department of Clinical Genetics and GROW School for Oncology and Reproduction, Maastricht University Medical Centre+, Maastricht, the Netherlands, [4]Department of Obstetrics and Gynecology and GROW School for Oncology and Reproduction, Maastricht University

Medical Centre+, Maastricht, the Netherlands, [5]Department of Obstetrics and Gynecology, University Medical Center Utrecht, Utrecht, The Netherlands, [6]Amsterdam UMC location University of Amsterdam, Center for Reproductive Medicine, Amsterdam, The Netherlands, [7]University of Groningen, University Medical Center Groningen Groningen, Department of Genetics, Groningen, The Netherlands

Myotonic Dystrophy type 1 (DM1) is an autosomal dominant disorder caused by a CTG repeat expansion in the *DMPK* gene. Upon transmission from parent to child, genetic anticipation often occurs. Despite the known genotype-phenotype correlation in DM1, prediction of disease manifestations in offspring is unreliable, complicating reproductive decision-making. Preimplantation genetic testing (PGT) is one of the available reproductive options to prevent affected offspring.

This study describes the success rate of PGT in a nationwide cohort of DM1 patients in the Netherlands and aims to identify factors influencing PGT outcomes.

A retrospective observational cohort study was conducted including all individuals who underwent PGT for DM1 in the Netherlands between January 1997 and May 2020. Data was collected on sex of the affected individual, CTG repeat size, fertility assessment, IVF cycles, PGT analysis, embryo transfers, and pregnancy complications and outcomes. Mixed-effects logistic regression analysis was performed to evaluate factors associated with pregnancy outcomes.

A total of 130 couples were included. In 53% the affected individual was female. Subfertility or infertility was identified in 28% of DM1-affected males and 19% of DM1-affected females during pre-IVF evaluation. The transfer of 300 non-risk haplotype embryos resulted in 72 clinical pregnancies and 60 live deliveries. Clinical pregnancy rate and live delivery rate were 24.5% and 20.4% per cycle, and 24.0% and 20.4% per embryo transfer, respectively. At least one clinical pregnancy was attained in 45% of couples. A CTG repeat ≥150 in the affected individual was associated with significantly lower chance of pregnancy per embryo transfer (OR 0.24, 95% CI 0.12-0.51, $p<0.001$). Sex of the affected individual did not significantly modify outcomes.

This nationwide study provides an overview of PGT success rates for DM1 in the Netherlands and offers valuable data to support genetic counseling and informed reproductive decision-making for DM1-affected couples.

Session: Cell and Animal Models for DM

11 - A repressible CUG repeat RNA mouse model to study the neurological manifestations and their reversibility in myotonic dystrophy type 1

Larissa Nitschke[1], Thomas Cooper[1]

[1]Baylor College of Medicine

Myotonic Dystrophy Type 1 (DM1) is a multisystemic disorder caused by a CTG repeat expansion in the 3' untranslated region of the *DMPK* gene. While primarily known for skeletal muscle dysfunction, over 80% of DM1 patients exhibit neurological symptoms including cognitive impairment, sleep disturbances, mood disorders, and anxiety. The severity of these symptoms varies with age of onset, with congenital and childhood-onset individuals experiencing more severe neurological manifestations than those with adult-onset. Despite the high prevalence and impact of the neurological symptoms in DM1, the underlying mechanisms remain poorly understood.

To address this gap, we developed a doxycycline-repressible transgenic mouse model (CUG960) that uses the NEFH promoter to drive the expression of CUG repeat RNA in neurons starting from embryonic development. CUG960 mice recapitulate key molecular DM1 features including nuclear RNA foci formation, sequestration of Muscleblind-Like (MBNL) proteins, and alternative splicing dysregulation. Phenotypically, the CUG960 mice exhibit reduced brain weight and display multiple behavioral abnormalities including hyperactivity and deficits in learning and memory. Notably, we observed mis-splicing of the *Mapt* gene encoding Tau and genes involved in synaptic function and calcium signaling, which may contribute to the observed cognitive phenotypes.

Feeding CUG960 mice on doxycycline-containing chow successfully suppresses CUG repeat RNA expression, allowing us to test for phenotype reversibility. We show that suppression of CUG repeat RNA starting from conception or birth rescues brain weight changes while suppression in adulthood does not, suggesting limited reversibility due to developmental effects. We are currently assessing the reversibility of the behavioral phenotypes to define critical therapeutic windows. Conversely, we also demonstrate that CUG repeat RNA expression can be turned on in adulthood by maintaining CUG960 mice on doxycycline-containing chow and then switching to regular chow, enabling future investigations of adult-onset mechanisms independent of developmental effects.

24 - Bioengineered 3D Muscle Tissues Identify an MBNL1-Independent Mechanism of Calcitriol-Mediated Myotonia Rescue

Xiomara Fernández-Garibay[1, 2], Maria Sabater-Arcís[1, 2], Ainoa Tejedera-Villafranca[1, 2], Judit Núñez-Manchón[3, 4], Mònica Suelves[3, 4], Rubén Artero[5, 6], Gisela Nogales-Gadea[3, 4], Javier Ramón-Azcón[1, 2, 7], Juan M. Fernández-Costa[1, 2]

[1]Institute for Bioengineering of Catalonia (IBEC), [2]Barcelona Institute of Science and Technology (BIST), [3]Germans Trias i Pujol Research Institute (IGTP), [4]Universitat Autònoma de Barcelona, [5]University Institute for Biotechnology and Biomedicine (BIOTECMED), University of Valencia, [6]Incliva Health Research Institute, [7]ICREA-Institució Catalana de Recerca i Estudis Avançats

Myotonic Dystrophy Type 1 (DM1) is a severe, multisystemic genetic disorder characterized by progressive muscle weakness, atrophy, and myotonia. Although traditional 2D cell cultures and animal models have advanced our understanding of DM1 molecular mechanisms, they fail to capture the contractile and structural complexity of human muscle tissue. To address these limitations, we engineered contractile three-dimensional (3D) human skeletal muscle tissues using immortalized myoblasts derived from three DM1 patient lines representing juvenile, adult, and late-onset forms of the disease. The cells were embedded in biocompatible hydrogel scaffolds and anchored between flexible posts, promoting alignment, maturation, and spontaneous contraction. These 3D tissues faithfully recapitulated hallmark DM1 features, including MBNL1 sequestration in ribonuclear foci and widespread alternative splicing defects. For the first time *in vitro,* we observed splicing alterations in CLCN1, the chloride channel gene causally linked to myotonia. Functionally, the model reproduced patient-specific phenotypes such as transient and fixed muscle weakness and myotonia, previously observed only *in vivo*. Pharmacological treatment with small molecules that enhance MBNL1 levels partially rescued both molecular and functional defects. Strikingly, treatment with calcitriol markedly reduced myotonia without restoring MBNL1 localization or CLCN1 splicing, revealing an MBNL1-independent mechanism of action. RNA sequencing further showed that calcitriol normalized dysregulated gene expression in DM1 tissues by upregulating genes involved in neuromuscular transmission, metabolic activity, and synaptic signaling, while downregulating pathways associated with stress, inflammation, fibrosis, and aberrant development. Altogether, this 3D DM1 muscle model provides a physiologically relevant, patient-specific platform for therapeutic testing and mechanistic studies. It enables detailed investigation of contractile dysfunction and identifies calcitriol as a promising modulator of DM1 pathology acting through an MBNL1-independent transcriptional mechanism.

108 - Transcriptomic and molecular characterization of a neuronal mouse model for myotonic dystrophy type 1 (DM1)

Juan D. Arboleda[1], Bethlehem A. Bekele[2], Emily Davey-Osuch[1], Belinda S. Pinto[1], Gary J. Bassell[2], Eric T. Wang[1]

[1]Department of Molecular Genetics & Microbiology, Center for NeuroGenetics, University of Florida, Gainesville FL 32610, [2]Department of Cell Biology, Emory University School of Medicine, Atlanta, GA 30322

Myotonic dystrophy type 1 (DM1) is caused by expanded CTG repeats in the *DMPK* gene and is characterized by widespread RNA-mediated molecular dysfunction, including alternative splicing defects. While central nervous system (CNS) symptoms are increasingly recognized as a major contributor to disease burden, cell-type specificity and reversibility of CNS molecular pathomechanisms remain incompletely defined. Here, we characterize the transcriptome of a *CamKIIa*-driven, tet-off mouse model expressing a 960-CTG repeat *DMPK* transgene (*CamKIIa-tTA;TREDT960i*), enabling postnatal and reversible expression of toxic repeat RNA selectively in excitatory neurons. Bulk RNA sequencing of frontal cortex and hippocampus at three months of age revealed robust mis-splicing of transcripts previously observed in human DM1 brain regions (Mbnl1, Gabrg2, Snap25, Grin1), demonstrating that postnatal repeat expression restricted to excitatory neurons is sufficient to induce DM-relevant transcriptomic defects. RNA fluorescence in situ hybridization confirmed abundant nuclear RNA foci across multiple brain regions in the forebrain. Suppression of transgene expression mediated by doxycycline feeding resulted in partial splicing rescue by 14 days and more substantial rescue by 30 days, suggesting that molecular defects remain reversible following postnatal repeat silencing. We additionally tested adeno-associated virus (AAV) miRNA-mediated knockdown of *DMPK* as an alternate and therapeutic-relevant avenue to assess relevant transcriptomic and behavioral changes mediated by repeatsilencing. Together, our findings establish that excitatory neuron-restricted CTG expression is sufficient to drive DM relevant transcriptomic pathology in the brain and highlights the capacity for postnatal molecular rescue, providing a powerful platform for dissecting CNS-specific RNA toxicity mechanisms and evaluating therapeutic strategies targeting toxic repeat RNA.

122 - Consequences of congenital myotonic dystrophy during neuromuscular development

Caroline Hermitte[1], Mathurin Bodin[1], Denis Furling[2], Cécile Martinat[1], Morgan Gazzola[1]

[1]Institut des cellules souches pour le traitement et l'étude des maladies monogéniques (I-Stem), Corbeil-Essonnes, [2]Institut de myologie, Hôpital de la pitié Salpêtrière, Paris

Objective: Congenital myotonic dystrophy (CDM) is the most severe form of myotonic dystrophy type 1, a multisystemic disorder caused by CTG repeat expansion in the DMPK gene. CDM is characterized by hypotonia and progressive muscle weakness associated with developmental delay. While skeletal muscle disorders have been extensively studied, increasing evidence suggests that the broader neuromuscular system is affected. However, the developmental origins and cellular mechanisms underlying neuromuscular dysfunction in CDM remain poorly understood.

Methods: To model human neuromuscular development in a disease context, we generated neuromuscular organoids (NMOs) from three control and three CDM patient-derived hiPSC lines. Organoids were differentiated for up to 100 days. Cell population dynamics were assessed by immunofluorescence and flow cytometry. Functional properties were evaluated using calcium imaging.

Results: By day 20, both control and CDM NMOs showed efficient specification of early myogenic progenitors and motor neuron precursors, indicating proper lineage commitment. By day 50, NMOs displayed a polarized organization with distinct neural and muscular compartments. Electron microscopy revealed organized sarcomeric structures and synaptic contacts between neurons and myotubes. At day 100, we observed a disproportion of myosin isoforms in CDM NMOs, suggesting the persistence of embryonic fibres and impaired muscle fibre maturation. Functionally, calcium imaging revealed a significant increase in calcium flux in CDM NMOs following electrical stimulation. To further dissect muscle-specific dysfunction, genetically modified organoids expressing a muscle-specific calcium-sensitive fluorescent probe are being generated. In parallel, snRNA-seq and ATAC-seq datasets at day 50 are being processed and will allow the identification of transcriptional alterations and the molecular and cellular defects underlying impaired neuromuscular maturation in CDM.

Conclusion: Our results demonstrate that NMOs recapitulate human neuromuscular development and provide a platform to study CDM physiopathology. We identified

defects in muscle fibre maturation and calcium dynamics in CDM organoids, potentially contributing to muscle weakness and fatigue.

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179 - RNA and RAN Protein Gain-of-Function Effects in a Novel DM2 BAC Transgenic Mouse Model

Hannah Golliher[1,2], Tala Ortiz[1,2], Avery Engelbrecht[1,2], Lisa Romano[1,2], Laura Ranum[1,2]

[1]Center for NeuroGenetics, University of Florida, [2]Department of Molecular Genetics and Microbiology, Univerity of Florida

Myotonic Dystrophy type 2 (DM2) is a multisystemic disease caused by an intronic CCTG·CAGG expansion in *CNBP*. Sense and antisense expansion transcripts and repeat-associated non-AUG (RAN) proteins accumulate in human tissues. Unfortunately, there are no mouse models available for DM2.

Here we report that we have generated two lines of DM2 transgenic mice using a human bacterial artificial chromosome (BAC). Both lines contain a single copy of *CNBP*, and initially ~750 CCTGs. Transgene expression in both lines is similar to a single copy of the endogenous *Cnbp* mouse locus. These mice show marked somatic and intergenerational repeat instability. Using selective breeding we have generated mice with repeats ranging from ~300 to 7,000 CCTGs. RNA foci and alternative splicing changes are repeat length-dependent and are found in mice with >3,000 CCTGs in skeletal muscle, brain, and heart. In the brain, sense LPAC and antisense QAGR RAN protein aggregates accumulate in regions with neuroinflammatory changes including activated microglia, astrogliosis, white matter loss, and neurodegenerative abnormalities. The CCTG repeat in these mice is highly unstable from one generation to the next, which has made generating mouse cohorts with specific repeat lengths difficult. Surprisingly, we saw a dramatic stabilization of the CCTG repeat in F1 animals generated by crossing our DM2 BAC mice on an FVB background to C57BL/6 mice.

In summary, we have generated a DM2 BAC transgenic mouse model with somatic and intergenerational repeat instability, robust RNA foci, alternative splicing abnormalities, and RAN protein pathology, all of which are features of disease in DM2 patients. This model will improve our understanding of the molecular mechanisms of DM2 and provide a novel tool for therapeutic development.

Session: Pathogenic Mechanisms II

90 - Evidence of nuclear DMPK transcript degradation and cytoplasmic export in DM1 cells using dSTORM Super Resolution Microscopy

Petter Hamilton-Stanley[1], Xiaomeng Xing[1], Robert Markus[1], Marzena Wojciechowska[2], Tushar Ghosh[1], Sarah Buxton[1], Daniel J. Nieves[3], David Brook[1]

[1]University of Nottingham, [2]Polish Academy of Sciences, [3]University of Birmingham

Foci from repeat expanded *DMPK* transcripts are a hallmark of DM1 and a main driver of the toxic pathomechanism. Despite repeat expanded transcripts' central role in DM1, the extent of their cytoplasmic transport, along with their potential degree of nuclear and cytoplasmic degradation, has not been established. To answer these questions, fluorescent *in situ* hybridization was performed on DM1, *MBNL1&2* KO and wild-type fibroblasts with Direct Stochastic Optical Reconstruction Microscopy (dSTORM) compatible fluorophore-conjugated probe sets: CTG repeat-expansion, and probe binding either 5' or 3' of the repeat expansion. Images were acquired using an Elyra 7 microscope with a 100x objective. Signals were filtered, then clustered using DBSCAN algorithm, followed by colocalization through Nearest Neighbour Analysis and number of transcripts were estimated. Foci could be detected in both DM1 and *MBNL1&2* KO nuclei, along with detectable micro foci in their respective cytoplasm. *MBNL1&2* KO led to both fewer large and micro foci compared to DM1 cells. Colocalization analysis between the 5' and 3' probes to the repeat-expansion found a high degree of colocalization between large foci in DM1 nuclei, and a lesser degree of colocalization between micro foci, but no colocalization in either *MBNL1&2* KO nuclei or cytoplasm. Both 5' and 3' cluster numbers and estimated transcript were reduced to wild-type levels upon *MBNL1&2* KO compared to DM1 levels. In conclusion, dSTORM allows for highly accurate imaging of foci in cells; with simultaneous colocalization of the different probe sets and estimation of the number of transcripts through the analysis algorithm. Furthermore, our data demonstrates that MBNL1&2 are important factors in the stabilization of both full-length and fragments of *DMPK* transcripts, and upon *MBNL1&2* KO, the number of fragments return to wild-type levels, whereas some large foci remain.

128 - Axon initial segment disruption and impaired vesicle transport reveal neuron-intrinsic mechanisms of brain dysfunction in DM1

Louison Daussy[1], Louison Lallemant[1], Johanna Cormenier[2], Aline Huguet-Lachon[1], Gilles Moulay[1], Stéphane Vassilopoulos[1], Frédéric Saudou[2], Geneviève Gourdon[1], Mario Gomes-Pereira[1]

[1]Sorbonne University, Inserm, Centre de Recherche en Myologie, Paris, France, [2]Grenoble Institut des Neurosciences, Grenoble Alpes University, Inserm, Grenoble, France

Cognitive, behavioural and sleep problems are prominent yet poorly understood manifestations of myotonic dystrophy. DM1 is caused by expanded CUG repeats in *DMPK* transcripts, which accumulate in nuclear foci and dysregulate RNA-binding proteins, such as MBNL. While this RNA toxicity mechanism is well established, how it translates into neuronal dysfunction and brain pathology remains largely unresolved. We hypothesise that neuron-intrinsic structural and functional abnormalities contribute to impaired neuronal function in DM1.

To test this hypothesis, we analysed primary cortical neurons derived from the DMSXL mouse model, which carries a human *DMPK* transgene with >1000 CTG repeats and exhibits behavioural, electrophysiological and neurochemical abnormalities. Imaging and morphological analyses revealed overall impaired neuritogenesis and an altered proportion of excitatory neurons in culture, consistent with altered neuronal differentiation and/or selective vulnerability of specific neuronal subtypes. Notably, we identified a striking and underappreciated defect affecting the axon initial segment (AIS), a specialised axonal domain essential for neuronal polarity, action potential initiation and excitability. In both excitatory and inhibitory DMSXL neurons, the AIS was consistently displaced to a more distal position along the axon, while its length remained unchanged. Given the critical role of the AIS in organising axonal transport, we next investigated vesicle dynamics using live imaging of fluorescent VAMP2-labelled vesicles. DMSXL neurons displayed reduced vesicle transport speed and increased pausing along axons, demonstrating a global impairment of vesicular trafficking.

Together, these data suggest that abnormal AIS localisation and/or maintenance, as well as defective axonal vesicle transport are neuron-intrinsic phenotypes in DM1. Ongoing functional analyses, combined with subcellular transcriptomic and proteomic approaches, aim to define the molecular pathways underlying these defects and their contribution to DM1 brain pathology. Our work provides new insight

into DM1 brain pathology and highlights novel cellular substrates for neuronal dysfunction in the disease.

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134 - Toxic CUG RNA repeats disrupt developmentally regulated splicing in oligodendrocytes causing transient hypomyelination in a mouse model of myotonic dystrophy

Gabriele Ordazzo[1], Sandra Braz[1], Louison Lallemant[1], Angel González-Barriga[1], Paul Magneron[1], Aurélien Cordier[1], Aline Huguet-Lachon[1], Rebecca Goulancourt[2], Fiorella Grandi[1], Piera Smeriglio[1], Cyril Bourgeois[3], Cecile Martinat[4], Genevieve Gourdon[1], Mario Gomes-Pereira[1]

[1]Sorbonne Université, Inserm, Institut de Myologie, Centre de Recherche en Myologie, Paris, France, [2]Institut de Myologie, Centre de Recherche en Myologie, Paris, France, [3]ENS de Lyon, Inserm, CNRS UMR 5239, Lyon, France, [4]Université Paris Saclay - I-STEM, Inserm/UEVE UMR861, Corbeil-Essonnes, France

Myotonic dystrophy type 1 (DM1) presents debilitating cognitive and behavioural impairments. Neuroimaging has consistently revealed white-matter abnormalities, and more recently reduced volume of the corpus callosum. While RNA toxicity is established in neurons and astrocytes, the contribution of oligodendrocytes to brain pathology remains unexplored, despite the expression of the *DMPK* gene in this cell type. Oligodendrocytes produce myelin and ensheath axons in the central nervous system (CNS), enabling efficient neurotransmission. We hypothesise that *DMPK* expression in oligodendrocytes exposes them to CUG RNA toxicity, driving intrinsic defects in this cell type. We examined myelin formation through a longitudinal analysis of white-matter tracts in the corpus callosum, together with the quantification the density of oligodendroglia at different stages of differentiation. To this end, we used DMSXL mice, which display developmentally regulated expression of an expanded *DMPK* transgene. DMSXL mice exhibited hypomyelination of the corpus callosum during early postnatal stages, which normalised in adulthood. This delay correlated with elevated *DMPK* RNA levels, abundant nuclear foci accumulation, reduced density of myelinating oligodendrocytes and high proliferation of oligodendrocyte progenitor cells (OPCs). Cell-intrinsic mechanisms were investigated in primary OPCs, combined with live-cell imaging and RNA sequencing. DMSXL OPCs showed impaired differentiation and process ramification, phenotypes that were reproduced in DM1 hiPSC-derived oligodendroglia, supporting a cell-autonomous mechanism operating in this cell lineage. Transcriptomics revealed prominent splicing alterations in mature DMSXL oligodendrocytes, affecting

primarily cytoskeletal and morphogenetic pathways, and recreating a profile signature resembling immature OPCs. These findings identify oligodendrocytes directly affected by RNA toxicity in DM1 brains and uncover a transient myelination defect during a critical developmental window for the establishment of neuronal circuits and synaptic connectivity. Ongoing spatial transcriptomics will define regional vulnerability of specific cell populations. Together, our data suggest impaired oligodendroglial maturation as a novel contributor to CNS pathology in DM1.

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162 - Converging mechanisms of DMPK and TCF4 CTG repeat expansions underpin Fuchs endothelial corneal dystrophy

Christina Zarouchlioti[1], Marcos Abreu Costa[1], Siyin Liu[2], Nihar Bhattacharyya[1], Amirah Ally[1], Nikoletta Nikolenko[3], Haris Qurashi[1], Scott Hau[4], Lubica Dudakova[5], Pavlina Skalicka[6], Darren G. Monckton[7], Arianna Tucci[8], Kirithika Muthusamy[4], Petra Liskova[9], Stephen Tuft[2], Chris Turner[10], Alice E. Davidson[2]

[1]UCL Institute of Ophthalmology, London, UK, [2]UCL Institute of Ophthalmology, London, UK; Moorfields Eye Hospital, London, UK, [3]National Hospital for Neurology and Neurosurgery, Queen Square, University College London Hospitals NHS Foundation Trust, London, UK, [4]Moorfields Eye Hospital, London, UK, [5]Department of Paediatrics and Inherited Metabolic Disorders, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic, [6]Department of Ophthalmology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic, [7]School of Molecular Biosciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK, [8]William Harvey Research Institute, Queen Mary University of London, London, UK, [9]Department of Paediatrics and Inherited Metabolic Disorders, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic; Department of Ophthalmology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic, [10]National Hospital for Neurology and Neurosurgery, Queen Square, University College London Hospitals NHS Foundation Trust, London, UK; Queen Square Department of Neuromuscular Disease, University College London, London, UK

Fuchs endothelial corneal dystrophy (FECD) is a common, typically late-onset eye disease characterised by the accelerated loss of corneal endothelial cells (CECs). Up to 80% of European cases are associated with a pathogenic expansion (≥50 repeat units) of a CTG repeat element located within an intron of *TCF4*. *TCF4* repeat-

mediated FECD displays non-mutually exclusive pathogenic mechanisms similar to other repeat expansion diseases, including myotonic dystrophy type 1 (DM1), such as high levels of tissue-specific repeat instability, CUG-specific RNA foci and aberrant splicing. Despite other established genetic causes of FECD, missing heritability remains high in *TCF4* expansion-negative (Exp-) FECD cases. Here, we applied ExpansionHunter (v5.0.0) to whole genome sequencing (WGS) data generated from 125 *TCF4* Exp- FECD cases to interrogate other known disease-associated repeat expansions. In total, 2/125 cases harboured a *DMPK* expansion (≥50 repeats), confirmed by polymerase chain reaction (PCR)-based fragment analysis. This represented a significant enrichment (adjusted p-value=0.0035) compared to 16,326 WGS from gnomAD (v4.1.0, EH-v5.0.0). We subsequently screened an additional 200 *TCF4* Exp- FECD by PCR. Overall, 6/325 (1.85%) *TCF4* Exp- FECD patients harboured *DMPK* repeat expansions. Strikingly, *DMPK* repeat expansions display extreme levels of tissue-specific somatic instability in diseased CECs. Optical genome mapping revealed molecules harbouring on average 5,000 repeats, similar to instability observed in *DMKP* Exp+ muscle biopsies. In addition, affected CECs display CUG RNA foci that sequester the RNA binding protein MBNL1. Alternative splicing analysis (rMATS) revealed comparable signatures between *DMPK* and *TCF4* Exp+ FECD cases. Finally, corneal phenotyping of a DM1 cohort (n=8) suggests that FECD is more common in this patient group than in the general population. Collectively, our data suggest that *DMPK* expansions can cause FECD through converging molecular mechanisms to *TCF4* Exp+ FECD including high levels of CTG repeat instability, CUG-specific RNA foci with sequestration of MBNL1, and aberrant splicing.

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165 - Autism-related traits in myotonic dystrophy type 1

Łukasz Sznajder[1], Mahreen Khan[2], Adam Ciesiołka[3], Mariam Tadross[4], Curtis Nutter[5], Katarzyna Taylor[3], Christopher Pearson[2], Mark Lewis[4], Rochelle Hines[1], Maurice Swanson[4], Krzysztof Sobczak[3], Ryan Yuen[2]

[1]University of Nevada, Las Vegas, NV, USA, [2]The Hospital for Sick Children, Toronto, ON, Canada, [3]Adam Mickiewicz University, Poznań, Poland, [4]University of Florida, Gainesville, FL, USA, [5]University of Missouri, Columbia, MO, USA

Genome-wide enrichment of gene-specific tandem repeat expansions has been linked to autism spectrum disorder. One such mutation is the CTG tandem repeat expansion in the 3' untranslated region of the *DMPK* gene, which is known to cause myotonic dystrophy type 1. Although there is a clear clinical association between

autism and myotonic dystrophy, the molecular basis for this connection remains unknown. Here, we show that sequestration of MBNL splicing factors by mutant DMPK RNAs with expanded CUG repeats alters the RNA splicing patterns of autism-risk genes during brain development, particularly a class of autism-relevant microexons. We demonstrate that both *DMPK*-CTG expansion and Mbnl null mouse models recapitulate autism-relevant mis-splicing profiles, along with social behavioral deficits and altered responses to novelty. These findings support our model that myotonic dystrophy-associated autism arises from developmental mis-splicing of autism-risk genes.

Flash Talk

173 - Methylation of CCG variant repeats is associated with heterogeneous methylation of CpG sites surrounding DMPK expansion in DM1 patients

Jovan Pesovic[1], Pavel Bashtrykov[2], Milica Poljicak[1], Lana Radenkovic[1], Igor Davidovic[3], Nemanja Radovanovic[1], Milos Brkusanin[1], Vidosava Rakocevic Stojanovic[4], Stojan Peric[4], Dusanka Savic-Pavicevic[1]

[1]Center for Human Molecular Genetics, University of Belgrade-Faculty of Biology, Belgrade, Serbia, [2]Department of Biochemistry, Institute of Biochemistry and Technical Biochemistry, University of Stuttgart, Stuttgart, Germany, [3]Center for Genome Sequencing and Bioinformatics, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Belgrade, Serbia, [4]Neurology Clinic, Clinical Center of Serbia, University of Belgrade-School of Medicine, Belgrade, Serbia

Myotonic dystrophy type 1 (DM1) is among the most clinically variable monogenic diseases. We previously showed that variant repeats act as individual-specific genetic modifiers, delaying age-at-onset in DM1 patients by stabilizing CTG expansions within the *DMPK* gene in somatic cells. Since CCG variant repeats were most common, we aimed to investigate whether they were methylated themselves as well as associated with methylation of surrounding CpG sites, as observed with GC-rich repeats in other repeat expansion disorders.

Our study included 22 patients from 13 families with *DMPK* expansions carrying different patterns of CCG variant repeats. To examine methylation of CCG repeats, we designed methyl-specific repeat-primed PCR on bisulfite-converted genomic DNA using primers for both unmethylated and methylated CCG repeats. For confirmation, we performed repeat-primed PCR on genomic DNA digested with the methyl-sensitive *Ssi*I enzyme. We assessed methylation of CpG sites located 1.5kb

upstream and 1 kb downstream of the expansion using targeted Illumina and Oxford Nanopore bisulfite sequencing.

We discovered that CCG variant repeats were heterogeneously methylated in all patients. CpG sites both downstream and upstream of the repeat tract also showed heterogeneous methylation. Importantly, the extent and level of methylation, ranging 10-50%, depended on the structure of variant *DMPK* expansions. Patients with more CCG repeats generally had higher methylation in the downstream region. Moreover, upstream CpG sites also showed increased methylation in patients with the most abundant and complex CCG repeat patterns. These findings suggest that methylation initiates at the CCG repeats and spreads locally to adjacent CpG sites.

The discovery of methylation in variant CCG repeats raises questions about the role of epigenetic mechanisms in stabilizing the *DMPK* locus and their potential clinical relevance in DM1 patients beyond those with the congenital form.

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186 - Development and Expert Evaluation of a Clinical Checklist for Adult Myotonic Dystrophy Type 1 Care

Cynthia Gagnon[1], Homira Osman[2], Charles Kassardjian[3]

[1]Universite Sherbrooke, [2]Muscular Dystrophy Canada, [3]University of Toronto

Objective: To develop and evaluate a pragmatic clinical checklist, with a corresponding patient-analog version, to support implementation of consensus-based DM1 care in adult neuromuscular clinics.

Methods: Adult DM1 care recommendations were compiled from the published consensus-based care recommendations and corroborated through a scoping review conducted in 2022, confirming their scope and supporting evidence. Checklist development began with an existing DM1 checklist developed by Dr. Charles Kassardjian, which was used as an initial structure and subsequently evaluated against the consensus-based care recommendations and expert review.

To assess implementation-relevant outcomes, a structured survey was completed by 26 DM1 clinical experts, all neurologists. Experts rated each recommendation on overall quality and suitability for use in their clinical context using a 7-point Likert scale. Consensus was defined a priori as ratings of 6 or 7. Quantitative ratings were

summarized, and qualitative feedback was reviewed through expert focus groups. Recommendations with lower agreement or feasibility concerns were revised or clarified through a structured expert consensus process.

Results: Most recommendations achieved high expert consensus for both quality and suitability, particularly for diagnostic referral, cardiovascular and respiratory assessment, and anticipatory guidance. Recommendations with lower suitability ratings reflected contextual practice variability and were refined rather than excluded.

Recommendations were translated into a visual checklist organized into three domains: initial evaluation, follow-up assessment, and general management considerations. In parallel, a patient-analog checklist was developed using plain language and a mirrored structure to support patient understanding and care planning.

Conclusion: This consensus-informed, visual checklist and patient-analog companion addresses low awareness of existing DM1 care recommendations and provides a feasible, implementation-ready approach to supporting more standardized care and clinical readiness in an evolving therapeutic landscape.

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206 - Apathy as a Distinct Executive Phenotype in Adult Myotonic Dystrophy Type 1

Melissa M. Dixon[1]

[1]University of Utah

Central nervous system (CNS) involvement in myotonic dystrophy type 1 (DM1) is well documented; however, adult studies have rarely distinguished apathy from depression, quantified real-world executive dysfunction using ecological measures, or integrated behavioral, cognitive, and genetic data to clarify mechanisms of functional impairment. To address these gaps, this study characterized behavioral executive dysfunction and apathy as distinct neurobehavioral features in adults with DM1 and examined their relationships with cognition and CTG repeat length. Adults with DM1 (n=22) completed the Behavior Rating Inventory of Executive Function-Adult (BRIEF-A), Apathy Evaluation Scale (AES), Beck Depression Inventory-II (BDI-II), Beck Anxiety Inventory (BAI), Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV), and Wechsler Memory Scale-Fourth Edition (WMS-IV). Pairwise deletion addressed missing data. One-sample Wilcoxon signed-rank tests compared BRIEF-A T-scores and WAIS-IV/WMS-IV Index scores to normative reference values; associations were examined using Spearman correlations and partial Spearman

correlations controlling for depressive symptoms. BRIEF-A scales were significantly elevated, most prominently Initiate, Working Memory, Metacognition Index (all p's <0.001), and Global Executive Composite ($p<0.01$), indicating a selective initiation-based dysexecutive profile. WAIS-IV revealed disproportionate reductions in Processing Speed ($p<0.00001$) and Working Memory ($p<0.0001$), with relatively preserved Verbal Comprehension ($p>0.05$) and a higher General Ability Index relative to FSIQ ($p<0.01$), consistent with cognitive inefficiency rather than global intellectual decline. WMS-IV demonstrated elevated Auditory Memory with reduced Visual Working Memory, supporting executive mediation of memory performance. AES scores significantly correlated with BRIEF-A GEC and Initiate; this association remained significant after controlling for depressive symptoms. CTG repeat length was not associated with executive or processing speed outcomes ($p>0.05$). These findings provide evidence that apathy in adult DM1 represents a distinct executive phenotype characterized by impaired initiation, independent of depression and global IQ, reframing CNS involvement as driven by real-world executive and processing inefficiency rather than affective or primary amnestic pathology.

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210 - Proteogenomic Discovery of Splice-Junction Peptides as Novel Biomarkers in Cerebrospinal Fluid of Myotonic Dystrophy Type 1 (DM1)

Marwa Zafarullah[1], Eric Wang[2], Glendon Parker[3], Jacinda B. Sampson[1], John W. Day[1]

[1]Department of Neurology and Neurological Sciences, Stanford School of Medicine, Stanford, CA, [2]Department of Molecular Genetics & Microbiology, University of Florida, Gainesville, FL, USA., [3]Department of Environmental Toxicology, University of California Davis, One Shields Ave., Davis, CA 95616, USA

Myotonic Dystrophy Type 1 (DM1), caused by expanded CTG repeats in the *DMPK* gene, is a multisystemic disorder characterized by widespread RNA mis-splicing and protein dysfunction. While aberrant splicing is a key pathogenic mechanism, its detection at the protein level in accessible biofluids remains largely unexplored, limiting biomarker development and therapeutic monitoring capabilities. This study employed an innovative multi-omics approach integrating cerebrospinal fluid (CSF) proteomics with RNA sequencing data from DM1 post-mortem brain tissue to identify protein biomarkers and splice-junction peptides. We analyzed CSF samples from DM1 patients (n=5) and healthy controls (n=4) using high-resolution mass spectrometry (TIMS-TOF Ultra coupled with nanoElute 2), followed by spectral analysis using Spectronaut. A novel bioinformatics workflow was developed to detect splice-junction peptides corresponding to previously identified brain mis-splicing

events. We quantified 2,056 proteins, identifying 14 with differential expression between DM1 patients and controls. Five proteins were upregulated (LAMA2, ANTXR2, FCER2, TCTN3, FREM2), while nine were downregulated (TAGLN, CALB2, NTNG2, IGHV3-38, OLR1, FAM177A1, SLITRK6, RPS10, NCAM1). Pathway enrichment analysis revealed alterations in key biological processes relevant to DM1 pathophysiology. Critically, splice-junction peptide analysis revealed differential expression of Prosaposin (PSAP) isoforms, with Exon 7/9 showing elevated peptide area in DM1 samples. This provides proof-of-concept for detecting aberrant splice variants at the protein level in CSF. This pioneering approach successfully translates RNA-level splicing defects into detectable protein biomarkers, establishing a framework applicable across neuromuscular disorders characterized by splicing dysregulation. These splice-junction peptides offer unprecedented potential as pharmacodynamic markers for clinical trials, providing direct molecular evidence of therapeutic correction of splicing defects. Ongoing enrichment strategies for low-abundance proteins will further expand biomarker discovery, potentially transforming treatment monitoring in DM1 and related neuromuscular diseases.

Oral presentation Friday May 29, 2026

Session: Development of Biomarkers and Clinical Outcome Assessments II

61 - Developing digital endpoints to assess ambulation in DM1: analytical validation and feasibility of using a wearable sensor in daily living

Margaux Poleur[1], Stéphanie Delstanche[1], Manon Hustinx[1], Guillaume Parinello[2], Stéphane Motola[2], Noor Benmhammed[1], Camille Bisson[2], Charline Dubois[1], Manon Duclos[1], Thao Nguyen Le Lam[2], Laurie Médard[1], Damien Eggenspieler[2], Laurent Servais[3, 4]

[1]University department of neurology, CHR Citadelle, Liège, Belgium, [2]Sysnav, Vernon, France, [3]University of Oxford, United Kingdom, [4]Department of Paediatrics, University and University Hospital of Liège, Belgium

Myotonic Dystrophy Type 1 (DM1) lacks reliable and sensitive endpoints to evaluate drug efficacy. The European Medicines Agency qualification of stride velocity 95th centile (SV95C) in Duchenne muscular dystrophy raised interest in using wearable digital health technology (wDHT) to passively assess ambulation in daily life and develop sensitive endpoints to evaluate treatment response in DM1.

The Mocap study aims to assess the wDHT precision and accuracy in stride detection and measurement of gait parameters. Patients performed several exercises to compare wDHT sensor outputs to a motion capture reference. Two natural history studies (NHS) aim to determine the feasibility of using wDHT in daily living and assess digital endpoint psychometric performance, starting with SV95C, maximal walking distance (WD95C), number of strides per hour (NbStrides/h). Participants undergo clinical evaluation every 6 months and wear ankle sensors daily for the first 3 months, followed by 1 month every 6 months.

The Mocap study enrolled 9 patients (median age [range]: 42 years [5-72]). The wDHT algorithm correctly identified >99% of strides. The mean difference between the wDHT and reference on stride length and velocity were 0.6 cm and 0.5 cm/s, respectively. To date, the NHS have enrolled 21 patients (37 years [6-72]). All but 2 patients recorded ≥50 hours at baseline. As of August 2025, intra-class correlation coefficients for SV95C, WD95C and NbStrides/h were 0.99, 0.78 and 0.92 (N=12), respectively. Mean baseline values were significantly different between patients and controls for all 3 measures ($p<0.01$). SV95C Spearman correlation coefficients with 6MWT and 10MT were 0.92 and -0.65, respectively. As expected, limited changes were seen between baseline and 6 months. All available results will be presented at the congress.

Future work will evaluate the sensitivity to detect change of digital measures in a larger cohort and explore distal weakness-specific endpoints.

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132 - Beyond balance: exploring cerebellar cognition in Myotonic Dystrophy Type 1

Carola Rita Ferrari Aggradi[1], Andrea Lizio[1], Jacopo Casiraghi[1], Susanna Pozzi[1], Maria Beretta[1], Valeria Galli[1], Lucia Greco[1], Alice Zanolini[1], Giovanni Colacicco[1], Alessandra Di Bari[1], Alice Valenza[1], Valeria Ada Sansone[1]

[1]NeMO Clinical Center, Milan, Italy

It is well established that DM1 is also a brain disorder. Recent studies in the DMSXL mouse model demonstrated the characteristic RNA foci and mis-splicing in cerebellum and midbrain. Specific cerebellar areas involvement can lead to cognitive deficits, comprised in the Cerebellar Cognitive Affective Syndrome (CCAS). Interestingly, the CCAS and DM1 cognitive profile present striking clinical overlap.

The aim of our study was to explore cerebellar cognition using the CCAS-Scale, and to correlate the scores with a validated battery of cognitive tests.

Adult DM1 patients regularly followed at the NeMO Clinical Center underwent an extensive cognitive protocol comprising tests addressing executive, visuospatial, and attention function in addition to the CCAS-S, a brief cerebellar cognition specific 10-item scale.

52 patients (median age 45 years, median disease duration 20 years) were recruited. 25 (48%) patients had a pathological CCAS-S, while 27 (52%) had a non-pathological CCAS-S. The two groups had similar demographic characteristics. Good correlation between CCAS-S and standard tests was found. Patients failing the CCAS-S had a significant higher probability of failing the standard tests (c-index for Raven=0.8, Rey-Figure=0.74, WAIS-IV=0.8, Wisconsin=0.73), with high sensitivity (Sn for Raven=0.9, Rey-Figure=0.78, WAIS-IV=0.82, Wisconsin=0.75) and negative predictive value (NPV for Raven=0.95, Rey-Figure=0.85, WAIS-IV=0.85, Wisconsin=0.79).

This was the first study assessing cerebellar cognition in DM1. The CCAS-S was able to capture cognitive impairment in our cohort in a fast and easy way, showing correlation with other tests. The CCAS-S good sensitivity suggests its potential role as a cognitive screening tool, identifying patients to send to more extensive and time-consuming assessments. Data from wider cohorts and neuroradiological correlations will confirm these preliminary results and establish whether the CCAS-S could serve as a biomarker of cognitive decline and response to brain-targeting drugs.

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141 - Cross-sectional and 3-year longitudinal analysis of RNA mis-splicing in vastus lateralis muscle in a DM1 cohort

Cécilia Légaré[1, 2, 3, 4], Lori Planco[4], Robert Merritt[4], John Ripollone[5], Sarah Conner[5], Laura Desrochers[5], Fares Nigim[5], Marie-Pier Roussel[2, 3], Cynthia Gagnon[3, 6, 7], John Douglas Cleary[4], Andrew Berglund[4, 8, 9], Elise Duchesne[1, 2, 3, 9]

[1]Centre de Recherche du Centre Hospitalier de l'Université Laval (CR-CHUL), Axe Neurosciences, Université Laval, Québec City, Canada, [2]École des sciences de la réadaptation, Faculté de médecine, Université Laval, Québec, Canada, [3]Groupe de Recherche Interdisciplinaire sur les Maladies Neuromusculaires (GRIMN), Centre intégré universitaire de santé et de services sociaux du Saguenay-Lac-Saint-Jean, Saguenay, Québec, Canada, [4]RNA Institute, College of Arts and Sciences, University at Albany-SUNY, Albany, NY 12222, USA, [5]Vertex Pharmaceuticals, Boston, MA, USA, [6]Centre de recherche Charles-Le Moyne-Saguenay-Lac-Saint-Jean sur les innovations en santé (CR-CSIS), Université de Sherbrooke, Québec, Canada, [7]Faculté

de médecine et des sciences de la santé, Université de Sherbrooke, Québec, Canada, [8]Department of Biological Sciences, College of Arts and Sciences, University at Albany-SUNY, Albany, NY 12222, USA, [9]Co-last authors

RNA mis-splicing, measured using a splicing index (SI), is a key pathogenic phenomenon in myotonic dystrophy type 1 (DM1). However, little is known about the relationship between SI and clinical status, nor how the SI score changes over multiple years. Here we: 1) evaluated the association between clinical measures of muscle strength and function with SI scores derived from *vastus lateralis* (*VL*) biopsies and 2) assessed changes in SI scores over a 3-year period.

RNA was extracted from *VL* biopsies from 51 DM1 participants at baseline and 20 DM1 participants at 3 years. Clinical measurements of muscle strength and function were assessed at both time points. SI score was calculated based on Provenzano *et al.* (PMID: 39836447).

At baseline (n=51), participants (mean age 47 years; 57% female; 41% juvenile, 35% adult, 24% late-onset) had mean SI of 0.26. At this timepoint, a higher (worse) SI score correlated with weaker strength: percentage predicted muscle strength values for ankle dorsiflexors, knee extensors, or grip were respectively r = -0.57 [95%CI: -0.74 to -0.33], r = -0.48 [95%CI: -0.68 to -0.23]), and r = -0.60 [95%CI: -0.76 to -0.36]. Among participants with 3-year biopsies (n = 20), SI increased from 0.34 to 0.50 (mean difference = 0.16 [95%CI: 0.05, 0.26]). Among participants with mis-splicing at baseline (SI > 0; n = 17), a higher baseline SI score was associated with less change in SI over 3 years, indicating a potential ceiling effect in the progression of mis-splicing (r = -0.53 [95%CI: -0.81 to -0.05]; the association is weaker when participants with SI ≤ 0 (n = 3) are included in the analysis (r = -0.18 [95%CI: -0.59 to 0.30]).

These findings support a link between *VL* RNA mis-splicing and DM1 disease severity and progression, consistent with findings from previous *tibialis anterior* biopsy studies.

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203 - Multicenter Multimodal Imaging Reveals System-Level CNS Disruption in Pediatric Myotonic Dystrophy Type 1

Tahereh Kamali[1], Katharine Hageman[1], Rajanikant Panda[2], George Lin[1], Meng Yao[1], Nathan Hageman[1], Kelvin Lim[3], Bryon Mueller[3], Gayle Deutsch[1], Jeffrey Wozniak[3], Jacinda Sampson[1], John Day[1]

[1]Stanford University, [2]University of California, San Francisco, [3]University of Minnesota

Background: Central nervous system (CNS) involvement is a major contributor to disability in pediatric myotonic dystrophy type 1 (DM1), yet prior investigations have been constrained by single-site cohorts, single-modality imaging, and limited integration of neuroimaging with cognitive outcomes. Consequently, system-level relationships among brain microstructure, functional networks, and neurocognitive impairment in pediatric DM1 remain incompletely characterized.

Methods: We conducted a multicenter case-control study including two independent pediatric cohorts (total n = 62; ages 8-18 years) of genetically confirmed DM1 participants and age-matched controls. All participants underwent diffusion tensor imaging (DTI), resting-state functional MRI (rs-fMRI), and standardized neurocognitive assessment. White-matter microstructure was quantified across major association, commissural, and projection tracts, while large-scale functional connectivity was evaluated using cortical and subcortical parcellations. Imaging features were harmonized across sites, and multimodal integration was performed using an AI-driven fusion framework to derive an individualized imaging-based CNS burden index.

Findings: Compared with controls, pediatric DM1 exhibited widespread and spatially specific white-matter microstructural disruption, accompanied by reduced within-network coherence and diminished segregation of frontoparietal and default-mode systems. Structural and functional abnormalities independently predicted executive and visuospatial deficits, demonstrating convergent structure-function-cognition relationships. The AI-derived CNS burden index correlated with global intelligence and executive dysfunction consistently across acquisition sites.

Interpretation: This multicenter multimodal study provides evidence that CNS involvement in pediatric DM1 manifests as a unified system-level disturbance linking white-matter integrity, functional network organization, and neurocognitive performance. By integrating structural, functional, and cognitive data into a single individualized metric, this work advances biomarker development for CNS monitoring in pediatric DM1 and establishes a scalable framework for evaluating therapeutic response in future clinical trials.

Session: Clinical Manifestations, Activity and Participation II

3 - Frailty in DM1: Prevalence and Associations with Disease-Specific Factors

Joana Garmendia[1, 2], Irati Larrañaga[1, 2], Garazi Labayru[1, 2, 3], Pablo Iruzubieta[2, 3, 4, 5], Patricia Garay[2, 3, 4], Adolfo López de Munain[2, 3, 4], Andone Sistiaga[1, 2, 3]

[1]Department of Clinical and Healthy Psychology and Research Methodology Psychology Faculty, University of the Basque Country, [2]Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Institute Carlos III, Madrid, Spain., [3]Área de Neurociencias; Biogipuzkoa Instituto de Investigación Sanitaria, Donostia - San Sebastián, Guipúzcoa, España, [4]Departamento de Neurología; Hospital Universitario Donostia, Donostia- San Sebastián, Guipúzcoa, España., [5]Department of Neurology and Neurosurgery, Montreal Neurological Hospital and Institute, McGill University, Montreal, QC H3A 2B4, Canada

INTRODUCTION: Myotonic dystrophy type 1 (DM1) is a progressive multisystemic disease, often considered a model of premature aging. Frailty, a state of increased vulnerability — physical, psychological and social —, is associated with aging and adverse health outcomes. Patients with DM1 share several characteristics with the frailty phenotype; however, no studies to date have explored this construct in DM1 and its relationship with the disease-specific factors.

OBJECTIVES: To estimate the prevalence of frailty in DM1, and examine its relation with genetic, clinical, neuropsychological and other CNS-related symptoms.

METHOD: A total of 108 DM1 patients were included (mean age= 47.62 ± 12.12). Frailty was addressed through Tilburg Frailty Indicator (physical, social and psychological), and patients were classified as frail (≥5 points) or robust (<5 points) according to Gobbens' criteria. Genetic data, clinical measures (muscular impairment, phenotype, inheritance pattern, age of onset, and disease duration), neuropsychological performance (IQ and five cognitive domains), and CNS-related symptoms (apathy, fatigue, and hypersomnolence) were evaluated. Comparative analyses were conducted between frail and robust DM1 groups.

RESULTS: 64.6% (n=73) of patients were classified as frail. Compared with robust patients, frail DM1 patients had significantly longer disease duration, greater muscular impairment, higher levels of apathy and fatigue, lower IQ, and poorer performance in attention/processing speed, and visuoconstruction. Patients with a late-onset phenotype showed lower levels of frailty than those with other phenotypes.

CONCLUSSION: Frailty is highly prevalent in DM1 and is associated with greater disease burden, cognitive impairment, and CNS-related symptoms. Whether frailty in DM1 is driven by disease-specific mechanisms, accelerated aging, or a combination of both warrants further investigation. These findings support

incorporating frailty screening into routine DM1 assessment to improve risk stratification and guide multidisciplinary care.

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86 - Everyday Cognitive Failures in Myotonic Dystrophy Type 1 (DM1): A Longitudinal Study

STEFAN WINBLAD[1], Olöf Eliasdottir[2], Valgeir Thorvaldsson[1], Ulrika Edofsson[3], Sara Nordström[2], Christopher Lindberg[2]

[1]Department of Psychology, University of Gothenburg, Sweden, [2]Neuromuscular Centre, Department of Neurology, Sahlgrenska Unversity Hospital, Gothenburg, Sweden, [3]Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gotheburg, Sweden

DM1 is associated with cognitive dysfunction as assessed by objective neuropsychological tests. However, cognitive failures—defined as subjective experiences of errors in real-world, planned thought and action—have been investigated to a lesser extent. In the present study, we examined self-reported cognitive failures in 125 patients with childhood-, juvenile-, adult-, and late-onset DM1 using the Cognitive Failures Questionnaire (CFQ). We investigated changes in CFQ scores over four years at both the group and individual levels, as well as the relationships between cognitive failures, objective cognitive measures, and other clinical and disease-related factors at baseline.

Results showed that few patients reported a high prevalence of everyday cognitive failures (12% above proposed cut-off = 43). CFQ scores remained relatively stable over time (*M1* = 29.68, vs *M2* = 29.08, *p* = ns), and changes were minor (*M* change = -.60, SD = 8.4, min = -23, max = 21). Higher levels of fatigue (β= .23, $p < 0.01$) and depression/anxiety (β= .29, $p < 0.01$) were independently associated with higher ratings of cognitive failures. Nevertheless, these variables accounted for only 14 % of the variance in CFQ scores (adjusted $R^2 = .142$).

In summary, individuals with DM1 reported low and stable levels of self-reported cognitive failures over time. CFQ scores were not associated with objective cognitive measures but were related to other disease-related factors influencing self-ratings. The discrepancy observed in the present study between objectively measured cognitive impairments in DM1 and low self-reported cognitive failures may be explained in several ways, non-mutually exclusive factors: (1) cognitive impairments in the patient group are marginal; (2) patients may have limited insight into their own cognitive difficulties; (3) cognitive failures may reflect real-world cognitive

functioning rather than laboratory-based performance; and/or (4) objective impairments may not translate into everyday difficulties when cognitive demands are low.

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114 - Vitamin D Deficiency and Respiratory Muscle Dysfunction in Myotonic Dystrophy Type 1

Daniel Jaraj[1], Ólöf Elíasdóttir[2, 3], Christopher Lindberg[1]

[1]Department of Neurology, Sahlgrenska University Hospital, Gothenburg university, Sweden, [2]University of Gothenburg, [3]Landspítali-The National University Hospital of Iceland, Reykjavik, Iceland

Respiratory complications are one of the leading causes of death in Myotonic Dystrophy (DM1). It is therefore imperative to find factors that might be amenable to treatment. Although Vitamin D plays an integral role in muscle function - and patients with DM1 often have deficient levels - its role in respiratory muscle function has previously not been examined. The aim of this study was therefore to examine the association between vitamin D-levels and respiratory function in patients with DM1.

Data from a prospective cohort study was utilized for cross-sectional analysis. Patients with genetically verified DM1 (n = 129) aged 18 years or more were included. All patients underwent a series of examinations including blood tests and measurement of Vitamin D levels. Forced vital capacity (FVC) was measured by specialized physical therapists, and values adjusted for age, gender and height. Data analysis was made with R software for statistical computing.

Median vitamin D level was 53 nmol/L (IQR 34.4) and 43 % of the participants had insufficency (< 50 nmol/L). FVC % was, on average, 16 % lower among those with vitamin D <50 nmol/L compared to those with > 50 nmol/L: FVC 57 % vs 73 %, $p<0.001$.

These findings indicate that vitamin D deficiency is associated with respiratory muscle dysfunction in patients with DM1. Although there are a number of limitations and possible confounders, the present data may warrant further analysis regarding mechanisms and the possibility of treatment with vitamin D supplementation.

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148 - Identifying an Appropriate Patient-Reported Outcome Measure for Oropharyngeal Dysphagia in Myotonic Dystrophy Type 1

Claudia Côté[1, 2], Kiera N. Berggren[3], Catharina Faber[4], Walmari Pilz[3], Karlien Mul[5], Hilde Braakman[5], Isis Joosten[4], Ingemar Merkies[4], Marloes Lagarde[5], Armelle Magot[6], Raphaèle Chasserieau[6], Xavier Rodrigue[1], Eli Abra Atsakou[2, 7], Cynthia Gagnon[2, 7]

[1]Université Laval, [2]GRIMN, [3]Center for Inherited Myology Research, Virginia Commonwealth University Health, Richmond, USA, [4]Maastricht University Medical Center, Masstricht, the Netherlands, [5]Radboud University Medical Center, Nijmegen, the Netherlands, [6]Neuromuscular Disease Center, Laboratoire d'Explorations Fonctionnelles, Hotel Dieu, Chu de Nantes, France, [7]Université de Sherbrooke, Sherbrooke, Canada

Background: Oropharyngeal dysphagia (OD) is highly prevalent in neuromuscular diseases, including myotonic dystrophy type 1 (DM1). Accurate assessment of OD is essential, as it is associated with clinically meaningful outcomes such as weight loss and aspiration pneumonia. Patient-reported outcome measures (PROMs) are valuable tools for capturing patients' experiences of dysphagia; however, no PROM has been specifically recommended for use in individuals with DM1.

Objectives: This study aimed to identify existing PROMs that could be recommended for the assessment of OD in individuals with DM1 within the context of clinical research.

Methods: A two-step literature review was conducted to identify dysphagia-related symptoms reported in DM1 and PROMs currently used to assess OD. Identified symptoms were rated by a multidisciplinary expert panel (N = 54) using a Delphi process, based on clinical relevance, potential to change, and detectability by patients. Each PROM was then evaluated according to its coverage of the symptoms deemed relevant by the experts.

Results: 32 symptoms were rated, leading to the identification of eight highly relevant symptoms spanning four categories: oral symptoms, pharyngeal symptoms, coping strategies, and impacts on activities and participation. All symptoms were considered having a potential to change; however, patient detectability was less consistently rated. Among the identified PROMs, the Dysphagiameter and the SOAL questionnaire covered the greatest number of highly relevant symptoms, each addressing at least three of the four categories identified. Both instruments included few symptoms not specific to DM1, making them promising candidates for adaptation.

Conclusion: Existing PROMs can be used to assess dysphagia in individuals with DM1 but may require adaptation to fully reflect the specific dysphagia experience in this population. As symptom relevance was evaluated exclusively by clinical experts, further qualitative interviews with patients are needed to ensure that selected symptoms align with lived experiences, patient priorities, and symptom clarity.

Session: Clinical Management, Rehabilitation and Quality of Life Improvement I

53 - Energy Expenditure and the Accuracy of Predictive Equations in Myotonic Dystrophy Type 1

Wander J.A. Aarts[1], Basil P.A.P. van Veen[1, 2], Cas J. Fuchs[3], Luc J.C. van Loon[3], Catharina G. Faber[1], Isis B.T. Joosten[1]

[1]Department of Neurology and School for Mental Health and Neuroscience, Maastricht University Medical Centre+, Maastricht, The Netherlands, [2]Department of Gastroenterology and Hepatology, Maastricht University Medical Centre+, Maastricht, The Netherlands, [3]Department of Human Biology, NUTRIM Institute of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre+, Maastricht, The Netherlands

Myotonic Dystrophy type 1 (DM1) is associated with reduced physical activity, increasing the risk of overweight and cardiovascular morbidity. Nutritional management can support a healthy body weight, but requires estimation of total daily energy expenditure (TEE) derived from basal metabolic rate (BMR) and physical activity level (PAL). In clinical practice, BMR is commonly estimated by using predictive equations. However, disease-related alterations in body composition may compromise their accuracy in DM1, while estimations of PAL are also challenging. This study evaluated the accuracy of conventional BMR predictive equations in DM1, and assessed PAL and respiratory quotient (RQ).

In this prospective case-control study, 15 DM1 patients were compared with 15 age-, sex- and BMI-matched controls. Overnight metabolic rate (OMR) was measured using 24-hour room calorimetry and compared with predicted BMR derived from Harris-Benedict, WHO, and Mifflin-St Jeor equations, as well as body composition equations (Wang, Structure 4-5-11, Nelson). TEE was measured over 15 days under free-living conditions using doubly labeled water. Body composition was assessed by dual-energy X-ray absorptiometry. PAL was calculated as TEE/OMR, and RQ from the ratio of CO_2 production to O_2 consumption.

Standard predictive equations significantly overestimated metabolic rate in DM1 patients, with a median bias ranging from +100 to +165 kcal/day (+7% to +11%, $p<0.01$), with no significant bias observed in controls. Among equations incorporating body composition, *Structure 4* demonstrated the best agreement in DM1 (median bias +7 kcal/day; +0.5%, $p=0.98$). PAL was significantly lower in DM1 patients compared with controls (1.42 vs. 1.69, $p<0.001$). RQ did not differ between groups.

In conclusion, commonly used BMR predictive equations overestimate energy requirements in DM1. Incorporating body composition or applying correction factors may be necessary to avoid systematic overestimation of caloric needs. When estimating TEE in DM1, PAL values corresponding to low physical activity level appear most appropriate.

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71 - Feasibility, acceptability and effects of a telerehabilitation-based Respiratory Training Program in Myotonic Dystrophy Type 1

Elie Fiogbé[1, 2, 3], Élise Duchesne[1, 4, 5, 6], Livia Pinheiro Carvalho[2], Cynthia Gagnon[1, 2, 7]

[1]Groupe de recherche interdîsciplinaire sur les maladies neuromusculaires (GRIMN), Saguenay-Lac-St-Jean Integrated University Health and Social Services Center, Saguenay, Quebec, Canada, [2]School of Rehabilitation, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Sherbrooke, Quebec, Canada, [3]Centre de recherche du Centre hospitalier universitaire de Sherbrooke (CRCHUS), Université de Sherbrooke, Québec, Canada, [4]School of Rehabilitation Sciences, Faculty of Medicine, Université Laval, Quebec City, Quebec, Canada, [5]Center for Interdisciplinary Research in Rehabilitation and Social Integration (Cirris), Capitale-National Integrated University Health and Social Services Center, Quebec City, Quebec, Canada, [6]CHU de Québec-Université Laval Research Center, Quebec City, Quebec, Canada, [7]Centre de recherche et d'innovation du Centre intégré universitaire du Saguenay-Lac-St-Jean, Clinique des maladies neuromusculaires, Hôpital de Jonquière, Jonquière, Québec, Canada

Background: The success of any rehabilitation intervention depends on multiple factors, including accessibility and patient engagement.

Objective: To evaluate the adherence, quality of execution, and acceptability of a telerehabilitation-based respiratory muscle training (RMT) program in twelve individuals diagnosed with DM1.

Methods: The eight-week protocol was designed as a hybrid model, consisting of three weekly sessions that alternated between synchronous and asynchronous formats. To ensure safety and efficacy, we implemented a personalized prescription for every participant, strictly defining the adequate training intensity (ATI) and duration (ATD). We measured adherence (ratio of completed vs. prescribed sessions) and fidelity (ratio of actual vs. prescribed load). Furthermore, we calculated the Quality of Execution using the Average Effective Load per Session (AELS), a composite metric integrating ATI, ATD, and total session volume. Acceptability was assessed using a theoretical framework of acceptability.

Results: The program demonstrated high acceptability, with a mean score of 3.64±0.47 on a 5-point Likert scale. Notably, adherence to the RMT protocol was excellent; participants exceeded expectations by completing an average of 2.1 times the number of prescribed sessions. Fidelity was equally excellent, showing a median ratio of 1.00 [IQR: 0.99-1.00], indicating precise compliance with prescribed intensities. Analysis of the quality of execution revealed a significant inverse correlation between baseline health status and training effort: participants with lower functional capacity (assessed via the 6-minute walk test) and lower maximal inspiratory pressure at inclusion engaged significantly greater intensity and duration into each session (AELS, r=-0.84, p=0.001 and r=-0.61, p=0.04, respectively).

Discussion/Conclusion: This pilot study provides preliminary evidence that telerehabilitation is a feasible and highly accepted modality for the DM1 population. It highlights remarkable engagement and adherence, particularly among individuals with more severe functional impairments, suggesting that remote monitoring may effectively bridge the gap in respiratory care for vulnerable patients.

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74 - The Current Landscape of Perinatal Information Provision and Genetic Counseling in Congenital Myotonic Dystrophy Type 1 in Japan

Ayumi Yonei[1], Yuzuha Ichimura[2], Yuko Shimizu-Motohashi[3], Minobu Shichiji[4], Rie Honda[2], Michio Kobayashi[5], Tsuyoshi Matsumura[6], Hotake Takizawa[3], Toshio Saito[6], Akinori Nakamura[7], Kazuma Sugie[8], Atsuko Ishii[9], Tomoya Kubota[2], Yasuhiro Takeshima[10], Harumasa Nakamura[3], Haruo Fujino[9, 11], Hirofumi Komaki[3], Keiko Ishigaki[4], Masanori P. Takahashi[1, 2, 9]

[1]Department of Genetic Counseling, The University of Osaka Hospital, [2]Clinical Neurophysiology, The University of Osaka Graduate School of Medicine, [3]Department of Child Neurology, National Center of Neurology and Psychiatry, [4]Tokyo Women's

Medical University School of Medicine, [5]Department of Neurology, NHO Akita National Hospital, [6]Department of Neurology, NHO Osaka Toneyama Medical Center, [7]Department of Neurology, NHO Matsumoto Medical Center, [8]Department of Neurology, Nara Medical University, [9]United Graduate School of Child Development, The University of Osaka, [10]Department of Pediatrics, Hyogo Medical University, [11]Graduate School of Human Sciences, The University of Osaka

Congenital myotonic dystrophy type 1 (cDM1) typically requires perinatal management of both the mother and the fetus. Although adequate understanding of DM1, including its congenital form, among patients and at-risk individuals is essential for appropriate perinatal care, the extent of perinatal information provision and its perception by patients and families in clinical practice remains unclear.

The objective of this study was to examine the provision of perinatal information to parents of children with cDM1, and parental perceptions of its importance, and to explore their experiences with perinatal complications.

We analyzed a subset of data from a nationwide, multi-item survey conducted primarily through a patient registry (Remudy) involving parents of individuals with congenital or childhood-onset DM1 in Japan. The survey assessed the provision and perceived importance of information across key DM1-related domains, as well as experiences of perinatal complications. In this analysis, we focused on parents of children with cDM1 and their reported experiences.

Of 470 questionnaires distributed, 145 were returned, and responses from 48 parents of children with cDM1 were included in the analysis. Information related to general DM1 features was frequently provided (mean 86.1%); however, information regarding precautions during pregnancy and perinatal complications was provided to only 38.1% of respondents, and 53.5% did not recognize its importance. Although 75.0% reported receiving genetic information, only 52.4% had been informed about referral to genetic medicine departments capable of providing comprehensive perinatal information, despite 70.5% recognizing its importance. Regarding perinatal experiences, 45.5% of women with DM1 reported symptom worsening during pregnancy, and 56.5% reported delivery complications.

These findings indicate that routine clinical care alone is insufficient to provide adequate perinatal-related information in cDM1, and suggest that collaboration with genetic medicine department capable of delivering comprehensive information is essential.

183 - Impact of assisted reproductive technologies on reproductive outcomes in women with myotonic dystrophy: a retrospective study

Patricia Garay-Albízuri[1, 2, 3], Roberto Fernández-Torrón[1, 2, 3], Pablo Iruzubieta[1, 2, 3, 4], Juan José Poza[1, 2, 3], Maria José Iñarra-Velasco[5], María Lure-Berregui[5], Loreto Martorell[6, 7], Adolfo López de Munain[1, 2, 3, 8, 9]

[1]Department of Neurology, Donostialdea Integrated Health Organisation, Osakidetza, San Sebastian, Spain, [2]Neuromuscular Diseases Group, Neurosciences Area, Biogipuzkoa Health Research Institute, San Sebastian, Spain, [3]CIBERNED, CIBER, Spanish Ministry of Science & Innovation, Carlos III Health Institute, Madrid, Spain, [4]Department of Neurology and Neurosurgery, Montreal Neurological Hospital and Institute, McGill University, Montreal, QC H3A 2B4, Canada, [5]Department of Gynecology, Donostialdea Integrated Health Organization, Osakidetza, San Sebastian, Spain, [6]Department of Genetic and Molecular Medicine-IPER, Hospital Sant Joan de Déu and Institut de Recerca Sant Joan de Déu, Barcelona, Spain., [7]Center for Biomedical Research Network on Rare Diseases (CIBERER), ISCIII, Madrid, Spain., [8]Department of Neurosciences, University of the Basque Country UPV-EHU, San Sebastian, Spain, [9]Faculty of Medicine, University of Deusto, Bilbao, Spain

Introduction: To date, few studies have evaluated the impact of assisted reproductive technologies for preimplantation genetic testing (PGT) in women with myotonic dystrophy type 1 (DM1). PGT represents an alternative to prenatal diagnosis for patients at risk of transmitting inherited disorders such as DM1 to their offspring and provides women with the opportunity to conceive without the risk of transmitting the monogenic disorder.

Objectives: To study the effect of PGT in the fertility and reproductive health of women with myotonic dystrophy type 1 (DM1).

Methods: We conducted a single-center retrospective observational study including women with a diagnosis of DM1 followed at Hospital Universitario Donostia (Gipuzkoa, Spain) between January 2011-November 2025. We selected patients who had the fertile years during and after the introduction of PGT in Gipuzkoa in 2001. Reproductive variables assessed included the number of pregnancies, miscarriages and deliveries, the use of PGT, as well as the success of this technique, together with other demographic variables.

Results: A total of 135 women were included, with a median follow-up time of 14.95 years (IQR 14.75-14.95). Thirty-two patients (23.7%) underwent preimplantation

genetic testing (PGT). Among patients who underwent PGT, 18 (56%) achieved a term pregnancy. Of these, 12 patients (66%) were successful on the first attempt; 3 (16.6%) on the second attempt and some required three to four cycles. In patients undergoing PGT with oocyte donation (N=10, 31.2% of women who underwent PGT), 90% achieved a successful outcome. Of the 103 women who did not undergo PGT, 16 (15.2%) were diagnosed after their pregnancies.

Conclusions: Despite the implementation of preimplantation genetic testing (PGT), women with DM1 show a moderate-to-low success rate. Several factors may contribute to this outcome, including involvement of the reproductive system in the disease, as women undergoing PGT with oocyte donation may have higher success rates, although the sample size is small.

Session 5: Preclinical and Clinical Drug Development

42 - Multiscale imaging uncovers xenogeneic regenerative capacity of human pericytes as a cell therapeutic vehicle

Renée H.L. Raaijmakers[1, 2], Marieke Willemse[2], Esther Wagena[2], Ellen van Beusekom[1], C. Rosanne M. Ausems[1, 2], Lisa Rahm[1, 2], Derick G. Wansink[2], Hans van Bokhoven[1]

[1]Radboud university medical center, Radboud Institute for Medical Innovation and Donders lnstitute for Brain Cognition and Behaviour, Department of Human Genetics, 6500 HB, Nijmegen, The Netherlands, [2]Radboud university medical center, Radboud Institute for Medical Innovation, Department of Medical BioSciences, 6500 HB, Nijmegen, The Netherlands

Background. Pericytes hold potential as therapeutic cells in skeletal muscle regeneration, particularly in cell therapy for neuromuscular disorders, including DM1. While preclinical studies have examined the role of pericytes in muscle repair, robust evidence of myogenesis *in vivo* remains limited due to insufficient understanding of pericyte migration and fusion capacity. Using an optimized multiscale imaging approach, we assessed survival, localization and myogenic capacity of primary human pericytes following intramuscular and intra-arterial injection in an acute muscle injury mouse model.

Methods. Cardiotoxin was administered to the tibialis anterior muscle of *Rag2*$^{-/-}$ immunodeficient mice to induce muscle regeneration, followed by intramuscular or intra-arterial delivery of primary human pericytes. One month post-treatment, organs

were harvested for qPCR analysis and whole muscles were cleared using an ethanol-ethyl cinnamate protocol and immunolabeled with a human-specific lamin A/C antibody. Light-sheet fluorescence microscopy enabled 3D visualization of transplanted pericyte distribution, guiding the selection of samples for cryosectioning and subsequent confocal laser scanning microscopy.

Results. Combining 3D whole muscle visualization with confocal laser scanning microscopy, showed that transplanted human pericytes contributed to muscle regeneration in mice *in vivo* upon intramuscular delivery. Variability in the traceability of human nuclei after intramuscular delivery highlighted the procedural complexity, underscoring the need for systemic, intra-arterial injections. Application of our microscopy-based pipeline highlighted that 0.2-1% of intra-arterially injected human pericytes homed to the tibialis anterior muscle at the site of injection, with a lower fraction in the gastrocnemius muscle. Human-specific qPCR analysis of filter organs showed no detectable human DNA outside muscle tissue.

Discussion. We offer a versatile multiscale imaging pipeline with broad applicability for tracking cell fate and enhancing the preclinical evaluation of regenerative interventions. Our results provide new insights into pericyte behavior and support their potential in cell-based therapy for neuromuscular diseases.

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82 - Scaling therapeutic discovery in DM1: A validated high-throughput platform combining in vitro screening and machine learning

Andrea López-Martínez[1], Abdullah Al-Ani[1], Solange Kapetanovic-García[1, 2], Nadia Osegui-Barcenilla[1], Sonia Arrasate[3], Humberto González-Díaz[3, 4, 5], Virginia Arechavala-Gomeza[1, 5]

[1]Nucleic Acid Therapeutics for Rare Diseases (NAT-RD), Biobizkaia Health Research Institute, Barakaldo, Spain, [2]ALS and Neuromuscular Unit, Department of Neurology, Hospital Universitario Basurto, Bilbao, Spain, [3]Department of Organic and Inorganic Chemistry, University of the Basque Country UPV/EHU, Leioa, Spain, [4]Basque Center for Biophysics CSIC-UPV/EHU, University of Basque Country UPV/EHU, 48940 Leioa, Spain, [5]Ikerbasque, Basque Foundation for Science, Bilbao, Spain

While the molecular drivers of myotonic dystrophy type 1 (DM1) are well-defined, the transition from mechanistic understanding to effective clinical therapies remains a significant bottleneck. Addressing this requires screening pipelines that are physiologically relevant in robust, high throughput platforms. We previously established an *in vitro* platform utilising in-cell western and digital PCR to quantify

MBNL1 restoration and splicing correction. Validation in myogenic models confirmed the platform's sensitivity, successfully detecting MBNL1 release following treatment with a *DMPK* gapmer and a repeat-blocker antisense oligonucleotide, while providing a clear negative readout for a siRNA.

We have now integrated this validated biological assay into a larger discovery pipeline, ScreenDM1, which uses a Perturbation Theory and Machine Learning (PTML) methodology to guide drug repurposing. To date, we have conducted an unbiased phenotypic screen of 711 FDA/EMA-approved compounds, with 327 evaluated across three doses. Using an MBNL1 restoration threshold, we identified 159 potential hits. Notably, 22 candidates demonstrated MBNL1 release exceeding 50% compared to untreated controls.

These top-tier hits are currently undergoing comprehensive characterisation to establish dose-response relationships and validate splicing correction via ddPCR in patient-derived myogenic cultures. In parallel, we are curating a database of ChEMBL assays for different compounds in order to construct a new cheminformatic model for predicting potential lead compounds and their activities using Artificial Intelligence/ML (AI/ML) algorithms . By feeding these experimental results back into the PTML model, we are iteratively refining its predictive accuracy for future lead selection. This dual-track approach allows for the rapid, unbiased identification of high-potency candidates from established drug libraries. These findings identify several novel hits with therapeutic potential *in vitro*, providing a systematic framework for further preclinical development in DM1.

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83 - Tricyclo-DNA antisense oligonucleotide compounds to tackle toxic CUGexp-RNA in a mouse model of Myotonic Dystrophy type 1

Julie FAGIOLI[1], Cyriaque BELEY[2], Marine GEOFFROY[2], Geneviève GOURDON[1], Luis GARCIA[2, 3], Denis FURLING[1], Arnaud KLEIN[1]

[1]Sorbonne Université, Inserm, Institut de Myologie, Centre de Recherche en Myologie, Paris, France, [2]SQY-Therapeutics, Montigny-le-Bretonneux, France, [3]Université Paris-Saclay, UVSQ, Inserm, END-ICAP, Versailles, France

Antisense oligonucleotides (ASOs) represent a promising therapeutic approach for neuromuscular disorders such as Myotonic Dystrophy type I (DM1). ASOs have been developed to directly degrade the mutated *DMPK* (Dystrophia myotonica protein kinase) transcripts containing expanded-CUG repeats (CUGexp) or to interfere with the abnormal binding of MBNL RNA-binding proteins to CUGexp and associated with

RNA toxicity. However, their efficacy and delivery to muscle tissue after systemic administration remain an ongoing challenge. Here, we describe the use of a highly potent ASO chemistry, the tricyclo-oligodeoxynucleotide (Tc-DNA) as a potential antisense approach for DM1. These conformationally constrained DNA analogs have shown enhanced RNA binding properties, high biostability, resistance to exonuclease as well as promising therapeutic potential for other neuromuscular diseases such as Duchenne muscular dystrophy. As a proof of concept, we evaluated a Tc-DNA-gapmer compound targeting mutant HSA-CUGexp transcripts in the skeletal muscle of the well-established HSA-LR DM1 transgenic mouse model expressing the Human Skeletal Actin (HSA) gene containing 220 CTG repeats. Intravenous injection of a single 20mg/kg dose of Tc-DNA-HSA in these mice resulted in a near complete degradation of CUGexp-RNAs, accompanied by a decrease in the number and the intensity of CUGexp-RNA foci. Consistent with these results, we observed a significant correction of alternative splicing defects in skeletal muscles, the normalization of the muscle transcriptome, and the suppression of myotonia. Beneficial molecular and functional effects of a single injection at 20mg/kg, or two injections at 10mg/kg lasted up for 6 months without adverse effects. In addition, evaluation of repeated injections of Tc-DNA-HSA at doses as low as 1, 2.5 or 5 mg/kg showed very promising results, confirming the enhanced properties of these ASO compounds and their potential as therapeutic approach for DM1. Based on these findings, the next step will consist to develop a Tc-DNA-gapmer targeting the human *DMPK* sequence.

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135 - Sensor-Regulated Decoy Gene Therapy for Myotonic Dystrophy Type 1

Ludovic Arandel[1], Aurélien Cordier[1], Alain Sureau[1], Gilles Moulay[1], Krizia Ronquillo[1], Antoine Muchir[1], Méganne Lemaitre[2], Julianne Perronnet[2], Arnaud Klein[1], Frédérique Rau[1], Denis Furling[1]

[1]Sorbonne Université, Inserm, Institut de Myologie, Centre de Recherche en Myologie, Paris, France, [2]Sorbonne Université, UMS28 Phénotypage du petit animal, Paris (France)

Myotonic dystrophy type 1 (DM1) is an autosomal dominant neuromuscular disorder caused by CTG repeat expansion in the 3' untranslated region of the DMPK gene. This mutation leads to the retention of CUG-expanded RNAs into nuclear foci through abnormal interactions with Muscleblind-like (MBNL) proteins. Sequestration of MBNL1 and its subsequent functional loss in skeletal muscle and heart disrupts RNA processing, including alternative splicing, contributing to muscle weakness,

myotonia, and cardiac conduction defects. Furthermore, due to somatic instability, the size of CTG repeats varies between tissues and increases over the patient's lifetime, complicating therapeutic interventions and highlighting the need for their regulation. Despite advances and ongoing trials, no treatment is currently available. We developed a gene therapy strategy based on a modified MBNL protein, so-called "Decoy", which lacks splicing activity but retains high binding affinity for expanded CUG repeats. Following binding to CUG-expanded repeats, the Decoy releases endogenous MBNL proteins from nuclear foci and restores their functions in the cell. To optimize efficacy and therapeutic benefit, we designed a sensor-based regulation system that adjusts Decoy expression in muscle according to CTG repeat size, CUGexp RNA levels, and associated loss of MBNL function, ensuring appropriate levels of therapeutic protein in the pathological context. The Sensor-Decoy cassette was packaged into a myotropic adeno-associated virus (AAV) vector for systemic delivery to striated muscles. Wild-type and DM1 mice carrying different CTG expansion sizes were treated, and molecular and functional outcomes were evaluated six weeks and/or six months post-injection. In DM1 mice, Decoy expression in skeletal and cardiac muscles normalized alternative splicing misregulation and improved myotonia, muscle strength, and cardiac conduction defects. Limited Decoy protein expression was detected in DM1 skeletal muscles, whereas it was absent in wild-type conditions, confirming strict regulation by the sensor system. Overall, this sensor-controlled strategy effectively corrects RNA toxicity in DM1.

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193 - Interventionally Contracting Somatic CTG Repeat Expansions as a Disease-Modifying Strategy for Myotonic Dystrophy Type 1

Shuqian Tang[1, 2], Kristie Feng[1], Mustafa Mehkary[1, 2], Isabelle Quick[1, 2], Peixiang Wang[1], Terence Gall-Duncan[1], Christopher Pearson[1, 2]

[1]Program of Genetics & Genome Biology, The Hospital for Sick Children., [2]Department of Molecular Genetics, University of Toronto.

DM1 is caused by inheritance of expanded CTG/CAG repeats in *DMPK*, which continue to undergo somatic expansion in affected tissues, including muscle, heart, and brain, as individuals age. Somatic expansions occur in DM1 mice, as they do in humans. DM1 is associated with progressive neuromuscular and cardiac manifestations, neurodevelopmental and neuropsychiatric phenotypes, including cognitive impairment and an increased risk of autism spectrum disorder (ASD), highlighting the importance of targeting repeat instability in the central nervous system.

Somatic expansions, mediated by slipped-CTG/CAG DNA structures, drive disease onset, progression, and severity. Therefore, slowing, arresting, or reversing somatic repeat expansions is expected to be therapeutically beneficial, although *in vivo* evidence for this strategy in DM1 remains limited.

The Pearson Lab has demonstrated that the slipped-CAG-binding small molecule Naphthyridine-Azaquinolone (NA) induces contractions of expanded repeats and improves molecular, neural, and motor phenotypes in Huntington's disease and DRPLA mice (both CAG/CTG repeat disorders). The goal of this study is to determine whether ligands specific to slipped-CTG/CAG structures can modify somatic CTG expansions in DM1 mice.

Our preliminary data show that Compound CP302, that binds specifically to slipped-CTG/CAG DNA structures induces repeat contractions in the brain, heart, and muscle of DM1 mice, and improves the downstream molecular phenotypes, such as reduced CUG RNA foci, decreased MBNL1 sequestration, and reduced central nucleation of muscle fibers, highlighting its therapeutic potential as a disease-modifying treatment. In parallel, we define age- and tissue-specific patterns of somatic instability in the brains and muscles of DM1 mice, identifying optimal windows for such a therapeutic intervention.

This work will determine whether the root cause of DM1—somatic repeat expansions—can be modified by pharmacological intervention with a small-molecule, which would be proof-of-principle data towards developing a new disease-modifying strategy for neuromuscular, cardiac, and neurodevelopmental manifestations of DM1, including those relevant to ASD.

Poster presentations

4 - Balance and coordination in myotonic dystrophy type 1

Sarah Mollet[1], Rachael Taylor[1], Joseph Donnelly[2], Catherine Watts[1], Juno Collins[1], Michael Sanders[1], Miriam Rodrigues[1, 2], Marie-Claire Smith[1], Richard Roxburgh[1, 2]

[1]University of Auckland, [2]Auckland City Hospital

Falls are ten times more common in myotonic dystrophy type 1 (DM1) than in age matched healthy volunteers. This has been attributed to muscle weakness, however, because it is a multisystem disorder we wanted to look at all five components that contribute to balance.

20 adult participants with DM1 able to walk 10m unaided were recruited. Balance was assessed using the Gait and Balance App (G&B App).

Contributors to balance were assessed with the 6m Visual Acuity (VA) chart, Manual Muscle Testing (MMT), the modified Inflammatory Sensory Sumscore (mISS) (maximum = 36), Scale for Assessment and Rating of Ataxia (SARA) (maximum = 40), and 3D video Head Impulse Test (vHIT) (vestibular function).

Our 20 participants had an average age of 47.2. 30% of participants had abnormal balance scores on basic tasks in the G&B App increasing to 50% of participants for more complex tasks.

70% had visual impairment (VA <6/9). Muscle weakness was found throughout the lower limb musculature, not just around the ankle. Joint position sense in the leg was the most affected sensory component, and participants had the most difficulty with gait and stance on the SARA. 30%-35% of participants had either bilateral or unilateral problems with their horizontal and posterior canals. Those with slow saccades tended to have lower vestibular ocular reflex gains and otolith functions.

Multiple regression analysis showed that strength improved performance in the hardest standing condition p = 0.026. Repeat length approached significance in this condition and vHIT approached significance in the hardest walking condition.

We have confirmed that our participants had balance difficulties that involve all five components of balance: vision, strength, sensation, coordination and vestibular. However, multiple regression analysis showed that the stronger they were the better they performed in the hardest standing condition of standing on foam with eyes closed.

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5 - The FREEDOM-DM1 clinical trial demonstrated unprecedented splicing correction with single doses of PGN-EDODM1, with an acceptable safety profile.

Johanna Hamel[1], Jean-Denis Brisson[2], Hanns Lochmuller[3], Thurman Wheeler[4], Jacinda Sampson[5], Namita Goyal[6], Jordi Diaz-Manera[7], Gerald Pfeffer[8], James Lilleker[9], Nicholas Johnson[10], Erin O'Ferrall[11], Jeffrey Statland[12], Christopher Turner[13], Brijesh Garg[14], Greg Song[14], Pallavi Lonkar[14], Sarah Vacca[14], Stephen Babcock[14], Sejal Batra[14], Shaoxia Yu[14], Paul Streck[14], Ann Barbier[14], Jane Larkindale[14]

[1]University of Rochester, [2]CIUSSS du Saguenay-Lac-Saint-Jean, Canada, [3]Ottawa Hospital Research Institute, Canada, [4]Massachusetts General Hospital, Boston, MA, [5]Stanford University Medical Center, Stanford, CA, [6]University of California - Irvine Medical Center, Irvine, CA, [7]John Walton Muscular Dystrophy Research Center, Newcastle University and Newcastle Upon Tyne NHS Trust, UK, [8]University of Calgary,

Canada, [9]Northern Care Alliance NHS Trust, UK, [10]Virginia Commonwealth University Health System, VA, [11]McGill University, and Montreal Neurological Institute Hospital, Montreal, Canada, [12]University of Kansas Medical Center (KUMC), KS, [13]University College London Hospital, UK, [14]PepGen

PGN-EDODM1 is an investigational peptide-conjugated oligonucleotide (PPMO) in clinical trials for myotonic dystrophy type 1 (DM1), based on PepGen's enhanced delivery oligonucleotide (EDO) cell-penetrating peptide technology. EDOs are engineered to optimize tissue delivery and nuclear uptake of therapeutic oligonucleotides. PGN-EDODM1 binds to pathogenic CUG trinucleotide repeat expansions in *DMPK* mRNA, liberating MBNL1 protein through steric blocking, and is expected to restore splicing of downstream transcripts: the central cause of DM1 pathology. Delivery to target tissues and correction of mis-splicing have been demonstrated in nonclinical models and in the FREEDOM-DM1 clinical trial (NCT06204809).

FREEDOM-DM1 is a Phase 1 randomized, double-blind, placebo-controlled, single ascending dose (SAD) study of PGN-EDODM1 in people with myotonic dystrophy type 1 (DM1) (NCT06204809). This study demonstrated dose-dependent improvements in mean splicing correction 28 days postdose of 12.3%, 29.1% and 53.7% at 5mg/kg, 10mg/kg and 15mg/kg, respectively (22-gene panel), substantially higher than previously reported in people with DM1. No significant changes in muscle function were observed after a single dose. PGN-EDODM1 was generally well-tolerated at 15mg/kg, with no serious treatment-related adverse events. Transient mild-moderate changes in renal biomarkers were observed, which met the dose limiting toxicity criteria in one participant. These were asymptomatic and resolved without intervention within 48 hours of dosing.

Nonclinical data suggest that further splicing improvement may be anticipated with repeat doses administered every 4 weeks, along with improvements in function over time. FREEDOM2-DM1 is an ongoing multiple ascending dose study of PGN-EDODM1 in adults with DM1 (NCT06667453). Three ascending dose levels will be studied (n=8, randomized 3:1); each cohort will receive 4 doses administered every 4 weeks. Endpoints include safety, tolerability, pharmacokinetics, pharmacodynamics (correction of mis-splicing), and multiple measures of function. *Data from the first cohort of this study will be presented*.

6 - Differentiated Cognitive Profiles in Myotonic Dystrophy Type 1: A Cluster Analysis

Irati Larrañaga[1, 2], Joana Garmendia[1, 2], Garazi Labayru[1, 2, 3], Adolfo Lopez de Munain[2, 3, 4], Andone Sistiaga[1, 2, 3]

[1]Department of Clinical and Health Psychology and Research Methodology; Faculty of Psychology, University of the Basque Country (EHU), Donostia - San Sebastian, Spain, [2]Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Institute Carlos III, Madrid, Spain, [3]Área de Neurociencias; Biogipuzkoa Instituto de Investigación Sanitaria, Donostia - San Sebastián, Guipúzcoa, España., [4]Departamento de Neurología; Hospital Universitario Donostia, Donostia - San Sebastián, Guipúzcoa, España.

INTRODUCTION: Myotonic dystrophy type 1 (DM1) is a multisystemic hereditary disease with heterogeneous symptoms affecting the CNS, including cognitive deficits, as well as apathy, fatigue, and somnolence. These alterations may contribute to heightened frailty, a state of increased vulnerability. Characterizing cognitive profiles and their clinical features is essential to better understand CNS involvement in DM1.

OBJECTIVES: To identify cognitive clusters in patients with DM1 and examine their associations with sociodemographic, frailty and disease-specific factors.

METHOD: 81 non-congenital DM1 patients were evaluated neuropsychologically, alongside sociodemographic, clinical, genetic, frailty, and other CNS outcomes. K-means clustering analysis was performed based on IQ and five cognitive domains. Clusters were compared across, sociodemographic, frailty and disease-specific factors.

RESULTS: In this sample (mean age 46.2 ± 11.9; 50% men), three cognitive clusters emerged: 1) high average IQ with preserved cognition (n=20); 2) low average IQ with mild deficits in attention/processing speed and visuoconstruction (n=38); and 3) markedly below average IQ with global cognitive impairment, more prominently in attention/processing speed and visuoconstruction (n=23). Patients in Cluster 1 displayed a higher educational level and less muscular impairment than the other two groups, and they were mostly partial and adult phenotypes; Cluster 2 showed higher apathy levels than the other groups. Frailty differed overall across clusters, although pairwise comparisons were not significant. There were no significant differences in other sociodemographic, clinical, and genetic outcomes.

CONCLUSION: Three distinct cognitive profiles were found in DM1, each associated with certain clinical and genetic characteristics. Frailty outcomes were not sufficiently powered to detect group-specific differences, although results suggest a

possible direction of increasing frailty scores in Cluster 2 and 3 compared to Cluster 1, warranting further study. Overall, findings explain the cognitive heterogeneity of DM1 and can help to identify more precise clinical subgroups, which would be useful for designing personalized interventions.

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7 - Respiratory function in Myotonic dystrophy type 1 - a prospective single center study

Olöf Eliasdóttir[1], Valgeir Thorvaldsson[2], Sara Nordström[1], Christopher Lindberg[1]

[1]Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Blåa stråket 7, 41345, Gothenburg, Sweden, [2]University of Gothenburg- Department of Psychology - Neuro, Cognition, Developmental Psychology Haraldsgatan 141314 Gothenburg, Sweden

Introduction

Myotonic dystrophy type 1 (DM1) is a multiorgan, progressive hereditary disease that commonly affects respiratory function over time. The aim of this study was to characterize the respiratory function in individuals with DM1 and to examine demographic factors, associated with respiratory impairment.

Patients and methods

This prospective study included 127 patients with DM1 and was conducted at the Neuromuscular Center, Sahlgrenska University hospital, Gothenburg, Sweden. Forced vital capacity (FVC%) and peak expiratory flow (PEF) were measured at baseline and follow up. Additional information was gathered on age, gender, CTG repeat length, Muscular Impairment Rating Scale (MIRS), and body mass index (BMI). Latent change score (LCS) models were used to examine associations of CTG repetitions, MIRS, DM1 type, and BMI with baseline FVC% and PEF, as well as with longitudinal changes in the respiratory measures.

Results

The mean follow up time was 4.3 years. The Mean FVC at baseline was 65.7% with SD 17.1 and it changed signficanly over time;65.7 vs 62.7% (p=0.002). The PEF did not change over time (p =0.147). Baseline FVC% was lower among participants with higher CTG repeat length (-1.52, SE=0.39 p<0.001), higher BMI (-0.683; SE=0.225 p=0.002), and higher MIRS scores (-8.197 SE=1.346; p=<0.000). For FVC%, higher MIRS scores was associated with a steeper decline over time (-3.25, SE=1.47 p=0.027). The biggest change in FVC% over time was in patients that where 35-60 years old at baseline.

Discussion

Our study suggests that a relatively long follow up is necessary to detect changes in FVC over time, the individual variation is high and that a higher MIRS score at inclusion correlates with a steeper decline in FVC over time.

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8 - Investigating the basis of sleep dysregulation in myotonic dystrophy type 1

Belinda Pinto[1], Emily Davey[1], Juan Arboleda[1], Miguel Gutierrez[1], Charles Thornton[2], Karyn Esser[1], Eric Wang[1]

[1]University of Florida, [2]University of Rochester Medical Center

Myotonic Dystrophy Type 1 (DM1) has profound CNS symptoms, with sleep dysregulation and hypersomnia being particularly debilitating. However, the physiological basis for these symptoms is unknown. Interestingly, actigraphic studies of DM1 patients suffering from hypersomnia show low amplitude sleep-wake rhythms with a ~2 hour delayed sleep phase or non-24-hour sleep wake disorder suggesting that disruption of circadian mechanisms could contribute to sleep dysregulation in DM1. To determine the basis of this phenotype, we have undertaken circadian activity analyses of multiple DM1 mouse models in which MBNL function is perturbed to different degrees: 1) the KI^{480}, which has 480 CTG repeats knocked into the mouse *Dmpk* 3' UTR, representing a mild form of the disease 2) the $Mbnl2^{-/-}$, which lacks the dominant MBNL in the CNS, representing a severe form of the disease and 3) KI^{1700}, with 1700 CTG repeats, and $KI^{480}/KI^{480}; Mbnl2^{+/-}$, representing intermediate symptomology. We find a variety of circadian activity phenotypes ranging from a shorter circadian period in the KI^{480} model to a phase delay of 2-3 hours in the KI^{1700} and $KI^{480}/KI^{480}; Mbnl2^{-/+}$ mice with a loss of rhythmic activity in the $Mbnl2^{-/-}$ mice. Interestingly, the models which display a phase delay reminiscent of DM1 patient symptomology, have a normal circadian period length as determined in the absence of light cues. This suggests that this phenotype may be due to altered photic entrainment. To further determine whether these mice have entrainment defects, we will examine phase response curves and response to phase advances and phase delays. As MBNL2 plays an important role in splicing regulation, we will perform transcriptomic analyses of key tissues involved in entrainment; the SCN and the ipRGCs. Findings from these studies will shed light on how circadian disruption contributes to sleep dysregulation in DM1 and other repeat expansion diseases.

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9 - Harmonization and federated analysis of myotonic dystrophy registries to model heterogeneous disease trajectories. Results from the 287th ENMC International Workshop

Leandre Fontaine[1], Daniël van As[2], Guillaume Bassez[3], Nicholas Johnson[4], Catharina Faber[1], Peter-Bram 't Hoen[2]

[1]Maastricht University Medical Center, [2]Radboud university medical center, [3]Hôpitaux Universitaires Henri Mondor, [4]Virginia Commonwealth University

The 287th ENMC International Workshop convened experts from ten countries to address the harmonization and federated analysis of Myotonic Dystrophy Type 1 (DM1) registries. With over 10,500 patients enrolled globally, registries remain fragmented, limiting their utility in modeling disease trajectories and supporting clinical trials. As new therapies enter advanced clinical testing, registries must evolve - not only to enable trial readiness but also to support downstream functions like pharmacovigilance. The workshop focused on four objectives: re-defining a core dataset, enabling FAIRification of registries, establishing federated analysis infrastructure, and developing longitudinal modeling strategies. Key outcomes included a revised core set of clinical and patient reported outcome measures that is feasible to collect in a routine care setting, strategies for FAIR data integration, and governance models for federated analysis. Pragmatic and interpretable statistical approaches such as latent variable modeling and unsupervised clustering were discussed, with key prediction targets identified across motor, cardiac, and pulmonary domains. The workshop emphasized the need for sustainable funding, patient-centered design, and international collaboration.

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10 - Responsiveness and the minimal clinically important difference of the DM1-ActivC in Myotonic Dystrophy type 1

Leandre la Fontaine[1], Sander van Kuijk[1], Ingemar Merkies[1,2], Catharina Faber[1], Karlien Mul[3]

[1]Maastricht University Medical Center, [2]Curaçao Medical Center, [3]Radboud university medical center

Myotonic Dystrophy type 1 (DM1) is a slowly progressive neuromuscular disorder with multisystem involvement. Most treatment thus far is focused on symptom management, however, numerous advancements in understanding the complex pathophysiology have led to various approaches targeting the underlying gene defect that demonstrate great promise in clinical trials. The cardinal features of DM1 are

progressive muscle weakness and myotonia, alongside a wide range of multisystemic disease manifestations, such as gastro-intestinal issues, pulmonary insufficiency and cardiac abnormalities. These disease manifestations contribute to impaired performance in daily life, and restrictions in everyday activities. The Rasch-built Myotonic Dystrophy type 1 activity and participation scale (DM1-Activ^{C}) is a disease-specific scale that has been constructed to capture limitations in activities of daily living and social participation. The validity and reliability of the DM1-Activ^{C} have been determined, but there is lacking knowledge on the responsiveness of the scale. Previous research has demonstrated statistically significant changes over time, but the use of a scale should not be determined solely by the ability to capture statistical significance. Therefore, it is imperative to determine the minimal clinically important difference (MCID) in order to capture changes in disease status that are relevant to the patient. Consequently, the objective of this study is to investigate the responsiveness to change of the DM1-Activ^{C} over a one-year period. Moreover, the study aims to estimate the MCID using a combination of anchor-based and distribution-based methods. By establishing the MCID, this study will help in facilitating better interpretation of longitudinal changes thereby improving its utility in clinical trials. Results will be presented at the IDMC.

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12 - Natural history of PR interval and QRS duration in Myotonic Dystrophy Type 1

David Bovenkerk[1], Wander Aarts[2], Leandre La Fontaine[2], Sander van Kuijk[3], Lotte Put[2], Karlien Mul[4], Kevin Vernooy[1], Dominik Linz[1, 5], Catharina Faber[2], Isis Joosten[2]

[1]Department of Cardiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, Maastricht, The Netherlands, [2]Department of Neurology, Maastricht University Medical Centre (MUMC+), School for Mental Health and Neuroscience, Maastricht, the Netherlands, [3]Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre (MUMC+), Maastricht, the Netherlands, [4]Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands, [5]Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Cardiac conduction disorders develop in approximately 80% of patients with myotonic dystrophy type 1 (DM1) and may lead to life-threatening complications. As targeted therapies are being evaluated in clinical trials, insight into natural history of cardiac conduction is essential but remains incomplete. This study aims to assess longitudinal changes in PR interval and QRS duration in patients with DM1. A

retrospective cohort study was conducted at Maastricht University Medical Center+ and Radboud University Medical Center, The Netherlands, including all genetically confirmed DM1 patients aged ≥18 years from the Dutch DM1 registry (MYODRAFT study). Data were collected between January 2017 and December 2025 and included demographics, CTG repeat length, ECG parameters and neuromuscular characteristics. Mixed-model regression was performed to assess longitudinal changes in PR interval and QRS duration and their associations with demographics and disease-related factors. 310 patients were included, of whom 155 (50%) were male. Median age was 44 [31-57] years and median follow-up was 37.7 [13-66.5] months. In men, mean PR interval at baseline was 174 ms and prolonged over time at a rate of 3.1 ms/year (CI 1.6-4.5). Compared to male sex, female sex was associated with a shorter baseline PR interval (-11 ms, CI -21 to -2.3) and a significantly slower rate of progression (interaction -2.3 ms/year, CI -4.5 to -0.21; corresponding to an increase of 0.8 ms/year, p = 0.031). Baseline QRS duration was 103 ms in men and increased significantly over time at a rate of 1.5 ms/year (CI 0.72-2.4). Baseline and progression were similar in both sexes. Considerable inter-individual variability was observed. In conclusion, these findings indicate a slow but progressive deterioration of cardiac conduction in DM1. Prolongation of the PR interval progresses more rapidly in male than in female patients, whereas no sex-specific difference is observed in the progressive prolongation of QRS duration.

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13 - Addressing gastrointestinal symptoms in myotonic dystrophy: consensus-based recommendations for clinical practice and research

Saskia Scholten[1], Janel Peterson[2], Lynn Orriëns[3], Luca Pastorelli[4], Giovanni Meola[5], Benedikt Schoser[6], Hilde Braakman[3], on behalf of the 288th ENMC workshop participants[7]

[1]Department of Rehabilitation, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, Amalia Children's Hospital, Nijmegen, The Netherlands, [2]Genetics & Genomics Graduate Program and Department of Pathology & Immunology, Baylor College of Medicine, Houston, Texas, USA, [3]Department of Paediatric Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical centre, Nijmegen, Amalia Children's Hospital, The Netherlands, [4]Department of Health Sciences, University of Milan, Milan, Italy.; Hepatology and Gastroenterology unit, San Paolo University Hospital, Milan, Italy, [5]Department of Neurorehabilitation Sciences, Casa di Cura Igea; Department of Biomedical Sciences for Health, University of Milan, Milan, Italy, [6]Friedrich-Baur-Institute,

Department of Neurology, LMN Clinics, Ludwig Maximilian University, Munich, Germany, [7]European Neuromuscular Centre, Baarn, The Netherlands

Gastrointestinal (GI) symptoms in myotonic dystrophy (DM) are highly prevalent, clinically significant, and often overlooked in routine care. They affect all segments of the digestive tract and can severely impair quality of life for patients and families. Despite this burden, GI issues remain underdiagnosed and undertreated, partly due to their complexity and frequent underreporting.

During the 288th ENMC International Workshop (May 2025), a multidisciplinary group of clinicians, researchers, and patient representatives reviewed current evidence and shared clinical experiences to address this gap. Alongside the already published scientific report of the workshop findings, increasing awareness and catalyzing broader discussion among a wide range of professionals was highlighted as a key priority.

The workshop highlighted the wide spectrum of GI manifestations in both children and adults with DM1 and DM2, including oropharyngeal dysphagia, oesophageal motility disorders, reflux, delayed gastric emptying, constipation, diarrhoea, and pelvic floor dysfunction. These symptoms often coexist with cognitive and behavioural challenges, complicating recognition. Registry data show that up to 80% of individuals with DM experience GI symptoms, yet fewer than 40% have ever been evaluated by a gastroenterologist.

To support proactive identification, we co-developed, together with patient representatives, a set of practical questions for use during routine consultations. These questions aim to help clinicians initiate conversations about GI symptoms in everyday practice, ensuring that issues are not missed. In addition, preliminary recommendations for diagnostic evaluation and management were formulated, and research priorities were defined, including the development of DM-specific outcome measures and integration of GI endpoints into clinical trials.

Improving recognition and management of GI symptoms in DM has the potential to significantly enhance patient well-being and reduce complications. It is time this domain receives the clinical and research attention it deserves.

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14 - Investigating the role of the transcriptional kinase, CDK13, in mutant DMPK transcription and RNA foci formation.

Jessie Brown[1]

[1]University of Nottingham

Myotonic Dystrophy (DM) is a complex autosomal dominant genetic disorder that affects 1 in 8000 people worldwide. The disorder is characterised by multisystemic manifestations including progressive myotonia, myopathy, muscle atrophy, and cataracts, with further abnormalities presenting in the cardiovascular, respiratory, endocrinal and gastrointestinal systems. DM is classified as a repeat expansion disorder. DM type 1 is caused by a CTG trinucleotide repeat expansion in the 3'untranslated region of the *dystrophia myotonica protein* kinase gene (*DMPK*). The mutant expansion RNA is primarily retained in the nucleus and sequesters the RNA binding protein, muscle blind-like 1 (MBNL1), to form nuclear RNA foci resulting in downstream cellular consequences. Cyclin dependent kinases 12 and 13 (CDK12/13) are transcriptional kinases which promote and maintain RNA polymerase II transcriptional elongation and processivity. Knockdown of either kinase has been shown to negatively impact transcription, DNA repair mechanisms, R-loop resolution and cell viability with greater effects seen upon dual knockdown. Previous reports show CDK12 knockdown in DM1 cell lines and mouse models results in reduced nuclear RNA foci and improved myotonia. Using techniques such as lentiviral transduction, siRNA transfection, western blotting and fluorescence *in-situ* hybridisation we demonstrate preliminary evidence that a 30% knockdown of CDK13 results in decreased foci area, intensity and abundance. Using the same techniques, we also show that the knockdown of ALYREF, a member of the TRanscription-EXport (TREX) complex functioning as an export adaptor and 5-methylcytosine (5mC) reader, results in reduced foci area, abundance and intensity. Further replicates and experiments are needed in order to understand how transcriptional elongation and post-transcriptional modifications influence the metabolism of the mutant *DMPK* transcript.

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15 - Hepatic insulin resistance in myotonic dystrophy type 1 is highly associated with acquired factors

HIROTO TAKADA[1], SEIKO KON[1], YOSHINOBU OYAMA[1], TAMAKI KIMURA[1], YASUHITO WAKASAYA[1]

[1]NHO Aomori National Hospital

Background

We previously reported that not only muscle insulin resistance (MIR) but also hepatic insulin resistance (LIR) is elevated in myotonic dystrophy type 1 (DM1), using the index developed by Abdul-Ghani et al. (2007). Although abnormal splicing of muscle mRNA insulin receptor has been reported as the primary cause of MIR in DM1, the

details of LIR remain unclear. In this study, we investigated the relationship between LIR and factors related to liver fibrosis and insulin resistance.

Methods

Sixty-four DM1 patients (42 ± 12 years old; mean ± SD, CTG repeat count: 897 ± 486) with no alcohol consumption, negative for HBV antigen and HCV antibody, and a confirmed genetic diagnosis who underwent 75g oral glucose tolerance test (OGTT) were studied. Regression analysis was performed on the following factors: MIR, LIR, insulin index (I-I), HOMA-R, and FIB-4 index calculated from the OGTT results; HbA1c, AST, ALT, γ-GTP, platelets, triglycerides, LDL cholesterol, and HDL cholesterol; body mass index (BMI); CT value liver-spleen ratio (LSR) and visceral fat area (VFA) on abdominal CT; skeletal muscle mass index (SMI) and body fat percentage (BFR) measured by DEXA.

Results

LIR was significantly correlated with age, HDL cholesterol, ALT, BMI, I-I, HOMA-R, FIB-4 index, LSR, VFA, SMI, and MIR. MIR was significantly correlated with CTG repeat number, HDL cholesterol, BMI, I-I, HOMA-R, VFA, and BFR.

Conclusion

While MIR correlated with the number of CTG repeats, LIR did not. Our results suggest that LIR is associated with many factors potentially involved in insulin resistance, including the FIB-4 index, an index of liver fibrosis. These findings suggest that LIR may be improved by treating glucose and lipid metabolism disorders and managing body weight.

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16 - Intensive speech therapy training in people with myotonic dystrophy type 1.

Amber Römkens[1], Jan Groothuis[1], Sanne Diepeveen[2], Karlien Mul[3], Simone Knuijt[1]

[1]Donders institute for brain, cognition and behavior, Radboud university medical center, Department of rehabilitation, Nijmegen, the Netherlands., [2]University of Applied Sciences, Nijmegen, the Netherlands, [3]Donders institute for brain, cognition and behavior, Radboud university medical center, Department of neurology, Nijmegen, the Netherlands

Dysarthria is a common symptom in myotonic dystrophy type 1 (DM1). Where patients are encouraged to do physical exercises, speech therapy focuses mainly on compensations such as reducing speaking rate. Because orofacial muscles have a different muscle composition than skeletal muscles, we do not know what the training effect on the orofacial muscle quality will be.

We are going to investigate whether there is a positive effect on speech with two months of intensive speech therapy training in people with DM1, followed by ten months of maintenance exercises. 25 participants will receive articulation exercises with tongue force training. Exclusion criteria are an insufficient physical or cognitive capacity to participate and co-morbidity that affects speaking.

Given the exploratory nature of this study, we include several outcome measures. The primary outcome measure is intelligibility, measured with intelligibility experiments. Secondary outcome measures are tongue force and communicative participation measured using a questionnaire. Orofacial muscle ultrasound is used to measure the effect of muscle strength training. The experiences of people with DM1 and their speech therapists will be subject to a qualitative study using semi-structured interviews.

The participants are treated as much as possible in primary care, so close to their home. To transfer the specific treatments, the participating speech therapists will be trained and coached by the researchers. Treatment intensity is supported using Physitrack, an online platform with demonstrations of all exercises. Compliance to the treatment is supported by access to PhysiApp for all participating patients and therapists, an app that can be used to send reminders and register the use of exercises.

This study will teach us whether orofacial muscles can be trained in people with DM1 and what the effect is on speaking.

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17 - Measurement properties and clinical relevance of outcome measures for myotonia in myotonic dystrophy type 1: protocol of the MyoMeasure study

Elise Taken[1], Harm Weekenstroo[1], Simone Knuijt[1], Nicole Voet[1], Nens van Alfen[1], Karin Faber[2], Karlien Mul[1]

[1]Radboud University Medical Center, the Netherlands, [2]Maastricht University Medical Center, the Netherlands

Delayed muscle relaxation (myotonia) is one of the hallmark symptoms of myotonic dystrophy type 1 (DM1). In preclinical models myotonia showed a rapid response to targeted therapies, making it a potential early indicator of therapeutic efficacy in clinical trials. It is therefore now selected as a primary outcome for various clinical trials on targeted therapies in DM1. However, the currently used myotonia assessment, the video Hand Opening Time (vHOT), has limitations as it is susceptible to variability, and not purely a measure of myotonia. For oropharyngeal myotonia,

there are currently no clinical outcomes. To establish the most optimal clinical trial endpoints, we aim to identify the most valid, sensitive, and clinically relevant myotonia measurements.

Therefore, a prospective observational study is conducted in Radboud University Medical Center aiming to include 50 adult patients. Transcranial magnetic stimulation (TMS), muscle ultrasound, handgrip relaxation time, and vHOT are assessed before and after four weeks of treatment with mexiletine, used as a pharmacological challenge agent to induce a change in myotonia. Additionally, muscle ultrasound of the oropharyngeal region is used to assess oropharyngeal muscle myotonia. Parameters reflecting the relaxation time of the forearm and oropharyngeal muscles are assessed and compared between measurement instruments.

Inclusions are ongoing and results are expected in 2027. This study will contribute to optimalization of outcome measures for myotonia as an endpoint in clinical trails. The ability to quantify treatment effects accurately within short trial periods would reduce trial duration, improve study feasibility, and accelerate drug development. Evaluating the clinical relevance of measurements is essential for the accurate interpretation of treatment effects in clinical trials.

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18 - Assessment of sleep-wake patterns in adults with the infantile-onset form of myotonic dystrophy type 1: an actigraphy study

Luc Laberge[1], Alexandre Maltais[1], Olivier Turcotte[1], Nathalie Angeard[2], Yohann Savinsky[3], Isabelle Gaudet[4], Cynthia Gagnon[3]

[1]ÉCOBES - Recherche et transfert, Cégep de Jonquière, [2]4 Laboratoire Mémoire, Cerveau et Cognition, Université Paris Cité, [3]Faculté de médecine et des sciences de la santé, Université de Sherbrooke, [4]Département des sciences de la santé, UQAC

Introduction. Sleep problems are common in the adult-onset form of myotonic dystrophy type 1 (DM1), but few studies have focused on the childhood-onset form of the disease.

Objectives. The objective of the present study is to evaluate the sleep-wake cycle of adults with childhood-onset DM1 using actigraphy.

Methods. Seventeen patients with the childhood-onset form of DM1 and 17 age- and sex-matched controls (12 females, mean age 40.2 years) wore an actimeter for four weeks and one week, respectively. R software v4.1.3 was used for intergroup comparisons.

Results. Patients went to bed ($p < 0.01$) and woke up ($p < 0.001$) later than controls. Additionally, patients exhibited longer sleep latency ($p < 0.05$), more frequent and longer nocturnal awakenings ($p < 0.001$), and lower sleep efficiency ($p < 0.001$) compared to controls. Furthermore, patients showed lower inter-daily stability (IS, $p < 0.001$) and relative amplitude (RA, $p < 0.001$) than controls. Finally, two patients presented with delayed sleep phase syndrome, and one patient exhibited a non-24-hour rhythm.

Discussion. Compared to healthy subjects, the sleep of adult patients with the infantile form of DM1 is of poorer quality. Additionally, their sleep-wake rhythm is less stable and less robust. Furthermore, this study confirms that the presence of intrinsic circadian sleep-wake rhythm disorders in DM1 is not coincidental. Furthermore, this study confirms that the presence of intrinsic circadian sleep-wake rhythm disorders in DM1 is not coincidental. Consequently, future research should focus on longitudinal assessments to determine how these rhythm instabilities affect long-term cognitive health, while exploring the potential benefits of targeted chronotherapy for this patient group.

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19 - Serum Proteomic Profiling Reveals Acute Inflammatory Response as a Key Pathogenic Mechanism in Myotonic Dystrophy Type 1

Elena Abati[1], Lorenzo Benigni[2], Linda Ottoboni[2], Melania Filareti[3], Giacomo Comi[1, 2], Stefania Corti[2, 4], Giovanni Meola[3, 5]

[1]Neurology Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [2]Department of Pathophysiology and Transplantation, Dino Ferrari Center, Università degli Studi di Milano, Milan, Italy, [3]Department of Neurorehabilitation Sciences, Casa Di Cura Igea, Milan, Italy, [4]Neuromuscular and Rare Diseases Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [5]Department of Biomedical Sciences for Health, Università degli Studi di Milano, Milan, Italy.

Myotonic dystrophy type 1 (DM1) is a multisystemic disorder caused by CTG repeat expansion, with poorly understood systemic proteomic changes. Circulating protein biomarkers could provide insights into disease mechanisms, facilitate monitoring and shed light on new potential therapeutic targets. The aim of the study is to characterize serum proteomic profiles across DM1 subtypes and identify

differentially expressed proteins correlating with clinical manifestations and disease severity.

We conducted a cross-sectional proteomic analysis of serum from 35 DM1 patients (25 classic, 4 juvenile, 2 infantile, 4 congenital) versus 15 controls. Following protein depletion and TMT10plex labeling, mass spectrometry analysis was performed. Bioinformatics included Principal Component Analysis (PCA), differential expression analysis using limma with MIRS/sex covariates, and Gene Ontology enrichment.

PCA revealed disease severity gradient with congenital DM1 most distinct from controls. Differential expression identified 35 significantly dysregulated proteins (adjusted $p<0.05$, $|\log_2 FC|>0.5$). Acute inflammatory response was most enriched ($p.adj=9.97\times10^{-10}$), involving 7 proteins. Classic DM1 showed pronounced inflammatory signature: ORM1, ORM2, A2M, HP, HPR significantly upregulated ($p<0.0001$), APOA2 downregulated ($p<0.001$). Congenital DM1 demonstrated severe early inflammation, juvenile DM1 intermediate changes. Disease enrichment revealed associations with acute kidney insufficiency ($p.adj=1.84\times10^{-7}$) and drug toxicity ($p.adj=1.63\times10^{-6}$).

This first comprehensive serum proteomic study reveals acute inflammatory response as central to DM1 pathogenesis, with subtype-specific signatures suggesting distinct mechanisms. Novel kidney and drug metabolism associations expand understanding of systemic involvement. Acute phase proteins represent promising biomarkers, identifying inflammation as a potential therapeutic target beyond RNA toxicity mechanisms.

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20 - Splicing modulation of DMPK exon 15 as a therapeutic approach for myotonic dystrophy type 1

Mireia Gromaz Iborra[1, 2], Katarzyna Taylor[1, 2], Prof. Krzysztof Sobczak[1, 2]

[1]Department of Gene Expression, Adam Mickiewicz University, Poznan, Poland, [2]Institute of Molecular Biology and Biotechnology

Myotonic dystrophy type 1 (DM1) is caused by an expansion of CTG repeats in the last exon of *DMPK* gene. Mutant RNAs with expanded CUG repeats are deposited in nuclear foci that sequester MBNL splicing factors, disrupting alternative splicing regulation, and contributing to disease development. Therapeutic strategies that reduce toxic RNA while keeping normal gene expression are still needed. In this project, we explore a splicing-based approach to remove the CUG repeat region from the *DMPK* mRNA. The expansion is located within the 5' part of terminal exon 15.

Importantly, a downstream splice acceptor site can be used to generate an alternative terminal exon (exon 16) that does not contain the repeat region. Our goal is to promote this splicing event using antisense oligonucleotides (ASOs). So far, two ASOs have been tested in human control and DM1 patients-derived fibroblasts to establish the experimental system and evaluate their effect on *DMPK* splicing. RT-PCR analysis show that both ASOs induce efficient exon 15 skipping and increase the use of exon 16, suggesting that *DMPK* splicing can be modulated in human cells. Additional ASOs will be designed and tested to identify more efficient candidates. The effect of exon 15 skipping on RNA foci formation, MBNL redistribution, and selected alternative splicing events affected in DM1 will also be investigated. Overall, this work aims to evaluate exon 15 skipping as a potential strategy to reduce RNA toxicity in DM1.

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21 - Gut microbiota profiles in children with myotonic dystrophy type 1 are marked by reduced Faecalibacterium abundance

Anne M. van Uden[1, 2], Heidi Zweers[3], Alejandro Arias Vasquez[4], Derick G. Wansink[2], Peter A.C. 't Hoen[2], Alem Gusinac[2, 5], Anja de Baaij-Daalmeyer[3], Karlijn Gerrits[3], Willem J.G. Melchers[6], Baziel van Engelen[7], Thomas H.A. Ederveen[2], Hilde M.H. Braakman[1]

[1]Department of Paediatric Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, Amalia Children's Hospital, Nijmegen, the Netherlands, [2]Department of Medical BioSciences, Radboud university medical center, Nijmegen, the Netherlands, [3]Department of Gastroenterology and Hepatology - Dietetics, Radboud university medical center, Nijmegen, The Netherlands, [4]Department of Psychiatry, Radboud university medical center, Nijmegen, the Netherlands, [5]Department of Pathology, Radboud university medical center, Nijmegen, The Netherlands, [6]Department of Medical Microbiology, Radboud university medical center, Nijmegen, The Netherlands, [7]Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, Nijmegen, The Netherlands

Myotonic Dystrophy type 1 (DM1) is a complex, multisystem disorder, with gastrointestinal and neurodevelopmental challenges being especially prominent in children. Although emerging research suggests the gut microbiome plays a role in various neuromuscular diseases, its involvement in DM1 remains largely unexplored. Therefore, this pilot study explores gut microbiota profiles of children with DM1. The gut microbiota of 11 children with DM1 were compared to that of their unaffected

siblings (n=11). 3-day food records and faecal samples were collected, with bacterial taxa analysed through 16S rRNA marker-gene sequencing. A within-family paired-sample design accounted for potential confounders, such as diet and lifestyle. Results revealed a significant reduction in the relative abundance of the bacterial genus *Faecalibacterium* in children with DM1 (mean 4.9% ± 2.1%) compared to their unaffected siblings (mean 9.1% ± 4.4%) (p=0.005). However, this finding should be considered exploratory, as its univariate analysis was uncorrected for multiple testing. Microbial diversity (alpha diversity) and community structure (beta diversity) were similar between the two groups. *Faecalibacterium*, a key gut bacterium, has been associated with DM1-associated disorders, but it is unclear whether this shift contributes to DM1 pathogenesis or is a result of the disease. If further studies confirm its role, targeting *Faecalibacterium* relative abundance could become a potential therapeutic strategy for alleviating gastrointestinal and neurodevelopmental symptoms in DM1.

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22 - Defining Epitranscriptomic Shifts in Myotonic Dystrophy Type 1

Nathaniel Beam[1, 2], Ulrike Begley[1, 2], Cecilia Legare[1, 3, 4, 5], Elise Duchesne[3, 4, 5], Andrew J. Berglund[1, 2], Thomas J. Begley[1, 2]

[1]RNA Institute, [2]University at Albany, [3]Centre de Recherche du Centre Hospitalier de l'Université Laval (CR-CHUL), Axe Neurosciences, Université Laval, Québec City, Canada, [4]École des sciences de la réadaptation, Faculté de médecine, Université Laval, Québec, Canada, [5]Groupe de Recherche Interdisciplinaire sur les Maladies Neuromusculaires (GRIMN), Centre intégré universitaire de santé et de services sociaux du Saguenay-Lac-Saint-Jean, Saguenay, Québec, Canada

RNA modifications in the form of the enzyme-catalyzed epitranscriptome regulate processes such as RNA splicing, localization, translational fidelity, and the cell cycle. The epitranscriptome is reprogrammed in response to stress caused by increased reactive oxygen species and DNA damage to regulate gene and protein expression. In Myotonic Dystrophy Type 1 (DM1), expression of expanded CUG repeats can stress cells and disrupt cellular function, resulting in aberrant splicing, RNA foci formation, and increased levels of senescence. These molecular mechanisms, along with the physical symptoms of muscle wasting and early balding, lead to DM1 being considered a progeroid condition. **We hypothesize** that in DM1, alterations in RNA modifications impair the cell's ability to respond to stresses inherent in the disorder, leading to increased levels of DNA damage and senescence**.** Preliminary data confirm increased levels of senescence in DM1 fibroblasts at basal conditions and

that these cells are more sensitive to genotoxic stress. Furthermore, longitudinal RNA-seq data reveal upregulation of DNA damage and senescence-associated genes, including p21, that worsen over time in DM1 patients. Inversely, there is broad down-regulation of mitochondrial genes and RNA modifiers, with changes in these genes strongly correlating with disease markers such as repeat length and splicing index. **Our study aims** to define the spectrum of modifications dysregulated in DM1 in response to cellular stress and how RNA modifications contribute to senescent programs in DM1. We will perform absolute quantification RNA sequencing (AQRNA-seq) to identify sequence-specific modifications of tRNA and mRNAs, including the repeat-expanded DMPK transcript. The sequence-specific location of RNA modifications will identify pathways and shifts in RNA pools that occur between disease states and stress induction. We will then test whether modulating RNA-modifying enzymes can alleviate or exaggerate DM1 etiology and/or senescence onset. These findings could help explain DM1's marked heterogeneity and open new therapeutic strategies.

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23 - Harmonization of DM registries through the Neuromuscular Domain Ontology

Peter A.C. 't Hoen[1], Leandre LaFontaine[2], Alberto Camara Ballesteros[3], Lilli Schuckert[4], Petar Horki[5], Ruby Langeslay[6], Marcel Heidemann[7], Daniel van As[1], Daphne Wijnbergen[8], Rachel Thompson[9], Marco Roos[8], Martijn G. Kersloot[4], Anita Burgun[10], Nicole Vasilevsky[11], Guillaume Bassez[12], Hanns Lochmuller[9], Catharina Faber[2], Nicholas Johnson[6], Cynthia Gagnon[13], Mark D. Wilkinson[3], Benedikt Schoser[14]

[1]Department of Medical Biosciences, Radboud university medical center, Nijmegen, The Netherlands, [2]Department of Neurology, Maastricht University Medical Center, Maastricht, The Netherlands, [3]Departamento de Biotecnología-Biología Vegetal, Escuela Técnica Superior de Ingeniería Agronómica, Alimentaria y de Biosistemas, Centro de Biotecnología y Genómica de Plantas. Universidad Politécnica de Madrid (UPM) , Madrid, Spain, [4]Department of Medical Informatics, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands, [5]Clinical Trials Unit, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany, [6]VCU Health, Richmond, Virginia, USA, [7]TREAT-NMD Neuromuscular Network, Newcastle upon Tyne, United Kingdom, [8]Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands, [9]Children's Hospital of Eastern Ontario Research Institute, Ottawa, Canada, [10]University of Paris Cité, Paris, France, [11]Critical Path Institute, USA, [12]Institute of

Myology, Sorbonne Université, AP-HP, Paris, France, [13]Université de Sherbrooke, Quebec, Canada, [14]Ludwig Maximilian University, Munich, Germany

Myotonic dystrophy (DM) registries are fundamental resources to characterize phenotype heterogeneity, and to evaluate and predict disease course and response to therapy. However, even the largest DM registries do not contain sufficient numbers of patients to construct accurate prediction models. This requires the combination of data from multiple registries. However, this is hampered by the use of different phenotype descriptions and clinician- and patient-reported outcome measures. In the 287th ENMC workshop “Harmonization and federated analysis of myotonic dystrophy registries to model heterogeneous disease trajectories”, we concluded that the standardization of phenotype descriptions, outcome measures and protocols to assess them would be essential steps towards DM registry harmonization. Therefore, after the workshop, we decided to create a domain ontology that covers the phenotypes and outcome measures unique to the neuromuscular disease (NMD) domain. In this process, we realized that there are many initiatives in the neuromuscular domain performing similar activities in parallel: SIMPATHIC, END-DM1, iDM-Scope, EURO-NMD, ERDERA, TREAT-NMD, PROMOT, PaLaDIn. These initiatives have now joined forces in the creation of the NMD domain ontology. This ontology preferably reuses terms from existing ontologies, such as Human Phenotype Ontology (HPO) and the International Classification of Functioning, Disability and Health (ICF). The data elements that are currently in use in the END-DM1 natural history study and the MYODRAFT, iDM-Scope and EURO-NMD registries have been mapped to common ontology terms and the Clinical And Registry Entries Semantic Model (CARE-SM) , making them unequivocally interpretable for humans and computers. In the next step, we will start a consensus process to connect these terms to standard operating procedures for the assessment of phenotypes and outcome measures. By harmonizing terminology and standardizing descriptions and procedures, this initiative improves interoperability and advances DM research and real-world evaluation of emerging therapies.

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25 - Glymphatic dysfunction mediates white matter microstructural damage and cognitive impairment in myotonic dystrophy type 1

Daisuke Yamanaka[1], Shuhei Kasama[1], Takashi Kimura[1]

[1]Hyogo Medical University

Objective Myotonic dystrophy type 1 (DM1) often involves cognitive impairment and diffuse white matter abnormalities, yet the underlying mechanisms remain unclear.

This study aimed to determine whether glymphatic dysfunction, assessed using the analysis along the perivascular space (ALPS) index, mediates the relationship between genetic severity, white matter microstructure, and cognitive performance in DM1.

Methods Eighteen patients with DM1 and twenty-four healthy controls underwent 3 T diffusion MRI and cognitive assessments (MMSE, TMT-A/B). Fixel-based analysis (FBA) was performed to derive fiber density (FD), fiber cross-section (FC), and their combined metric (FDC) in major white matter tracts. The ALPS index was calculated from projection and association fiber regions near the lateral ventricle. Group differences were evaluated using ANCOVA controlling for age and sex. Correlation and structural equation modeling (SEM) analyses were conducted to test mediation pathways (CTG → ALPS → WM → Cognition).

Results The ALPS index was significantly reduced in the DM1 group compared with controls ($p < 0.01$). FBA revealed reduced FDC in multiple white matter tracts, and tract-level FDC values—particularly in the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and occipital segment of the superior temporal tract—were positively correlated with MMSE ($r \approx 0.70$, $p < 0.01$) and negatively with TMT-B ($r \approx -0.60$, $p < 0.01$). SEM demonstrated a significant indirect pathway from CTG to MMSE through ALPS and white matter integrity ($p = 0.03$).

Conclusion Glymphatic dysfunction appears to contribute to white matter microstructural damage and cognitive impairment in DM1. This study links reduced ALPS index with fixel-based white matter alterations and cognition, suggesting the glymphatic pathway as a potential therapeutic target for central nervous system involvement in DM1.

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26 - Study for Caregivers of Patients with Myotonic Dystrophy type 1 focusing on Well-Being and Psychological distress.

Momoko Goto[1], Kaori Odaira[1], Go Kurauchi[1], Shizuko Taima[1], Asami Akasaka[1], Seiko Kon[1], Haruo Fujino[2], Makiko Endo[3], Tsuyoshi Matsumura[4], Masanori P Takahashi[5], Hiroto Takada[1]

[1]NHO Aomori National Hospital, [2]2) Graduate School of Human Sciences, The University of Osaka, [3]3) National Center of Neurology and Psychiatry, [4]NHO Osaka Toneyama Medical Center, [5]5) The University of Osaka Graduate School of Medicine

Background In myotonic dystrophy type 1 (DM1), there is little research on caregivers while basic and clinical study on the underlying disease is progressing. We planned a patient-reported outcome (PRO) and questionnaire survey focusing on well-being and Psychological distress for caregivers, with the aim of clarifying the current situation regarding care burden.

Method Twenty-five caregivers of DM1 patients participated. PROs were administered using the K6 (psychological distress scale), the WHO-5 Mental Health Status Inventory (WHO-5), and the Japanese version of the SF12v2 (QOL scale; SF_N: social functioning; RE_N: daily role functioning). A questionnaire survey regarding background factors was conducted in person. With informed consent, patient information was obtained from medical records and interviews.

Results The average of caregiver age was 61.8 ±13.5 years (mean ± SD). K6 score was 2.0 ± 2.8 (5 or above; 5 patients, 13 or above; 0 patients), and WHO-5 was 17.5 ± 6.4. SF12v2 scores were 53.5 ± 6.5 for SF_N and 51.4 ± 7.8 for RE_N. The patient's age was 48.1 ± 12.0 years, and the Barthel Index was 72.4 ± 23.4. All caregivers with a K6 score of 5 or higher reported that the total annual income of the household including the patient and caregiver was less than 3 million yen, and SF_N and RE_N were below the average and the national standard value. Four of these five caregivers selected "financial issues" as a major caregiving difficulty.

Conclusion Although results varied widely, caregivers with DM1 tended to have high well-being and low levels of psychological distress. The results of K6 indicated that a certain number of them experienced above-average levels of psychological distress, suggesting that factors behind this were low annual income, financial difficulties, and a lack of awareness of their role in daily life for social functioning and mental health.

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27 - Improving Awareness of Multisystem Manifestations and Multidisciplinary Management of Myotonic Dystrophy Type 1 Through Global Education

Cynthia Gagnon[1], Melissa Glasner[2], Emily Peck[2], Jas Chahal[2], Sean Conlan[2]

[1]Université de Sherbrooke, [2]The France Foundation

Myotonic dystrophy type 1 (DM1) remains underrecognized due to its multisystem manifestations, variable progression, and the need for coordinated multidisciplinary care. Significant gaps remain in clinician understanding of how underlying pathophysiology, genetic determinants, and early diagnostic approaches influence disease trajectory. To address these gaps, a three-part global educational initiative (EXPLORE™) was launched for neurologists and multidisciplinary specialists,

facilitated by global clinical experts, supported by three Clinical Companion Guides, and reinforced through international digital promotion.

Between December 2024 and August 2025, over 14,000 health care professionals from the United States, Europe, Japan, and additional regions participated in the education. After completing this program participants were asked to complete an evaluation to assess their knowledge, confidence, and intent to make changes to their clinical practice. Baseline assessment demonstrated low knowledge of DM1 pathophysiology and prevalence (43%) and low confidence in managing DM1 across care domains (12%). Following participation, learners achieved a 42% relative gain in knowledge and competence across learning objectives.

Most learners (82%) reported intent to change practice. The most frequently selected intended practice changes included improving multidisciplinary team awareness of the multisystem impact of DM1 (73%), obtaining detailed family histories when clinical suspicion exists (42%), and ordering confirmatory genetic testing for CTG repeat expansion in the *DMPK* gene when DM1 is suspected (37%). Qualitative thematic analysis revealed improved clinician recognition of early symptoms, enhanced understanding of genetic counseling, and stronger commitment to coordinated management strategies.

These findings demonstrate that scalable, multidisciplinary education can significantly improve DM1 awareness, diagnostic readiness, and care coordination. Ongoing education should prioritize case-based learning to further strengthen clinician confidence in early detection and longitudinal management to reduce diagnostic delay and improve patient outcomes.

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28 - Evaluating the usefulness of the Motor Function Measure (MFM-32) in children and adolescents with Myotonic Dystrophy type 1

Ulrika Edofsson[1], Marie Gudmundsson[1], Anne-Berit Ekström[1, 2]

[1]Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden, [2]Department of Paediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Myotonic dystrophy type 1 (DM1) presents with clinical heterogeneity in childhood, which complicates the development of standardized clinical guidelines. The Neuromuscular Team at Queen Silvia Children's Hospital, one of two national referral centers in Sweden for patients aged 0-18 years integrates clinical care with research to implement diagnosis-specific assessment tools for longitudinal monitoring,

clinical decision-making and transition planning. This study aimed to characterize the paediatric DM1 population, examine associations between phenotype and motor function and identify appropriate outcome measures. This study included 40 paediatric patients with DM1, followed by the neuromuscular team. Motor function data were obtained during routine clinical follow-up using the MFM-32 alongside standard motor function assessments. Of the 40 children included, 22 had the congenital form, 17 the childhood form, and 1 the juvenile form of DM1. A total of 29 children were assessed using the MFM-32. Differences in MFM-32 scores were observed between phenotypes, with similar patterns noted in the 10-meter run test and the 6-minute walk test. Children performed best on items within axial and proximal motor function, whereas the most challenging items were within standing and transfers and distal motor function. Comparisons of the most difficult items across phenotypes revealed both shared and distinct challenges, highlighting phenotype-specific motor function patterns. Assessment using the MFM-32 could not be completed in five children with severe congenital DM1 over six years of age, and in six children under six years of age, due to difficulty understanding instructions and the instrument's age range. The study has provided in-depth knowledge of the patient cohort and the use of the MFM-32. The instrument proved well-suited for children with the childhood form and mild congenital form of DM1. The findings have contributed to improved understanding for clinical care, supporting evidence-based practice, and facilitating the transition to adult healthcare.

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29 - Functionally mature bioengineered 3D DM1 muscle tissue demonstrates first in vitro CLCN1 mis-splicing and myotonic pathophysiology across clinical subtypes

Maria Sabater Arcís[1, 2, 3, 4], Xiomara Fernández-Garibay[1, 2], Ainoa Tejedera-Villafranca[1, 2], Judith Núnez-Manchón[5], Mònica Suelves[5], Gisela Nogales-Gadea[5, 6], Rubén Artero[4, 7, 8], Javier Ramón-Azcón[1, 2, 9], Juan Manuel Fernández-Costa[1, 2]

[1]Institute for Bioengineering of Catalonia (IBEC), [2]Barcelona Institute of Science and Technology (BIST), [3]Neuromuscular Diseases Research Group, Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [4]CIBERER ISCIII, Av. Monforte de Lemos 3-5, 28029 Madrid, Spain, [5]Germans Trias i Pujol Research Institute (IGTP), [6]Universitat Autònoma de Barcelona, [7]Institute for Biotechnology and Biomedicine (BIOTECMED), University of Valencia, [8]Incliva Health Research Institute, [9]ICREA-Institució Catalana de Recerca i Estudis Avançats

Myotonic dystrophy type 1 (DM1) is characterized by muscle weakness, fatigue, and myotonia caused by aberrant *CLCN1* splicing. Although conventional 2D cultures and

animal models have advanced our understanding of DM1 pathophysiology, they fail to recapitulate the complexity and functional deficits of the disease, limiting therapeutic discovery. To address these limitations, we developed a functionally mature, patient-derived 3D skeletal muscle model from human immortalized myoblasts representing three DM1 clinical subtypes (juvenile, adult, late-onset). Our tissue engineering approach consisted of encapsulating myoblasts within PDMS-based scaffolds with flexible mechanical supports to create contractile 3D human muscle tissue capable of responding to electrical stimulation, enabling both physiological maturation and recapitulation of DM1 genetic and clinical heterogeneity.

Critically, for the first time in a patient-derived *in vitro* system, the 3D environment uniquely enabled expression and pathogenic *CLCN1* mis-splicing—completely undetectable in matched 2D myoblast cultures—accompanied by quantifiable myotonia-like delayed relaxation during repeated electrical stimulation. Fiber-type analysis revealed characteristic DM1 pathology: marked shift toward oxidative slow-twitch type I fibers and pathological MyHC-I/IIx hybrids reflecting loss of glycolytic capacity, in contrast to control tissues dominated by fast-twitch type IIx and physiological IIa/IIx fibers. Functionally, human DM1 tissue exhibited impaired calcium handling, severe contractile weakness and rapid fatigue.

Comparative transcriptomic analysis revealed that human 3D muscle tissue selectively acquired gene expression programs silent in 2D myoblast cultures but present in human muscle biopsies. Genes involved in sarcomere assembly, contractile fiber organization, and mitochondrial metabolism were expressed in both our human 3D tissue and native muscle tissue, demonstrating advanced physiological maturation.

This study establishes the first in vitro system recapitulating both CLCN1 mis-splicing and myotonia-like physiology in human DM1 muscle, bridging RNA toxicity with mature muscle architecture and functional outcomes—a critical platform for mechanistic discovery and therapeutic testing across DM1 subtypes.

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30 - Feasibility, Acceptability, and Reproducibility of Rehabilitation Programs for Individuals with Myotonic Dystrophy Type 1: A Scoping Review

Anne-Gabrielle Brassard[1], Alexis Gelinas[1], Kelly-Anne Forest[2], Gabriel Bélanger[2], Gracia Imelda Foidien Monkam[2], Léa Gervais[2], Elise Duchesne[3]

[1]1. School of Rehabilitation Sciences, Faculty of Medicine, Université Laval, Quebec City, Quebec, Canada. 2. Center for Interdisciplinary Research in Rehabilitation and

Social Integration (Cirris), Capitale-National Integrated University Health and Social Services Center, Quebec City, Quebec, Canada, [2]1. School of Rehabilitation Sciences, Faculty of Medicine, Université Laval, Quebec City, Quebec, Canada., [3]1. School of Rehabilitation Sciences, Faculty of Medicine, Université Laval, Quebec City, Quebec, Canada. 2. Center for Interdisciplinary Research in Rehabilitation and Social Integration (Cirris), Capitale-National Integrated University Health and Social Services Center, Quebec City, Quebec, Canada. 3. CHU de Québec-Université Laval Research Center, Quebec City, Quebec, Canada. 4. Groupe de recherche interdisciplinaire sur les maladies neuromusculaires (GRIMN), Saguenay-Lac-St-Jean Integrated University Health and Social Services Center, Saguenay, Quebec, Canada.

Background: Myotonic dystrophy type 1 (DM1) is an incurable rare neuromuscular disease with a particularly high prevalence in the Saguenay-Lac-Saint-Jean region (Province of Quebec, Canada). Rehabilitation plays a central role in the management of clinical manifestations experienced by individuals living with DM1. However, the current scientific literature remains limited and does not provide clear clinical guidelines for exercise prescription in this population. Exercise programs reported in the literature are often insufficiently detailed, limiting their applicability in clinical practice. The aim of this study is to map the existing literature to synthesize current knowledge on the documentation of feasibility, acceptability, and reproducibility, key components for the successful implementation of rehabilitation programs.

Methods: This study was conducted according to the Joanna Briggs Institute framework. The MedLine, Embase, and CINAHL databases were searched, and article selection was managed using the Covidence software. A total of 1,723 records were identified. Following duplicate removal and screening based on predefined inclusion and exclusion criteria, 12 studies were retained for final analysis. Criteria of feasibility were determined. The theoretical framework of acceptably of Sekhon and the Consolidated Exercise Reporting Template (CERT) were respectively used to assess acceptability and reproductibility.

Results: The included studies were characterized by small sample sizes. Reporting on the feasibility of exercise programs was variable and often incomplete. In addition, very limited information was available regarding program acceptability, including participant adherence, tolerance, and satisfaction. The reproducibility of exercise interventions was also poorly described, which restricts their transferability and application in real-world clinical settings.

Conclusion: Important gaps in the rehabilitation literature related to DM1 have been identified. The findings emphasize the need for more rigorous and better-

documented research that systematically reports feasibility, acceptability, and reproducibility outcomes. Addressing these elements is essential to support clinicians in exercise prescription in DM1.

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32 - Towards Explainable Speech-Acoustic Biomarkers for Myotonic Dystrophy Type 1

Mattys Gervais[1], Florentin Thullier[1], Élodie Gagnon[1], Kévin Bouchard[1], Bruno Bouchard[1], Vincent Martel-Sauvageau[2, 3], Cynthia Gagnon[4, 5, 6], Elise Duchesne[2, 3, 6, 7], Sébastien Gaboury[1]

[1]Université du Québec à Chicoutimi, Chicoutimi, Québec, Canada, [2]School of Rehabilitation Sciences, Faculty of Medicine, Université Laval, Quebec City, Quebec, Canada, [3]Center for Interdisciplinary Research in Rehabilitation and Social Integration (Cirris), Capitale-National Integrated University Health and Social Services Center, Quebec City, Quebec, Canada, [4]Faculté de médecine et des sciences de la santé, Université de Sherbrooke, Sherbrooke, Québec, Canada, [5]Centre de recherche et d'innovation du Centre intégré universitaire du Saguenay-Lac-St-Jean, Clinique des maladies neuromusculaires, Hôpital de Jonquière, Jonquière, Québec, Canada, [6]Groupe de recherche interdîsciplinaire sur les maladies neuromusculaires (GRIMN), Saguenay-Lac-St-Jean Integrated University Health and Social Services Center, Saguenay, Quebec, Canada, [7]CHU de Québec-Université Laval Research Center, Quebec City, Quebec, Canada

Background: Myotonic dystrophy type 1 (DM1) is a multisystemic neuromuscular disorder categorized by a broad phenotypic spectrum, ranging from congenital to late-onset presentations. It can involve bulbar and vocal musculature, leading to characteristic speech disturbances. Despite these manifestations, diagnosis relies on genetic testing, and patients often experience prolonged diagnostic delays. Speech constitutes a promising non-invasive biomarker for early screening in several other diseases; however, machine-learning approaches have not yet been applied to DM1 speech analysis.

Objective: To develop and interpret an explainable machine-learning pipeline for DM1 detection based on acoustic features extracted from speech.

Methods: Speech recordings from 35 individuals with DM1 and 28 healthy controls were collected during a standardized oral diadochokinesis task. A comprehensive set of 288 acoustic features capturing phonatory, articulatory, spectral, prosodic, and cepstral characteristics was extracted. Three classifiers, Random Forest, CatBoost, and L2-regularized Logistic Regression, were evaluated using repeated stratified

cross-validation with strict data leakage control. Data augmentation was applied within training folds to improve generalization. Model interpretability was assessed using SHAP (SHapley Additive exPlanations).

Results: Random Forest achieved the best performance, with balanced accuracy of 0.81 ± 0.08 and ROC-AUC of 0.89 ± 0.08 when late-onset participants were excluded. Optimal performance was obtained using three augmentations per original instance. Feature ablation showed that MFCCs alone were insufficient, while comparable performance was maintained when MFCCs were excluded, highlighting the importance of broader acoustic descriptors. SHAP analyses revealed that classification was primarily driven by formant variability, energy redistribution around fundamental frequency, spectral irregularity, and temporal fluency measures—patterns consistent with flaccid dysarthria.

Discussion/Conclusion: These results demonstrate that explainable machine learning applied to speech acoustics can reliably capture clinically meaningful markers of DM1. This work provides a foundation for non-invasive, interpretable screening tools and supports the integration of speech-based biomarkers into clinical and research protocols for DM1.

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33 - Differential pathology and susceptibility to MBNL loss across muscles in myotonic dystrophy mouse models

Mackenzie Davenport[1, 2], Amaya Fong[1, 2], Gloria Montoya-Vazquez[1, 2], Maria Fernanda Alves de Moura[1, 2], Jodi Bubenik[1, 2], Maurice Swanson[1, 2]

[1]University of Florida Center for NeuroGenetics, [2]University of Florida Department of Molecular Genetics and Microbiology

There are two subtypes of myotonic dystrophy, DM1 and DM2, each caused by repeat expansion mutations. The leading pathogenic mechanism for both diseases is RNA mediated toxicity whereby (C)CUG expansions sequester the muscleblind-like (MBNL) family of RNA binding proteins. However, key differences exist in muscle involvement patterns and histopathology between DM1 and DM2. The cause of these disparities both in how the muscles are affected within each disease and between the two diseases is unknown, and it is unclear if current DM mouse models recapitulate these differences or develop differential muscle susceptibility. Here, we examined the expression of disease-relevant genes across healthy human muscles from a transcriptomic atlas and collected a series of muscles from *Mbnl* knockout mice to evaluate characteristic histologic and molecular features of DM pathology. Our results indicate that MBNL loss discordantly affects muscles, likely through a

splicing independent mechanism, and results in a fiber atrophy profile more like DM1 than DM2. These findings point to a predominant role for MBNL loss in muscle pattern involvement in DM1, provide further evidence for additional DM2 pathomechanisms, and have important implications for muscle choice when performing analyses in new mouse models and evaluating therapeutic modalities and biomarkers. Our next steps are to identify the mechanisms responsible for the discordant effects of MBNL loss across muscles.

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34 - Developing a Treatment for Myotonic Dystrophy 1 (DM1) - Small Molecules Screening and in vivo Splicing Studies

Oliver Chukwuma Orji[1], Sarah Memarzadeh[2], Jozef Park[2], Rebecca Trueman[1], Chris Hayes[2], David Brook[1]

[1]School of Life Sciences, Faculty of Medicine and Health Sciences, University of Nottingham Medical School, Queen's Medical Centre, NG7 2UH, Nottingham, United Kingdom., [2]School of Chemistry, Faculty of Science, University of Nottingham, University Park Campus, NG7 2RD, Nottingham, United Kingdom

Myotonic dystrophy 1 (DM1) is a progressive, debilitating multi-system genetic disorder which is inherited in autosomal dominant pattern. The disease mechanism is underpinned by a CTG repeat expansion mutation on the 3'UTR of the Dystrophia Myotonica Protein Kinase (DMPK) gene, leading to the formation of toxic RNA and the nuclear sequestration of RNA binding proteins such as the Muscleblind-Like protein-1 (MBNL-1), the formation of intranuclear inclusions known as RNA foci, and defects in the alternative splicing of key transcripts which underly the clinical symptoms associated with muscle, heart and brain dysfunction. DM1 is an orphan disease, and current clinical trials for treatment mostly rely on RNA-based strategies and use of repurposed small molecules. However, target tissue delivery and biodistribution challenges with RNA-based strategies remain, necessitating research into small molecules which are more potent, more specific and possess superior biodistribution to multiple target tissues and simpler drug administration methods. Our lab has previously identified CDK12 as a druggable target for DM1. Using high content imaging modalities for high throughput screening, we have identified potent small molecules which are selective for CDK12 inhibition, and which produced significantly reduced RNA foci number, area and intensity following visualisation via in situ hybridisation. We have also tested some of these compounds in HSA^{LR} DM1 mouse models for efficacy and are developing RNA-based techniques for assessing mis-splicing correction after treatment.

Here, we present our ongoing small molecules screening efforts for developing a treatment for DM1 using CDK12 targets.

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35 - A Magnetic Actuator-Based Platform for Functional Assessment of 3D Human Skeletal Muscle Bioengineered Tissues in Myotonic Dystrophy

Timothée Caboche[1], Carolina Rodríguez-Gallo[1], Maria Sabater-Arcís[1], Javier Ramón-Azcón[1, 2], Juan M. Fernández-Costa[1]

[1]Institute for Bioengineering of Catalonia (IBEC), The Barcelona Institute of Science and Technology (BIST), C/Baldiri Reixac 10-12, E08028 Barcelona, Spain, [2]Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain

Myotonic dystrophy type 1 (DM1) is the most common muscular dystrophy and is characterized by multisystemic symptoms such as myotonia, muscle weakness or cardiac muscle dysfunction. No treatment options are currently available. In this context, three-dimensional (3D) tissue has emerged as a relevant approach to develop more relevant biological models compared to traditional 2D cultures. It has previously been demonstrated that controlling the cellular microenvironment can enhance tissue morphogenesis, cell differentiation, and functionality. In our laboratory, we have developed a contractile DM1 3D skeletal muscle tissues model using immortalized myoblasts derived from DM1 patients encapsulated in biomaterials, attached between two flexible, biocompatible pillars. This model is combined with an electrical pulse stimulation (EPS) platform (MyoMoves) to reproduce muscle contraction and to quantify the muscle-generated force by measuring pillar displacement. These models recapitulate DM1 phenotypes *in vitro*, including muscle myotonia and CLCN1 splicing abnormalities.

In this project, we aim to develop a magnetic actuator-baseds platform that can reproduce DM1 phenotypes and induce percussive myopathy, complementing the existing MyoMoves approach. To achieve this, we are designing chips with flexible pillars with magnetic nanoparticles to support 3D tissues. By aligning the magnetic moments of these particles, we can induce pillar bending through magnetic torque in response to an external magnetic field. To generate this deflection, we will develop a magnetic actuation system based on electromagnets, installed under 24-well plates and will be compatible with the MyoMoves system.

By varying magnetic field strength, the applied torque can be controlled to define stretching regimes. This system provides a controlled mechanical environment to investigate the effects of mechanical loading on muscle differentiation, gene expression, and muscle fiber-type specification.

This platform will enable deeper investigation of DM1 pathophysiology and can be readily extended to cardiac tissue models and high-content drug screening applications.

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36 - Focusing on Foci: Expansion Microscopy for High-Resolution Characterization of Repeat RNA-Protein Aggregates in DM

Sofia Gaspari[1], Marieke Willemse[1], Thomas D. Hoekman[1], Hans van Bokhoven[2], Derick G. Wansink[1]

[1]Dept of Medical BioSciences, Radboud University Medical Centre, Nijmegen, The Netherlands, [2]Dept of Human Genetics, Radboud University Medical Centre, Nijmegen, The Netherlands

A hallmark of the molecular pathogenesis of myotonic dystrophy type 1 (DM1) and type 2 (DM2) is the occurrence of RNA-protein aggregates, formed respectively by CUG- and CCUG-repeat containing RNAs. These aggregates accumulate primarily in the nucleus and appear as distinct foci when visualized by *in situ* hybridization and immunofluorescence microscopy. The best-characterized protein components of these foci are members of the muscleblind family, whose sequestration leads to functional depletion and widespread missplicing, ultimately contributing to their classification as spliceopathies. One of the main challenges in DM research remains unravelling the structure, dynamics, and function of repeat RNA foci. To resolve their ultrastructure, we introduced Expansion Microscopy (ExM) as an innovative approach to DM research. With this technique, immunolabeled samples are uniformly enlarged via hydrogel expansion, enabling super-resolution imaging using confocal fluorescence microscopy. Moreover, RNA expansion can be enhanced by utilizing molecules (e.g. LabelX) that allow RNAs to covalently attach to the swellable polyelectrolyte gel synthesized throughout a biological specimen. We combined ExM with single-molecule inexpensive FISH (smiFISH), which enables RNA localization by imaging individual mRNAs in single cells, alongside employing sets of probes targeting different regions of the transcripts. In the context of DM, ExM with smiFISH provides high-resolution visualization of MBNL-C(C)UG repeat transcript complexes in cell types relevant to DM pathology. Our initial findings in muscle progenitor cells (human myoblasts expressing >2600 CTGs) indicate that nuclear foci are polymorphic and significantly smaller than previously reported. We are currently extending this work to other cellular models, including neurons and astrocytes. This approach enhances our ability to achieve nanoscale resolution of RNA foci, and to investigate the mechanisms underlying their formation and dissolution after

exposure to antisense oligonucleotides, drugs that are currently being evaluated in clinical trials for DM1.

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37 - Tracing Ancestral Haplotypes to Map the Transmission and Evolution of Myotonic Dystrophy Type 1 in a French-Canadian Founder Population

Claudia Moreau[1], Gilles-Philippe Morin[1], Jean Mathieu[2], Élise Duchesne[3], Cynthia Gagnon[4], Simon Girard[1]

[1]Université du Québec à Chicoutimi, [2]CIUSSS du Saguenay-Lac-St-Jean, [3]Université Laval, [4]Université de Sherbrooke

Microsatellite repeat expansions underlie several neuromuscular disorders, including myotonic dystrophy type 1 (DM1). DM1 is caused by large, unstable CTG repeat expansions in the *DMPK* gene. The disease shows a strong founder effect in Quebec's Saguenay-Lac-Saint-Jean (SLSJ) region, where its prevalence is among the highest worldwide. This unique context provides exceptional access to well-characterized patient cohorts. Analysis of genealogical, genotyping, and phenotyping data from 200 DM1 patients revealed two major haplotype groups strongly associated with DM1 expansions, supporting a role for genomic background in repeat instability. We applied a novel approach integrating genetic and genealogical data to investigate these haplotype groups and to align genetic lineages with genealogical trajectories. We identified two ancestral couples who likely introduced the DM1-associated haplotype into the SLSJ population. We traced their descendants carrying this haplotype and examined its present-day geographic distribution within the region to estimate expected carrier frequencies across subregions. We also followed haplotype transmission across generations to assess disease evolution over time and its effects on fitness, including offspring survival and lifespan. Together, these analyses provide new insights into the mechanisms governing repeat instability evolution and its population-level consequences. Moreover, by characterizing repeat length variability and validating haplotypes as a cost-effective diagnostic proxy our project has the potential to help improve early detection and genetic counseling, reduce diagnostic costs, and enable population-level screening strategies. Additionally, this unique transmission cartography that we report constitutes a unique public health resource that can be used for understanding the population-level dynamics of rare diseases transmission.

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38 - Tissue-specific CTG•CAG expansion rate and disease severity are modified by DNA repair genes expression levels in DM1 patients

Melissa Palma-Jiménez[1], Lisbeth Ramírez-Carvajal[1], Hailey Olafson[2], Eric T. Wang[2], Fernando Morales[1]

[1]INISA, Universidad de Costa Rica, [2]University of Florida

Myotonic dystrophy type 1 (DM1) is an autosomal dominant disorder caused by the expansion of CTG repeats in the *DMPK* gene, leading to multisystemic complications. This study examined whether differential expression of DNA repair genes in skeletal muscle, peripheral blood, and skin from the same DM1 patient contributes to tissue-specific somatic instability of the CTG repeat. RNA-Seq was used to quantify expression levels of eight DNA repair genes (*MSH2, MSH3, MSH6, MLH1, MLH3, PMS2, LIG1,* and *FAN1*). Results indicate that the expression levels varied significantly across tissues, with no inter-tissue correlations, suggesting independent regulation and patient-specific differences. Somatic expansion of the CTG•CAG repeat in blood and muscle was effectively predicted by a complex interaction of ePAL and age, while in muscle it was further influenced by *MSH3* and *PMS2* gene expression, confirming their role as tissue-specific genetic modifiers in DM1. Although only marginally significant, muscle expression of *PMS2* and *FAN1* appeared to affect age-at-onset: higher *FAN1* expression was associated with reduced somatic expansion and later onset. Our findings also suggest a complex competitive balance between promoters and stabilizers of repeat instability, shaping muscle expansion dynamics and potentially modifying clinical onset. Overall, these results indicate that certain DNA repair genes exert stronger, tissue-dependent effects on somatic instability. In particular, we confirm that *MSH3, PMS2,* and *FAN1* act as key modifiers not only of repeat expansion, especially in skeletal muscle, but also of DM1 severity. These genes therefore represent promising therapeutic targets for modulating disease progression.

39 - Plasma Neurofilament Light Chain and Phosphorylated Tau Are Elevated in Myotonic Dystrophy Type 1

Mika Yoshida[1], Harutsugu Tatebe[2], Hiroto Takada[3], Takahiro Nakayama[4], Michio Kobayashi[5], Kosuke Yoshida[6], Satoshi Kuru[7], Natsuki Kira[1], Tomoya Kubota[1], Yasuaki Mizutani[8], Hirohisa Watanabe[8], Yuhei Takado[9], Takahiko Tokuda[10], Masanori P. Takahashi[1]

[1]Clinical Neurophysiology, The University of Osaka Graduate School of Medicine, [2]Institute for Quantum Medical Science, National Institutes for Quantum Science and Technology, [3]Department of Neurology, NHO Aomori National Hospital, [4]Department of Neurology, Division of Neuromuscular Diseases, Yokohama Rosai Hospital, [5]Department of Neurology, NHO Akita National Hospital, [6]Department of Neurology, NHO Asahikawa Medical Center, [7]Department of Neurology, NHO Suzuka National Hospital, [8]Department of Neurology, Fujita Health University School of Medicine, [9]Institute for Quantum Life Science, National Institutes for Quantum Science and Technology, [10]Department of Neuroetiology and Diagnostic Science, Healthy Longevity Medicine

Myotonic dystrophy type 1 (DM1) is a multisystem disorder that affects the central nervous system. Despite previous studies, blood-based biomarkers have not been sufficiently characterized. This study investigated plasma neurofilament light chain (NfL), phosphorylated tau (p-tau181), amyloid-β (Aβ42/40), and glial fibrillary acidic protein (GFAP) in a Japanese cohort with DM1 to assess their potential as biomarkers.

Forty patients with genetically confirmed DM1 were enrolled in this study. Plasma NfL, p-tau181, Aβ42/40, and GFAP were quantified using single-molecule array technology. Clinical and genetic variables, including age, CTG repeat size, Mini-Mental State Examination (MMSE) score, modified Rankin Scale (mRS) score, and creatine kinase levels, were analyzed for correlations.

NfL and p-tau181 were significantly elevated in patients with DM1 compared with controls, with 95% exceeding the p-tau181 cut-off. NfL was moderately correlated with age, age at onset, and mRS, and no significant associations were observed between p-tau181 and other biomarkers, although a correlation was noted with serum creatine kinase.

These findings support that NfL is a marker of disease severity in DM1 and identified plasma p-tau181 as a potential novel biomarker. While the mechanisms underlying the increased p-tau181 levels remain unclear, they may reflect DM1-related pathologies in the brain and possibly in skeletal muscle. Study limitations include a small sample size and lack of age-matched controls, highlighting the need for

longitudinal validation. This study demonstrates the utility of NfL and suggests that p-tau181 is an emerging biomarker for DM1, supporting future work toward biomarker-guided monitoring and therapeutic evaluation.

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41 - Natural history of dysarthria in children with congenital and childhood myotonic dystrophy type 1: a 3-year longitudinal cohort study

Saskia Scholten[1], Marloes Lagarde[1], Lynn Orriëns[2], Corrie Erasmus[2], Saskia Houwen - van Opstal[1], Simone Knuijt[3], Jan Groothuis[3], Hilde Braakman[2]

[1]Department of Rehabilitation, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, Amalia Children's Hospital, Nijmegen, The Netherlands, [2]Department of Paediatric Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical centre, Nijmegen, Amalia Children's Hospital, The Netherlands, [3]Department of Rehabilitation, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, The Netherlands

In myotonic dystrophy type 1 (DM1), weakness of oropharyngeal and respiratory muscles causes dysarthria, impairing speech intelligibility and limiting social interactions. Although clinical features of dysarthria in children with DM1 have been described, long-term progression remains unclear. This study investigates the prevalence and progression of dysarthria and intelligibility problems in children with DM1, distinguishing between congenital and childhood-onset DM1 and describes affected speech aspects.

We retrospectively analyzed 3-year of data from children with DM1 (ages 5-18). Data were obtained from speech language therapy (SLT) reports, in which dysarthria severity and speech intelligibility were graded using the pediatric Radboud Dysarthria Assessment (pRDA), a validated tool with good reliability and construct validity. The pRDA includes six-point scales for functional and activity levels ranging from 'no dysarthria' to 'very severe dysarthria' and from 'effective communication' to 'no oral communication possible'. From the SLT reports, information was extracted on speech aspects, including articulation, phonation, resonance, respiration, and prosody.

We present repeated measurements from 119 visits of 46 children (19 congenital-onset DM1, 27 childhood-onset DM1with 1-4 assessments per child. Preliminary results from the index measurement show that 80% of the children exhibit dysarthria and 82% have intelligibility problems. All aspects of speech were affected, in decreasing order of frequency: articulation, resonance, phonation, respiration and prosody. Across all visits, children with congenital DM1 show more severe dysarthria

compared to childhood DM1. Dysarthria and intelligibility problems are plotted against age for congenital DM1, childhood DM1, and the total group.

Both congenital and childhood DM1 show a high prevalence of dysarthria and speech intelligibility problems, with more severe impairment observed in congenital DM1. Overall, articulation is the most prominently affected aspect, characterized primarily by weakness.

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43 - Characterising Patient-Derived iPSC Models of the Neuroimmune System to Study RNA Pathology in Repeat Expansion Disorders

Daisy Stringfellow[1], Rebecca Trueman[1], Luisa Martinez-Pomares[1], David Brook[1], Daniel Scott[1]

[1]University of Nottingham

Myotonic Dystrophy (DM) is an RNA-based disorder in which expanded RNA transcripts accumulate into toxic nuclear foci. This RNA pathology has been well characterised in various tissues, but the impact on the immune system remains unclear.

Growing evidence indicates the immune system is affected in DM and may contribute to disease mechanisms. As the immune system interacts with, surveys, and responds to all tissues, understanding how the immune system is affected could provide a more holistic understanding of pathology in DM.

The nervous system is also vulnerable to DM, and most other RNA foci disorders. Neuroimmune pathology is associated with many neurological conditions and has also been reported across disorders that express RNA foci such as C9orf72 Amyotrophic Lateral Sclerosis and Huntington's Disease. This proposes that the neuroimmune environment may be similarly affected in DM, and some studies have alluded to this. We aim to investigate how the immune system may be affected by RNA foci, and how this could contribute to nervous system changes reported in patients.

We have generated a collection of three paired iPSC lines (3 DM1 patient-derived lines and respective isogenic control lines) via CRISPR-mediated excision of the repeat expansion. We have characterised foci expression, off target analysis and changes to expansion length in these lines. Using these lines, we compare the effects of the repeat expansion on cellular function in iPSC-derived macrophages, microglia and motor neurones based on published protocols. We are currently using these models to study DM1 pathology in different cell types, such as RNA foci and MBNL

sequestration. Further, we explore the effect of DM1 pathology on immune cell motility, inflammatory responses to stimuli, phagocytosis and trophic support to neurones. We also aim to investigate how RNA foci-clearing compounds could rescue phenotypic changes in our cell models.

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44 - Urinary Titin Fragment as a Biomarker of Disease Severity in Patients with Myotonic Dystrophy Type 1

Mika Yoshida[1], Tsuyoshi Matsumura[2], Hiroto Takada[3], Akinori Nakamura[4], Satoshi Kuru[5], Michio Kobayashi[6], Kazuma Sugie[7], Ryosuke Niwa[1], Tomoya Kubota[1], Hotake Takizawa[8], Makiko Endo[8], Harumasa Nakamura[8], Masafumi Matsuo[9], Masanori P. Takahashi[1]

[1]Clinical Neurophysiology, The University of Osaka Graduate School of Medicine, [2]Department of Neurology, NHO Osaka Toneyama Medical Center, [3]Department of Neurology, NHO Aomori National Hospital, [4]Department of Neurology, NHO Matsumoto Medical Center, [5]Department of Neurology, NHO Suzuka National Hospital, [6]Department of Neurology, NHO Akita National Hospital, [7]Department of Neurology, Nara Medical University, [8]Department of Neurology, National Center of Neurology and Psychiatry, [9]Graduate School of Science, Technology and Innovation, Kobe University

Fragments of titin protein have recently been detected in urine following muscle injury and shown to correlate with disease severity in Duchenne muscular dystrophy and other neuromuscular disorders. However, the utility of urinary titin in myotonic dystrophy type 1 (DM1) remains insufficiently established. This study investigated urinary titin as a biomarker of disease severity in patients with DM1.

Patients with DM1 were recruited from eight institutions in Japan. Urinary titin was measured using a Titin N-Fragment Assay ELISA Kit (Immuno-Biological Laboratories, Japan) and analyzed as creatinine-corrected urinary titin/Cr ratios. Associations with serum creatine kinase (CK) and clinical parameters were assessed using Spearman's rank correlation and the Jonckheere-Terpstra test, with $p < 0.05$ considered statistically significant.

A total of 81 patients with DM1 were included in the analysis. The median age of the patients was 46 years (IQR 37-54) and 46.9% were male. The median urinary titin/Cr ratio was 34.6 pmol/mgCr (IQR 15.9-58.7). Urinary titin showed a significant increasing trend across modified-Rankin Scale (mRS) scores from 0 to 4, whereas serum CK did not show a significant trend. Across the four ambulation status groups (independent, with aids, assisted walking, and non-ambulatory), urinary titin showed

a significant monotonic increase, whereas serum CK exhibited a monotonic decrease. In addition, urinary titin was significantly correlated with ankle dorsiflexion strength and 10-m walk/run time at a comfortable pace (ρ = −0.4436 and 0.4596, respectively). Urinary titin also showed a moderate correlation with serum CK (ρ = 0.371). In ambulatory patients who participated in a natural history study, urinary titin showed an increasing trend over time.

The urinary titin/Cr ratio correlated more strongly with disease severity than serum CK. In ambulatory patients, urinary titin showed a longitudinal increasing trend, and further data are being collected for validation.

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45 - Mortality risks in Myotonic dystrophy: Insights from a single-center retrospective study

Tsuyoshi Matsumura[1], Yuhei Hasuike[1], Misa Matsui[1], Naoko Kawamura[1], Yuiko Watanabe[1], Tomoko Saito[1], Motohiro Sudo[1], Rika Yamashita[1], Yuki Yonenobu[1], Tomohiro Yata[1], Daisuke Nakatsu[1], Tomomi Furushima[1], Takuyuki Endo[1], Akinori Iyama[1], Makoto Kinoshita[1], Misaki Yamadera[1], Kimiko Inoue[1], Keiko Toyooka[1], Toshio Saito[1], Hideki Mochizuki[1]

[1]NHO Osaka Toneyama Medical Center

Myotonic dystrophy (DM) is a multisystem disorder characterized by impaired symptom recognition, which complicates appropriate medical management and contributes to limited improvements in life expectancy relative to other neuromuscular diseases. To clarify the factors influencing prognosis, we assessed causes of death in 134 patients with DM (69 men, 65 women) who received care at our institution and died between 1989 and 2025. The most prevalent category was respiratory failure and infections, accounting for 56.7% of cases. A comparison of two periods, 1998-2015 (n=64) and 2016-2025 (n=70), demonstrated a significant decline in the age at diagnosis of respiratory impairment (52.9±11.2 vs. 48.9±11.1 years, p=0.027), accompanied by an extension of respiratory management duration (3.4±3.1 vs. 8.3±6.3 years). Notwithstanding these changes, the mean age at death did not differ significantly between periods (55.7±12.7 vs. 57.1±11.7 years, p=0.382). Among the 39 patients who underwent tracheostomy, 11 procedures followed resuscitation during acute deterioration, with four cases complicated by anoxic encephalopathy. In four additional cases, resuscitation attempts were unsuccessful despite intubation. The application of time-dependent Cox analysis identified significant associations between mortality and male sex (hazard ratio (HR): 1.567), younger age at onset (HR: 0.982/year), respiratory impairment (HR: 8.582), cardiac

impairment (HR: 2.251), and enteral nutrition (HR: 1.817). These findings indicate that respiratory failure and infection remain the predominant causes of death in DM, highlighting the necessity of rigorous management of respiratory and swallowing dysfunction. Although earlier diagnosis has been achieved through improved clinician awareness, limited patient insight and poor adherence continue to hinder gains in survival. Enhancing risk communication through repeated presentation of objective data and tailoring support systems to individual risk profiles are essential for improving long-term outcomes.

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46 - Enhancing Antisense Oligonucleotide Activity in Myotonic Dystrophy Type 1 by Genetic and Chemical Modulation

Yasmine Ferchichi[1], Arturo Lopez-Castel[2]

[1]Universitat de València, BIOTECMED,ENTRY-DM Marie Skłodowska-Curie Doctoral Network, [2]Arturo López Castel - Assistant Professor, PhD, MBA Facultad de Ciencias Biológicas Human Translational Genomics Group BIOTECMED - Genetics Department Universitat de València

Antisense oligonucleotides (ASOs) are a promising therapeutic strategy for Myotonic Dystrophy Type 1 (DM1), yet their efficacy is limited by inefficient endocytosis and/or endosomal sequestration, which prevents efficient delivery to nuclear RNA targets. Proof-of-concept studies have shown that small molecules can promote endosomal escape and markedly increase ASO activity, highlighting intracellular trafficking as a key therapeutic bottleneck. Building on this foundation, the present work aims to identify novel chemical and genetic modulators capable of shifting ASO fate toward productive release.

A dual screening strategy is implemented using the HeLa IVS2-654 EGFP splice-switching reporter system, a rapid, low-stress, low-cost, and scalable platform that enables direct visualization of ASO activity. The chemical screen evaluates thousands of compounds from the Prestwick and PureTitre libraries, complemented by literature-selected molecules implicated in membrane dynamics, vesicle acidification, lipid remodeling, or endosomal maturation. These compounds are assessed for their ability to enhance gymnotic ASO delivery, providing a high-throughput route to identifying small-molecule adjuvants.

In parallel, a literature-driven analysis of endocytic and vesicular trafficking pathways guides the selection of key regulatory proteins involved in cargo sorting, endosomal maturation, recycling, fusion, and lysosomal degradation. Targeted knockdown, knockout, or overexpression of these genes will be used to determine how specific

trafficking nodes influence ASO sequestration and cytosolic release, enabling mechanistic dissection of the pathways governing ASO intracellular fate.

By integrating chemical screening with targeted genetic perturbation, this work aims to uncover translatable strategies that enhance cellular uptake and/or endosomal escape, reduce required ASO dosing, and ultimately improve the safety and therapeutic performance of ASO-based treatments for DM1. The most promising candidates will advance to validation in DM1-relevant muscle cells and *in vivo* models, establishing a robust and scalable pipeline for optimizing ASO delivery.

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47 - Self-perceived change in daily living competence in patients with Myotonic Dystrophy type 1

Ulrika Edofsson[1, 2], Stefan Winblad[3], Christopher Lindberg[2, 4], Olöf Eliasdottir[2], Sara Nordström[2]

[1]Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden, [2]Department of Neurology, Neuromuscular Center, Sahlgrenska University Hospital, Gothenburg, Sweden., [3]Icon Lab, Department of Psychology, University of Gothenburg, Gothenburg, Sweden., [4]Department of Neuroscience and Rehabilitation, Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden.

Myotonic dystrophy type 1 (DM1) is a chronic, progressive multisystem disorder characterized by increasing muscle weakness and functional decline. The complexity of the disease, its wide spectrum of symptoms, reduced adherence to clinical recommendations and a tendency among individuals with DM1 to minimize or underreport difficulties pose substantial challenges for healthcare professionals. Performance in activities of daily living is influenced by multiple interacting factors, and the underlying mechanisms of functional limitations, as well as their progression over time, are not always easily identifiable. Consequently, current knowledge in this area remains limited.

The aim of this study was to investigate longitudinal changes in self-perceived occupational competence in performing activities of daily living and to examine whether these changes are associated with objective performance measures.

Ninety-seven adult patients with childhood, juvenile, adult or late-onset DM1 completed a self-report questionnaires, including Occupational Self-Assessment (OSA) and the Myotonic Dystrophy Type 1 Activity and Participation Scale (DM1-Activ), as well as measures of muscle function (MIRS) and cognition (MoCA).

Assessments were conducted on two occasions, with a four-year interval between them.

Results showed that patients reported significantly lower self-perceived occupational competence at follow-up (M_1 = 57.12, SD = 14.05; M_2 = 55.14, SD = 14.18; p = 0.039, d = 0.21), whereas the perceived importance of daily activities remained stable. Similar negative changes were observed in activity performance and muscle function, while cognitive measures remained stable.

The study indicates that changes over time in self-perceived occupational competence, despite stable valuation of activities, may increase the risk of dissatisfaction with daily activities. Over time, this could negatively affect quality of life for this patient group. The findings have clinical relevance for healthcare professionals by highlighting the need for continuous follow-up, individualized goal-setting, and interventions that enhance patients' motivation and engagement in rehabilitation within a multidisciplinary expert team.

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48 - Intensive speech therapy to address bulbar problems in children with myotonic dystrophy type 1

Karlijn Beckers[1], Simone Knuijt[2], Hilde Braakman[3], Saskia Houwen-van Opstal[1], Saskia Scholten[1], Jan Groothuis[2], Corrie Erasmus[3], Marloes Lagarde[1]

[1]Department of Rehabilitation, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, Amalia Children's Hospital, Nijmegen, The Netherlands., [2]Department of Rehabilitation, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, The Netherlands, [3]Department of Paediatric Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical centre, Nijmegen, Amalia Children's Hospital, The Netherlands

The study aims to assess the effectiveness of intensive speech language therapy (SLT) in children with Myotonic Dystrophy type 1 (DM1), specifically targeting orofacial muscle strength training, articulation, and swallowing. Oropharyngeal dysphagia (mastication and swallowing difficulties) and dysarthria (speech disorders) are common symptoms in children with DM1, which can severely impact their quality of life, leading to complications such as aspiration pneumonia and difficulties with social participation.

The study will include 25 children, aged 5-18 years, diagnosed with clinically and genetically confirmed DM1, who will participate in an 8-week intensive therapy program followed by 10 months of maintenance exercises. The interventions will

focus on orofacial muscle strength training (including chin tuck against resistance and masticatory muscle exercises) and articulation training. The primary outcomes will include orofacial muscle quality, assessed using quantitative muscle ultrasound, and the impact on speech intelligibility and swallowing capacity. Secondary outcomes will include mastication function and participant-reported experiences of the therapy.

Data will be collected at three time points: before (T0), immediately after (T1), and 10 months post-intervention (T2). These will be compared to retrospective data from previous studies. The study will employ a mixed-methods design, combining quantitative measurements with qualitative interviews from children, their parents, and speech therapists to capture the personal impact of the therapy.

This study aims to provide new insights into the effects of intensive SLT in treating dysarthria and dysphagia, with the potential to guide clinical practice and improve daily care for children with DM1.

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49 - Zeleciment basivarsen targets the underlying cause of DM1 to enable functional improvement in the Phase 1/2 ACHIEVE trial

Shauna Andresson[1], Guillaume Bassez[2], Jordi Diaz-Manera[3], James B. Lilleker[4], Karlien Mul[5], Marika Pane[6], Richard H Roxburgh[7], Benedikt Schoser[8], Christopher Turner[9], Soma Ray[1], Huaihou Chen[1], Douglas Kerr[1], Valeria Sansone[10]

[1]Dyne Therapeutics, Inc., Waltham, MA, USA, [2]Institut de Myologie, Paris, France, [3]John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle-Upon-Tyne, UK, [4]Muscle Disease Unit, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK, [5]Radboud University Medical Center, Nijmegen, Netherlands, [6]Fondazione Policlinico Universitario A. Gemelli, Rome, Italy, [7]Neurogenetics Clinic Centre for Brain Research, University of Auckland, Auckland, NZ, [8]Friedrich-Baur-Institute, Dep. of Neurology LMU Clinics, Ludwig-Maximilians University, Munich, Germany, [9]University College London Hospitals, London, UK, [10]Centro Clinico NeMO, University of Milan, Milan, Italy

Introduction: Myotonic dystrophy type 1 (DM1) is a spliceopathy that results in multi-system clinical manifestations. Zeleciment basivarsen (z-basivarsen, also known as DYNE-101) consists of a TfR1-binding Fab conjugated to an ASO designed to target mutant nuclear *DMPK* RNA in both muscle and CNS to correct splicing with the goal of enabling functional improvement.

Objective: Assess the safety, tolerability, and efficacy of z-basivarsen in adults with DM1 in the Phase 1/2 ACHIEVE trial (NCT05481879).

Design/Methods: In the completed 24-week placebo-controlled Multiple Ascending Dose (MAD) portion of ACHIEVE, 56 participants received one of 5 IV dose regimens of z-basivarsen or placebo. Eligible participants subsequently entered the long-term extension portion at 6.8 mg/kg Q8W z-basivarsen.

Results: In six participants who received 6.8 mg/kg Q8W z-basivarsen in the MAD portion, substantial knockdown of *DMPK* RNA levels and improvement in splicing were noted as early as 3 months post-treatment. Improvement from baseline in myotonia, measured by video hand opening time (vHOT), was also noted at 3 months and sustained through 12 months of treatment. Improvement from baseline across multiple measures of muscle strength and function, including Quantitative Muscle Testing (QMT) total score, 10-meter walk/run test, 5 times sit-to-stand, and 9-hole peg test was sustained through 12 months. Clinical meaningfulness of improvements observed with z-basivarsen were supported and further contextualized by patient-reported outcomes measured by the myotonic dystrophy health index (MDHI) total score. Improvement from baseline on clinician-reported global impression of change scales was reported by 83% of patients at 12 months. As of April 23, 2025, z-basivarsen has demonstrated a favorable safety profile, with no serious related TEAEs.

Conclusions: These data suggest that z-basivarsen has a favorable safety profile and showed functional improvement across several clinical measures, including myotonia, muscle strength and function, further contextualized by improvement in patient assessment of DM1 disease burden.

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50 - Genetic and Clinical Characterisation of DM1 Patients from Costa Rica with DMPK Variant Repeats

Harshavardhini Gnanasekaran[1], Fernando Morales[2], Darren G. Monckton[1]

[1]Institute of Molecular, Cell and Systems Biology, College of Medical, Veterinary and Life Sciences, University of Glasgow, UK, [2]Instituto de Investigaciones en Salud, Universidad de Costa Rica, Costa Rica

Approximately 5% of all DM1 patients harbour variant repeats in their CTG expansions which are usually associated with stabilisation of the expansions, later onset and reduced disease severity. Detection of variant repeats is traditionally done using restriction digestion and Southern blotting. However, this method offers limited

resolution regarding the sequence architecture, which can be enhanced by sequencing. In this study, whole blood genomic DNA of 35 DM1 patients from Costa Rica were initially screened for CCG/CGG variant repeats using small pool-PCR followed by AciI digestion and Southern blotting. Through this, three patients were confirmed to possess AciI-sensitive variants. To further characterise the variants, long-read sequencing was employed. This approach allowed for the determination of accurate sequence of the variants which was subsequently used to assess genotype-phenotype relationships. Analysis of the sequencing data revealed the repeat variations in the *DMPK* locus across the three patient samples. Comparison of the genetic profiles with the clinical presentation suggest that variants stabilise the repeats and thus the alter the age of onset and severity of DM1. The findings from this study demonstrate the need to screen for variant repeats and characterise them using next-generation sequencing, as they are crucial for studying the disease prognosis and aid patients with disease management.

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51 - MiSeq sequencing of the CTG repeat expansion in 250 DM1 patients reveals a complex picture of DNA sequence variants

Sarah Cumming[1], Tolulope Oyeniyi[1], Darren Monckton[1]

[1]University of Glasgow, Glasgow, UK

The symptoms of DM1 are highly variable. Age at disease onset largely depends on inherited CTG repeat length, modified by somatic repeat instability and the presence of variant repeat (VR) interruptions, most commonly CCG, which typically delay onset. We used blood DNA samples from a cohort of 250 Scottish DM1 patients to identify genetic variants, aside from CTG repeat length, that could contribute to the observed phenotypic variability in DM1. We used an Illumina MiSeq repeat-primed PCR assay to sequence both ends of the repeat expansion. We have previously described three families with apparent *de novo* CCG VRs in this cohort. We identified three further families with CCG VRs, each with a complex pattern of VRs which differed slightly between the members of each family. Pedigree analysis indicated the exact pattern could be modified during both paternal and maternal transmission. Three further individuals with VRs included one highly unusual single CTTG interruption near the 5' end of the repeats. Flanking sequence variants were also detected multiple times, including an AAT insertion upstream of the first repeat that was found in 12 individuals/families both with and without CCG VRs. A C to A mutation in the first CTG repeat was also seen four times. At the 3' end of the expansion, a G to C mutation in three individuals from two families generated an AciI

restriction site downstream of the final CTG repeat, resulting in false positives in the small-pool PCR screen often used for CCG and CGG VRs. In four other individuals/families, a deletion of one G immediately after the final CTG repeat was seen. These flanking sequence variants likely result from the high genetic instability in the CTG repeat region extending into nearby sequences. Assessing the impact of these additional variants on symptoms will require a much larger study.

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52 - Gastrointestinal Involvement in Myotonic Dystrophy Type 1: An Integrated Retrospective Analysis

B.P.A.P. van Veen[1, 2], I.B.T. Joosten[1], C.G. Faber[1], D. Keszthelyi[2], W.J.A. Aarts[1], K. Mul[3], J.M. Conchillo[2]

[1]Department of Neurology and School for Mental Health and Neuroscience, Maastricht University Medical Centre+, Maastricht, The Netherlands, [2]Department of Gastroenterology and Hepatology, Maastricht University Medical Centre+, Maastricht, The Netherlands, [3]Department of Neurology, Radboudumc, Nijmegen, The Netherlands

Gastrointestinal (GI) manifestations are common in patients with myotonic dystrophy type 1 (DM1) and substantially contribute to disease burden. Symptoms may affect all segments of the GI tract, ranging from dysphagia and gastroesophageal reflux to constipation and fecal incontinence. Although motility disturbances have been proposed as an underlying mechanism, existing evidence is often limited by small sample sizes and focus on isolated aspects of GI function. Consequently, the relationship between patient-reported symptoms and objective diagnostic findings remains insufficiently understood.

In this retrospective study, we aim to describe the prevalence and spectrum of GI abnormalities in a large cohort of DM1 affected individuals. In addition, we will investigate associations between reported GI symptoms and objective findings during functional assessment and explore the presence of distinct phenotypic subgroups. We will include genetically confirmed DM1 patients who underwent routine GI diagnostic evaluation at Maastricht University Medical Centre+ between 2009 and 2019. Data were collected as part of standard clinical care and includes esophageal manometry, videofluoroscopic swallowing studies, gastroscopy, colonoscopy, abdominal radiography, abdominal ultrasound and systematically documented gastrointestinal symptoms.

The results of this analysis will be presented at the International Myotonic Dystrophy Consortium Meeting and are expected to contribute to the development of more targeted diagnostic strategies and to the design of future prospective studies.

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54 - A Feasibility Study of a Multi-Module At-Home Digital Assessment Platform for DM1

Florentin Thullier[1], Élie Fiogbé[2, 3, 4], Claudia Côté[2, 5], Pascal Fortin[1], Élise Duchesne[2, 6, 7, 8], Sowmya Chary[9], Prashant Bansal[9], Sébastien Gaboury[1], Allison Kreuzer[9], Cynthia Gagnon[2, 3, 10]

[1]Département d'Informatique et Mathématique (DIM), Université du Québec à Chicoutimi, Chicoutimi, Québec, Canada, [2]Groupe de recherche interdisciplinaire sur les maladies neuromusculaires (GRIMN), Saguenay-Lac-St-Jean Integrated University Health and Social Services Center, Saguenay, Quebec, Canada, [3]Faculté de médecine et des sciences de la santé, Université de Sherbrooke, Sherbrooke, Québec, Canada, [4]Centre de recherche du Centre hospitalier universitaire de Sherbrooke (CRCHUS), Université de Sherbrooke, Québec, Canada., [5]Faculté des sciences de l'agriculture et de l'alimentation, Université Laval, Québec City, Québec, Canada, [6]Center for Interdisciplinary Research in Rehabilitation and Social Integration (CIRRIS), Capitale-National Integrated University Health and Social Services Center, Quebec City, Quebec, Canada, [7]CHU de Québec-Université Laval Research Center, Quebec City, Quebec, Canada, [8]School of Rehabilitation Sciences, Faculty of Medicine, Université Laval, Quebec City, Quebec, Canada, [9]Dyne Therapeutics, Waltham, Massachusetts, USA, [10]Centre de recherche et d'innovation du Centre intégré universitaire du Saguenay-Lac-St-Jean, Clinique des maladies neuromusculaires, Hôpital de Jonquière, Jonquière, Québec, Canada

DM1 is one of the most common neuromuscular disorders in adults. Previous studies have reported deficits in muscle strength, mobility, physical activity, speech, and sleep, leading to early functional decline, reduced participation, and quality of life. Clinic-based assessments are episodic, clinically burdensome, often require long travel, and are sensitive to fatigue for participants. This feasibility study aims to address some of these limitations by developing and pilot-testing a multi-module at-home digital assessment platform.

Methods The platform will be co-designed with patient partners to address feasibility with consideration for DM1-specific functional impairments. It will integrate connected devices, including a smartwatch for physical activity and sleep monitoring, a wireless spirometer for respiratory assessment, and a microphone for

speech. A tablet will be provided to guide participants and record standardized test videos of the 30 second sit-to-stand and 80ml drinking tests. Following baseline clinical assessments at a neuromuscular clinic, up to 20 participants will receive supervised at-home installation and training, followed by daily platform use over a predefined schedule, supported by weekly check-ins. The study will measure task completion, protocol adherence, technical issue frequency, surveys and qualitative interviews, to assess whether the platform is feasible and/or acceptable.

Expected Outcomes Expected deliverables include a user-centered at-home digital assessment platform and evidence of high feasibility and acceptability. Secondary outputs include preliminary longitudinal real-world data and insights into implementation barriers and facilitators, providing proof-of-concept for remote monitoring. The multimodal dataset will support future AI-driven analyses that are expected to derive digital biomarkers of disease severity and progression.

Conclusions This study will lay the groundwork for scalable, feasible, continuous, and patient-centered home monitoring of DM1. By reducing travel burden and contextual biases associated with clinic visits, the platform has the potential to improve accessibility, support earlier detection of functional decline, and enhance readiness for future clinical trials.

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55 - Life at the interface of data, care, and clinical trials: living as a DM researcher and caregiver through clinical trials

Lori Planco[1], Cécilia Légaré[1, 2, 3, 4], Tammy Reid[1], John Cleary[1], Andrew Berglund[1, 5]

[1]RNA Institute, College of Arts and Sciences, University at Albany-SUNY, Albany, NY 12222, USA, [2]Centre de Recherche du Centre Hospitalier de l'Université Laval (CR-CHUL), Axe Neurosciences, Université Laval, Québec City, Canada, [3]École des sciences de la réadaptation, Faculté de médecine, Université Laval, Québec, Canada, [4]Groupe de Recherche Interdisciplinaire sur les Maladies Neuromusculaires (GRIMN), Centre intégré universitaire de santé et de services sociaux du Saguenay-Lac-St-Jean, Saguenay, Québec, Canada, [5]Department of Biological Sciences, College of Arts and Sciences, University at Albany-SUNY, Albany, NY 12222, USA

Myotonic dystrophy (DM) presents a unique intersection of scientific complexity and human vulnerability. As a bioinformatics researcher immersed in unraveling the molecular underpinnings of DM, I have spent years parsing genomic datasets, modeling RNA toxicity, and exploring therapeutic targets. Yet, my professional journey is deeply intertwined with a personal one: supporting family members living with DM and guiding them through the uncertainties of clinical trials. This dual perspective has

profoundly shaped my understanding of translational research and patient-centered care.

From the research standpoint, the experience underscores the importance of data integrity and nuanced interpretation. Bioinformatics offers powerful tools to identify biomarkers and predict disease trajectories, but these insights gain true meaning only when contextualized within lived realities. Observing trial protocols firsthand revealed gaps between theoretical endpoints and what patients value most - quality of life, functional independence, and emotional resilience. With my observations I seek to challenge researchers to design studies that prioritize patient-reported outcomes alongside molecular metrics.

As a caregiver, the lessons are equally transformative. Navigating consent forms, managing logistics, and witnessing the emotional toll of progressive symptoms illuminated the ethical and practical dimensions of clinical research. Advocacy becomes a daily practice, ensuring clear communication, fostering trust, and balancing hope with realism. This role reinforced that scientific progress is not merely a function of algorithms and assays but of empathy, accessibility, and sustained dialogue between stakeholders.

Ultimately, occupying both roles has cultivated a holistic vision: precision medicine must integrate precision compassion. By bridging computational rigor with human experience, we can advance therapies that honor not only biological complexity but also the lived narratives of those we aim to serve.

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57 - Social cognition impairments in myotonic dystrophy type 1: A scoping review

Simon-Pierre Gagnon[1, 2], Nathalie Angeard[3], Cynthia Gagnon[1, 2]

[1]Groupe de Recherche Interdisciplinaire sur les Maladies Neuromusculaires (GRIMN), [2]Faculté de médecine et des sciences de la santé, Université de Sherbrooke (UdS), [3]Laboratoire Mémoire, Cerveau et Cognition (LMC2), Université Paris Cité

Background: Myotonic dystrophy type 1 (DM1) is the most prevalent neuromuscular disorder in adults and is associated with five distinct phenotypes. Cognitive impairments are reported across all phenotypes, with more severe deficits in earlier-onset forms. In addition to cognitive impairments, individuals with DM1 also exhibit social cognition difficulties such as impaired emotion recognition and reduced Theory of Mind (ToM) abilities. These difficulties may contribute to the reported reduced social participation in this population. However, studies with social cognition assessment in individuals with DM1 remain limited.

Objective: To identify studies assessing social cognition in individuals with DM1 in order to 1) map the clinical outcome assessments (COA), 2) document the impaired and preserved components referring to the Hierarchical Interdependent Taxonomy of Social Cognition (HITS) and 3) identify the gaps in the current literature.

Methods: The review is currently being conducted in accordance with the Joanna Briggs Institute guidelines for scoping reviews. Multiple databases (MedLine, PsycINFO, CINAHL, Scopus and Embase) were queried in October 2025 with a search strategy validated by a trained librarian. Eligible studies underwent data extraction, and results were organized into a social cognition framework.

Results: From 157 initial studies, 16 studies met inclusion criteria. Findings were mapped onto the HITS. Preliminary analysis indicated that emotion recognition and ToM are the most frequently assessed components of social cognition (n=7), while other components (e.g., empathy, social knowledge) were less frequently assessed (n=2 for both components).

Discussion/Conclusion: The review is the first comprehensive literature synthesis on social cognitive functioning across all DM1 phenotypes. Its findings will help clarify the extent of social cognition impairments in DM1, guide future studies on this topic, inform of appropriate assessment tools for social cognition as well as improve clinical management of social and cognitive difficulties in this population.

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58 - Investigating cell type-specific contributions to central nervous system disease mechanisms in myotonic dystrophy type 1

Emily E. Davey-Osuch[1], Juan D. Arboleda[1], M. Carmen Valero[1], Kendra K. McKee[1], Katharine A. Hagerman[2], Jacinda B. Sampson[2], John W. Day[2], Eric T. Wang[1]

[1]Department of Molecular Genetics & Microbiology, Center for NeuroGenetics, Genetics Institute, University of Florida, Gainesville, FL, USA, [2]2Department of Neurology, Stanford University, Palo Alto, CA, USA

Myotonic dystrophy type 1 (DM1) is a multisystemic disease caused by a CTG repeat expansion in the 3'UTR of *DMPK*. The expanded repeats sequester MBNL RNA binding proteins, resulting in global transcriptomic dysregulation. While central nervous system (CNS) symptoms are reported by patients to be a significant burden to their everyday lives, our understanding of how specific CNS cell types are affected in DM1 remains limited. We first profiled global transcriptomic dysregulation across specific brain regions by performing bulk RNA-seq using postmortem tissue from 9 DM1 patients. We initially focused on five regions (caudate/putamen/accumbens,

cerebellum, anterior hippocampus/entorhinal cortex, hippocampal body, amygdala) and compared to publicly available control RNA-seq data and observed widespread transcriptomic dysregulation across all five regions, including numerous shared mis-splicing signatures. Using unaffected control postmortem tissues from matched brain regions, ongoing studies will expand these analyses to quantitate global transcriptomic dysregulation across 11 brain regions. Furthermore, to determine whether specific cell types may be contributing to this dysregulation, we performed snRNA-seq using postmortem frontal cortex tissue from DM1 patients and controls and observed an increased proportion of both microglia and endothelial cells in DM1 patients. Interestingly, we also observed a correlation between endothelial cell proportion and severity of overall splicing and gene expression dysregulation. In future studies, we will use an immunofluorescence-based approach to sort out specific cell types by leveraging antibodies against cell type-specific proteins and fluorescence-activated nuclei sorting; these bulk populations of specific cell types will be utilized for downstream bulk RNA-seq and repeat length sizing to characterize cell type-specific transcriptomic dysregulation and repeat length measurements. These studies will elucidate how specific CNS cell types may be differentially affected on a transcriptomic level and whether there may be differences in repeat lengths between cell types in DM1 patients.

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59 - Investigating the basis of circadian activity disruption on a cellular level in myotonic dystrophy type 1

Emily E. Davey-Osuch[1], Belinda S. Pinto[1], Eric T. Wang[1]

[1]Department of Molecular Genetics & Microbiology, Center for NeuroGenetics, Genetics Institute, University of Florida, Gainesville, FL, USA

Myotonic dystrophy type 1 (DM1) is a neuromuscular disease characterized by numerous central nervous system symptoms, one of the most prevalent being hypersomnolence. One possible cause of hypersomnia is disrupted circadian rhythms and interestingly, circadian activity analyses of DM1 patients have shown that these individuals display a low amplitude rest-wake rhythm. However, the molecular mechanisms driving dysregulated activity rhythms are unknown. We aim to investigate the basis of circadian activity disruption in DM1 on a cellular level. To determine how expanded CTG repeats affect the core molecular clock, we generated stable cell lines by introducing 480 or 0 CTG repeats into U2OS reporter cells expressing a *Per2*:LUCIFERASE (*Per2*:LUC) fusion protein, as real-time bioluminescence recordings of *Per2*:LUC oscillations can be used to track circadian

rhythms. We found that cells expressing 480 CTG repeats exhibit a shorter period than control lines. To test whether this period shortening may be due to MBNL loss, we are also generating MBNL1 knockout, MBNL2 knockout, and MBNL1/2 double knockout U2OS *Per2*:LUC reporter lines, which we will utilize to test how loss of MBNL affects the circadian clock on a cellular level. Furthermore, to determine whether circadian activity rhythms are also perturbed in patient-derived cell models, we subsequently introduced the *Per2*:LUC reporter into DM1 patient and control myoblasts. Upon differentiation to myotubes and measuring *Per2*:LUC oscillations, we similarly observed a shorter period in DM1 patient myotubes as compared to controls. We are further investigating potential mechanisms that may be driving this period shortening phenotype in DM1 cells. These studies suggest that circadian rhythms are disrupted in DM1 and will help to uncover whether this dysregulation is a direct result of the effect of the CTG repeat expansion on the core circadian clock mechanism or may be driven by other downstream pathways.

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60 - Comprehensive Bioinformatic Analysis of Genome-Wide Variation in 3,000 DM1 Patients Using Long-Read Sequencing

Luis Orduña[1, 2], Raquel Pérez-Gómez[1, 2], Marc Corral-Juan[3], Clara Moliner[3], Eva Coll-Liesa[3], Alicia López-Martín[3], Alba Herrero[3], Álvaro S. Larran[3], Usua Laresgoiti[4], Daniel Borras[3], Virginia Arechavala-Gomeza[4, 5], Arturo López-Castel[1, 2, 6], Gisela Nogades-Gadea[3]

[1]INCLIVA Biomedical Research Institute, Av. Menendez Pelayo 4, 46010 Valencia, Spain, [2]Human Translational Genomics Group, University Institute for Biotechnology and Biomedicine (BIOTECMED), University of Valencia, Av. Dr. Moliner 50, 46100 Valencia, Spain, [3]Badalona Neuromuscular Research Group (GRENBA), Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol (IGTP), Campus Can Ruti, Universitat Autònoma de Barcelona, 08916 Badalona, Spain, [4]Nucleic Acid Therapeutics for Rare Disorders (NAT-RD), Biobizkaia Health Research Institute, Barakaldo, Spain, [5]Ikerbasque, Basque Foundation for Science, Bilbao, Spain, [6]CIBERER ISCIII, Av. Monforte de Lemos 3-5, 28029 Madrid, Spain.

Myotonic dystrophy type 1 (DM1) is caused by a pathogenic CAG repeat expansion at the DMPK locus, yet its pronounced clinical heterogeneity cannot be fully explained by repeat length alone. To systematically characterize the genomic and epigenomic landscape underlying this variability, we are performing long-read whole-genome sequencing of 3,000 Spanish DM1 patients from the DM1-Hub registry using Oxford Nanopore technology. We are developing a scalable bioinformatic framework

tailored to population-scale long-read data, enabling robust variant calling across repetitive and low-complexity regions, accurate phasing over megabase scales, and direct inference of epigenetic modifications.

Our analytical pipeline enables unified detection and integration of multiple variant classes directly from native DNA reads. These include base-resolution DNA methylation profiles, single-nucleotide variants, small insertions and deletions, structural variants, copy number variants, regions of loss of heterozygosity, and haplotype-resolved, allele-specific features. At the DMPK locus, dedicated workflows are used to measure repeat length, identify repeat interruptions, assess somatic mosaicism, and characterize allele-specific methylation. At the genome-wide level, the approach captures structural and copy number variation that is often missed by gold standard short-read sequencing. All derived features data are combined into a high-dimensional genomic feature matrix and integrated with longitudinal clinical data. Machine learning methods are then applied for feature selection, patient stratification, and prediction of clinical outcomes.

Overall, this work provides a practical bioinformatic framework for large-scale long-read genomics in repeat expansion disorders and demonstrates the potential of integrating multiple layers of genomic information with clinical phenotypes to better resolve complex genotype-phenotype relationships in DM1.

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62 - Long-Read Amplicon Sequencing Method to Measure CTG Repeat Length and Mosaicism in Myotonic Dystrophy Type 1

Omari McMichael[1], Lola Holmes[1], Dove Enicks[1], Marina Provenzano[1], Julia Hartman[1], Nicholas Johnson[1], Samuel Carrell[1]

[1]Virginia Commonwealth University

Myotonic dystrophy type 1 (DM1) is a multisystemic neuromuscular disease caused by an expanded CTG repeat in the 3` untranslated region of the *DMPK* gene. Pathogenic inherited repeats commonly range in the 100s to 1000s triplets in blood cells of affected individuals. Using current methods, the length of the inherited repeat in the blood is broadly correlated with disease severity (Pearson's R » -0.44; Age-of-onset x modal CTG length), but accurate measurement of individual repeat lengths has technical limitations, particularly with larger alleles.

We set out to develop a method to measure CTG repeat length and mosaicism that is amenable to low sample input, economically feasible for large-scale analyses, and allows for sequence-level data. Using Southern blot as the standard, we evaluate (1)

Cas9-mediated genomic DNA enrichment and PacBio long-read sequencing, (2) a novel long-range PCR using strand-displacing polymerase, and (3) PacBio sequencing of long-range PCR products. Fidelity of all three methods are examined using a test-set of patient-derived blood gDNA samples and a gDNA mixing experiment of known repeat lengths from patient-derived cell lines. We show that our novel long-range PCR can amplify highly-expanded CTG repeat alleles in blood genomic DNA, including with LNA blocker based de-targeting of the wild-type allele. We analyze concordance between the methods and examine the limitations of various detection methods regarding input DNA, detection of longer or shorter alleles, and quantification of mosaicism. Tagging of input molecules with unique molecular identifiers prior to amplification to allow for correction of amplification bias is explored.

Identifying an accurate, cost-effective method for repeat length measurement will aid in ongoing efforts to identify novel genetic modifiers of DM1 and develop robust assays to test repeat stabilizing therapeutics.

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63 - TRACK DM: Design of longitudinal natural history study in people with myotonic dystrophy linking retrospective data with prospective follow-up

Guillaume Bassez[1], Melinda Gyenge[1], Jean-Yves Hogrel[1], Alla Zozulya-Weidenfeller[2]

[1]Constitutive Reference Center for Neuromuscular Diseases, Neuro-Myology Department, Institute of Myology, AP-HP Pitié-Salpêtrière, Paris, France, [2]Lupin Neurosciences, Zug, Switzerland

Myotonic dystrophy (DM) is a heterogeneous group of hereditary rare diseases, classified as DM1 and DM2, with a common and defining symptom of myotonia. Knowledge of the daily physiological burden of myotonia and its psychological impact are lacking, including how these aspects can change over time.

TRACK DM is a longitudinal noninterventional study, linking retrospective data captured from the French DM-Scope Registry with a prospective 24-month follow-up period. The study consists of a detailed retrospective medical history assessment of selected participants over an 18-month period up to the start of the study. This is followed by the prospective study period, with assessment visits at 12 and 24 months. TRACK DM is due to run from Q2 2026 to Q2 2028.

The primary objective is to study the natural history of DM, focusing on functional tests of the impact of myotonia symptoms, quality of life, and ability to perform daily activities as assessed by patient questionnaires. Other objectives include assessing

the prevalence of systemic involvement of DM in relation to cardiopulmonary, gastrointestinal, hepatic and renal organ systems. Myotonia treatments will be assessed retrospectively.

Participants genetically diagnosed with DM1 or DM2 will be selected from those within the DM-Scope registry with a confirmed medical history covering ≥18 months prior to enrolment; they will be ≥16 years at study entry, with confirmed clinical signs of handgrip myotonia (DM1 participants), or other myotonia subtypes (DM2 participants). The anticipated participant population is N=100 in total (N=90 DM1; N=10 DM2). Descriptive statistics will be used to summarise baseline characteristics, retrospective, and prospective assessments; DM1 and DM2 patients will be analysed separately.

TRACK DM aims to demonstrate the value of enhancing knowledge of the natural history of DM, by providing insight into extramuscular disease manifestations of DM while symptoms of myotonia and weakness persist.

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64 - Circulating Immune Biomarkers in Myotonic Dystrophy Type 1

Sylvia Nieuwenhuis[1], Daniël van As[2], Liesbeth van Emst[3], Isabelle Cote[4], Baziel G.M. van Engelen[5], Elise Duchesne[4], Cynthia Cagnon[6], Peter-Bram A.C. 't Hoen[1], Jeffrey C. Glennon[7]

[1]Department of Medical Biosciences, Radboud university medical center, Nijmegen, The Netherlands, [2] Department of Neurology, Donders Institute for Brain, Cognition, and Behaviour, Radboud university medical center, Nijmegen, The Netherlands, [3]Department of Internal Medicine, Radboud university medical center, Nijmegen, The Netherlands, [4]School of Rehabilitation Sciences, Faculty of Medicine, Université Laval, Quebec City, Quebec, Canada, [5] Faculty of Medicine and Health Sciences, University of Sherbrooke, Quebec, Canada [6] Conway Institute of Biomolecular and Biomedical Research, School of Medicine, University College Dublin [7]D04 V1W8 Dublin, Ireland

Transcriptomic data from the OPTIMISTIC clinical trial indicate dysregulated inflammatory and immune pathways in DM1 patients. Here, we determined the associations between serum cytokine and other immune-related protein levels with disease severity and clinical outcomes in the OPTIMISTIC cohort, with replication in an independent cohort of Canadian patients.

In the OPTIMISTIC cohort, serum levels of 92 serum cytokines and other immune-related proteins were quantified using the OLINK® Target 96 Inflammation panel (PCR

ELISA Proximity Extension Assay). Data from 55 participants with matching RNA seq, CTG repeat length, 6-minute walk test distance (6MWT), fatigue and daytime sleepiness score (FDSS), Kurtzke Functional Systems Score (KFSS) and checklist individual strength-fatigue (CIS Fatigue) measures were analyzed at baseline and after 10 months of intervention (cognitive behavioural therapy (CBT), CBT plus graded exercise therapy (CBT+GET) or care as usual (CAU). Associations with clinical and genetic variables were assessed by linear regression, with Benjamini Hochberg correction for multiple testing. For replication, seven cytokines were evaluated with an OLINK® FLEX assay in serum from 57 patients in the Canadian cohort at two time-points along with clinical measurements.

In the OPTIMISTIC cohort, 10 cytokines showed significant ($p<0.05$, FDR<0.2) (associations with disease measures: CD8A, SCF, DNER, and MMP1 with CTG repeat length; IL17C, CCL20, and IL6 with 6MWT; and MMP1, TWEAK, and CX3CL1 with FDSS. No cytokines were associated with CIS Fatigue. In the Canadian cohort, IL6 was the only cytokine significantly linked to functional motor outcomes and KFSS, but did not show significant changes over a period of 4 years.

Across both cohorts, IL6 consistently emerged as a biomarker associated with disease severity and impaired motor performance in DM1. These findings underscore the contribution of immune inflammatory mechanisms to DM1 and support further studies of IL6 as a biomarker for therapeutic response.

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65 - CoreDMScope_ENSA (RevEal the burdeN in daily life in myotonic dyStrophy due to myotoniA): study design compares patient-reported and clinical outcomes

Guillaume Bassez[1], Melinda Gyenge[1], Razak Ellafi[2], Alla Zozulya-Weidenfeller[3], Regis Dufresne[4]

[1]Constitutive Reference Center for Neuromuscular Diseases, Neuro-Myology Department, Institute of Myology, AP-HP Pitié-Salpêtrière, Paris, France, [2]admedicum, Cologne, Germany, [3]Lupin Neurosciences, Zug, Switzerland, [4]Medisol, LUPIN group company, Paris, France

Up to 80% of people living with myotonic dystrophy types 1 (DM1) or 2 (DM2) experience myotonia, yet evidence of its daily physiological and psychological burden is limited. Furthermore, there is debate among DM specialists regarding the relative burden of myotonia compared to other multisystemic symptoms of the disease. The CoreDMScope_ENSA study aims to evaluate myotonia burden in the broader context of DM1.

This study builds on earlier findings from the international ENSA (RevEal the burdeN in daily life in myotonic dyStrophy due to myotoniA) survey. It investigates experiences of living with DM in individuals from France, and utilises data from the French DM-Scope registry. CoreDMScope_ENSA is conducted in collaboration with AFM Téléthon, the French Myopathy Association.

CoreDMScope_ENSA is a non-interventional, observational, anonymous, online, patient-reported, questionnaire survey. Data are collected from individuals with DM1 or DM2 in France. First, new ENSA survey data will be analysed descriptively. Next, ENSA data will be compared with data from the DM-Scope registry, to identify potential correlations between patient-reported daily impact of myotonia and clinical data recorded in DM-Scope.

The study includes participants with a confirmed genetic diagnosis of DM1 or DM2 who are also in the DM-Scope registry, with recorded clinical signs of hand myotonia (DM1) and other types of myotonia (DM2). Individuals who received mexiletine for myotonia treatment in the 18 months preceding the study are excluded. Target study population is N=100, anticipated as N=90 with DM1 and N=10 with DM2. Study recruitment began mid-2025. Study objectives and design are presented at the conference.

CoreDMScope aims to provide a comprehensive understanding of the health status of individuals living with DM. Ultimately it aims to guide improvements in DM management, by enhancing our understanding of the daily challenges faced by affected people.

Submitted by authors on behalf of DM Study Group.

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66 - Understanding the burden of care in myotonic dystrophy: Findings from a caregiver survey in Canada and the United States

Nadine Ann Skinner[1], Mindy Buchanan[1], Tanya Stevenson[1]

[1]Myotonic Dystrophy Foundation

Myotonic Dystrophy (DM) is a progressive multisystemic disease, with physical, cognitive, and behavioral symptoms, including apathy, executive dysfunction, and hypersomnolence, further increasing caregiving demands. Neuromuscular disease caregiving is associated with emotional strain, financial impact, and limited respite, yet caregiver experiences specific to DM remain understudied. The Myotonic Dystrophy Foundation surveyed 238 caregivers in the United States (92%) and Canada (8%) supporting individuals with DM1 (84%) and DM2 (13%). Analyses in

Stata/SE 15 included descriptive statistics, Wilcoxon signed-rank tests, Spearman correlations, and OLS regression on a validated seven-item caregiver burden index (α = 0.82). Findings were subsequently validated and refined through a caregiver focus group. Respondents were predominantly female (74%), white (82%), and over age 50 (83%). Nearly one third (32%) provided major care, and 56% provided moderate care.

Pairwise Wilcoxon tests (Bonferroni α = 0.00238) showed mental/emotional (M = 3.36, SD = 1.15) and physical exhaustion (M = 3.09, SD = 1.11) exceeded financial burden, personal health impacts, future worries, and ability to care for others (all $p < 0.002$), though physical exhaustion did not differ from strength needed for care ($p = 0.067$) or future worries ($p = 0.0012$). The burden domains were strongly interrelated, reflecting cumulative emotional, physical, and practical demands. Regression indicated caregiver burden is significantly predicted by level of care and frequency of breaks, with higher burden for moderate (0.347, $p = 0.024$) and major care (0.567, $p = 0.002$) and for caregivers with rare or no breaks (0.422-0.447, $p \leq 0.01$). Age, number of individuals cared for, and availability of other support were not significant. The model explained 15% of variance in burden ($R^2 = 0.146$, F $p = 0.0028$). Findings highlight the importance of accessible, meaningful respite opportunities and coordinated support strategies that address the multifaceted and cumulative nature of DM caregiver burden.

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67 - What shapes DM1 severity? A modifier gene quest in the SLSJ founder population

Claudia Moreau[1], Jean Mathieu[2], Élise Duchesne[3], Cynthia Gagnon[4], Simon Girard[1]

[1]Université du Québec à Chicoutimi, [2]CIUSSS du Saguenay-Lac-Saint-Jean, [3]Université Laval, [4]Université de Sherbrooke

Myotonic dystrophy type 1 (DM1) is an autosomal dominant disorder characterized by marked interindividual variability in symptom presentation, disease severity, and progression. Although DM1 is caused by the expansion of a CTG repeat in the *DMPK* gene, repeat length alone only partially accounts for the observed variability in age at onset and clinical course. Increasing evidence suggests that genetic modifier genes contribute to the repeat instability and to the multisystemic manifestations of the disease. The Saguenay-Lac-Saint-Jean (SLSJ) region of Quebec has the highest reported prevalence of DM1 worldwide, a consequence of a strong founder effect. This unique demographic context provides access to exceptionally well-characterized patient cohorts. By analyzing genealogical, genotyping, and phenotyping data from 200 DM1 patients and more than 2,500 population-matched

controls, we identified two major haplotype groups flanking the DM1 expansion that are strongly associated with the broad DM1 phenotype. We subsequently searched for founder haplotypes in known modifier genes implicated in other repeat expansion disorders using the newly developed FoundHaplo method. In addition, we conducted haplotype-based association analyses using DASH and GCTA to identify novel modifier genes that may underlie variability in age at onset among DM1 patients with comparable CTG repeat lengths. Identifying genetic modifiers shared among patient subgroups may represent a critical step toward stratified patient care and early preventive interventions for individuals predicted to develop earlier or more severe disease.

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68 - In vitro and in vivo effects of lipid mediators targeting muscle stem cell alterations in myotonic dystrophy type 1 (DM1)

Inès Mokhtari[1], Thomas Molina[1], Pauline Garcia[1], Taeyeon Kim[1], Tati Koike[1], Paul Fabre[1], Élise Duchesne[2], Nicolas Dumont[1]

[1]Université de Montréal, CHU Sainte-Justine, [2]Université Laval

Introduction: Myotonic dystrophy type 1 (DM1) is the most common adult-onset myopathy, affecting approximately 1 in 8,000 individuals worldwide. DM1 is caused by a CTG repeat expansion in the *DMPK* gene leading to progressive skeletal muscle weakness, myotonia, and atrophy. Muscle stem cells (MuSCs), essential for muscle regeneration, are profoundly altered in DM1, exhibiting impaired proliferation and differentiation as well as premature senescence. Single-cell RNA sequencing analyses from our laboratory identified a subpopulation of senescent MuSCs characterized by a strong inflammatory signature consistent with a senescence-associated secretory phenotype (SASP). To date, no curative treatment exists for DM1. **Objectives:** The aim of this study was to evaluate the therapeutic potential of omega-3 derived pro-resolving lipid mediators in reducing inflammation and senescence while restoring myogenic capacity in DM1, both *in vitro* and *in vivo*. **Methods:** MuSCs isolated from DM1 patient biopsies and healthy controls were treated *in vitro* with lipids. Myogenesis was assessed by using immunofluorescence. Inflammatory and senescence related gene expression was evaluated by transcriptomic analyses, while lipidomic and proteomic profiling were performed using mass spectrometry and multiplex assays. *In vivo*, DMSXL mice were treated daily with RvD2 for seven days. Muscle function was assessed *ex vivo*, and histological analyses were performed to evaluate myogenesis, fibrosis, and inflammatory profiles. **Results:** DM1 MuSCs displayed increased secretion of pro-

inflammatory factors and a deficiency in precursors of pro-resolving lipid mediators. Treatment with lipids significantly reduced inflammatory gene expression, with RvD2 showing the strongest effects on MuSC. *In vivo*, RvD2 treatment led to a reduction in inflammatory and fibrotic pathways, decreased collagen deposition, increased muscle fiber size, and significantly improved muscle strength. **Conclusion:** These findings demonstrate that RvD2 effectively rescues MuSC dysfunction and attenuates inflammation and fibrosis in DM1, supporting pro-resolving lipid mediators as a promising therapeutic strategy to improve muscle regeneration and function in DM1.

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69 - Long-read sequencing reveals CCG and TCTG variability within pathogenic expansions in DM1 and DM2

Sonia Lameiras[1], Eirini Maria Lampraki[2], Duncan Kilburn[3], Ismail Jamail[1, 4], Nicolas Servant[4], Sylvain Baulande[1], Sarah Kingan[3], Jeff Zhou[3], Harsharan Dillon[3], Sam Holt[2], Valeriya Gaysinskaya[3], Guilherme De Sena Brandine[2], David Stucki[2], Natalia Pinzón[5], Tanya Stojkovic[6], Guillaume Bassez[6, 7], Denis Furling[7], Geneviève Gourdon[7], Stéphanie Tomé[7]

[1]ICGex Next-Generation Sequencing Platform, Institut Curie, PSL Research University, Paris, France, [2]Pacific Biosciences UK Ltd - London (United Kingdom), [3]Pacific Biosciences, Menlo Park, CA94025, USA, [4]Institut Curie, INSERM U900, Mines Paris Tech, PSL University, [5]Institut de Myologie, plateforme MyoData, Paris, F-75013, France., [6]Centre de Référence des Maladies Neuromusculaires Nord-Est/Île-de-France, Institut de Myologie, GHU Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France, [7]Sorbonne Université, Inserm, Centre de Recherche en Myologie, Institut de Myologie F-75013 Paris, France

Accurate molecular characterization of repeat expansions is critical to understand the clinical heterogeneity of myotonic dystrophy type 1 (DM1) and type 2 (DM2) and to define reliable biomarkers for patient stratification and clinical trials. DM1 is caused by an unstable CTG repeat expansion that can reach up to 4,000 triplets. Repeat dynamics and clinical variability depend on multiple factors, including CTG repeat length, the presence of variant triplets interrupting the CTG expansion, somatic mosaicism, and DNA methylation. However, current diagnostic tools cannot assess all of these parameters simultaneously, particularly in the context of large expansions, limiting precision in clinical management and trial design. DM2 is associated with an unstable CCTG repeat expansion that can reach up to 11,000 units and is embedded within a complex (TG)x(TCTG)y(CCTG)n motif that varies between

individuals. As in DM1, detailed molecular characterization of the DM2 locus remains challenging using conventional approaches.

To overcome these limitations, we applied amplification-free long-read sequencing (PacBio) in DM patients. PacBio enabled accurate sequencing of expansions >1,000 repeats, with detailed assessment of nucleotide composition, somatic mosaicism, and DNA methylation. In DM1, while most expanded alleles consist of pure CTG repeats, we identified CCG-interrupted expansions in several patients. In these cases, the overall CTG expansion length appeared relatively stable, whereas the CCG interruption motifs displayed marked somatic and intergenerational instability, suggesting distinct mutational dynamics within the same expanded allele. In DM2, analysis of several patients revealed pronounced genetic heterogeneity, including variable-length TCTG motifs downstream of the CCTG tract. The impact of this motif on clinical variability remains to be determined.

These findings highlight the power of long-read sequencing to refine molecular diagnosis, improve genotype-phenotype correlations, and provide measurable molecular parameters that could inform patient stratification and endpoints in future clinical trials of DM1 and DM2.

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70 - Respiratory function in individuals with myotonic dystrophy type 1: a scoping review

Elie Fiogbé[1, 2, 3], Alec Bass[4, 5], Élise Duchesne[1, 6, 7, 8], Livia Pinheiro Carvalho[2], Cynthia Gagnon[1, 2, 9]

[1]Groupe de recherche interdîsciplinaire sur les maladies neuromusculaires (GRIMN), Saguenay-Lac-St-Jean Integrated University Health and Social Services Center, Saguenay, Quebec, Canada, [2]School of Rehabilitation, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Sherbrooke, Quebec, Canada, [3]Centre de recherche du Centre hospitalier universitaire de Sherbrooke (CRCHUS), Université de Sherbrooke, Québec, Canada, [4]École de réadaptation, Université de Montréal, Montréal, Canada, [5]Savoirs partagés - Centre de recherche du CIUSSS Nord-de-l'Île-de-Montréal, Montréal, Canada, [6]School of Rehabilitation Sciences, Faculty of Medicine, Université Laval, Quebec City, Quebec, Canada, [7]Center for Interdisciplinary Research in Rehabilitation and Social Integration (Cirris), Capitale-National Integrated University Health and Social Services Center, Quebec City, Quebec, Canada, [8]CHU de Québec-Université Laval Research Center, Quebec City, Quebec, Canada, [9]Centre de recherche et d'innovation du Centre intégré

universitaire du Saguenay-Lac-St-Jean, Clinique des maladies neuromusculaires, Hôpital de Jonquière, Jonquière, Québec, Canada

Background: Respiratory impairment is a major contributor to morbidity and mortality in myotonic dystrophy type 1 (DM1). Despite its clinical importance, respiratory assessment practices in DM1 remain heterogeneous, with variability in both the methods and clinical outcome assessments (COAs) used. A comprehensive synthesis of current assessment practices is needed to inform clinical decision-making and research standardization.

Objective: To map the methods and clinical outcome assessments used to evaluate respiratory function in individuals with DM1.

Methods: A scoping review was conducted in accordance with the Joanna Briggs Institute (JBI) methodology. Five databases were searched for original studies reporting respiratory function assessments in individuals with DM1. All study designs were eligible if they included at least one respiratory-related COA. Extracted data included study design, population characteristics (including age group and DM1 phenotype), and the respiratory COAs employed.

Results: Eighty studies were included. Most were observational (88.8%), using cross-sectional, retrospective, or prospective designs. Only seven studies (8.8%) were interventional, and few employed longitudinal designs. Adult-onset DM1 was the predominant phenotype studied, while pediatric populations were markedly underrepresented. CTG repeat length was infrequently reported. Respiratory assessments primarily focused on static lung volumes (slow vital capacity, forced vital capacity, and forced expiratory volume in one second), respiratory muscle strength (e.g., maximal inspiratory and expiratory pressures) and gas exchange parameters (partial pressures of oxygen and carbon dioxide). Non-volitional assessments, such as sniff nasal inspiratory pressure, were rarely used.

Conclusion: This scoping review highlights a predominance of observational research centered on conventional pulmonary function tests in DM1. The findings underscore the need for standardized, DM1-specific respiratory assessment protocols and for longitudinal, functionally oriented studies that better capture disease progression across phenotypes. Such efforts are essential to optimize timing of interventions and support personalized respiratory care in DM1.

72 - Nanopore sequencing shows positive molecular diagnosis for Facioscapulohumeral Muscular Dystrophy (FSHD) in known Myotonic Dystrophy Type 2 (DM2) patient case.

Beth Osia[1], Hannah Chan[1], Gor Bazoyan[1], Lusine Abgaryan[1], Gor Sarkisyan[1]

[1]GrittGene Therapeutics, USA

Myotonic Dystrophy Type 2 (DM2) is an autosomal dominant multisystem disorder that typically presents with symmetrical musculoskeletal weakness, myotonia, and muscle pain and fatigue. DM2 is caused by CCTG-repeat expansion mutations in intron 1 of the CNBP gene, with expansions ranging from 75 to >11,000 repeat units in patient cases. Facioscapulohumeral Muscular Dystrophy (FSHD) is an unrelated autosomal dominant multisystem disorder affecting the muscles in the face and upper body. Similarly, FSHD is caused by a deletion mutation of repeat units in the DUX4 gene, where non-pathogenic allele lengths are >35 Kilobase pairs.

Typical diagnostic tests for DM2 and FSHD include PCR and southern blot techniques to confirm alleles with expanded or contracted repeats respectively. However, molecular characterization using these methods remains challenging because the structure of mutated repeat alleles can be complex or may exceed sequence length limitations. Nanopore sequencing offers an additional avenue to study repeat instability in disorders like DM2 and FSHD while preserving sequence structure. Here, we performed Long- and Ultra-long read nanopore sequencing on a patient previously diagnosed with DM2 that also exhibits FSHD-like symptoms. We confirmed the presence of a 6.2 kilobase pair expansion in the repeat region of the CNBP gene and a 15 kilobase pair deletion in the repeat region of the DUX4 gene as compared to the patient's normal alleles for each respective gene, representing a positive molecular diagnosis for both DM2 and FSHD. Broadly, these findings highlight the utility of a genome-wide long-read sequencing approach in identifying genomic variations that occur concurrently with DM2.

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73 - Paternal transmission of congenital and severe childhood myotonic dystrophy type 1; a case series

Francisca Smulders[1], Lotte Put[2], Catharina Faber[2], Ilse Karnebeek[1], Sylvia Klinkenberg[2], Thatjana Gardeitchik[3], Karlien Mul[1], Hilde Braakman[4]

[1]Department of Neurology, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center, Nijmegen, The Netherlands, [2]Department of Neurology, Maastricht University Medical Center, Maastricht, The Netherlands;

Mental Health and Neuroscience Research Institute, Maastricht University, Maastricht, The Netherlands., [3]Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands, [4]Department of Pediatric Neurology, Radboud University Medical Center, Amalia Children's Hospital, Nijmegen, The Netherlands

Myotonic dystrophy type 1 (DM1) is characterized by anticipation, whereby subsequent generations show an earlier onset and increasingly severe clinical manifestations. This phenomenon results from progressive expansion of the CTG repeat in the *DMPK* gene, which underlies the disease and contributes to the substantial variability in symptom severity between generations. The most severe phenotypes of DM1 are congenital myotonic dystrophy (CDM1) and childhood myotonic dystrophy (ChDM1).

Over the past decades, the prevailing view has been that CDM1 occurs almost exclusively following maternal inheritance. In recent years, however, there have been more frequent reports of CDM1 after paternal transmission. These observations have been mentioned within larger cohort studies, although this specific issue was not examined in detail. At the DM1 expertise center in the Netherlands, we observed a striking number of CDM1 and severe ChDM1 cases after paternal inheritance. Notably, almost all fathers carried relatively short CTG repeat expansions (< 150 repeats) and exhibited at the time of transmission no or only mild DM1 manifestations. This case series describes several children diagnosed with CDM1 or severe ChDM1 and their fathers.

With this case series, we intend to increase awareness for paternal transmission of CDM1 and severe ChDM1. Further investigation is required to deepen the understanding of the differences between maternal versus paternal inheritance of CDM1 and ChDM1, and to collect more objective data on this topic. Ultimately, this may contribute to improved understanding and the optimization of clinical guidelines, enabling more personalized counselling.

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75 - Patient-derived iPSC models suggest astrocytic involvement in DM1 neuropathology

Lisa Rahm[1], Anton M. Simoes[1], Marieke Willemse[2], Derick G. Wansink[2], Hans van Bokhoven[1]

[1]Department of Human Genetics, Radboudumc, Netherlands, [2]Medical BioSciences, Radboudumc, Netherlands

Myotonic dystrophy type 1 (DM1) arises from a CTG trinucleotide repeat expansion in the 3' untranslated region of the *DMPK* gene, causing a multisystem disorder with profound brain involvement. Patients exhibit executive dysfunction, visuospatial impairments, and memory deficits, yet the underlying molecular pathways and cellular mechanisms remain poorly understood.

To elucidate the molecular and functional phenotypes driving DM1-related cognitive deficits, we generated patient-derived induced pluripotent stem cells (iPSCs) and isogenic controls in which the repeats were excised. These iPSCs were differentiated into neurons (iNeurons) and astrocytes, providing a robust platform for modeling DM1 neuropathology.

We found that iNeurons cultured in the absence of diseased astrocytes showed no or only minor sequestration of MBNL1 and MBNL2 in nuclear RNA foci, a hallmark of DM1 pathology. Consistently, analyses of neuronal branching, and network activity revealed only subtle differences compared to repeat-excised isogenic control neurons. In contrast, patient-derived astrocytes displayed clear nuclear sequestration of MBNL1 and MBNL2, accompanied by altered splicing of a subset of DM1-relevant target genes. Additionally, preliminary data show that antisense oligonucleotides reduce these neuropathological features in DM1 astrocytes.

Taken together, these results suggest a predominant role of glial cells in DM1-related cognitive dysfunction. To test this hypothesis, we are currently co-culturing patient-derived iNeurons and astrocytes with their respective isogenic controls, to gain mechanistic insights into DM1 brain pathology. By dissecting neuron-astrocyte interactions in DM1, this work will clarify whether and how astrocyte dysfunction contributes to neuronal impairment.

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76 - Challenging the Limits: Enhancing Physical Potential in Children with Myotonic Dystrophy Type 1 - A Case Series on the Effect of Training

Lieze Hoogveld[1], Lynn Orriëns[2], Maaike Pelsma[1], Hilde Braakman[2]

[1]Radboud University Medical Center, Amalia Children's Hospital, Department of Rehabilitation, Pediatric Physical Therapy, Nijmegen, the Netherlands, [2]Radboud University Medical Center, Department of Pediatric Neurology, Donders Institute for Brain, Cognition and Behavior, Amalia Children's Hospital, Nijmegen, the Netherlands

Myotonic dystrophy type 1 (DM1) is a progressive neuromuscular disorder with multisystemic involvement. In children, DM1 can significantly impact motor

development, mobility, and overall functioning. While physical training has shown positive effects in adults with DM1, evidence for its impact on children is limited. Early interventions targeting strength, fitness and mobility may help improve daily functioning and potentially slow disease progression.

This case series explores the clinical effects of various training interventions in children with DM1, including intensive physical therapy, personal training, and the use of assistive devices. The study evaluates both self-reported improvements and measured effects through physical therapy assessments, mobility, and functional performance.

This case series includes 6 children (ages 14-17) with congenital and childhood-onset DM1 who underwent physical training in various settings, including a gym, physical therapy practice, personal training sessions, and/or the use of assistive devices. The interventions aimed to improve muscle strength, endurance, core stability, scapular kinesis and/or functional mobility. Clinical measures were assessed annually, with physical therapy tests repeated each year as part of routine clinical care at the Amalia Children's Hospital, Radboudumc, Nijmegen, the Netherlands.

Positive trainings effects emerged in endurance strength, muscle strength, core stability, walking distance (6MWT), and scapular kinesis. These children reported reductions in perceived symptoms and a sense of increased strength. Some also found the training enjoyable, which boosted their motivation.

Despite the progressive nature of DM1, our clinical experience shows that physical training interventions can lead to clinically relevant improvements in strength, conditioning, and mobility in children. The diverse outcomes observed demonstrate that tailored interventions can lead to a wide range of improvements, customized to meet individual needs. This emphasizes the importance of early intervention and the potential of personalized training to enhance muscle function, fitness, and daily functioning in children with DM1.

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77 - Somatic Instability and Repeat Interruptions in Japanese Patients with Myotonic Dystrophy Type 1: A Comparative Analysis Using Multiple Genomic Approaches

Yuzuha Ichimura[1], Mika Yoshida[1], Fuuka Takahashi[1], Konomi Okada[1], Haruka Shioi[1], Haruna Shimamura[1], Monami Toba[1], Tomoya Kubota[1], Tsuyoshi Matsumura[2], Kenichi Yamamoto[3], Masayuki Nakamori[4], Masanori P. Takahashi[1]

[1]Clinical Neurophysiology, The University of Osaka Graduate School of Medicine, [2]Department of Neurology, NHO Osaka Toneyama Medical Center, [3]Child Healthcare

and Genetic Science, The University of Osaka Graduate School of Medicine, [4]Department of Neurology, Yamaguchi University Graduate School of Medicine

Myotonic dystrophy type 1 (DM1) is caused by an abnormal expansion of CTG repeats. The repeat length, however, is not uniform and exhibits somatic instability. In addition, repeat interruptions, defined as the insertion of non-CTG sequences within the repeat tract, have been suggested to influence somatic instability. This study investigated somatic instability and repeat interruptions in Japanese patients with DM1 by comparing multiple analytical methods.

Genomic DNA extracted from lymphocytes was analyzed. Clinical data, including age at onset and Southern blot results, were obtained from medical records. Somatic instability was assessed using small-pool PCR (SP-PCR), and long-read sequencing (LRS) with the Pacific Biosciences PureTarget™ Repeat Expansion Panel was performed in a subset of samples. Repeat interruptions were screened by triplet-primed PCR (TP-PCR), followed by Sanger sequencing and LRS.

Genomic DNA was obtained from 116 Japanese patients with DM1. LRS analysis (12 cases) demonstrated that somatic instability was more pronounced in four samples with modal repeat lengths under 600 repeats, showing a right-shifted distribution, whereas an apparent plateau in repeat expansion was observed in eight samples with modal repeat lengths over 600 repeats, lacking rightward skew. Comparison with SP-PCR revealed minor discrepancies in some samples, particularly in congenital cases. Screening of 116 patients identified CCG interruptions in six samples from four families. Sanger sequencing revealed variability in the number and position of interruptions among clones, which was also confirmed by LRS in three samples from the same family. LRS showed that interruptions were clustered toward the 3’ region, while variability was observed in the central and 5’ regions of the repeat tract. Within-family comparisons showed interruptions at relatively conserved positions.

These findings demonstrate that combined analytical approaches enable detailed characterization of somatic instability and repeat interruptions in Japanese patients with DM1.

78 - Mitochondrial characterisation of myotonic dystrophy type 1 human skeletal muscle

Valeria Di Leo[1, 2], Marie-Pier Roussel[3], Laura Girard-Cote[4, 5, 6], Bethany Hunter[7], George O. T. Merces[8, 9], Conor Lawless[1], Tiago Bernardino-Gomes[1, 2, 10], Elise Duchesne[4, 5, 6, 11], Amy E. Vincent[1, 2, 12]

[1]Mitochondrial Research Group, Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, UK, [2]NIHR Newcastle Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University, Newcastle upon Tyne, England, [3]Department of Fundamental Sciences, Université du Québec à Chicoutimi, Quebec, Canada, [4]School of Rehabilitation Sciences, Faculty of Medicine, Université Laval, Quebec City, Quebec, Canada, [5]CHU de Québec-Université Laval Research Center, Quebec City, Quebec, Canada, [6]Neuromuscular Diseases Interdisciplinary Research Group (GRIMN), Saguenay-Lac-St-Jean Integrated University Health and Social Services Center, Saguenay, Quebec, Canada, [7]Flow Cytometry Core Facility, Newcastle University, UK, [8]Biosciences Institute, Innovation, Methodology and Application (IMA) research Theme, Faculty of Medical Sciences, Newcastle University, UK, [9]Image Analysis Unit, Faculty of Medical Sciences, Newcastle University, UK, [10]NHS Highly Specialised Service for Rare Mitochondrial Disorders, Royal Victoria Infirmary, Newcastle Upon Tyne, UK, [11]Center for Interdisciplinary Research in Rehabilitation and Social Integration (Cirris), Capitale-National Integrated University Health and Social Services Center, Quebec City, Quebec, Canada, [12]John Walton Muscular Dystrophy Research Centre, Clinical and Translational Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle, UK

Background: Myotonic dystrophy type 1 (DM1) is a rare autosomal dominant neuromuscular disorder caused by CTG repeat expansion in the *DMPK* gene. Resistance exercise training is currently the most effective intervention to improve physical function in DM1, enhancing skeletal muscle (SKM) strength and promoting hypertrophy. However, the contribution of mitochondrial dysfunction to DM1 pathology and its modulation by exercise remains poorly understood.

Aims: This study aims to characterise SKM mitochondrial features in DM1 patients before and after a 12-week resistance exercise training programme.

Methods/Materials: SKM biopsies were obtained from the quadriceps of DM1 patients (men, n=11; women, n=9) pre- and post-training and compared with age- and

sex-matched controls. Immunofluorescence was used to assess oxidative phosphorylation (OXPHOS) defects, and mitochondrial function was further examined using MACSima (Miltenyi Biotec), a cutting-edge spatial proteomics technology.

Results: The 12-week resistance training increased mitochondrial mass and partially restored OXPHOS deficiencies in complex I and/or complex IV in DM1 patients. These exercise-induced mitochondrial improvements were independent of CTG repeat length, clinical phenotype, and sex. Spatial single-cell analysis enabled quantification of protein abundance and comparison of mitochondrial signalling pathways in OXPHOS-deficient versus normal fibres before and after resistance exercise training.

Conclusion: Enhanced characterisation of SKM mitochondrial function in DM1 provides new insight into the molecular contributors to disease pathology and may support the identification of novel therapeutic targets for DM1.

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79 - Parental Transmission Patterns and Phenotypic Differences in Congenital and Childhood Myotonic Dystrophy Type 1

Lotte Put[1], Francisca Smulders[2], Isis Joosten[1], Thomas Hoekman[3], Peter 't Hoen[3], Derick Wansink[3], Yavuz Ariyurek[4], Els Vanhoutte[5], Thatjana Gardeitchik[6], Karlien Mul[2], Catharina Faber[1], Sylvia Klinkenberg[1], Hilde Braakman[7]

[1]Department of Neurology, Maastricht University Medical Center, Maastricht, The Netherlands; Mental Health and Neuroscience Research Institute, Maastricht University, Maastricht, The Netherlands, [2]Department of Neurology, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center, Nijmegen, The Netherlands, [3]Department of Medical BioSciences, Radboud University Medical Center, Nijmegen, The Netherlands, [4]Department of Human Genetics, Leiden Genome Technology Center, Leiden University Medical Center, Leiden, The Netherlands, [5]Department of Clinical Genetics, Maastricht University Medical Center, Maastricht, The Netherlands, [6]Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands, [7]Department of Pediatric Neurology, Radboud University Medical Center, Amalia Children's Hospital, Nijmegen, The Netherlands

Congenital and childhood DM1 represent the most severe subtypes of DM1, with early onset and pronounced clinical manifestations. Congenital DM1 (CDM1) is predominantly maternally inherited, although paternal transmission has been documented. In contrast, childhood DM1 (ChDM1) shows no clear parental

transmission bias. The mechanisms underlying this phenomenon remain poorly understood. Growing evidence suggests that epigenetic factors, especially DNA methylation, may play a central role in the etiology of CDM1. Moreover, phenotypic differences potentially associated with maternal versus paternal inheritance have not been systematically evaluated. This study investigates methylation patterns associated with maternal and paternal transmission and explores phenotypic variation across parental inheritance in CDM1 and ChDM1. We will conduct a retrospective analysis of all genetically confirmed patients with these subtypes within the Dutch Expertise Center for DM1 (Maastricht UMC+ and Radboudumc) by extracting clinical data from medical records and analyzing residual DNA material using amplification-free targeted long-read sequencing. Correlations will be examined between parental inheritance, methylation profiles, CTG repeat length, degree of anticipation, and several clinical features including cardiopulmonary, cognitive, and musculoskeletal involvement, as well as fatigue. By integrating genetic and phenotypic data, this study aims to gain important associative insights into the factors driving maternal bias in CDM1 and identify clinically relevant differences between parental inheritance patterns. These insights may improve genetic counseling and optimize personalized care for patients with DM1.

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81 - Causes of Acute Death in Myotonic Dystrophy Type 1: The Importance of Aspiration and Choking—A Single-Center Retrospective Study in Japan

Yuhei Hasuike[1], Tsuyoshi Matsumura[1], Misa Matsui[1], Naoko Kawamura[1], Yuiko Watanabe[1], Tomoko Saito[1], Motohiro Sudo[1], Rika Yamashita[1], Yuki Yonenobu[1], Tomohiro Yata[1], Daisuke Nakatsu[1], Tomomi Furushima[1], Takuyuki Endo[1], Akinori Iyama[1], Makoto Kinoshita[1], Misaki Yamadera[1], Kimiko Inoue[1], Keiko Toyooka[1], Toshio Saito[1], Hideki Mochizuki[1]

[1]NHO Osaka Toneyama Medical Center

Myotonic dystrophy type 1 (DM1) is a multisystem disorder, often leading to sudden death. However, the precipitating factors remain inadequately characterized. Therefore, we retrospectively analyzed “acute death” (defined as death within 24 hours of a documented acute change in clinical status) to clarify its characteristics and precipitants. We assessed causes of death in 134 DM1 patients who received care at our institution and died between 1989 and 2025; 50 cases (26 men, 24 women) met the criteria for acute death. Clinical profiles, including care settings and interventions, were evaluated. Respiratory-related death was the most frequent cause (60%), followed by cardiac death due to heart failure/arrhythmia (16%),

thromboembolism/hemorrhage (6%), accidents (6%), and unknown causes (12%). Among respiratory deaths, 70% were aspiration-related, comprising choking (n=13), reflux aspiration (n=6), and aspiration pneumonia (n=2). Notably, five of the six reflux aspiration cases involved tube-fed patients. Documentation in several hospitalized cases revealed that hypoxemia preceded the transition to a lethal arrhythmia. Additionally, discrepancies in advance care planning (ACP) were also observed between expressed preferences during stable phases and real-time decisions during acute deterioration. We found that respiratory events were major contributors to acute death, consistent with the respiratory-dominant mortality profile in DM1. In particular, reflux aspiration, predominantly in tube-fed patients, often progressed more abruptly than typical aspiration pneumonia, leading to fatal consequences in our study. This pattern may reflect DM1-related gastrointestinal dysfunction including gastroesophageal reflux disease. Moreover**,** aspiration-related events can precipitate lethal arrhythmias through hypoxemia; thus, plans for acute deterioration such as choking should be discussed and shared with community care providers in advance. In conclusion, alongside arrhythmia prevention, respiratory-focused strategies should be integrated into both chronic management and prevention of acute deterioration in DM1.

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84 - Therapeutic Innovation, Clinical Trial Acceleration, and Lifestyle Interventions in Myotonic Dystrophy Type 1: A Systematic Review

Yasmine Ferchichi[1], Angela Natividad I Mateu[2], Arturo Lopez-Castel[3], Ruben Artero Allepuz[4]

[1]Doctoral Candidate, Marie Skłodowska-Curie ENTRY-DM Network, Translational Genomics Group, Universitat de València, Valencia, Spain, [2]Marie Skłodowska-Curie Doctoral Candidate (ENTRY-DM), Translational Genomics Group, Universitat de València, Spain, [3]Arturo López Castel - Assistant Professor, PhD, MBA Facultad de Ciencias Biológicas Human Translational Genomics Group BIOTECMED - Genetics Department Universitat de València, [4]Ruben Artero, Professor, Human Translational Genomics, University of Valencia

Myotonic dystrophy type 1 (DM1) is a multisystemic disorder caused by a CTG repeat expansion in the *DMPK* gene, leading to toxic CUG-expanded RNA, MBNL sequestration, spliceopathy, and progressive dysfunction across muscle, cardiac, gastrointestinal, and central nervous systems. Despite decades of research, no disease-modifying therapy has reached approval, yet recent years have shown

unprecedented acceleration in therapeutic development, including major pharmaceutical investments.

A PRISMA-guided search of PubMed, EMBASE, Scopus, and clinical trial registries was conducted to identify the most advanced therapeutic candidates in preclinical and clinical development and the growing evidence supporting exercise-based interventions, extracting data on mechanisms of action, delivery strategies, biomarkers, safety, and translational readiness.

This compilation effort shows that therapeutic pipeline has expanded dramatically, involving different strategies in type of molecules and biological targets. Repurposed small molecules such as mexiletine, metformin or amlodipine, among others, have progressed to Phase II-III trials targeting myotonia, splicing defects, metabolic dysfunction, and CNS symptoms. Otherwise, biologics such has JUV-161 introduce novel therapeutic strategies in the field, allowing a regenerative approach via the modulation of MAPK/ERK and PI3K/AKT routes. Finally, the use of nucleic acid-based therapies represent the most transformative wave, including siRNA, antisense oligonucleotides, antimiRs, and AAV-delivered RNAi constructs (AOC 1001, DYNE-101, ATX-01,SAR446268), several now in late-stage trials with encouraging biomarker and functional outcomes. Parallel preclinical innovation includes RNA□targeted small molecules, DNA□directed GeneTAC compounds, mismatch□repair modulators, PPR□based RNA binders, and CRISPR/Cas9 or CRISPRi genome□editing strategies.

Beyond pharmacology, structured aerobic and resistance exercise is increasingly recognized as safe and effective for improving muscle function, mitochondrial health, and quality of life. Altogether, these advances highlight a pivotal moment for DM1, with multiple therapeutic candidates nearing potential approval, emerging genetic strategies reshaping long-term prospects, and lifestyle interventions offering immediate functional benefits, providing a consolidated resource to guide clinical practice and future translational efforts.

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85 - Evaluating drug potential of macrolide azithromycin in Myotonic Dystrophy 1 (DM1)

Tushar Ghosh[1], Junting wang[1], Anjani Kumari[1], Pavel Gershkovich[1], Rebecca Trueman[1], J David Brook[1]

[1]University of Nottingham

Background: Myotonic dystrophy type 1 (DM1) is a neuromuscular disease with clinical symptoms of that include myotonia, muscle wasting, cardiac conduction defects, cataracts and insulin resistance. It is the most common adult form of muscular dystrophy affecting 1 in 8000 individuals and as of now there is no cure. DM1 is caused by an expanded CTG repeat at the 3' untranslated region of the dystrophia myotonica protein kinase gene (*DMPK*). The expanded CUG repeat RNAs form secondary structures that sequester regulatory RNA-binding proteins including MBNL1, forming toxic nuclear foci and affecting normal cellular functions.

Objectives: We have investigated a macrolide antibiotic azithromycin for its potential as a drug treatment for DM1 and compared its effect to that of another macrolide erythromycin.

Methods: We employed a cell-based foci assay to analyse foci elimination following drug treatment. We looked for the tissue distribution of the macrolides in HSA^{LR} mice by LC-MS. Using RT-PCR we will be analysing splicing correction in mouse muscle tissue and in DM1 cells. For molecular mechanism of the macrolides, we will carry out RNA sequencing.

Results: Azithromycin (AZM) was found to be more potent than erythromycin (ERM) in our foci assay. Wash out experiments suggested that the AZM was more stable than ERM inside DM1 cells. Tissue distribution studies in the HSA^{LR} mouse found that AZM accumulated more in muscle and heart and least in the brain. Currently we are examining the efficacy of AZM via splicing correction of key genes in DM1 cells and HSA^{LR} mouse muscle tissues. Also, we are doing direct RNA sequencing from the treated HSA^{LR} mice and DM1 cells to understand the molecular mechanism of the drug.

Conclusion: The macrolide azithromycin is more potent than erythromycin in foci assay and more accessible to muscle and heart tissues in mouse.

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91 - The inducible ACTA1-TurboDMXL mouse model exhibits DM1 phenotypes in skeletal and cardiac muscle as well as specific molecular signatures.

Alain SUREAU[1], Arnaud KLEIN[1], Ludovic ARANDEL[1], Corentin ROUXEL[1], Aurélien CORDIER[1], Gilles MOULAY[1], Aline HUGUET[1], Pauline MEGALLI[1], Mégane LEMAITRE[2], Julianne PERRONNET[2], Nathalie MOUGENOT[2], Antoine MUCHIR[1], Geneviève GOURDON[1], Denis FURLING[1]

[1]Sorbonne Université, Inserm, Institut de Myologie, Centre de Recherche en Myologie, Paris (France), [2]Sorbonne Université, UMS28 Phénotypage du petit animal, Paris (France)

The autosomal dominant Myotonic Dystrophy type 1 (DM1) disease, a frequent neuromuscular disease in adult, displays multisystemic disorders including myotonia, muscle weakness and wasting as well as heart defects and cognitive impairments. We developed a new mouse model expressing the *DMPK* gene with large and pure CTG repeats in a tissue-specific and dose-dependent manner. Thanks to the Crispr-Cas9 technology we have replaced the human DMPK promoter with the inducible TRE3G promoter in the well-known DMSXL mouse model carrying 1500 repeats. The resulting mice (TurboDM^{XL}) were crossed with transgenic mice expressing a doxycycline-inducible rtTA activator under the control of the ACTA1 promoter allowing expression of the CTG expansions in striated muscles. We showed that the resulting ACTA1-TurboDM^{XL} mice fed with doxycycline diet express CTG expansions in skeletal muscles and heart in a dose dependent manner and display DM1 features such as RNA foci, splicing defects and centralized nuclei. These mice also display reversible phenotypes among which robust myotonia, muscle strength reduction, fiber type switching towards oxidative fibers and heart conduction defects. Next, RNA-seq transcriptomic analysis were performed to examine global splicing and gene expression changes during time-course expression of CTG repeats and after doxycycline removal, allowing the identification of molecular signatures of the pathology. In parallel, we characterized a natural variant of the TurboDM^{XL} mouse carrying 450 instead of 1500 repeats. While these contracted 450 CTG expansions are expressed at comparable levels, ACTA1-TurboDM^{450} mice show little or no splicing defects and do not display skeletal muscle phenotypes such as myotonia or strength reduction. In conclusion, the ACTA1-TurboDM^{XL} mouse turns out to be a relevant model to study the molecular mechanisms involved in DM1 pathogenesis in muscle and heart and to assess therapeutic candidates.

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92 - Targeting Musashi-2 with antisense oligonucleotides mitigates muscle pathology in myotonic dystrophy type 1

Dulce Peris-Moreno[1], Natalia Riedel[1, 2, 3], Alberto García-Martín[4], Jorge Espinosa[1, 5], Ariadna Bargiela-Schönbrunn[1, 4], Rubén Artero-Allepuz[1, 2, 4], Àngela Natividad-Mateu[2, 4, 6]

[1]CIBERER ISCIII, Madrid, Spain, [2]Human Translational Genomics Group, Department of Genetics, University of Valencia, [3]INCLIVA Biomedical Research Institute, Valencia, Spain., [4]INCLIVA Biomedical Research Institute, Valencia, Spain, [5]Experimental and Applied Biomedicine Research Group, Health Sciences Faculty,

Universidad Particular Internacional SEK, Quito, Ecuador, [6]Institute for Biotechnology and Biomedicine (BIOTECMED)

We recently identified the RNA-binding protein Musashi-2 (MSI2) as a key contributor to myotonic dystrophy type 1 (DM1) pathology. MSI2 is overexpressed in DM1, represses miR-7 biogenesis, disrupts autophagy regulation, and exacerbates muscle loss, suggesting that MSI2 inhibition may complement approaches targeting toxic CUG-expanded RNA. Here, we evaluated MSI2 as a therapeutic target using antisense oligonucleotides (ASOs) to knockdown its expression in vitro and in vivo. We designed 127 ASOs targeting MSI2 mRNA in silico and selected 27 non-overlapping candidates based on bioinformatic criteria for in vitro screening in human DM1 myotubes (hDM1-myo). Candidate ASOs were identified based on efficient MSI2 silencing, improved myogenic fusion, and transcriptomic changes. In hDM1-myo, MSI2 knockdown produced marked phenotypic rescue, including a >75% increase in myogenic fusion and restoration of gene programs related to muscle function and cytoskeletal integrity. Selected ASOs were subsequently administered subcutaneously to HSALR mice to assess tissue-level MSI2 silencing, with protein levels quantified by Jess Simple Western and ASO exposure by ELISA. While a single systemic dose significantly reduced MSI2 expression in liver, skeletalmuscle knockdown was limited. Optimization of ASO chemistry and dosing substantially improved MSI2 silencing in skeletal muscle and other tissues without evidence of renal or hepatic toxicity. In a durability study, one optimized ASO achieved sustained MSI2 knockdown in liver and skeletal muscle for at least 45 days post-treatment. Together, these findings highlight the therapeutic potential of MSI2-directed ASOs for DM1, demonstrating that optimized delivery and dosing can achieve durable target engagement in vivo without overt toxicity.

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93 - Characterization of the Myotonic Dystrophy type 2 miRNome

Àngela Natividad-Mateu[1, 2], Javier Poyatos-García[2, 3, 4], Juan Vilchez[1, 4], Luis Orduña-Rubio[2], Rubén Artero-Allepuz[1, 2, 3], Ariadna Bargiela-Schönbrunn[2, 3], Arturo Lopez-Castel[1, 2, 3]

[1]Human Translational Genomics Group, University Institute of Biotechnology and Biomedicine (BIOTECMED), University of Valencia, Burjassot, Spain, [2]INCLIVA Biomedical Research Institute, Valencia, Spain, [3]CIBERER ISCIII, Madrid, Spain, [4]Neuromuscular and Ataxias Research Group, Health Research Institute Hospital, La Fe (IIS La Fe), Valencia, Spain.

Despite significant advances in elucidating myotonic dystrophy type 1 (DM1) pathogenesis, type 2 (DM2) remains relatively unexplored compared to DM1, highlighting unmet needs in understanding its molecular basis and developing effective therapies. DM1 is caused by a CTG repeat expansion in the DMPK gene, whereas DM2 results from a CCTG repeat expansion in the CNBP gene. In both conditions, these repeat expansions lead to toxic RNA transcripts that accumulate as nuclear foci and sequester RNA-binding proteins of the Muscleblind-like (MBNL) family, key splicing regulators, causing widespread splicing defects. However, MBNL sequestration in DM2 is less pronounced and shows a weaker correlation with clinical severity than in DM1, suggesting that additional mechanisms contribute to the disease.

In DM1, beyond MBNL sequestration, dysregulation of multiple microRNAs contributes to disease mechanisms, with miR-23b and miR-218 upregulated and acting as endogenous repressors that further exacerbate MBNL depletion. AntimiRs targeting these microRNAs have been shown to restore functional MBNL levels, correct splicing defects, and reduce nuclear RNA foci in preclinical models. Based on these observations and previous evidence of microRNA dysregulation in DM2 detected by microarrays, we hypothesized that microRNAs may play a key role in DM2 pathogenesis. To test this, we performed Small RNA-seq on six muscle biopsies from DM2 patients and controls, followed by bioinformatic and gene ontology analyses to identify dysregulated microRNAs with potential functional relevance. Simultaneously, mRNA-seq on these same samples enabled global transcriptome profiling, capturing both gene expression changes and mis-splicing events, with the latter recognized as prognostic biomarkers of muscle strength and function in DM1. Integrating these datasets provides a framework to link microRNA dysregulation with splicing defects and transcriptome alterations in DM2, offering insight into disease mechanisms, their potential relationship with clinical severity, and highlighting novel molecular targets for therapeutic intervention.

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94 - Quantitative muscle ultrasound as an assessment and phenotyping tool for oro-pharyngeal dysphagia in myotonic dystrophy type 1

Jodi Allen[1], Tom Parry[2], Nens van Alfen[3], Simone Knuijt[4], Chris Turner[5], Christina Smith[6], Roganie Govender[7], Sue Mallett[2], Stuart Taylor[2]

[1]The National Hospital for Neurology and Neurosurgery, University College London NHS Foundation Trust, UK, [2]University College London Centre for Medical Imaging, UK, [3]Radboud University Medical Centre Department of Neurology and Clinical

Neurophysiology, Netherlands, [4]Radboud University Medical Centre Deparment of Rehabilitation, Netherlands, [5]The National Hospital for Neurology and Neurosurgery, University College London NHS Foundation Trust, London, UK, [6]University College London Division of Psychology and Language Sciences, [7]University College London Division of Psychology & Language Sciences, UK

Current dysphagia phenotyping focuses on biomechanical function while neglecting pathophysiology. This limits treatment selection in conditions like myotonic dystrophy type 1 (DM1), where dysphagia may result from central nervous system impairment, muscle abnormalities, or both. We integrated biomechanical and muscle pathophysiology assessments to characterise DM1 dysphagia phenotypes.

Ninety-four adults with DM1 and 63 healthy controls were recruited from across the UK (July 2023 to August 2024). Participants underwent videofluoroscopic swallowing study using the Modified Barium Swallow Impairment Profile (MBSImP) and quantitative muscle ultrasound (QMUS) of five swallowing-related muscles (geniohyoid, anterior digastric, masseter, temporalis, tongue). Participants were stratified by MBSImP oral and pharyngeal sum score tertiles. QMUS echogenicity and thickness were converted to sex-, age-, and BMI-adjusted z-scores and compared between tertiles. Sample size was calculated based on changes to geniohyoid muscle thickness and echogenicity.

Median age was 45 years (IQR 38, 52) for DM1 participants and 43 years (30, 56) for controls; 52 DM1 participants and 32 controls were female. Muscle thickness and echogenicity varied by dysphagia type and severity. For pharyngeal dysphagia, median geniohyoid echogenicity z-scores decreased across MBSImP tertiles: 2.60 (IQR 2.25, 2.79; n=22), 2.34 (1.48, 3.05; n=38), and 1.73 (1.43, 2.31; n=30), while thickness was reduced in tertiles 1-2 (medians -1.09 and -1.06) but less affected in tertile 3 (-0.40). All oral dysphagia tertiles showed elevated echogenicity (2.18-2.30) and reduced thickness (-1.01 to -1.07). Results for remaining muscles, including the tongue (z-scores near zero), QMUS reliability, and measurement agreement will be presented. For geniohyoid echogenicity, ICC ranged from 0.73-0.99 in controls and 0.80-0.97 in pwDM1, with 95% LoA of ±23 and ±34 grayscale units (scale 0-255) respectively.

QMUS indicators of altered muscle thickness and echogenicity were associated with biomechanical dysphagia in DM1, but the relationship was inconsistent, potentially indicating multifactorial dysphagia mechanisms beyond muscle abnormality alone.

95 - A cross-sectional study exploring the alignment between patient-reported and biomechanical dysphagia outcomes in myotonic dystrophy type1 (DM1)

Jodi Allen[1], Tom Parry[2], Caroline Waszkiewicz[1], Chris Turner[1], Christina Smith[3], Roganie Govender[4], Sue Mallett[2], Stuart Taylor[2]

[1]The National Hospital for Neurology and Neurosurgery, University College NHS Foundations Trust, UK, [2]University College London Centre for Medical Imaging, UK, [3]University College London Division of Psychology & Language Sciences, UK, [4]University College London Division of Surgery & Interventional Science

Studies in myotonic dystrophy type 1 (DM1) consistently demonstrate poor association between patient-reported dysphagia symptoms and instrumental assessment findings. This disconnect, potentially reflecting disease-related anosognosia or reduced symptom awareness, complicates clinical assessment and may lead to underdiagnosis of dysphagia. We investigated relationships between biomechanical dysphagia severity and patient-reported symptoms.

Ninety-four adults with DM1 were recruited from across the UK to a tertiary neuromuscular centre (July 2023 to August 2024). During the same visit, participants completed the Sydney Swallowing Questionnaire (SSQ), and Swallowing Quality of Life Questionnaire (SWAL-QOL), followed by a videofluoroscopic swallowing study using the Modified Barium Swallow Impairment Profile (MBSImP). Participants were stratified into three dysphagia severity groups based on MBSImP oral and pharyngeal sum score tertiles for comparison of symptom scores. Descriptive and graphical analysis was used.

Median age was 45 years (IQR 38, 52); 52 were female. MBSImP oral scores ranged from 3 to 17 (max 22) and pharyngeal scores from 1 to 23 (max 29), with higher scores indicating greater impairment. SSQ scores ranged from 20 to 1096 (max 1700), with higher scores indicating greater symptom burden; scores increased across oral dysphagia tertiles: median 136 (IQR 70, 350; n=27), 224 (84, 426; n=20), and 264 (106, 578; n=45), and pharyngeal dysphagia tertiles: median 152 (57, 270; n=22), 194 (78, 398; n=39), and 350 (183, 663; n=31). SWAL-QOL swallowing symptom scores (range 0-100, with higher scores indicating fewer symptoms) decreased across oral tertiles: median 68 (43, 81), 57 (41, 82), and 46 (34, 66), and pharyngeal tertiles: 68 (46, 86), 65 (38, 86), and 43 (30, 59). Individual questionnaire items will be presented, highlighting those with poor sensitivity for detecting differences in dysphagia severity.

These findings suggest that limitations in measurement sensitivity, rather than anosognosia, may explain previously observed disconnect between patient-reported and instrumental measures.

96 - Congenital and Childhood Myotonic Dystrophy Health Index

Kiera Berggren[1], Michelle Bernard[1], Chad Heatwole[2], Nicholas Johnson[1]

[1]VCU, [2]URMC

The Congenital and Childhood Myotonic Dystrophy Health Index (CCMDHI) is a disease-specific outcome measure designed to quantify symptom burden in individuals with congenital or childhood onset myotonic dystrophy type 1 (CDM or ChDM, respectively). The CCMDHI has parent- and self-report versions with questions covering 21 symptomatic themes and subscales regarding disease-specific symptoms for the pediatric forms of this disease rated on a 6-point Likert scale from “does not experience” to “affects life severely.” This measure is intended for clinical trial use and has been refined for use in children from the previously validated Myotonic Dystrophy Health Index.

To evaluate test-retest reliability of the CCMDHI parent-proxy instrument in CDM. To describe longitudinal data in a natural history cohort.

Children 0-13 years of age with genetically-confirmed CDM were enrolled in a longitudinal natural history study at the University of Utah with annual visits. As part of this larger study, the CCMDHI was administered at each visit with an additional data collection point ~1 week after baseline visit for test-retest reliability.

Forty-five children (0.2-13.2 years, average age 6.1±3.4 years, 22 female (49%)) were enrolled at baseline. CTG repeat length was 405-2530 (average 1271±416). Test-retest reliability was excellent (n=30; 6.3±2.9 years; ICC 0.939). A one-way repeated measures ANOVA analysis was not statistically significant from baseline to 24 months (n=25; 5.8±3.2 years; $F(2,48)=.104$, $p=.902$) or to 36 months (n=17; 6.3±2.9 years; $F(3,48)=.796$, $p=.502$).

The CCMDHI is a useful tool to quantify disease burden in individuals with CDM with excellent test-retest reliability. Symptoms of CDM may remain relatively stable in younger pediatric individuals. The CCMDHI instrument is a useful and reliable tool in clinical practice and future clinical trials.

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97 - Concept Analysis of Fatigue, Apathy and Sleepiness in Myotonic Dystrophy Type 1

Julie Fortin[1], Benjamin Gallais[2], Luc Laberge[3], Cynthia Gagnon[1]

[1]Groupe de Recherche Interdisciplinaire sur les Maladies Neuromusculaires (GRIMN), [2]Université du Québec à Chicoutimi (UQAC), [3]ÉCOBES-Recherche et Transfert, Cégep de Jonquière

Background: Fatigue, excessive daytime sleepiness, and apathy are highly prevalent and disabling symptoms in myotonic dystrophy type 1 (DM1). However, these constructs are variably defined and assessed across disciplines, and no disease-specific tools currently exist for DM1.

Objective: By integrating evidence from the literature with the perspectives of individuals with DM1, their relatives, and clinical experts, this study aims to examine how these symptoms are currently evaluated in DM1 and to identify key considerations to guide future assessment approaches in clinical care, research, and clinical trials.

Method: First, a literature review was conducted to examine how the concepts of fatigue, apathy, and sleepiness are currently defined and operationalized in DM1. Subsequently, in-depth interviews were conducted with 10 individuals with DM1 and 6 relatives to explore the manifestations, impacts, and coping strategies associated with these symptoms. Finally, a focus group involving 10 DM1 experts was held to further describe the expression and clinical interpretation of these symptoms. All qualitative data were analyzed using a combination of inductive and deductive approaches, and findings were integrated across data sources.

Results: Core results highlight several key challenges in the assessment of fatigue, sleepiness, and apathy in DM1. Distinguishing fatigue from apathy, particularly from a motivational perspective, remains difficult. In addition, patients often do not clearly distinguish between sleepiness and fatigue. Adaptive strategies must be systematically explored across all constructs, as tasks are often performed with compensatory modifications rather than without difficulty. Finally, reduced self-awareness represents a major barrier to patient-reported assessments, complicating the accurate characterization of these symptoms.

Discussion/Conclusion: Accurate characterization of fatigue, apathy, and sleepiness in DM1 is essential for valid measurement. The present findings challenge existing assessment scales and support the development of more adapted tools, with potential implications for both trial readiness and clinical care.

98 - DT-818: a clinical stage GeneTAC® molecule for the treatment of Myotonic Dystrophy Type 1

Sumon Datta[1], Raechel Peralta[1], Jon DiMaina[1], Peter Sheperd[1], Greg Miller[1], Darragh Buckley[1], Ryan Jordan[1], Anna De Somma[1], Tadimeti Rao[1], Chengzhi Zhang[1], Doane Chilcoat[1]

[1]Design Therapeutics

GeneTAC® molecules are novel small molecule drug candidates designed to target an individual gene to modulate transcription. DM1 is an autosomal dominant monogenic, progressive multisystem disease caused by CTG nucleotide repeat expansion in the 3' UTR of the DMPK gene. The mutant DMPK gene transcript containing the expanded repeat sequesters MBNL proteins, key regulators of RNA splicing, in toxic foci. This leads to global RNA splicing dysregulation and systemic manifestation of disease. DT-818 is a DM1 GeneTAC® molecule designed to selectively target expanded CTG repeats and reduce transcription of the mutant DMPK allele. In DM1 patient myotube cell models with repeat lengths ranging from 330-2600 CTG, DT-818 potently reduced the number of toxic foci, achieving >90% of foci elimination in cells treated for 7 days with an IC50 of ~8nM. Foci reduction was accompanied by a similar correction of spliceopathy (>90%) in cell models with similar potency. Importantly, DMPK protein abundance was not altered in DT-818 treated cells despite the reduction in mutant DMPK RNA foci, indicating selective targeting of the mutant DMPK allele. In nonclinical studies, DT-818 has shown favorable pharmacokinetic and tolerability profiles in rodents and non-human primates. Regulatory clearance has been obtained for clinical evaluation of DT-818.

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99 - A Structured Neuropsychological Assessment Protocol for Pediatric Myotonic Dystrophy Type 1: Preliminary Findings from the DM1-Hub Project

Irati Larrañaga[1, 2], Joana Garmendia[1, 2], Garazi Labayru[1, 2, 3], Daniel Natera[4], Stephanie Lotz[4], Andrés de Nascimento[4], Carlos Ortez[4], Clara Moliner[5], Mar Corral[5], Alvaro Larran[5], Alba Herrero[5], Sebastián Figueroa[6], Anna Revert[6], Virginia Arechavala[7], Gisela Nogales-Gadea[5], Arturo López[8], Andone Sistiaga[1, 2, 3]

[1]Deparment of Clinical and Health Psychology and Research Methodology; Faculty of Psychology, University of the Basque Country (EHU), Donostia - San Sebastian, Gipuzkoa, Spain, [2]Centro de investigación Biomédica en Red Sobre Enfermedades Neurodegenerativas (CIBERNED), Institute Carlos III, Madrid, Spain, [3]Área de Neurociencias; Biogipuzkoa Instituto de Investigación Sanitaria, Donostia - San

Sebastian, Gipuzkoa, Spain, [4]Neuromuscular Disorder Unit, Neurology deparment, Hospital Sant joan de Deu, Esplugues de Llobregat, Spain, [5]Badalona Neuromuscular Research Group (GRENBA), Institut d´Investigació en Ciències de la Salut Germans Trias i Pujol (IGTP), Campus Can Ruti, universitat Autònoma de Barcelona, Spain, [6]Neuromuscular Pathology Unit, Neurology Service, Hospital Universitari Germans Trias i Pujol, Spain, [7]Nucleic Acid Therapeutics for Rare Disrders (NAT-RD), Biobizkaia Health Research Institute, Barakaldo, Spain, [8]INCLIVA Biomedical Research Institue, Valencia, Spain

INTRODUCTION: CNS involvement often exceeds muscular impairment in pediatric DM1, and may represent an early, prominent clinical feature. The ongoing *DM1-Hub* project aims to characterize DM1 in Spain, with neuropsychological functioning being a key component. In this context, a neuropsychological assessment protocol has been designed for pediatric DM1 population.

OBJECTIVES: To describe a structured neuropsychological assessment protocol for pediatric DM1 population, and to present preliminary results from its implementation.

METHODS: The pediatric protocol assessed cognitive, emotional, and behavioral functioning. Cognitive evaluation included selected subtests from WISC-V and NEPSY-II, covering estimated IQ, memory and learning, attention and executive functions, social perception, visuoconstructive abilities, and language. Multi-informant tools were used, with parents completing three questionnaires: A-TAC as a screening tool for autism spectrum disorder (ASD); SENA to evaluate behavioral and emotional problems; and ABAS-II to assess adaptive functioning in daily life.

RESULTS: Cognitive assessment lasted a mean of 55.2 minutes (SD = 19.4). Preliminary results among the first 11 participants (mean age = 10.92 years, SD = 3.75) showed a mean estimated IQ below average (64.18, SD = 20.45), with 3 participants meeting the criteria for severe intellectual disability. The most affected domain was visuoconstructive ability, followed by language and attention/executive functions. Parents of 9 participants completed the questionnaires. 2 out of 9 screened positive for ASD. No global behavioural problems were observed on the SENA, though difficulties were identified in the Personal Resources Index. ABAS-II results indicated generalized adaptive functioning impairments, predominantly at the conceptual level.

CONCLUSION: Preliminary findings reveal low estimated IQ scores, domain-specific cognitive impairment, and generalized adaptive difficulties, consistent with expectations in pediatric DM1. These results support the clinical utility of this structured neuropsychological assessment in this population.

101 - Preliminary data from the first-in-human ArthemiRTM study of a novel antimiR drug, ATX-01, for the treatment of DM1

Guillaume Bassez[1], Judith Walker[2], Nicola McIntyre[2], Barbara Collins[2], Estefania Lucendo[2], Georgina Butler[2], Isabella Castano[2], Lucia Solaz[2], Lilian Chow[2], Estefania Cerro[2], Beatriz Llamusi[2], Julia Presanis[2], Nicholas Johnson[3], Valeria Sansone[4], The ArthemiR Trial Investigator Group[2]

[1]Institut de Myologie, [2]Arthex Biotech, [3]Virginia Commonwealth University, [4]Centro Clinico Nemo

ATX-01 is a novel anti-microRNA in clinical development for the treatment of Myotonic Dystrophy (DM). ATX-01 has a dual mechanism of action as a result of the inhibition of miR-23b, a key player in DM1 pathophysiology. In preclinical experiments, ATX-01 increases translation of the important RNA binding protein MBNL and decreases levels of toxic DMPK RNA foci, leading to an improvement in mis-splicing events characteristic of DM1. In animal models of DM1, this has led to functional improvement in muscle grip strength and to decreased myotonia. Preclinical pharmacology demonstrated broad tissue distribution, including to skeletal and cardiac muscle, and to the central nervous system, supporting the potential for ATX-01 to address the multisystemic manifestations of DM1. ArthemiR is a first-in-human randomized, double-blind, placebo-controlled clinical study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary clinical efficacy of ascending single and multiple doses of ATX-01 in adult participants with DM1. The study is an integrated single-ascending dose (Part 1) and multiple-ascending dose (Part 2) trial in participants with DM1 aged 18 to 64 years old. Key inclusion criteria include a CTG repeat count of >150 in the DMPK gene, the presence of grip myotonia (as determined by video hand opening time) of >3 seconds, and the ability to walk. Key exclusion criteria include congenital DM1, MRC Muscle Scale score of ≤3 on ankle dorsiflexion, moderate-advanced cardiac disease, contraindication to a muscle biopsy, and use of anti-myotonia medication. The ArthemiR study is ongoing at 12 sites across Canada, France, Italy, the Netherlands, Spain, the UK, and the US. Preliminary data from the first 2 cohorts of the single-ascending dose part (Part 1) of the study will be presented.

102 - A Global Phase 3 Trial Assessing the Efficacy and Safety of Z-basivarsen in Myotonic Dystrophy Type 1

Sowmya Chary[1], Soma Ray[1], Shuli Yu[1], Shauna Andersson[1], Douglas Kerr[1]

[1]Dyne Therapeutics, Inc., Waltham, MA, USA

Zeleciment basivarsen (z-basivarsen, also known as DYNE-101) is an investigational therapeutic that consists of a TfR1-binding Fab conjugated to an ASO designed to target mutant nuclear *DMPK* RNA in both muscle and CNS with the goal of correcting the underlying spliceopathy in those living with DM1.

The z-basivarsen clinical development plan includes ACHIEVE (NCT05481879), a global, Phase 1/2, randomized, placebo-controlled study consisting of a multiple ascending dose (MAD) period to identify the optimal dose regimen and a registrational expansion cohort (REC) to evaluate the selected dose. Based on a favorable benefit-risk profile observed in the MAD portion of ACHIEVE, the selected dose regimen of 6.8 mg/kg Q8W is currently being evaluated in the REC, with the primary endpoint being change from baseline in middle finger myotonia as measured by video hand opening time (vHOT) at 6 months compared with placebo. Myotonia is a hallmark feature of DM1 and was previously demonstrated to be rapidly responsive to splicing correction in animal models of disease (Wheeler et al., 2012; Tanner et al., 2021). Therefore, improvement in myotonia as demonstrated by vHOT supports its utility as an important clinical tool that is predicted to serve as an early indicator of functional improvement. Data from ACHIEVE, including vHOT and additional functional measures, will potentially serve to deliver a therapeutic option for individuals living with DM1. To further assess the multi-system impact of z-basivarsen, a global, randomized, double-blind, placebo-controlled Phase 3 study will be conducted. It will be powered to evaluate broader functional performance, including a clinically meaningful primary endpoint that captures abilities of high relevance to individuals living with DM1. The Phase 3 study will also include a broad set of secondary and exploratory assessments to measure impact across multiple systems. Details of the Phase 3 study design will be shared.

103 - Investigating the impact of light therapy on cognitive outcomes and central nervous system dysfunction in myotonic dystrophy type 1

Julie Fortin[1], Mercedes Aubin[2], Alexandre Maltais[2], Isabelle Lessard[2], Olivier Turcotte[2], Alexandre Girard[2], Marc Hébert[1], Cynthia Gagnon[3], Luc Laberge[2]

[1]CERVO, Université Laval, [2]ÉCOBES-Recherche et transfert, Cégep de Jonquière, [3]Groupe de Recherche Interdisciplinaire sur les Maladies Neuromusculaires (GRIMN)

Background. Myotonic dystrophy type 1 (DM1) is a progressive neuromuscular disorder frequently associated with circadian sleep-wake rhythm dysregulation. This disruption may exacerbate debilitating symptoms, including apathy, fatigue, excessive daytime sleepiness (EDS), sleep problems, and cognitive dysfunction. Light therapy, a known regulator of circadian rhythms, shows promises in alleviating these burdensome clinical features.

Objective. To assess the effect of light-based interventions on apathy, fatigue, EDS, sleep problems, and cognitive performance in patients with DM1.

Methods. Nineteen patients underwent a personalized three-week light therapy intervention (dawn simulator with or without bright light therapy). Pre- and post-intervention assessments included actigraphy as well as cognitive measures (Ruff 2 & 7, Stroop, Trail Making, and Digit Symbol tests), and questionnaires for fatigue (Fatigue Severity Scale), excessive daytime sleepiness (Epworth Sleepiness Scale), and apathy (Lille Apathy Rating Scale).

Results. Data analysis is underway; preliminary findings will be presented at the conference.

Discussion/Conclusion. This project introduces a novel approach to addressing the pervasive and impactful non-muscular symptoms of DM1. While individual responses to light therapy vary, the intervention can be life-changing for many patients. As a cost-effective, non-invasive, and home-based treatment, light therapy holds significant potential for broad clinical implementation.

104 - Understanding central nervous system impairments' impact on daily life in myotonic dystrophy type 1: an exploratory sequential mixed design study

Samar Muslemani[1, 2], Nathalie Bier[3], Marc Tremblay[2], Kathy Bouchard[2], Cynthia Gagnon[1, 2]

[1]Université de Sherbrooke, [2]Groupe de recherche interdisciplinaire sur les maladies neuromusculaires (GRIMN), [3]Université de Montréal

Background: Myotonic dystrophy type 1 (DM1) involves multisystemic impairments that can significantly restrict daily functioning, particularly the performance of instrumental activities of daily living (IADLs)—complex tasks essential for independent living, such as meal preparation and financial management. While previous research has focused on physical manifestations of the disease, the contribution of central nervous system (CNS) involvement on IADL performance remains largely underexplored. CNS impairments in DM1 include cognitive dysfunction (e.g., executive and memory deficits) as well as symptoms such as hypersomnolence and central fatigue. Existing studies are mostly descriptive and do not examine how these deficits affect daily functioning. Moreover, none have incorporated the perspectives of individuals with DM1, their families, or healthcare professionals. This gap limits both clinical assessment approaches and the development of targeted interventions for this population.

Objective: To characterize and explore the impact of CNS impairments on IADL performance in individuals with DM1.

Methods: An exploratory sequential mixed-methods design (QUAL → quan) was employed. The qualitative phase used a case study approach and focus groups with healthcare professionals to examine the phenomenon in real-life contexts. The qualitative results guided the quantitative phase that allowed to describe the phenomenon in a larger sample of participants.

Results: Six patients with DM1 participated in the multiple case study, each accompanied by a relative. Thirty patients participated in the quantitative phase (15 juvenile phenotype and 15 classic phenotype). Preliminary analyses suggest that executive dysfunction—particularly difficulties with task initiation and planning—plays a major role in IADL challenges. Full results are anticipated by March 2026.

Discussion/Conclusion: This project uses an innovative methodology which will allow a deep, rigorous, and structured in-depth understanding of the impact of CNS impairments on IADL performance, with the perspective of patients, relatives, and HCPs.

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105 - Strength training improves mitochondrial respiration and skeletal muscle integrity while reducing H2O2 emission in women with myotonic dystrophy type 1

Vincent Marcangeli[1, 2, 3], Laura Girard-Côté[4, 5, 6], Valeria Di Leo[7, 8], Marie-Pier Roussel[6, 9], Conor Lawless[7, 8], Olivier Charest[6], Anteneh Argaw[5], Maude Dulac[10], Guy Hajj-

Boutros[10], José A. Morais[10], Amy Vincent[7, 8, 11], Gilles Gouspillou[1, 2], Jean-Philippe Leduc-Gaudet[12], Elise Duchesne[4, 5, 6, 13]

[1]Department of Physical Activity Sciences, Université du Québec à Montréal, Montreal, Quebec, Canada., [2]Research Group for Adapted Physical Activity, Université du Québec à Montréal, Montréal, Quebec, Canada., [3]Department of Biological Sciences, Université du Québec à Montréal, Montreal, Quebec, Canada., [4]School of Rehabilitation Sciences, Faculty of Medicine, Université Laval, Quebec City, Quebec, Canada, [5]CHU de Québec-Université Laval Research Center, Quebec City, Quebec, Canada., [6]Groupe de recherche interdisciplinaire sur les maladies neuromusculaires (GRIMN), Saguenay-Lac-St-Jean Integrated University Health and Social Services Center, Saguenay, Quebec, Canada., [7]Mitochondrial Research Group, Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK., [8]NIHR Newcastle Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University, Newcastle upon Tyne, UK., [9]Department of Fundamental Sciences, Université du Québec à Chicoutimi, Chicoutimi, Québec, Canada., [10]Research Institute of the McGill University Health Center, Montreal, Québec, Canada., [11]John Walton Muscular Dystrophy Research Centre, Clinical and Translational Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle, UK., [12]Research Group in Cellular Signaling, Department of Medical Biology, Université du Québec À Trois-Rivières, Trois-Rivières, Quebec, Canada., [13]Center for Interdisciplinary Research in Rehabilitation and Social Integration (Cirris), Capitale-National Integrated University Health and Social Services Center, Quebec City, Quebec, Canada.

Background: Clinically, myotonic dystrophy type 1 (DM1) is characterized by progressive muscle weakness and atrophy, resulting in reduced physical capacity and quality of life. Recent evidence implicates mitochondrial dysfunction in DM1 pathophysiology. While aerobic exercise has been shown to improve skeletal muscle and mitochondrial health in individuals with DM1, the benefits of strength training remain unexplored.

Objective: We investigated the effects of a 12-week strength training program on mitochondrial respiration, reactive oxygen species (ROS) production and muscle integrity in women with DM1.

Methods: Vastus lateralis muscle biopsies were obtained from participants with DM1 before and after the training intervention, and once from unaffected, untrained individuals. Mitochondrial respiration and hydrogen peroxide (H_2O_2) emission, as an index of of reactive oxygen species (ROS) production, were measured in

permeabilized myofibers. Oxydative phosphorylation (OXPHOS) protein contents were quantified using immunoblotting and immunofluorescence. Histological analyses were performed to assess markers of myofiber denervation (NCAM+) and muscle integrity, including centrally located myonuclei, distrupted laminin, and nuclear clumps.

Results: At baseline, DM1 participants displayed reduced mitochondrial respiration compared to unaffected individuals. Strength training significantly increased mitochondrial respiration and mitochondrial content in the DM1 group. Baseline absolute ROS production was lower in DM1, whereas ROS production normalized to oxygen consumption (i.e. mitochondrial free radical leak) was elevated. Histological analyses revealed evidence of myofiber denervation and compromised muscle integrity. Strength training partially normalized mitochondrial free radical leak and improved selected markers of myofiber integrity.

Discussion/Conclusion: Taken together, our results demonstrate that strength training promotes mitochondrial health and improves myofiber integrity in women with DM1.

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106 - MBNL loss-of-function drives CELF1 and HNRNPA1 upregulation in mouse models of Myotonic Dystrophy Type 1 (DM1)

Ashwini Prasad[1, 2], Larissa Nitschke[1], Brandon Nguyen[1], Rong-Chi Hu[1], Thomas A. Cooper[1, 2]

[1]Baylor College of Medicine, Department of Pathology and Immunology, [2]Baylor College of Medicine, Genetics and Genomics Graduate Program

Myotonic dystrophy type 1 (DM1) is caused by expanded CTG repeats in the 3' untranslated region of the *DMPK* gene. Expanded CUG RNA from the mutant allele sequesters muscleblind-like (MBNL) RNA-binding proteins (RBPs), resulting in their loss of function (LOF). In addition to MBNL LOF, the CELF1 and HNRNPA1 RBPs are upregulated in DM1 striated muscles and overexpression studies in mice support a role for these proteins in DM1 pathogenesis. Whether CELF1 and HNRNPA1 upregulation are a direct consequence of MBNL LOF or through other mechanisms triggered by the toxic RNA has not been established.

We show that upregulation of CELF1 and HNRNPA1 proteins is induced by skeletal muscle-specific *Mbnl1* and *Mbnl2* conditional double knockout (skm*Mbnl* cdKO) in adult mice. CELF1 mRNA levels are not increased suggesting regulation at the level of protein stability or translation. CELF1 upregulation is reproduced by *MBNL1* and

MBNL2 double knockdown in mouse and human myoblasts, ruling out a secondary consequence of skeletal muscle regeneration. Furthermore, we show that the CELF1 coding sequence is sufficient for protein upregulation, consistent with a role for increased protein stability or translation efficiency.

HNRNPA1 protein, mRNA, and pre-mRNA are upregulated in skm*Mbnl* cdKO skeletal muscle indicating transcriptional upregulation and revealing transcriptional effects of MBNL LOF.

We also demonstrate CELF1 and HNRNPA1 upregulation in heart-specific *Mbnl1* and *Mbnl2* conditional double knockout (hrt*Mbnl* cdKO) in adult mice, supporting RBP dysregulation as a direct result of MBNL loss in DM1-relevant tissues. Ongoing studies will define the mechanisms underlying CELF1 and HNRNPA1 upregulation following MBNL loss. The discovery of a direct regulatory link between MBNL LOF and dysregulation of CELF1 and HNRNPA1 offers a framework for understanding how coordinated disruption of RBPs drives disease pathology in DM1.

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107 - Do clinical manifestations of DM1 differ between countries? A registry-based comparison of French and Canadian cohorts

Marianne Nury[1], Melinda Gyenge[2], Dhouha Meftah[2], Lola Lessard[3], Justine Dolbec[1], Tamara Burgess[4], Rachel Thompson[4], Isabelle Coté[5], Dalil Hamroun[6], Xavier Rodrigue[7], Hanns Lochmüller[3, 4], Cynthia Gagnon[8], Guillaume Bassez[2]

[1]Department of Medicine, Faculty of Medicine, Université Laval, Quebec City, Canada, [2]Institute of Myology, Pitie Salpetriere Hospital, Paris, France, [3]The Ottawa Hospital; and Brain and Mind Research Institute, University of Ottawa, [4]Children's Hospital of Eastern Ontario Research Institute; Division of Neurology, [5]UQAC, Chicoutimi, Canada, [6]CHU Montpellier, France, [7]CIUSSS Quebec, Canada, [8]CIUSSS du Saguenay-Lac-St-Jean, Jonquière, Canada

Myotonic dystrophy type 1 (DM1) is one of the most prevalent inherited neuromuscular disorders worldwide. It is characterized by marked clinical heterogeneity, reflecting both its multisystem involvement and wide range of ages at onset, from the prenatal period to late adulthood. This difference in disease expression and severity is in part explained by the size of the CTG repeat expansion. Whether the clinical phenotype of DM1 differs across countries remains unclear. Cross-country comparative studies may reveal population-specific differences and help inform international research efforts and clinical care strategies. To our knowledge, no such international comparative study has been previously reported. We used data from the international DM-Scope registry to compare French and

Canadian DM1 cohorts. To ensure comparability, Canadian participants (n = 275) were matched 1:2 with French individuals (n = 550) based on age, sex, age at onset, and disease duration. Key variables analyzed included age at diagnosis, disease duration, sex, clinical phenotype, cardiac device implantation (pacemaker or implantable cardioverter-defibrillator), diabetes, use of ventilatory support, muscular impairment assessed by the Muscular Impairment Rating Scale (MIRS), CTG repeat length, and presence of cataracts. Additional analyses were performed in the overall French DM1 registry population (n = 3,347). Mean age at diagnosis was 26.1 years in the French cohort and 26.7 years in the Canadian cohort. Mean disease duration was 21.0 versus 20.6 years, and mean age at last follow-up was 47.1 versus 47.3 years, respectively. A detailed comparison of muscular and multisystem involvement in the two cohorts will be presented at the meeting. Overall, French and Canadian DM1 populations share many clinical characteristics while also exhibiting distinct clinical variations. This cross-country comparative study provides insight into common clinical patterns and geographic variability, and may inform international research initiatives, clinical trial design, and patient care strategies.

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109 - Behavioral and Histological Characterization of a Neuronal Mouse Model for Myotonic Dystrophy Type 1 (DM1)

Bethlehem Bekele[1], Juan Arboleda[2], Jason Schroeder[1], Jingsheng Gu[1], Jie Jiang[1], Gary Bassell[1]

[1]Emory University, [2]University of Florida

Myotonic Dystrophy Type 1 (DM1) causes central nervous system (CNS) dysfunction, including learning and memory deficits, sleep disorders and behavioral changes such as anxiety and apathy. To determine how RNA toxicity in neurons alters behavior, we crossed CaMKIIα-tTA mice with TREDT960I mice, which express 960 interrupted CTG repeats in the human DMPK 3'UTR under Tet-Off control. This approach enables reversible expression of toxic RNA using doxycycline to turn off the transgene. Using fear conditioning paradigms, we found that 960-CUG mice show pronounced impairments in hippocampal-dependent contextual fear memory and delayed expression of cued fear responses. One month of doxycycline (Dox) feeding improved cued memory, whereas contextual memory remained impaired. Extending Dox treatment to two months increased freezing response to context, suggesting that hippocampal-dependent memory is more vulnerable and requires prolonged reduction of toxic RNA for functional recovery. To determine whether RNA toxicity

broadly affects behavior, we assessed motor, affective, and social function using rotarod, grip strength, Morris water maze, social interaction, and forced swim tests. We detected no significant genotype-dependent differences in these assays, suggesting that behavioral deficits in this model may be selective for fear-related memory circuits. Histological analysis revealed Dox treatment reduced both RNA foci burden and MBNL sequestration, while transcriptomic analysis showed significant rescue of mis-splicing events important for synaptic function demonstrating significant molecular rescue that parallels behavioral improvement. Together, our data show that CUG-repeat expression within forebrain circuits is sufficient to drive selective hippocampal-dependent memory deficits, linking reversible RNA-mediated splicing pathology to circuit-specific behavioral dysfunction.

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110 - Invisible Factors with Visible Impact: The Influence of Cognition and Behavior on Test Performance in Children with Myotonic Dystrophy.

Lisa Suppers[1], Lynn Orriëns[2], Hilde Braakman[2]

[1]Department of Rehabilitation, Amalia Children's Hospital, Radboud University Medical Centre, Nijmegen, the Netherlands, [2]Department of Pediatric Neurology, Amalia Children's Hospital, Radboud University Medical Centre, Nijmegen, the Netherlands

In children with myotonic dystrophy type 1 (DM1), clinical care traditionally focuses on limitations in muscle strength and motor performance. However, clinical practice indicates that cognitive and behavioral factors may have an equally important impact on daily functioning. As there is very little information on these factors in the literature, incorporating them effectively into treatment recommendations remains challenging.

At the Amalia Children's Hospital, Radboudumc in Nijmegen, the Netherlands, children with DM1 are seen annually by a multidisciplinary team in which occupational therapists and physiotherapists work closely together. During these consultations, in addition to assessing physical functioning, we identify how cognitive and behavioral characterisistics influence the performance of activities. This study presents an exploratory description of clinical cases in which the interaction between physical, cognitive, and behavioral factors becomes apparent.

Our observations indicate that cognitive and behavioral factors may substantially influence the assessment of functional performance and the feasibility of therapeutic recommendations in children with DM1. These factors may affect engagement, task execution, and consistency during assessments, potentially leading to a distorted

representation of a child's abilities and affecting the validity and reliability of outcome measures. For occupational therapists and other allied health professionals, attention to these cognitive and behavioral domains is therefore indispensable in both the evaluation and guidance of children with DM1. Future research should focus on systematically mapping these interactions to ensure that treatment recommendations better align with the child's meaningful activities and provide appropriate support within their environment, including family, peers, and school.

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111 - Inhibition of LIN28 reverses dysregulated ion channel and miRNA expression in myotonic dystrophy

Alok Kumar Behera[1], Peter Meinke Meinke[2], Benedikt Schoser Schoser[2], Jonathan Hall Hall[1]

[1]1Institute of Pharmaceutical Sciences, D-CHAB, ETH Zurich, [2]Freiderich Baur Institute, LMU Munich

Sequestration of MBNL proteins caused by expanded CUG or CCUG repeats causes myotonic dystrophy (DM). The pathology of the disease involves dysregulation of ion channels caused by mis-splicing due to MBNL1 sequestration or loss of target miRNAs controlled by RNA binding protein (RBP). It has been shown that disruption of MEF2 transcription network alters miRNA expression in both human and mouse DM1 model and heart samples; an overexpression of MEF2C restores MEF2A target miRNAs in a DM1 cell culture model Several groups are investigating peptides or small molecule inhibitors of the MBNL1.CUGexp interaction as potential therapeutic approaches for DM1. We are investigating an alternative approach by inhibition of an RNA binding protein LIN28 in DM with a small molecule approach to rescue reduced MEF2A expression and dysregulated ion channels in DM model. We have shown that a subset of primary and mature miRNAs which are controlled by either LIN28 or MEF2A are dysregulated in skeletal myotubes derived from DM1 and DM2 patient samples compared to healthy volunteers. We have shown MEF2A expression is depleted whereas LIN28 levels are elevated in DM patient samples. We used small molecule 1632 to inhibit LIN28 and de-repress MEF2A in myotubes from DM samples. We have further shown that 1632 treatment increased the levels of several of these altered miRNAs, and reduced the expression of KCNJ2, CACNA1S, ATP1B1 ion channels, which are involved in DM pathology. Our finding reveals LIN28 inhibition activity could be used as an RNA therapeutics strategy towards pathophysiology of DM or cardiac defects.

112 - Feasibility of pelvic floor muscle training in DM1: A pilot study

Émilie Petitclerc[1], Isabelle Fisette[1], Mélanie Morin[2], Cynthia Gagnon[1, 2]

[1]Groupe de recherche interdisciplinaire en maladies neuromusculaires (GRIMN), [2]School of Rehabilitation, Faculty of Medicine and Health Sciences, Université de Sherbrooke

Myotonic dystrophy type 1 (DM1) is characterized by progressive muscle weakness and myotonia affecting both striated and smooth muscles, including the pelvic floor muscles (PFM). In 2013, Voet et al. demonstrated that strength training in DM1 does not cause harm, establishing an important foundation for rehabilitation research in this population. Subsequent studies conducted in Saguenay showed that muscle training in individuals with DM1 leads to increased muscle fiber size and strength, with associated improvements in functional performance, apathy, hypersomnolence, and mental health. Despite the fact that urinary and gastrointestinal symptoms are among the most burdensome and quality-of-life-limiting manifestations of DM1, no studies to date have examined the feasibility or effectiveness of physical rehabilitation interventions targeting pelvic floor dysfunction in this population.

Objective: To assess the feasibility of a pelvic floor muscle training program in women with juvenile-, adult-, or late-onset DM1.

A pilot feasibility study was conducted in five women with DM1. Participants completed a 12-week pelvic floor muscle training program consisting of a structured home-based exercise regimen combined with one supervised physiotherapy session per week. Three standardized questionnaires were administered pre- and post-intervention to assess urinary and fecal incontinence, other pelvic floor disorders, and their impact on quality of life, social participation, and emotional well-being.

Three participants completed the intervention. All completers demonstrated reductions in both urinary and fecal incontinence, accompanied by a marked decrease in the negative impact of pelvic floor symptoms on quality of life and participation.

Despite challenges related to adherence, pelvic floor muscle training appears feasible in women with DM1 and shows promise for improving pelvic floor-related symptoms and quality of life. Larger, controlled studies are warranted to confirm these preliminary findings.

113 - A Wake-Up Call: Respiratory Dysfunction in Children with Myotonic Dystrophy Type 1

Lynn Orriens[1], Seline van der Kop[1], Haddia Ghafuri[1], Peter Merkus[2], Sylvia Klinkenberg[3], Hilde Braakman[1]

[1]Department of Paediatric Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Centre, Amalia Children's Hospital, Nijmegen, The Netherlands, [2]Department of Paediatric Pulmonology, Radboud University Medical Centre, Amalia Children's Hospital, Nijmegen, The Netherlands, [3]Department of Neurology, Maastricht University Medical Center, Maastricht, The Netherlands; Mental Health and Neuroscience Research Institute, Maastricht University, Maastricht, The Netherlands

Myotonic dystrophy type 1 (DM1) is a multisystem disorder in which respiratory complications represent the leading cause of death in adults. While respiratory dysfunction in adults with DM1 has been well described, evidence in paediatric populations is strikingly limited, leaving a critical gap in understanding whether respiratory involvement is also a concern in children with DM1 and how symptoms typically present.

We performed a retrospective cohort study at the Dutch Myotonic Dystrophy Expertise Center in 2025, evaluating respiratory function in children with congenital and childhood-onset DM1. Medical records of 88 children were reviewed, covering clinical data and results of pulmonary function testing, including spirometry and polysomnography. Children under one year of age with congenital-onset DM1 were excluded, due to the high prevalence of respiratory insufficiency in the neonatal period and the weeks and months hereafter.

Respiratory dysfunction was common and clinically relevant in this paediatric DM1 cohort, with a considerable proportion of children requiring non-invasive ventilation, even in those with an apparently mild phenotype. The findings suggest that respiratory dysfunction in children with DM1 predominantly originates from central nervous system involvement and weakness of the orofacial musculature, rather than primarily respiratory muscle weakness.

Excessive daytime sleepiness and fatigue were the most prevalent symptoms associated with nocturnal hypoventilation; however, these symptoms are often considered part of the intrinsic disease burden of DM1, potentially delaying recognition of respiratory dysfunction.

These results underscore the clinical relevance of respiratory involvement in children with DM1 and highlight the need for increased awareness and systematic respiratory

evaluation, even in the absence of clear symptoms. Further research is warranted to improve early detection, elucidate underlying pathophysiological mechanisms, and optimize respiratory management to reduce morbidity and improve quality of life in this population.

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115 - Rapid and Sensitive CTG Repeat Sizing and Somatic Instability Assessment: Toward Standardization in DM1 Repeat Sizing

M. Carmen Valero[1], Katharine Hagerman[2], Jacinda B. Sampson[2], Sub H. Subramony[3], Donovan J. Lott[4], John W. Day[2], Eric T. Wang[1]

[1]Department of Molecular Genetics & Microbiology, Center for NeuroGenetics, UF Genetics Institute, University of Florida College of Medicine, Gainesville, Florida, USA, [2]Department of Neurology and Neurological Sciences, Stanford University, Palo Alto, California, USA, [3]Department of Neurology, University of Florida College of Medicine, Gainesville, Florida, USA., [4]Department of Physical Therapy, University of Florida, Gainesville, Florida, USA

Accurate measurement of CTG repeat expansions in Myotonic Dystrophy Type 1 (DM1) is essential for diagnosis, prognosis, and therapeutic monitoring. Repeat length strongly correlates with disease severity and progression, yet traditional methods such as Southern blot are labor-intensive, require large amounts of high-quality DNA, and lack scalability for longitudinal studies. An ideal approach should not only determine repeat size but also capture somatic instability, which varies across tissues and influences phenotype. This capability is critical for tracking disease dynamics over time and evaluating responses to emerging treatments.

To address these limitations, we developed a protocol that combines low input amount of DNA, **Small-Pool PCR (SP-PCR) with capillary gel electrophoresis**, providing a high-resolution, efficient alternative to Southern blot. This method enables sensitive detection of expanded alleles in blood, skeletal muscle, and brain tissues from DM1 patients. Importantly, it allows longitudinal monitoring of somatic instability over 1-2 years in blood and muscle samples, revealing dynamic changes in repeat size that reflect ongoing mutational processes. By integrating SP-PCR with capillary electrophoresis, we achieved quantitative analysis of repeat length distributions across tissues and time, offering a scalable and less labor-intensive strategy for disease monitoring.

This comprehensive approach improves prognostic accuracy, supports personalized treatment strategies, and may accelerate the development of targeted therapies for DM1. Our findings demonstrate that SP-PCR combined with capillary gel

electrophoresis is a powerful tool for assessing tissue-specific repeat dynamics and tracking instability, paving the way for its application in clinical diagnostics and therapeutic trials.

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117 - Health insurance profile and health insurance literacy (HIL) in myotonic dystrophy type 1 (DM1)

Allison Kreuzer[1], Douglas Kerr[1], Aaron Novack[1], Tanya Stevenson[2], Andreas Rohrwasser[2], Nadine Ann Skinner[2], Ashish Dugar[3], Anne Melchior[4], Skyler Jackson[4], Katherine Beaverson[3]

[1]Dyne Therapeutics, Inc., Waltham, MA, USA, [2]Myotonic Dystrophy Foundation, Oakland, CA, USA, [3]Previously of Dyne Therapeutics, Inc., Waltham, MA, USA, [4]Engage Health, Inc., Eagan, MN, USA

Background: Health insurance literacy (HIL) is the extent to which individuals have knowledge, ability, and confidence to find/evaluate health plan information, choose a plan suited to needs, and use it effectively. HIL is critical in complex diseases where patients need optimal access to new/emerging therapies.

Objective: To understand the health insurance profile and HIL of individuals with DM1, compared with the general population.

Methods: Mixed-methods (survey & interview) PRO study comparing HIL to the general population.

Results: The study included 100 participants aged 18+ diagnosed with DM1 and in whom muscular symptoms began ≥ age 11, or their caregiver.92% were individuals diagnosed with DM1; 82 managed their own insurance, 10 did not, 8 were caregivers who managed insurance. Most (99%) were insured: private (51%), government (41%), private and government (7%), uninsured (1%). Private insurance was most often employer-based. Among government-insured participants, Medicare was most common (61%), then Medicaid (14.6%). Medicare recipients used more Advantage plans than traditional (57.7% vs. 42.3%). Most were not on a Medicaid waiver (79%), citing ineligibility (19.4%), not interested, believed they were insufficiently disabled (15.1% each), or unaware (7.5%). Few used co-pay support (4%), reduced co-pay (7%), free drug programs (5%), or received non-profit financial support (4%), despite difficulties paying medical bills.

Participants scored better than the general population on HIL. Caregivers who managed insurance scored better than patients, and patients managing their insurance scored better than those who did not. Only 8% correctly defined a patient

assistance program, 33% off-label use, and 54% prior authorization. Plan type was misidentified by 23%, most often related to managed Medicare.

Conclusions: While most participants were covered by health insurance and scored well on terminology, they had difficulty understanding their plan types and concepts related to new therapies. These findings are helpful to address educational/programming needs.

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119 - Growth, development, and social participation in congenital and childhood-onset myotonic dystrophy type 1: A nationwide survey in Japan

Yuzuha Ichimura[1], Yuko Shimizu-Motohashi[2], Minobu Shichiji[3], Rie Honda[1], Michio Kobayashi[4], Tsuyoshi Matsumura[5], Hotake Takizawa[6], Toshio Saito[5], Akinori Nakamura[7], Kazuma Sugie[8], Atsuko Ishii[9], Ayumi Yonei[10], Tomoya Kubota[1], Yasuhiro Takeshima[11], Harumasa Nakamura[6], Midori Senoo[12], Haruo Fujino[9, 13], Hirofumi Komaki[2], Keiko Ishigaki[3], Masanori P. Takahashi[1, 9, 10]

[1]Clinical Neurophysiology, The University of Osaka Graduate School of Medicine, [2]Department of Child Neurology, National Center of Neurology and Psychiatry, [3]Tokyo Women's Medical University School of Medicine, [4]Department of Neurology, NHO Akita National Hospital, [5]Department of Neurology, NHO Osaka Toneyama Medical Center, [6]Department of Neurology, National Center of Neurology and Psychiatry, [7]Department of Neurology, NHO Matsumoto Medical Center, [8]Department of Neurology, Nara Medical University, [9]United Graduate School of Child Development, The University of Osaka, [10]Department of Genetic Counseling, The University of Osaka Hospital, [11]Department of Pediatrics, Hyogo Medical University, [12]Myotonic Dystrophy Patient's Group of Japan (DM-Family), [13]Graduate School of Human Sciences, The University of Osaka

Pediatric-onset myotonic dystrophy type 1 (DM1) differs clinically from adult-onset DM1. Congenital DM1 presents with neonatal hypotonia, respiratory impairment, and intellectual disability, while childhood-onset DM1 is also frequently associated with intellectual disability and autistic traits; these neurodevelopmental features markedly affect schooling, employment, and quality of life (QOL). This study aims to clarify the epidemiology, development, symptoms, and QOL of patients with pediatric-onset DM1 in Japan.

Questionnaires, primarily completed by parents, were mainly distributed through a patient registry (Remudy) with additional distribution via patient groups and neuromuscular centers. Survey items included basic demographics, genetic testing results, growth and development, schooling, employment, and family information.

For comparative analyses, patients were classified by age at onset into congenital (CDM; <1 month), childhood-onset (ChDM; <10 years), and juvenile-onset DM1 (JDM; <18 years).

Of approximately 470 questionnaires distributed, 145 were returned, and 119 cases were included (48 CDM, 36 ChDM, 35 JDM). Mean current ages were 14.5, 22.9, and 36.5 years, respectively. In CDM pregnancies, polyhydramnios and massive hemorrhage during delivery occurred in 54.2% and 35.4%. In CDM, achievement rates for major developmental milestones (head control, sitting, independent walking) remained at 30-40% at ages when these milestones are normally achieved. At two years of age, approximately 20% had achieved single-word speech and 15% two-word sentences. Intellectual disability was twice as frequent in CDM/ChDM as in JDM. Regarding final education attainment (n=70), 92.9% of CDM and 82.6% of ChDM graduated from high school, predominantly from special education schools, whereas 53.3% of JDM patients attained education beyond high school. Employment rates were 64.3% (CDM), 73.9% (ChDM), and 56.3% (JDM); assisted commuting was required by 50.0%, 52.6%, and 33.3%, respectively. Median monthly income was 20,000, 40,000, and 70,000 Japanese yen, respectively.

These findings provide critical insights into growth, development, and social participation for pediatric-onset DM1 in Japan.

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121 - Diagnostic Support for Myotonic Dystrophy Type 1 Using Real-World Data at the German Portal for Medical Research Data (FDPG)

Jana Zschüntzsch[1], Elisabeth Nyoungui[2], Richard Röttger[3], Miriam Hübner[4], Marco Schaarschmidt[4], Harisa Muratovic[3]

[1]Department of Neurology, University medical Center Göttingen, [2]Institute of Medical Informatics, University medical Center Göttingen, [3]Department of Mathematics and Computer Science, Syddansk Universitet Odense, [4]Charité - University medical Center Berlin

Background Myotonic dystrophy type 1 (DM1) is a multisystem disorder with marked clinical heterogeneity that often leads to diagnostic delay. The emergence of disease modifying therapies highlights the need for precise phenotyping, early disease diagnosis and staging to ensure clinical trial readiness and optimized patient care.

This study evaluates the potential of real world data (RWD) from German University Data Integration Centers (DIC) to support early DM1 detection and trial preparedness. We aim to: (1) define phenotype specific and laboratory profiles in genetically

confirmed DM1; (2) assess the predictive value of a characteristic laboratory constellation—elevated CK, AST, ALT, and HbA1c with reduced IgG and TSH; (3) determine whether clinical features such as frontal baldness, gallstones, early cataract, or insulin resistance related complications enhance diagnostic accuracy; and (4) explore the feasibility of identifying undiagnosed DM1 through machine learning approaches applied to federated RWD.

Methods As DM1 lacks a disease specific ICD 10 code in Germany, feasibility analyses were performed via the German Portal for Medical Research Data (FDPG), providing federated access to DIC datasets using ORPHA code 273. Between June and July 2025, confirmed DM1 cases increased from 50 across four sites to 130 across six. Ongoing analyses track ORPHA code rollout, with comprehensive modeling planned once ≥500 cases are available. Supervised machine learning algorithms optimized by the Youden index will define predictive laboratory clinical signatures.

Results As of January 2026, 220 DM1 cases are registered across 11 FDPG sites. Preliminary analyses demonstrate the technical feasibility of detecting distinctive laboratory and clinical patterns consistent with DM1 within federated hospital RWD.

Conclusions A composite laboratory signature integrated with systemic comorbidities will potentially show promising predictive value. Applying machine learning models to such RWD derived patterns may enable earlier diagnosis, optimized patient stratification, and enhanced readiness for upcoming disease modifying trials.

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124 - The Genetic Landscape of DM1: Ancestry-Specific Insights from Nearly One Million Genomes

Rezbieara Rahman[1], Elijah Behr[1], Marta Futema[1], Emma Matthews[1]

[1]City St George's University of london

Background: Myotonic dystrophy type 1 (DM1) is a complex, multisystemic disorder caused by unstable CTG repeat expansions in the *DMPK* gene. While its clinical manifestations are well documented, the global genetic landscape remains poorly characterised. Most genomic studies to date have focused on individuals of European ancestry, leaving ancestry-specific patterns underexplored. This lack of diversity limits the generalisability of diagnostic criteria and may contribute to underdiagnosis in underrepresented populations.

Objectives: Leveraging large-scale whole genome sequencing (WGS) data, we aimed to identify *DMPK* repeat expansions across nearly one million participants, examining ancestry-specific differences.

Methods: We analysed WGS participants from Genomics England (n = 80,110), UK Biobank (n = 490,086), and the All of Us Research Program (n = 414,830). Repeat lengths at the *DMPK* locus were estimated using ExpansionHunter, with cohort-specific pipelines adapted to each platform. Individuals were classified into Normal (≤37 repeats), Premutation (38-49 repeats), and Pathogenic (≥50 repeats) groups. Genetic ancestry was determined using platform-specific approaches and grouped into six superpopulations: African (AFR), Admixed American (AMR), East Asian (EAS), European (EUR), Middle Eastern (MID), and South Asian (SAS). Subsequent analyses evaluated ancestry-specific variations in repeat length distributions and the prevalence of pathogenic expansions.

Results: We report the largest ancestry-informed dataset of *DMPK* repeat expansions to date. Significant variation in repeat length distributions and pathogenic expansion prevalence was observed across ancestries. European individuals showed the highest prevalence and larger expansions, while other groups exhibited lower frequencies. These findings raise questions about epidemiological modifiers, diagnostic bias, and the need for more inclusive genomic studies.

Conclusion: By integrating WGS data from nearly one million individuals, this study reveals ancestry-specific variation in *DMPK* repeat expansions, addressing a critical gap in DM1 research and supporting development of inclusive diagnostic and management strategies.

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127 - Screening by ECAS help defining cognitive and behavioral involvement in different DM1 phenotypes

Erica Frezza[1,2], Ilaria Petitta[1], Mariangela Goglia[1], Giulia Greco[1], Francesco Gruosso[1,2], Giovanni Vietri[1,2], Laura Boffa[3], Diego Centonze[2,4], Roberto Massa[1,2]

[1]Unit of Neuromuscular Diseases, Department of Systems Medicine, Tor Vergata University of Rome, Via Montpellier 1, 00133 Rome, Italy., [2]IRCCS Neuromed, Pozzilli (IS), Italy, [3]Unit of Neuromuscular Diseases, Policlinico Tor Vergata, Rome, Italy, [4]Department of Systems Medicine, Tor Vergata University of Rome, Via Montpellier 1, 00133 Rome, Italy

Myotonic dystrophy type 1 (DM1) is a multisystem disorder characterized by marked clinical heterogeneity across phenotypes. Although cognitive and behavioral aspects

are recognized features, their systematic assessment in a cross-sectional study, using a brief screening tool, across different phenotypes in adult DM1 is still lacking. The aim of this study is to evaluate the feasibility in clinical practice of the Edinburgh Cognitive and Behavioral ALS Screen (ECAS) as a screening instrument for cognitive and behavioral involvement across DM1 phenotypes, and to explore relationships between cognition, motor function, metabolic status, and sex. Fifty-eight genetically confirmed adult DM1 patients were consecutively recruited and classified by age at disease onset. Cognitive and behavioral functioning were assessed using ECAS. Motor performance, fatigue, daytime sleepiness, and body mass index (BMI) were systematically evaluated. Phenotype comparisons, correlation analyses, regression models, and cluster analyses were performed. Overall, 52% of patients showed pathological ECAS performance, most frequently affecting executive functions (47%) and language (38%). Early-onset phenotypes exhibited the greatest cognitive impairment, whereas adult-onset patients showed relatively preserved cognition. Patients with executive dysfunction showed significantly worse motor performance at 6MWT (p 0.028). Behavioral alterations were common, particularly apathy (64%) and reduced empathy (45%), with distinct associations with motor and cognitive outcomes, respectively. Cognitive impairment correlated with longer disease duration, poorer motor performance, and higher BMI, with stronger associations observed in male patients. Regression analyses identified sex and disease duration as primary predictors of cognitive performance. Cognitive impairment in DM1 is modulated by age of onset, disease duration, metabolic status, and sex, supporting the coexistence of alterations related to both neurodevelopment and neurodegeneration. ECAS may represent a valuable first-line instrument for cognitive and behavioral stratification in clinical practice and research settings in adult patients across DM1 phenotypes.

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129 - New insights into DM1 mechanism of pathogenesis: DMPK, MBNL and miR-23b balance as the master key of DM1 pathology

Diego Piqueras-Losilla[1], Argimiro Mayoral-Olmos[1], Andrea Garcia-Rey[1], Ana Díaz-Maqueda[1], Nuria Barquero[1], Rubén Artero[2, 3], Beatriz Llamusí[1], Estefanía Cerro-Herreros[1]

[1]ARTHEx Biotech, [2]University Institute of Biotechnology and Biomedicine (BIOTECMED), Valencia University (UV), [3]Translational Genomics Group, Incliva Biomedical Research Institute

Myotonic dystrophy type 1 (DM1) is a multisystemic genetic disorder caused by CTG repeat expansion in the 3' untranslated region of the *DMPK* gene, leading to the accumulation of toxic mutant RNA in ribonuclear foci and sequestration of muscleblind-like (MBNL) splicing regulators. In addition to sequestration, recent evidence indicates that upregulation of miR-23b, a negative regulator of MBNL1 translation, further contributes to MBNL loss of function and DM1 pathology. ATX-01 is a novel antisense oligonucleotide in clinical development that inhibits miR-23b, and has been shown to influence *DMPK* mRNA levels in vitro.

We investigated how miR-23b inhibition contributes to the reduction of mutant *DMPK* transcripts and provides broader insight into DM1 pathogenesis. Our data indicate that the reduction of mutant *DMPK* transcripts does not result from decreased transcription but rather from altered nuclear RNA processing. ATX-01 corrects the splicing of MBNL exon 5, promoting the expression of MBNL isoforms with increased cytoplasmic localization. This shift facilitates the nuclear export of mutant *DMPK* transcripts, leading to their rapid degradation in the cytoplasm. In parallel, the effects of ATX-01 were compared with those of a *DMPK*-targeting oligonucleotide to evaluate the relative therapeutic impact of these approaches. Importantly, ATX-01 exhibits superior modulation of the DM1 pathogenic cascade compared to other oligonucleotide approaches. By simultaneously enhancing MBNL1 expression and promoting the processing and clearance of mutant *DMPK* RNA, ATX-01 offers a dual, upstream mechanism of action that supports its potential as a first-in-class therapeutic strategy for DM1.

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130 - Targeting miR-23b uncovers a therapeutic opportunity for Myotonic Dystrophy Type 2

Estefanía Cerro-Herreros[1], Diego Piqueras-Losilla[1], Dulce Peris-Moreno[2, 3, 4], Argimiro Mayoral-Olmos[1], Bjarne Udd[5], Ariadna Bargiela[2, 3, 4], Rubén Artero[2, 3, 4], Beatriz Llamusí[1]

[1]ARTHEx Biotech, [2]University Institute of Biotechnology and Biomedicine (BIOTECMED), Valencia University (UV), [3]Translational Genomics Group, Incliva Biomedical Research Institute, [4]CIBERER ISCIII, [5]Neuromuscular Center, Tampere University Hospital, Tampere

Myotonic dystrophy type 2 (DM2) is a multisystemic neuromuscular disorder caused by the expansion of CCTG repeats within intron 1 of the *CNBP* gene, leading to the accumulation of toxic intronic RNA and sequestration of MBNL proteins in nuclear foci. This results in widespread splicing dysregulation that underlies disease

pathology. In contrast to DM1, there are no drugs in development for DM2 (or approved drugs), and mechanistic and translational studies in DM2 remain limited. ATX-01, an antisense oligonucleotide targeting miR-23b currently in clinical development for DM1, increases MBNL expression and restores regulation of splicing, raising the possibility of a shared therapeutic strategy across myotonic dystrophies.

In this study, we evaluated the effects of ATX-01 in primary cells derived from DM2 patients to assess the molecular impact of ATX-01 in the context of a disease driven by intronic repeat expansion. ATX-01 treatment resulted in a robust increase in MBNL protein levels, accompanied by correction of multiple DM2-associated splicing defects. Notably, a significant reduction in nuclear RNA foci was observed. This effect was linked to the correction of splicing of the *CNBP* intron harboring the CCTG expansion, promoting improved RNA processing, and reduced intron retention. Importantly, these molecular rescue events occurred without detectable changes in the amount of *CNBP* mRNA or protein, indicating that ATX-01 does not interfere with *CNBP* gene expression or function, which would be undesirable. Together, these findings demonstrate that miR-23b inhibition can ameliorate core molecular hallmarks of DM2 by restoring MBNL-dependent RNA processing and reducing toxic RNA accumulation. Given the absence of therapeutic options for DM2, this study suggests that anti-miR-23b may represent a promising disease-modifying therapeutic approach for DM2, and is worth further investigation.

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133 - HDAC inhibitors identified as myogenic modulators in DM1 context through a target-agnostic and high content imaging drug screening

Noemie Berenger-Currias[1], Laurine Mériadec[1], Corentin Rouxel[2], Ludovic Arrandel[2], Peter Sommer[3], Denis Furling[2], CECILE MARTINAT[4]

[1]CECS, IStem, [2]Institut de Myologie, Paris, [3]KSILINK, [4]Inserm UMR861, IStem

Myotonic Dystrophy Type 1 (DM1) is the most common form of muscular dystrophy in adults. Although the causal mutation has been well characterized, the development of an effective curative approach is challenged by its complex physiobiology.

To develop unbiased screening approaches recapitulating the complex biology of the disease, we combined the use of disease-specific human stem cells (hPSC), with high-content imaging and machine learning analysis. This works aims to highlight new pathways that may be involved in the disease and/or act on its pathological hallmarks and could be considered for therapeutics development.

More than 40 000 compounds were tested for their capacity to normalize the defective myogenic fusion of hPSC derived-DM1 myotubes, and 97 hits were further investigated through their ability to reduce DM1 molecular hallmarks.

Our results highlighted the family of HDACs inhibitors as modulators of both myogenic fusion and DM1 molecular hallmarks in hPSC derived-skeletal muscle cells. Interestingly, the inhibition of HDACs also led to a reduction of DM1 hallmarks in hPSC derived-cortical neurons. More precisely, the inhibition of HDAC6 seems to induce a significant reduction of DMPK expression and intranuclear foci number, leading to the correction of several disease related splicing defects.

Several HDACs inhibitors are currently in clinical development for other muscular diseases. The tubastatin A, an HDAC6 inhibitor that has been shown to improve muscle functions in Duchenne's myopathy, is now tested in DM1 mouse model to evaluate its clinical potential in a DM1 context.

The target-agnostic approach of our screening allowed to identify a new set of molecules able to both improve the fusion of DM1 skeletal muscle cells and reduce the pathological hallmarks in multiple cell types. The exploration of their mode of action, and the ongoing in vivo testing of these molecules will determine if they could be considered for potential therapeutics.

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136 - Single-Nucleus Long Read RNA-sequencing for DM1 improved precision medicine and advancing clinical transcriptomics.

Daniel Borràs[1], Marc Corral-Juan[1], Alicia López-Martín[1], Eva Coll-Liesa[1], Christian Escalona-Huerta[2], Damián García-Perdomo[2], Sebastián Figueroa-Bonaparte[3], Gisela Nogales-Gadea[1], Giuseppe Lucente[3], Eduard Juanola-Mayos[3]

[1]Neuromuscular Research Group of Badalona (GRENBA), Germans Trias i Pujol Research Institute (IGTP), Badalona, Spain., [2]Skeletal Muscle section, Radiodiagnostic Service, Hospital Universitari Germans Trias i Pujol, Badalona, Spain, [3]Neuromuscular Pathology Unit, Neurology Service, Neuroscience Department, Hospital Universitari Germans Trias i Pujol, Badalona, Spain

Myotonic dystrophy type 1 (DM1) is a progressive, multisystemic neuromuscular disorder caused by a CTG repeat expansion in the DMPK transcript, leading to toxic RNA accumulation and widespread cellular dysfunction of splicing mechanisms. Due to its clinical variability, the molecular mechanisms driving DM1 progression remain poorly understood, particularly at the level of single-cell compartments and composition. We are developing a unique multi-omics approach using single-

nucleus long-read RNA sequencing (SNLR-seq) to characterize full-length transcripts, splicing events, and coding variants in skeletal muscle biopsies from 40 DM1 patients (across DM1 clinical categories) and 8 healthy volunteers.

Leveraging third-generation sequencing technologies (such as Oxford Nanopore Technologies), our SNLR-seq will enable precision medicine by profiling of RNA isoforms at single-nucleus level, overcoming the limitations of short-read approaches and capturing the heterogeneity found in DM1. The integration of transcriptomics, splicing, epigenomics, and whole-genome data obtained through the DM1-Hub, Spain's DM1 patient registry, will provide insight into cell-type-specific mechanisms of DM1 pathology. Hence, establishing the first SNLR-seq database of DM1 muscle transcriptomes, with identified aberrant splicing, coding variants, and MBNL sequestration signatures, holds immense potential for linking molecular profiles to clinical outcomes in DM1. This database will enable the development of predictive models for improved patient stratification, patient management, and identification of potential therapeutic targets.

We leverage on our extensive preliminary infrastructure with access to 3,000 patient records in the DM1-Hub registry, validated (in-house) long-read sequencing protocols, high-performance supercomputing resources (RES), and close collaborations with clinical and translational experts (lead neurologists). This will generate the first multi-omics database of DM1 muscle pathology, and advance in precision medicine through biomarker discovery, patient stratification, and novel therapeutic strategies.

Metformin is a potential systemic treatment for Myotonic Dystrophy type 1 (DM1) since it can interfere with several pathomechanisms of the disease. We evaluated the effects of a 24-month metformin treatment on mobility and safety in adult DM1 patients.

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137 - Analysis of tissue organization defects in patients with muscular dystrophy

Khouloud Swalmi[1], Nicolas Dumont[2], Élise Duchesne[3], Marie-Claude Sincennes[1]

[1]INRS, [2]UdeM, [3]ULaval

Muscular dystrophies are characterized by progressive muscle weakness, muscle wasting and fatigue. Although they share similar symptoms, the molecular mechanism of the disease is distinct between different muscular dystrophies. For example, while Duchenne Muscular Dystrophy (DMD) and Myotonic Dystrophy (DM1) are caused by mutations in genes predominantly expressed in muscle tissue, other

subtypes such as oculopharyngeal muscular dystrophy (OPMD) are caused by ubiquitously expressed genes.

Muscle tissue is composed of several cell types, including muscle fibers, muscle stem cells, as well as immune, adipose, and endothelial cells. While most fundamental studies of muscular dystrophies focus on myogenic cells, it is expected that other cell types contribute as well to the disease phenotype. Targeting muscle-resident cells for therapy could alleviate the symptoms or delay disease progression.

In this project, we aim to develop a spatial proteomics approach to characterize cellular defects present in the muscles of individuals affected by muscular dystrophies. To achieve this, we will use the imaging technology MACSima, which enables high-resolution visualization of muscle tissue while preserving spatial organization and allowing simultaneous detection of numerous proteins. We will develop a panel of markers that can distinguish muscle-resident cells, in addition to markers for major cell processes that are frequently mis-regulated in muscular dystrophy, such as senescence, ubiquitin-proteasome system, autophagy, and mitochondrial function.

Staining will be performed on muscle samples from affected individuals and healthy control subjects. The resulting data will be analyzed using bioinformatics tools, and proteomic profiles will be compared with transcriptomic data to better understand disease-related alterations. Ultimately, this project aims to improve understanding of muscle defects associated with muscular dystrophy and support diagnostic and therapeutic strategies.

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138 - Long-term observational study of disease progression in DM1 - analysis of the Saguenay, Quebec DM1 Cohort

Isabelle Côté[1], Cynthia Gagnon[1,2], John Ripollone[3], Fares Nigim[3], Sarah Conner[3], Jean Mathieu[1]

[1]Centre de recherche et d'innovation du CIUSSS Saguenay-Lac-St-Jean, [2]Université de Sherbrooke, Sherbrooke, Quebec, CA, [3]Vertex Pharmaceuticals, Boston, MA, USA

Data on the mortality burden of myotonic dystrophy type 1 (DM1) and prognostic factors of mortality in DM1 are sparse. This study aimed to describe the mortality experience of the Saguenay-Lac-Saint-Jean (SLSJ, CA) DM1 Cohort over a 22-yr period and identify prognostic factors associated with mortality among DM1 adults.

At baseline (2002), 200 DM1 patients were recruited for a large prospective natural history study at the SLSJ Neuromuscular Clinic. All-cause mortality status was

determined on January 31, 2024. Several potential prognostic factors were considered, including muscle strength (quantitative muscle testing; % from normative value [ppQMT]), self-selected walking speed (10-meter Walk Test; cm/s [10MWT]), and respiratory function (ppFVC). Mortality rates were calculated, overall and by prognostic factor. Associations between mortality and ppQMT, 10MWT, and ppFVC were analyzed using Cox regression models, adjusted for baseline age, sex, phenotype, CTG, BMI, presence of diabetes and fatigue, ECG, respiratory variables, and income level.

At baseline, mean age was 47 yrs, 60.8% were female, and 45.2% had the juvenile phenotype. The overall mortality rate was 50.0 per 1000 person-years, compared to 7.6 in the SLSJ adult general population in 2021 (not matched). Higher rates were observed for participants with the juvenile phenotype (58.5 vs 49.2, adult phenotype and 35.1, late phenotype), and in individuals with ≥300 CTG repeats (59.1, vs 30.6, <300 CTG repeats). Hand grip, pinch, ankle dorsiflexion ppQMT, 10MWT, and ppFVC were associated with mortality, with an increase in mortality risk between 1.7% and 3.1% for each decrease of 1 percentage point (or 1 cm/s) of the factor. Models based on binary/quartile versions of these factors yielded the same directional conclusions.

The high mortality burden in DM1 and its association with worse strength, walking speed, and respiratory function highlights the need for novel therapies to treat the underlying cause of DM1.

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140 - Ultrastructural Alterations in DM1 Muscle Cells Revealed by Cryo Soft X-Ray Tomography

Pau Maestre-Mora[1], Judit Núñez-Manchón[1], Eva Coll Liesa[1], Alba Herrero-Gómez[1], Mònica Suelves[1], Ana Joaquina Pérez-Berná[2], Gisela Nogales-Gadea[1]

[1]Badalona Neuromuscular Research Group (GRENBA), Germans Trias i Pujol Research Institute (IGTP), Badalona, Catalonia, Spain., [2]ALBA Synchrotron Light Source, Cerdanyola del Vallès, Barcelona, Spain.

Myotonic dystrophy type 1 (DM1) is an autosomal dominant multisystem disorder that affects multiple organs, including skeletal muscle, the heart, nervous system, and eyes. DM1 is caused by expanded CTG repeats in the 3'-untranslated region of the dystrophin myotonic-protein kinase gene (DMPK). In DM1 the mutant transcripts aggregate as nuclear foci and sequester several RNA-binding proteins, leading to alternative splicing dysregulation. Beyond the detrimental effects at the RNA level, additional cell dysfunction contributes to pathological mechanisms observed in DM1 cells.

Pioneering experiments with full-field cryo soft X-ray tomography (cryo-SXT) at the MISTRAL beamline of the ALBA synchrotron, operating in the water-window photon energy range, have enabled the investigation of whole, unstained cells. These experiments revealed and characterized numerous previously undescribed cellular morphological alterations in mature DM1 patient-derived myotubes, providing new insights into DM1 pathogenesis under near-native conditions.

Our results show differences in organelle numbers in DM1 cells, namely a reduction in mitochondrion and an increased number of lipid drops, endocytic vesicles, and autophagosomes. Furthermore, differences were also observed in the volume and shape of these organelles in DM1 cells when compared to controls, manifesting organelle disorganization and morphological changes at mitochondrial, lipid vesicle, ER and lysosomal levels as result of a pathological mechanisms involved in DM1. Moreover, nuclear aggregates present in the nuclei were analyzed through linear attenuation coefficient (LAC), with DM1 cells presenting larger and denser aggregates, consistent with nuclear foci described in DM1 pathogenesis.

Our findings uncover significant organelle and nuclear alterations in DM1 muscle cells, offering new insights into disease mechanisms. Cryo-SXT proves a powerful tool for the characterization of complex multisystemic pathologies at the cellular level, paving the way for cellular biomarkers and potential therapeutic targets.

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142 - Role of cardiac magnetic resonance in Myotonic Dystrophy type 1

Eduard Juanola Mayos[1], Anna Revert[1], Ainhoa Sancho[2], Martín Rojas-Goldsack[3], Victoria Delgado[3], Albert Teis[3], Javier Sotoca[4], Raul Juntas-Morales[4], Maria Salvado-Figueras[4], Bernat Bertran-Recasens[5], Alba Ramos[6], Laura Llansó[7], Jorge Espinosa-García[8], Teresa Casadevall-Codina[9], Velina Nedkova-Hristova[10], Antonio Cano[11], Nicolau Guanyabens[11], David Reyes-Leiva[12], Daniel Borràs[2], Gisela Nogales-Gadea[2]

[1]Neuromuscular Pathology Unit, Neurology Service, Neuroscience Department, Germans Trias i Pujol University Hospital, Badalona, Spain, [2]Badalona Neuromuscular Research Group (GRENBA), Germans Trias i Pujol Research Institute (IGTP), Badalona, Catalonia, Spain, [3]Heart Institute. Cardiology Department. Cardiovascular Imaging Unit. Germans Trias University Hospital, [4]Clinic of Neuromuscular Disorders and Rare Diseases, Neurology Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute, European Reference Network for Neuromuscular and Rare Diseases EURO-NMD, Barcelona, Spain, [5]Neuromuscular Unit, Neurology Service, Hospital del Mar, Barcelona, Spain, [6]Neuromuscular Unit, Neurology Service, Hospital Clínic, Barcelona, Spain,

[7]Neuromuscular Diseases Unit, Department of Neurology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [8]Neuromuscular Unit, Neurology Service, Hospital Parc Taulí, Sabadell, Spain, [9]Neurology Department, Hospital Calella, Spain, [10]Neuromuscular Unit, Neurology Department, Bellvitge University Hospital-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain, [11]Neurology Department, Hospital Mataró, Barcelona, Spain, [12]Neurology Department, Hospital Sant Joan Despí Moisès Broggi, Barcelona, Spain

INTRODUCTION Approximately 80% of patients with Myotonic Dystrophy Type 1 (DM1) develop cardiac involvement throughout their lives, but there are no valid biomarkers for early detection. Cardiac magnetic resonance (CMR) is a promising tool due to its ability to identify early cardiac dysfunctions, fatty infiltration and myocardial fibrosis. The DM1-Heart project aims to evaluate CMR as a potential tool for detecting early myocardial damage in DM1.

METHODS We prospectively included genetically confirmed DM1 patients from different centers in Catalonia with adult onset (>18 years) and without cardiac symptoms (normal ECG, 24-hour Holter and echocardiogram; no symptoms or signs of cardiac disease). All patients underwent CMR and a comprehensive neuromuscular examination.

RESULTS Sixty-seven patients were included (aged 43±11 years, 64% female), 56% with mild neuromuscular involvement (MIRS 1-2) and 44% with moderate-severe (MIRS 3-4). CMR showed preserved left and right ventricular ejection fraction (LVEF 62±5% / RVEF 58±6%), normal atrial and ventricular volumes, and no strain abnormalities. In 17 individuals (25%), we identified early signs of myocardial damage, including 13 patients (19%) who had areas of late gadolinium enhancement (LGE), indicative of myocardial fibrosis, and 4 patients (6%) who showed areas of myocardial fatty infiltration, with no increase in extracellular volume (ECV 27.3±3.4%). The presence of myocardial fibrosis was significantly associated with age (P = 0.02) but did not correlate with other CMR variables or degree of neuromuscular involvement.

CONCLUSION In adult DM1 patients without prior evidence of cardiac involvement and despite normal conventional cardiac evaluations and absence of symptoms, CMR detected tissue abnormalities in up to 25% of cases, demonstrating its value as a sensitive tool for early detection of myocardial damage.

143 - High Resolution Characterization of the DMPK Repeat Expansion Using CRISPR/Cas9 Capture and Long Read Sequencing in DM1 Patients

Marc Corral-Juan[1], Alicia López-Martín[1], Alvaro S. Larran[1], Clara Moliner Diaz[1], Alba Herrero-Gómez[1], Anna Revert Barberà[2], Usua Laresgoiti Garay[3], Eva Coll Liesa[1], Eric Casellas-Sanfelix[1], Alejandro Montalvà[1], Ivàn Pajuelo-Navarro[1], Raquel Pérez Gómez[4], Luis Orduña Rubio[4], Eduard Juanola-Mayos[2], Jorge Alonso-Pérez[5], Daniel M. Borràs[1], Sebastián Figueroa-Bonaparte[2], Virginia Arechavala-Gomeza[3], Arturo López-Castel[4], Gisela Nogales-Gadea[1]

[1]1. Badalona Neuromuscular Research Group (GRENBA), Germans Trias i Pujol Research Institute (IGTP), Badalona, Catalonia, Spain., [2]2. Neuromuscular Pathology Unit, Neurology Service, Neuroscience Department, Germans Trias i Pujol University Hospital, Badalona, Spain, [3]3. Nucleic Acid Therapeutics for Rare Disorders (NAT RD), Biobizkaia Health Research Institute (IIS Biobizkaia), Barakaldo, Spain, [4]4. INCLIVA Biomedical Research Institute (INCLIVA), Valencia, Spain. Human Translational Genomics Group, University Research Institute for Biotechnology and Biomedicine (BIOTECMED), University of Valencia, Burjassot, Spain., [5]5. Neuromuscular Diseases Unit, Neurology Department, University Hospital of Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Tenerife, Spain.

Resolving the full complexity of the pathogenic CTG repeat expansion in the *DMPK* gene is critical for elucidating the molecular basis of Myotonic Dystrophy type 1 (DM1). Conventional assays such as PCR, TP-PCR, and Southern blotting provide limited resolution and fail to capture key structural and epigenetic features of the locus.

We are developing an innovative methodology that integrates CRISPR/Cas9-mediated targeted enrichment with Oxford Nanopore long-read sequencing to achieve comprehensive characterization of the *DMPK* locus. This strategy enables direct sequencing of native DNA molecules spanning the entire repeat region and its flanking sequences, thereby eliminating PCR-induced bias and delivering accurate measurements of repeat length, detection of sequence interruptions, structural rearrangements, and allele-specific methylation patterns. This targeted approach yields a 60x median coverage of the *DMPK* locus, which is 10x higher on-target coverage compared with whole-genome Oxford Nanopore sequencing, while maintaining an approximately 50:50 ratio between the sequenced wild-type and expanded alleles.

Custom bioinformatic pipelines will process these enriched reads to quantify somatic mosaicism and incorporate epigenetic signals, providing a multidimensional representation of repeat architecture.

This technology will be deployed to generate high-resolution molecular profiles of DM1-Hub participants, Spain's first DM1 patient registry collecting samples, clinical, cognitive and lifestlye data from 3,000 participants. These locus-specific datasets will be integrated with whole-genome sequencing, plasma biomarker analyses, and clinical records, creating a unique multi-layered resource for robust genotype-phenotype correlations and machine learning-driven biomarker discovery.

Overall, the combination of CRISPR/Cas9-based capture and long-read sequencing represents a paradigm shift from traditional Southern blotting, enabling high-resolution, allele-specific, and clinically actionable insights into repeat expansion disorders. Beyond advancing fundamental knowledge, these high-resolution insights open the door to new biomarker discovery and more precise patient stratification, paving the way for improved clinical management and therapeutic development for DM1 on a global scale.

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144 - A stepwise molecular workflow for efficient screening of DMPK CTG repeat expansions

Diana Shabshai[1], Rezbieara Rahman[2], Noushin Masoudi[2], Mason Connolly[2], Elijah Behr[2], Emma Matthews[2], Sarah Cumming[1], Marc Ciosi[1], Darren G. Monckton[1]

[1]School of Molecular Biosciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, G12 8QQ, UK., [2]City St Georges, University of London, London UK

Most individuals with myotonic dystrophy type 1 (DM1) receive molecular confirmation only after referral to neurology, often following a prolonged diagnostic pathway of 5-10 years. Although undiagnosed DM1 patients frequently present to other clinical specialties, the lack of awareness of DM1 as a potential diagnosis, frequently precludes a clinical DM1 diagnosis and the low relative prevalence of DM1 in these settings limits routine genetic testing. Efficient strategies are therefore needed to enable scalable genetic screening for *DMPK* expansions in large cohorts. We thus aimed to develop and evaluate a sensitive, stepwise molecular screening workflow optimised for studies with a low expected prevalence of DM1. Firstly, PCR and high-resolution NuSieve gel analysis was used to identify individuals carrying two clearly non-expanded alleles, allowing rapid exclusion of a substantial proportion of samples. This method also has the potential to identify small expansions. Cases that

could not be confidently resolved at this stage were analysed using Southern blotting of a smaller amount of PCR-amplified product to detect larger expansions. Repeat-primed PCR and small-pool PCR were subsequently applied to confirm expansion status and to estimate progenitor and modal allele sizes in positive cases. Using this workflow, approximately 67% of samples were confidently excluded at the initial PCR stage. Southern blotting of amplified material resolved most of the remaining cases, leaving only a small subset requiring higher-sensitivity analyses. During screening of a cohort of 202 undiagnosed cardiology cases, one expansion was detected, one pathogenic *DMPK* CTG expansion was identified. The stepwise design substantially reduced the number of samples progressing to labour-intensive assays, eliminated the need for Southern blot analysis of restriction enzyme-digested genomic DNA and reduced DNA requirements, analytical burden, and cost, and supports broader implementation of DM1 screening beyond traditional neurology-led diagnostic pathways.

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145 - DTDM1: Dyslipidaemia and transcriptional dysregulation in DM1

Emma Matthews[1], Meneka Kanagaratnam[2], Mark Mencias[1], Rezbieara Rahman[1], Alan Pittman[1], Myotonic Dystrophy Clinical Research Network Myotonic Dystrophy Clinical Research Network[3]

[1]City St George's University of London, [2]St George's University Hospitals NHS Foundation Trust, [3]Myotonic Dystrophy Clinical Research Network

Dyslipidaemia and metabolic syndrome are described in DM1 but the cause or causes of this are not clearly delineated and unlike many of the other clinical features, associations with specific splicing changes have not been made. Dyslipidaemia is considered a risk factor for adverse cardiovascular and cerebrovascular events in the general population. It has been suggested that such events are not frequent for those with DM1 despite dyslipidaemia being common. No large-scale longitudinal studies have been performed in DM1 populations to clarify this however. Current DM1 care guidelines assume a pragmatic approach and recommend monitoring serum lipids and treating as required.

We received funding from an MDF pilot grant to perform RNA sequencing in 100-150 individuals with DM1. We will analyse the sequencing data to identify mis-spliced genes genome-wide, but with a particular focus on metabolic genes. Clinical and demographic data will be collected including age, sex, smoking history, medication and past medical history (including MI and stroke), mobility and activity, presence or absence of OSA and cardiac disease, BMI and waist circumference, blood pressure,

hba1c, thyroid function, and serum lipid levels. In addition, with the MDCRN we will analyse data from 700 participants in the END DM1 study to determine the frequency of adverse vascular events (stroke and MI) compared with the general population.

An understanding of the transcriptional and metabolic pathways involved in dyslipidaemia, alongside a preliminary analysis of the influence of mobility, demographics and other cardiovascular risk factors will help to determine the best approach to management for DM1 patients. This would inform care guidelines. It may also indicate pathways that are either predictive of or protective against dyslipidaemia or reduce the risk of cardiovascular events even in the presence of dyslipidaemia. Identification of these pathways could be manipulated by the development of new lipid lowering drugs.

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146 - Development and Feasibility of a Pediatric Neuropsychological Assessment Protocol in Myotonic Dystrophy Type 1

Amélie D'Ambroise[1], Naomie Gilbert[1], Cindy Beaudoin[2], Cynthia Gagnon[3, 4, 5], Hamdi Ben Abdessalem[1], Isabelle Gaudet[1]

[1]Université du Québec à Chicoutimi, [2]Université de Montréal, [3]Université de Sherbrooke, [4]Groupe de recherche interdisciplinaire sur les maladies neuromusculaires (GRIMN), [5]CHU de Sherbrooke-Université de Sherbrooke research center,

Myotonic dystrophy type 1 (DM1) is a rare neuromuscular disorder affecting multiple organ systems, with notably high prevalence in the Saguenay-Lac-Saint-Jean region. The pediatric forms of the disease are more severe than adult-onset cases, leading to substantial cognitive and social impairments that negatively impact both academic achievement and social integration. Despite these challenges, this population remains significantly understudied in the literature, despite ongoing advances in targeted therapies. To support their meaningful inclusion in future clinical trials, there is a pressing need for standardized, age-appropriate assessment protocols specifically designed for this population. This pilot study aims to develop and evaluate a neuropsychological assessment protocol for children and adolescents with DM1, co-developed in collaboration with parent partners and clinicians. More precisely, the assessment will examine intellectual, attentional, executive, social, and motor domains, as well as daytime sleepiness, using validated and standardized measures. In addition, non-invasive neurophysiological measures, including portable electroencephalography and eye tracking, will be integrated to better characterize attentional and socio-emotional processes. This cross-sectional pilot

study will compare ten youth with DM1 to ten age- and sex-matched typically developing controls. Given the developmental and feasibility-oriented nature of the study, analyses will focus on protocol acceptability, feasibility, and data completeness, while also allowing for an initial descriptive characterization of cognitive functioning in youth with DM1. This work ultimately seeks to advance clinical care, strengthen readiness for future clinical trials, and enhance support systems for families and educational environments. Furthermore, it will support the co-development of a plain-language educational fact sheet and digital toolkit in partnership with parent partners, with the dual objectives of promoting school inclusion and equipping educational settings with evidence-informed, tailored resources.

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147 - Tideglusib in congenital myotonic dystrophy - an update on the AMO Pharma REACH-CDM programme

Hanns Lochmuller[1], Suzanne Ftouni[2], Emily Fantelli[2], Stuart Evans[2], Madhu Davies[2], Nikoletta Nicolenko[3], Mike Snape[2]

[1]CHEO Research Institute, [2]AMO Pharma UK, [3]University College London Hospitals NHS Foundation Trust

Introduction: Congenital myotonic dystrophy type 1 (cDM1) is characterised by early-onset variable multisystem involvement. Phenotypic variability poses challenges for clinical trial design. We report results from the largest randomised, double-blind, placebo-controlled trial in cDM1 (REACH-CDM) with updates on the open-label REACH-CDM-X study.

Methods: Children and adolescents aged 6-16 years with genetically confirmed cDM1 were randomised 1:1 to oral tideglusib or placebo for 20 weeks then offered continued open-label treatment.

The primary endpoint was change from baseline to end of treatment on the Congenital DM1 Rating Scale (CDM1-RS) with functional, cognitive, adaptive behaviour, and biomarker secondary endpoints. A post-hoc multi-domain responder index (MDRI) was applied to capture clinically meaningful treatment effects across the most relevant disease domains.

Results: Fifty-three participants were randomised (tideglusib n=27; placebo n=26), 50 completing the double-blind study and 49 opting for open-label extension.

In REACH-CDM, both groups demonstrated improvement on the CDM1-RS, resulting in no significant treatment differences. Substantial variability was observed across

outcome measures. Analysis of CDM1-RS items showed many participants having low baseline scores with insensitivity to change in multiple domains. In the post-hoc MDRI analysis, a statistically significant treatment effect favouring tideglusib was detected (p=0.04). A clinically significant effect on the 10MWRT was seen.

In both studies, safety and tolerability of tideglusib was excellent with 150+ patient-years of exposure showing few Serious Adverse Events, almost exclusively unrelated to study treatment. In REACH-CDM-X participants show continued benefit long-term open label treatment up to three years.

Discussion: The REACH-CDM study missed its primary endpoint partly due to phenotypic variability. A post-hoc MDRI analysis and ongoing open-label REACH-CDM-X study suggest signals of benefit and a good safety profile. These studies highlighted cDM1 is a complex and heterogeneous disorder where capturing disease activity and treatment response is difficult and MDRI approaches may be more informative.

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149 - A multidimensional registry capturing clinical, cognitive, functional, patient-reported, and molecular profiles in myotonic dystrophy type 1

Alvaro S. Larran[1], Clara Moliner Diaz[1], Alicia López-Martín[1], Marc Corral-Juan[1], Anna Revert Barberà[2], Usua Laresgoiti Garay[3], Eva Coll Liesa[1], Raquel Pérez Gómez[4], Luis Orduña Rubio[4], Irati Larrañaga[5], Andone Sistiaga[5], Gerardo Gutiérrez-Gutiérrez[6], Jorge Alonso-Pérez[7], Ana Lara Pelayo[8], Jorge García-García[9], Daniel M. Borràs[1], Sebastián Figueroa-Bonaparte[2], Virginia Arechavala-Gomeza[3], Arturo López-Castel[4], Gisela Nogales-Gadea[1]

[1]Badalona Neuromuscular Research Group (GRENBA), Germans Trias i Pujol Research Institute (IGTP), Badalona, Catalonia, Spain, [2]Neuromuscular Pathology Unit, Neurology Service, Neuroscience Department, Germans Trias i Pujol University Hospital, Badalona, Spain, [3]Nucleic Acid Therapeutics for Rare Disorders (NAT RD), Biobizkaia Health Research Institute (IIS Biobizkaia), Barakaldo, Spain, [4]INCLIVA Biomedical Research Institute (INCLIVA), Valencia, Spain. Human Translational Genomics Group, University Research Institute for Biotechnology and Biomedicine (BIOTECMED), University of Valencia, Burjassot, Spain, [5]Department of Clinical and Health Psychology and Research Methodology, Faculty of Psychology, University of the Basque Country (UPV/EHU), Donostia-San Sebastián, Gipuzkoa, Spain, [6]Neurology Department, Infanta Sofía University Hospital, Madrid, Spain, [7]Neuromuscular Diseases Unit, Neurology Department, University Hospital of Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Tenerife, Spain, [8]Service of

Neurology, Marqués de Valdecilla University Hospital, Santander, Spain, [9]Neurology Department, Albacete University Hospital (Complejo Hospitalario Universitario de Albacete), Albacete, Spain

Myotonic Dystrophy Type 1 (DM1) presents with complex, multisystemic involvement that requires comprehensive characterization to support precision medicine. The DM1-Hub registry in Spain addresses this need by integrating clinical, functional, neuropsychological, and molecular data from patients and matched controls. Data collection spans motor, respiratory, cardiac, endocrine, gastrointestinal, and cognitive domains, complemented by patient-reported outcome measures (PROMs) on fatigue, pain, sleep quality, apathy, physical activity, and adherence to the Mediterranean diet, including DM1-Activ. Functional assessments include standardized tests such as hand grip strength via dynamometry, the Muscular Impairment Rating Scale (MIRS), Medical Research Council (MRC) motor grading, the 6-Minute Walk Test (6MWT), the 10-Meter Walk/Run Test (10MWRT), and the 30 Second Sit to Stand Test (30CST). Complementary evaluations incorporate electrocardiogram (ECG), spirometry when available, and recent laboratory parameters from routine clinical care. Demographic and diagnostic data include age, education, occupation, geographic origin, age at onset, first symptoms, and family history, while clinical variables cover anthropometrics, cardiovascular risk factors, toxic habits, and multisystem involvement (cardiac, respiratory, gastrointestinal, genitourinary), along with current medications. Neuropsychological evaluations are based on WAIS-IV subtests assessing IQ, memory, attention, processing speed, visuoconstruction, language, and executive functions, administered by trained staff using harmonized protocols. Blood samples are collected for genomic and proteomic profiling, including long-read sequencing of the whole genome and *DMPK* locus to characterize CTG repeat length, methylation status, somatic mosaicism, and interruption motifs, while proteomic analysis via mass spectrometry supports biomarker discovery. Harmonization aligns with Treat-NMD, Euro-DMC, and EMA guidelines, ensuring compatibility with global datasets and clinical trial requirements. By integrating standardized outcome measures with advanced omics data, DM1-Hub provides a unique resource for biomarker validation, patient stratification, and trial readiness in DM1.

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150 - MEG and cognition in Myotonic Dystrophy

Nikoletta Nikolenko[1], Arjun Ramaswamy[2], Enza Leone[1], Rofael Jabr[1], Chris Turner[1], Umesh Vivekananda[1]

[1]National Hospital for Neurology and Neurosurgery, Queen Square, University College London Hospitals NHS Foundation Trust, London, UK, [2]Functional Imaging Laboratory, Department of Imaging Neuroscience, University College London, London, UK.

Myotonic Dystrophy Type 1 (DM1) is the most common form of adult-onset muscular dystrophy. While primarily known for affecting skeletal, respiratory and cardiac systems, the central nervous system (CNS) involvement is a major contributor to disease burden, manifesting as excessive fatigue, apathy and deficits in executive function, visuospatial processing and attention. Although neuroradiological studies show white matter lesions and neuropathological studies identify neurofibrillary tangles and abnormal tau protein expression, the functional neural mechanisms underlying these cognitive deficits remain unclear.

The primary objective of the study was to demonstrate that theta phase coupling strength and task performance are significantly altered in DM1 patients due to the condition's effect on temporal and frontal brain regions. The secondary objective was to prove that genetic burden will negatively correlate with both visuospatial and working memory task performance and underlying brain regional theta power.

This cohort study recruited 8 adults with genetically confirmed DM1 to identify neurophysiological biomarkers using magnetoencephalography (MEG). MEG is a non-invasive technique that offers superior source localization accuracy and better immunity to muscle artifacts compared to EEG because magnetic fields are minimally affected by the skull and scalp. Participants performed validated cognitive tasks during MEG recording, including visuospatial navigation in a virtual environment and reward-processing tasks.

The study focused on theta frequency oscillations (1-8 Hz), which integrate functional brain regions across spatiotemporal scales. Specifically, the hippocampal-medial prefrontal cortex (mPFC) pathway, a circuit heavily implicated in memory formation, planning and decision-making, was examined. Performance and physiological data were compared against a healthy control dataset and correlated with genetic severity, measured by CTG repeats number.

Identifying these functional biomarkers is critical for the clinical assessment of CNS-targeted therapies. These findings may provide unprecedented insight into DM1 brain physiology and establish a framework for future trials for CNS-targeted candidate therapies.

151 - Enabling Population Screening: Determining DM1 Germline Repeat Expansion Rates.

Hossameldin Ali[1], Roaa Ehab[2], Darren Monckton[1]

[1]University of Glasgow, [2]Cairo University

Myotonic dystrophy type 1 (DM1) is caused by a CTG repeat expansion in the *DMPK* gene. Although highly expanded alleles are typically genetically lethal, new DM1 families continue to emerge, implying that non-expanded alleles occasionally expand into the pathogenic range. While transitions from “premutation” alleles (35-50 repeats) are known, haplotype analysis suggests these arise from alleles in the 20-34 repeat range, and it is these alleles that are the ultimate source of new DM1 families.

We describe a three-pronged approach to characterize germline expansion dynamics at a population level. First, we will analyse large-scale whole genome sequencing datasets—including UK Biobank and All of Us—to reconstruct the evolutionary history of *DMPK* alleles and estimate sex-averaged mutation rates. Second, we will perform ultra-deep amplicon sequencing of longitudinal sperm DNA to directly measure male germline expansion rates and age-related effects. Third, we will use trio-based sequencing data from Genomics England to detect *de novo* CTG repeat mutations and quantify expansion and contraction events occurring during both maternal and paternal transmissions.

This work will provide insights into the different disease frequencies for different ancestral groups and allows for the prediction of future disease trajectories. By integrating these approaches into a unified modelling framework, we aim to infer the rates and patterns of CTG repeat expansion with sufficient resolution to identify key transition points between stable and pathogenic alleles and derive the roles of age, sex, CTG length and repeat sequence. This work will clarify how new DM1 mutations arise in the population and provide a foundation for population screening, individual risk assessment, and reproductive counselling in both research and clinical settings. Moreover, with effective therapies for DM on the horizon, this work should give helpful future insights on the population dynamics of DM1 when it becomes no longer genetically lethal.

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152 - A Comparative Overview of Current Biomarker Development in Myotonic Dystrophies

Malin Larsen[1], Peter Meinke[1], Benedikt Schoser[1]

[1]LMU Klinikum, Friedrich-Baur-Institut

Myotonic dystrophies (DM) are autosomal dominant, multisystemic disorders characterised by myotonia and progressive muscle weakness, with additional manifestations commonly including insulin resistance and respiratory, cardiac and central nervous system involvement. Despite substantial phenotypic overlap, largely attributed to shared alternative splicing pathology, myotonic dystrophy type 1 (DM1) and type 2 (DM2) differ in genetic origin, repeat motifs, disease progression and aspects of molecular pathology. At present, DM disease management is primarily symptomatic and pronounced clinical heterogeneity contributes to frequent diagnostic delays, highlighting the need for robust biomarkers to support diagnosis, prognosis and disease monitoring. In light of increasing insight into the molecular mechanisms underlying DM, new therapeutic strategies are rapidly emerging, emphasising the requirement for reliable and responsive biomarkers to evaluate treatment efficacy. This work presents an overview of current biomarker research in DM1 and DM2, encompassing imaging-based, muscle-derived and fluid-based approaches. Established DM biomarkers remain limited, with research disproportionately focused on DM1. Multiple markers of alternative splicing pathology underlying DM have shown promise but are challenged by their reliance on invasive sampling, which restricts cohort size and longitudinal assessment. Consequently, recent efforts have shifted towards minimally invasive biomarker development, a trend reinforced by the growing therapeutic pipeline. While several fluid-based markers, such as muscle-specific circulating microRNAs, correlate with clinical measures, inconsistent detection across studies and limited evaluation of disease specificity underscore the need for continued exploration in larger, more diverse longitudinal cohorts. Future progress will depend on validation of existing candidates, discovery of novel biomarkers addressing the outlined limitations, and concerted effort to reduce the imbalance between DM1- and DM2-focused research to advance DM diagnosis, disease management and therapeutic development.

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153 - Discovery of Orally Bioavailable Small Molecules that Bind CUG Repeats, Displace Muscleblind Protein, and Improve Pathogenesis of Myotonic Dystrophy Type 1

Domi Stickens[1], Sarah Mahoney[1], Emily Garcia Sega[1], Xuan Yang[1], Amy Andreucci[1], Griffin Schroeder[1], Zach Boswell[1], Amit Shahar[1], Pallavi Awate[1], Alexandre Amlie-

Wolf[1], Alyssa Cousineau Kelly[1], Alex Wu[1], Alexandra Gehring[1], Chuck Perry[1], Eric Schwartz[1], Jennifer Petter[1]

[1]Arrakis Therapeutics

Myotonic dystrophy type 1 (DM1) is a form of muscular dystrophy and a genetic neuromuscular disease affecting at least 1 in 8,000 people worldwide. It is a multi-system disease, affecting the skeletal muscle, heart, diaphragm, central nervous system, and gastrointestinal tract. DM1 is caused by a trinucleotide (CUG) repeat expansion in the mRNA encoding myotonic dystrophy protein kinase (DMPK) that results in the formation of nuclear aggregates that bind and sequester splicing factors such as Muscleblind-Like Splicing Regulator 1 (MBNL1). Depletion of critical splicing factors leads to global splicing abnormalities and widespread pathology. There are no approved disease-modifying treatments for DM1, but several muscle-targeted oligonucleotide therapies are in clinical development. These therapies show evidence of addressing skeletal muscle defects in patients but are unlikely to fully address systemic manifestations of the disease.

Here we present preclinical data on RNA-targeted small molecules (rSMs) that selectively bind the pathogenic CUG repeat RNA and release MBNL1 from nuclear aggregates. In DM1 donor cells with 2,600 CTG repeats, rSMs reduce nuclear aggregates by 90% and correct splicing defects in a dose-dependent manner. rSMs also modulate splicing in skeletal muscle and completely reverse myotonia in the HSA^{LR} mouse model. The compounds are orally bioavailable and broadly biodistributed to multiple impacted tissues.

Although muscle pathology is a significant component of DM1, an orally bioavailable, broadly biodistributed rSM has the potential to address systemic manifestations of the disease beyond skeletal muscle and establish that rSMs represent a new class of small-molecule genetic medicines that directly address the genetic basis of disease.

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154 - How to Optimize Patient Participation in Prospective DM1 Studies: Insights from One Study, Barriers to Enrollment, and Suggestions for Improvement

Anna Revert-Barberà[1], Ainhoa Sancho-Garcia[2], Eduard Juanola-Mayos[1], Bernat Bertran-Recasens[3], Javier Sotoca[4], Alba Ramos-Fransi[5], Laura Llansó[6], Teresa Casadevall[7], Antoni Cano[8], Jorge Espinosa[9], Maria Salvadó[4], Velina Nedkova-Hristova[10], Nicolau Guanyabens[8], David Reyes-Leiva[11], Nuria Cayuela-Caudevilla[11], Gisela Nogales-Gadea[2]

[1]Neuromuscular Pathology Unit, Neurology Service, Neuroscience Department, Germans Trias i Pujol University Hospital, Badalona, Spain., [2]Badalona Neuromuscular Research Group (GRENBA), Germans Trias i Pujol Research Institute (IGTP), Badalona, Catalonia, Spain., [3]Neuromuscular Pathology Unit, Neurology Department, Hospital del Mar, Barcelona, Spain, [4]Neuromuscular Diseases Unit, Department of Neurology, Hospital Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain., [5]Neurology Department, Hospital Clínic de Barcelona, Barcelona, Spain., [6]Neuromuscular Diseases Unit, Department of Neurology, Hospital de la Santa Creu i Sant Pau, Institut d'Investigació Biomèdica Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain., [7]Neurology Department, Hospital Comarcal Sant Jaume de Calella, Calella, Barcelona, Spain., [8]Neurology Department, Hospital Universitari de Mataró, Barcelona, Spain., [9]Neurology Department, Hospital Universitari Parc Taulí, Sabadell, Barcelona, Spain., [10]Neuropathology Unit, Department of Pathology and Neuromuscular Unit, Department of Neurology, IDIBELL-Hospital de Bellvitge, Hospitalet de Llobregat, Barcelona, Spain., [11]Neurology Department, Hospital de Sant Joan Despí Moisès Broggi, Barcelona, Spain.

Myotonic dystrophy type 1 is a complex multisystem disease. Observational studies have contributed to a better understandig of the natural history of DM1. However, few prospective studies have examined the specific involvement of different organs, and those that exist often struggle with low participant numbers. This may be partly due to the pronounced clinical heterogeneity of DM1, which makes it difficult to identify homogeneous cohorts that meet specific inclusion and exclusion criteria, as well as by lower disease awareness compared to other neuromuscular disorders.

We aimed to conduct a prospective study to investigate biomarkers of early cardiac involvement in DM1 using relatively strict inclusion and exclusion criteria. Although all study tests would take place at our hospital, we reached out to neurologists at 9 other hospitals to inform them about the study anticipating potential challenges in recruiting. Of all patients invited to participate, 39% were excluded from follow-up for various reasons: 19% declined participation, while non-compliance with inclusion criteria and inability to contact patients accounted for 13% and 7%, respectively. The main reasons to decline were difficulties travelling to the medical center, limited time availability, work schedule conflicts and the high number of required visits.

This high refusal rate makes us wonder which modifiable aspects should be optimized when designing prospective studies to improve DM1 patient participation, considering their specific features. Implementing strategies such as decentralizing data collection to more easily accessible centers, deploying trained personnel who

can visit patients in multiple sites, offering flexible scheduling, and promoting patient education to improve disease understanding and highlight the importance of follow-up and research can significantly improve patient recruitment and retention in prospective DM1 studies.

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155 - Early insights into clinical, cognitive, and lifestyle correlations in myotonic dystrophy type 1

Alba Herrero-Gómez[1], Clara Moliner Diaz[1], Luisa Tenorio[2], Cynthia Almeida[3], Estefania Bocanegra[4], Patricia Garay[5], Irati Larrañaga[6], Patricia Alonso[7], Maitane Bravo[7], Marc Corral-Juan[1], Alvaro S. Larran[1], Anna Revert Barberà[1], Alicia López-Martín[1], Solange Kapetanovic[7], Gerardo Gutiérrez-Gutiérrez[2], Andone Sistiaga[6], Jorge Alonso-Pérez[3], Daniel Borras[1], Arturo López-Castel[8], Gisela Nogales-Gadea[1]

[1]Badalona Neuromuscular Research Group (GRENBA), Germans Trias i Pujol Research Institute (IGTP), Badalona, Catalonia, Spain., [2]Neurology Department, Infanta Sofía University Hospital, Madrid, Spain., [3]Neuromuscular Diseases Unit, Neurology Department, University Hospital of Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Tenerife, Spain., [4]Neurology Department & Instituto de Biomedicina de Sevilla (IBiS), Virgen del Rocío University Hospital, Seville, Spain., [5]Neuromuscular Pathology Unit, Neurology Service, CIBERNED, Donostia University Hospital, Donostia, Spain, [6]Department of Clinical and Health Psychology and Research Methodology, Faculty of Psychology, University of the Basque Country (UPV/EHU), Donostia-San Sebastián, Gipuzkoa, Spain., [7]Nucleic Acid Therapeutics for Rare Disorders (NAT-RD), Biobizkaia Health Research Institute (IIS Biobizkaia), Barakaldo, Spain. University Hospital Basurto, Bilbao, Spain., [8]INCLIVA Biomedical Research Institute (INCLIVA), Valencia, Spain. Human Translational Genomics Group, University Research Institute for Biotechnology and Biomedicine (BIOTECMED), University of Valencia, Burjassot, Spain.

Myotonic Dystrophy Type 1 (DM1) is a multisystemic disorder with heterogeneous manifestations, and understanding phenotype variability is essential for improving care and guiding therapeutic development. We report preliminary findings from the DM1-Hub registry, a nationwide initiative collecting multidimensional data from 3,000 patients and matched controls across Spain.

Analyses of the initial cohort reveal clinically relevant associations, including a correlation between reduced forced vital capacity and increased apathy scores, suggesting interplay between respiratory impairment and central nervous system involvement. Symmetrical progression of muscle weakness is supported by strong

correlations between left- and right-hand grip strength, while poor dietary habits appear linked to greater daytime sleepiness, highlighting the impact of lifestyle factors on symptom burden and disease management. Additionally, individuals with affected relatives were more likely to be asymptomatic at diagnosis, underscoring how family awareness and disease education can facilitate early detection in undiagnosed relatives.

These preliminary findings illustrate the potential of integrated registries to uncover novel clinical correlations, inform patient stratification strategies and improve standard of care for DM1 patients globally. By combining standardized clinical assessments, neuropsychological testing, and lifestyle data with molecular profiling, DM1-Hub aims to accelerate biomarker discovery, refine prognostic models, and optimize trial readiness for DM1. Further analyses will explore genotype-phenotype relationships and longitudinal trajectories to support precision medicine approaches and ultimately improve prognosis for individuals living with DM1.

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157 - DM1-Heart: Searching Biomarkers of Cardiac Damage in Myotonic Dystrophy Type 1

Anna Revert-Barberà[1], Eduard Juanola-Mayos[1], Ainhoa Sancho-Garcia[2], Victoria Delgado[3], Martin Rojas-Goldsack[3], Bernat Bertran-Recasens[4], Javier Sotoca[5], Alba Ramos-Fransi[6], Laura Llansó[7], Teresa Casadevall[8], Jorge Espinosa[9], Antoni Cano[10], Maria Salvadó[5], Raul Juntas[5], Velina Nedkova-Hristova[11], Nicolau Guanyabens[10], David Reyes-Leiva[12], Nuria Cayuela-Caudevilla[12], Alicia López-Martín[2], Gisela Nogales-Gadea[2]

[1]Neuromuscular Pathology Unit, Neurology Service, Neuroscience Department, Germans Trias i Pujol University Hospital, Badalona, Spain., [2]Badalona Neuromuscular Research Group (GRENBA), Germans Trias i Pujol Research Institute (IGTP), Badalona, Catalonia, Spain., [3]Heart Institute, Cardiology Department, Cardiovascular Imaging Unit, Germans Trias I Pujol University Hospital, Badalona, Spain, [4]Neuromuscular Pathology Unit, Neurology Department, Hospital del Mar, Barcelona, Spain, [5]Neuromuscular Diseases Unit, Department of Neurology, Hospital Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain., [6]Neurology Department, Hospital Clínic de Barcelona, Barcelona, Spain., [7]Neuromuscular Diseases Unit, Department of Neurology, Hospital de la Santa Creu i Sant Pau, Institut d'Investigació Biomèdica Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain., [8]Neurology Department, Hospital Comarcal Sant Jaume de Calella, Calella, Barcelona, Spain., [9]Neurology Department, Hospital

Universitari Parc Taulí, Sabadell, Barcelona, Spain., [10]Neurology Department, Hospital Universitari de Mataró, Barcelona, Spain., [11]Neuropathology Unit, Department of Pathology and Neuromuscular Unit, Department of Neurology, IDIBELL-Hospital de Bellvitge, Hospitalet de Llobregat, Barcelona, Spain., [12]Neurology Department, Hospital de Sant Joan Despí Moisès Broggi, Barcelona, Spain.

Myotonic dystrophy type 1 (DM1) is a multisystem disease. Approximately 80% of patients present cardiac involvement, which is the second leading cause of death. The most common cardiac manifestations are conduction disturbances and arrhythmias. In a variable proportion of patients, left ventricular involvement is also observed, and has been correlated with conduction system disease.

Currently, no biomarkers reliably predict which DM1 patients are at risk of cardiac damage, hindering the ability to deliver individualized and improved clinical management. The DM1-Heart project aims to identify and validate these biomarkers of future cardiac damage.

The DM1-Heart is a prospective study that would last 2 years. ECG, echocardiography, and 24-hour Holter monitoring are performed at baseline, at 1 year, and at 2 years, as well as neuromuscular, functional, and respiratory assessments. Cardiac magnetic resonance (CMR) is performed at baseline and at the 2-year follow-up. In addition, blood samples are collected every six months for plasma biomarker analysis. The inclusion criteria are genetic diagnosis of DM1 and symptom onset after the age of 18. Patients with known structural heart disease or arrhythmia, abnormal baseline ECG, and those with pacemaker or implantable defibrillators have been excluded.

The recruitment phase took place from December 2024 to December 2025. A total of 144 patients were proposed to participate, of whom 96 were included, and none of them reported cardiac symptoms. The baseline evaluation revealed the following findings: 7 patients with PR interval longer than 200ms in ECG, 15 with some degree of left ventricular hypertrophy and 18 with valvular involvement on echocardiography. Although most findings are not considered clinically significant, longitudinal follow-up may uncover which alterations progress to clinically significant cardiac involvement and their correlation with potential biomarkers, supporting personalized preventive strategies in DM1.

158 - Dual Targeting ASO-based RiboTAC degrades CUG RNA and Rescues Mis-Splicing in HeLa-based DM1 Cell Model

Amy Mascorro[1, 2], Yu Sheng Chen[1, 2], Angela White[1, 2], Audrey Coons[3], Lucas Hooker[3], Shemari Blackwood[3], Sanjida Ahmed[3], Jia Sheng[1, 2], Andy Berglund[2, 3]

[1]Department of Chemistry, State University of New York at Albany, [2]RNA Institute, State University of New York at Albany, [3]Department of Biological Sciences, State University of New York at Albany

Myotonic Dystrophy type 1 (DM1) is an autosomal dominant, repeat expansion disease that results in RNA gain-of-function. Expression of the CTG repeat expansion from the 3' Untranslated Region (UTR) of the Dystrophia Myotonica Protein Kinase (DMPK) gene results in $(CUG)^{exp}$ that sequester the MBNL family of proteins. Given that yhese proteins are key regulators of splicing, their sequestration results in catastrophic dysregulation of alternative splicing. Many of these events are directly connected to DM1 patients symptoms such as myotonia, insulin resistance, GI tract issues, and cardiovascular defects. While there are some treatments on the verge of gaining FDA approval, it is vital to develop a broad range of potential treatments. Based on a different DM-targeting RiboTAC using small molecules to target the $r(CUG)^{exp}$, this work details the development and characterization of a **Du**al-Targeting **Ribo**nuclease **Ta**rgeting **C**himera (DuRTAC) that targets both the $r(CUG)^{exp}$ and the 3'UTR of the DMPK gene. Preliminary evidence shows that this dual targeting degradation method results in specific degradation of $r(CUG)^{exp}$ using RNase L - an RNA degradation enzyme that is involved in the innate immune response - both *in-vitro* and *in-cellulo*. This ongoing project has shown promising results in the use of two targeting oligos to degrade CUG repeats, resulting in the release of MBNL proteins and rescue of DM1 biomarkers in a DM1 HeLa cell model.

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159 - The GRIMN Biobank: A Longitudinal Biobank Coupling Biospecimens with Comprehensive Clinical Phenotyping in DM1

Melissa Verreault[1], Élise Duchesne[1, 2, 3, 4], Cynthia Gagnon[1, 5, 6]

[1]Groupe de recherche interdîsciplinaire sur les maladies neuromusculaires (GRIMN), Center for Research and Innovation of the Saguenay-Lac-St-Jean Integrated University Health and Social Services Center, Saguenay, Quebec, Canada, [2]School of Rehabilitation Sciences, Faculty of Medicine, Université Laval, Quebec City, Quebec, Canada, [3]Center for Interdisciplinary Research in Rehabilitation and Social Integration (Cirris), Capitale-National Integrated University Health and Social

Services Center, Quebec City, Quebec, Canada, [4]CHU de Québec-Université Laval Research Center, Quebec City, Quebec, Canada, [5]School of Rehabilitation, Faculty of Medicine and Health Sciences, Université de Sherboroke, Sherbrooke, Québec, Canada, [6]CHU de Sherbrooke-Université de Sherbrooke research center, Sherbrooke, Québec, Canada

Centralized access to high-quality, well-annotated biological resources linked to extensive phenotypic data, including CTG repeat length, remains limited in myotonic dystrophy type 1 (DM1). Biobanks play a critical role in advancing biomarker discovery by providing standardized biological samples connected to longitudinal clinical data. The Groupe de recherche interdisciplinaire sur les maladies neuromusculaires (GRIMN) has conducted multiple studies in neuromuscular disorders, including several DM1-focused projects, enabling systematic collection of biological material using harmonized clinical outcome assessments.

To describe the development, scope, and utilization of the Saguenay biobank and to document the availability of biological materials and clinical outcome data supporting neuromuscular research, innovation, and clinical trial readiness.

The biobank integrates biological samples and phenotypic data collected through GRIMN-led studies conducted since 2000, using standardized protocols and centralized data management. Data are curated and managed using the ATIM software platform to ensure traceability, quality control, and accessibility for academic and industry partners.

The biobank includes samples from DM1-specific studies with several timepoints including 239 individuals. They include a large natural history cohort with up to 25 years of follow-up, as well as central nervous system observational studies and exercise-based interventional trials. More than 4,000 phenotypic variables are available, covering multisystemic involvement including quantitative muscle strength, executive functions, sleep, participation, and quality of life. A total of 8,051 biological samples are stored, including 6,931 derived from individuals with DM1 from these studies. Sample types include derivatives from muscle biopsies (747), skin biopsies (113), blood draw (6,125), urine (492), saliva (292), and buccal swab (188), providing comprehensive biological representation.

Leveraging a unique founder population from the Saguenay-Lac-Saint-Jean region, the GRIMN biobank offers centralized access to high-quality biological resources for DM1. Expansion and harmonization will further strengthen collaboration, biomarker discovery, and clinical trial preparedness in rare neuromuscular diseases.

160 - Comparison between long-read sequencing technologies and the gold-standard Small Pool PCR in the study of Myotonic Dystrophy Type 1

Eva Coll Liesa[1], Alicia López-Martín[1], Ivàn Pajuelo-Navarro[1], Clara Moliner[1], Anna Revert Barberà[2], Eduard Juanola Mayos[2], Miriam Almendrote[2], Sebastián Figueroa-Bonaparte[2], Luis Orduña[3, 4], Marc Corral-Juan[1], Daniel M Borràs[1], Gisela Nogales-Gadea[1]

[1]Badalona Neuromuscular Research Group (GRENBA), Germans Trias i Pujol Research Institute (IGTP), Badalona, Catalonia, Spain., [2]Neuromuscular Pathology Unit, Neurology Service, Neuroscience Department, Germans Trias i Pujol University Hospital, Badalona, Spain., [3]INCLIVA Biomedical Research Institute (INCLIVA), Valencia, Spain., [4]Human Translational Genomics Group, University Research Institute for Biotechnology and Biomedicine (BIOTECMED), University of Valencia, Burjassot, Spain.

Although Small-Pool PCR with Southern blot (SP-PCR) is considered the gold-standard for the study of the CTG expansion that causes Myotonic Dystrophy Type 1 (DM1), its limited ability to capture the full extent of genetic heterogeneity restricts accurate patient characterization and biomarker discovery. Emerging long-read sequencing (lrGS) platforms, such as Oxford Nanopore Technologies (ONT) and Pacific Biosciences (PacBio), offer improved resolution of complex repeat expansions; however, their performance has not yet been systematically compared with SP-PCR. In our study, we sequence blood samples from a cohort of Spanish DM1 patients with two sequencing techniques: we use the Puretarget kit from PacBio and we establish a protocol for sequencing with ONT, we also use SP-PCR with the restriction enzyme AciI to measure the allele sizes (ePAL, modal allele and instability) and the presence of CGG interruptions in the DMPK gene.

We are comparing the performance of all sequencing technologies by evaluating the number of reads obtained, the estimated allele sizes, the presence and types of repeat interruptions, the proportion of interrupted reads, and the number of interruptions per interrupted read, among other metrics. In our cohort, the ePAL and modal allele values are similar in both lrGS technologies when compared to the results obtained in SP-PCR. Nevertheless, preliminary results show differences in the detection and quantification of CGG-interrupted reads between techniques. Characterizing these differences and understanding their impact on pathophysiology could aid in the search of molecular biomarkers of DM1.

In conclusion, long-read sequencing technologies provide novel and clinically relevant insights into repeat composition and structure. Given the profound clinical

and genetic heterogeneity of DM1 and the lack of molecular biomarkers, continued refinement of long-read sequencing protocols, together with larger and more diverse patient studies, will be essential to unlock their potential for improving stratification and patient care in DM1.

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161 - DM1 patient derived fibroblasts as an in vitro cell model for CTG somatic instability

Nehaa Kandasamy Packil Ponraj[1], Sarah Cumming[1], William Sands[1], Darren Monckton[1], Caroline Benn[2]

[1]University of Glasgow, [2]LoQus23

The length of the inherited CTG repeat in the *DMPK* gene is positively correlated with DM1 disease severity and inversely with age at onset. These repeats are somatically unstable in an expansion-biased, age-dependent, tissue-specific manner and individual specific rates of somatic expansion are correlated with the rate of disease progression. Skin cells have repeat sizes comparable to muscle cells and studying modifiers of somatic instability in fibroblasts should help identify potential therapeutic targets for the disease. Development of a cell model in which the CTG repeat is unstable will allow us to test the effects of modifier genes on somatic instability. Knockdown of known and predicted modifiers genes *MSH3*, *FAN1, PMS2 and MLH3,* most of which are involved in the DNA mismatch repair pathway, will inform on the role of mismatch repair in somatic instability. Fibroblast cells derived from the skin of donors with DM1 were obtained from the Coriell Institute. Fibroblasts from donors with alleles of approximately 66 CTGs, 400 CTGs and 1200 CTGs in blood were chosen to study the effects of modifiers on somatic instability. The fibroblasts were cultured and genotyped for CTG length. Cells from one donor were relatively homogenous for alleles of approximately 66 repeats. The other two cultures were polyclonal with common alleles of approximately 140, 250, 545, and 600 for one, and 631, 1200 and 1900 for the other. Small pool PCR analysis revealed that the CTG repeats of these fibroblasts were unstable over 10 weeks. These cells were immortalised using plasmid nucleofection of *hTERT*, selected using an antibiotic and will be cloned via serial dilution to have one repeat size per cell line. Fibroblast cells are easy to handle with observable somatic instability *in vitro*, making them an appropriate cell model for studying modifiers of somatic instability in DM1.

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163 - Implementing a Socially Assistive Robot-Guided Functional Assessment During Routine Outpatient Care in Myotonic Dystrophy Type 1

Élodie Gagnon[1, 2], Killian Lachaux[3], Florentin Thullier[3], Sébastien Gaboury[3], Cynthia Gagnon[1, 4, 5], Elise Duchesne[1, 6, 7, 8]

[1]Groupe de recherche interdisciplinaire sur les maladies neuromusculaires (GRIMN), Saguenay-Lac-St-Jean Integrated University Health and Social Services Center, Saguenay, Quebec, Canada, [2]Health Sciences Department, Université du Québec à Chicoutimi, Chicoutimi, Québec, Canada, [3]Department of Mathematics and Computer Science, Université du Québec à Chicoutimi, Chicoutimi, Québec, Canada, [4]School of Rehabilitation, Faculty of Medicine and Health Sciences, Université de Sherboroke, Sherbrooke, Québec, Canada, [5]CHU de Sherbrooke-Université de Sherbrooke research center, Sherbrooke, Québec, Canada, [6]School of Rehabilitation Sciences, Faculty of Medicine, Université Laval, Quebec City, Quebec, Canada, [7]Center for Interdisciplinary Research in Rehabilitation and Social Integration (Cirris), Capitale-National Integrated University Health and Social Services Center, Quebec City, Quebec, Canada, [8]CHU de Québec-Université Laval Research Center, Quebec City, Quebec, Canada

Background: Standardized physical and functional assessments are essential for monitoring disease progression in myotonic dystrophy type 1 (DM1). However, these assessments are time-consuming, prone to inter-rater variability, and increase clinician workload. Building on prior validation of socially assistive robots (SARs) for automated physical testing, this project aimed to evaluate the feasibility and acceptability of an innovative SAR-based, co-constructed clinical pathway embedded in a real-world outpatient neuromuscular clinic.

Objective: To evaluate the feasibility, completion rate, and user acceptability of a SAR-guided standardized assessment pathway implemented during routine outpatient visits at a neuromuscular clinic.

Methods: Using a co-construction approach, an interactive assessment pathway was deployed in a dedicated clinic waiting-room environment. Upon arrival, participants completed a standardized parcours guided by the SAR, including: 30-Second Chair Stand Test (with extraction of the 5-times sit-to-stand), 10-meter walk test and grip strength testing. Feasibility was defined as the proportion of contacted individuals who agreed to participate. Completion rate was defined as the proportion of participants who completed the entire robot-guided assessment pathway among those who initiated the protocol. Acceptability was explored through focus groups

and analyzed using the seven domains of Sekhon et al.'s Theoretical Framework of Acceptability.

Results: Of all DM1 patients and healthy controls contacted, more than 90% agreed to participate. Among the 35 participants with DM1, completion was high across all assessments (30-34 of 35 participants per test) Focus group findings (1 DM1 patient, 2 controls) indicated high overall acceptability. The intervention generated curiosity, minimal discomfort, and an effort level comparable to a physiotherapy session. Participants felt guided and engaged, while emphasizing the importance of human presence for introducing the SAR. Suggested improvements included enhanced robot interactivity and more natural encouragement.

Conclusion: Embedding a SAR-guided standardized assessment pathway within routine clinical visits is highly feasible and well accepted in DM1 population.

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164 - Development of Quantitative Muscle Imaging as a Biomarker of Disease Endpoints in Myotonic Dystrophy

Diana A. Madrid Fuentes[1], Elizabeth G. Hilber[1], Ashley A. Weaver[1], Araya Puwanant[1]

[1]Wake Forest University School of Medicine

Myotonic dystrophy (DM) is associated with progressive and heterogeneous muscle involvement. Quantitative, non-invasive biomarkers that capture regional muscle pathology are needed for natural history studies and therapeutic trials. Dixon MRI enables muscle fat fraction (MFF) estimation and may serve a sensitive imaging biomarker of disease severity.For an ongoing observational study, Dixon MRI scans covering the hip, thigh, and calf were acquired in individuals with DM type 1 or type 2 (N= 9, 5 females, ages 52±12) and unaffected controls (N= 5, 3 females, ages 42±13). To quantify MFF (%), muscles were segmented automatically using MuscleMap. Analyses were performed blinded to DM type. Groups were compared with a t-test and Spearman rank correlation (ρ) was used to measure associations of MFF with handheld dynamometry and 10-meter walk time (gait speed).Mean MFF in DM vs. controls was (mean ± SD): hip 33.5 ± 13.8% vs. 15.5 ± 6.8% (p-value=0.007), thigh 23.7 ± 16.0% vs. 9.8 ± 4.2% (p-value=0.03), calf 22.5 ± 12.8% vs. 11.8 ± 5.1% (p-value=0.05), and all muscles 27.1 ± 13.8% vs. 12.8 ± 5.8 (p-value=0.02). In eight DM participants with motor testing, mean elbow flexion strength was 6.4 ± 12.2 lbs, wrist extension strength was 16.5 ± 7.8 lbs, knee extension strength was 59.6 ± 25.1 lbs and 10-meter walk time was 7.7 ± 6.1 seconds. Higher average MFF across lower extremity muscles was associated with lower strength for elbow flexion (ρ=-0.74, p-value=0.037), wrist extension (ρ=-0.74, p-value=0.037), and knee extension (ρ=-0.71,

p-value=0.047). Higher thigh MFF was associated with longer 10-meter walk time (ρ=0.79, p-value=0.021).

MFF trended toward higher values in DM relative to controls and was significantly associated with muscle strength and walking speed. These interim findings suggest that MFF may serve as a useful imaging biomarker for DM disease severity.

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166 - A systematic review of the measurement properties of outcome measures for motor function for adults with myotonic dystrophy type 1

Demers Isabelle[1], Isabelle Côté[2], Elizabeth Angelevski[2], Marika Morin[2], Elise Duchesne[3], Nicoline BM Voet[4], Cynthia Gagnon[5]

[1]School of Rehabilitation, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Sherbrooke, Quebec, Canada; Groupe de recherche interdisciplinaire sur les maladies neuromusculaires (GRIMN), Quebec, Canada, [2]Groupe de recherche interdisciplinaire sur les maladies neuromusculaires (GRIMN); Centre de recherche et d'innovation du CIUSSS Saguenay-Lac-St-Jean, Quebec, Canada, [3]Groupe de recherche interdisciplinaire sur les maladies neuromusculaires (GRIMN); School of Rehabilitation Sciences, Faculty of Medicine, Université Laval, Quebec City; Center for Interdisciplinary Research in Rehabilitation and Social Integration (CIRRIS), Capitale-National Integrated University Health and Social Services Center, Quebec City; CHU de Québec-Université Laval Research Center, Quebec City, Quebec, Canada., [4]Rehabilitation center Klimmendaal, Arnhem, the Netherlands; Department of Rehabilitation, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands, [5]School of Rehabilitation, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Sherbrooke; Centre de recherche et d'innovation du CIUSSS Saguenay-Lac-St-Jean, Quebec, Canada

Background: Myotonic dystrophy type 1 (DM1) is a multisystemic neuromuscular disorder characterized by motor impairments such as muscle weakness, myotonia, and reduced endurance. Although several studies have documented DM1 natural history and evaluated interventions using various motor function clinical outcomes assessments (COA), evidence regarding the measurement properties of these COA remains limited and fragmented. A systematic review is therefore essential to identify and critically appraise the available evidence on the measurement properties of motor function COA. **Methods:** A comprehensive search was conducted for articles available in French or English. Four databases (PubMed, MEDLINE, CINAHL, and Scopus) were searched from 1992 to 2023, while ProQuest and EMBASE were

searched from 2012 to 2022. Eligible studies assessed the measurement properties of one or more motor function COA in adults diagnosed with DM1. A critical appraisal of psychometric properties was performed following the Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN) methodology. **Results:** The search identified 1,882 records; after duplicates removal, 59 articles underwent full-text review, and 39 met inclusion criteria for data extraction and analysis. Eighteen distinct motor function outcome measures were identified across these studies. None of the measures had been evaluated for all eight COSMIN psychometric properties. Reliability was the most frequently reported property, assessed in 30 studies and covering 94% of the identified outcome measures. When considering all reported psychometric properties across the 18 outcome measures, only 59.6% of these assessments met at least an adequate level according to COSMIN standards. **Conclusion:** This review highlights significant limitations in the methodological rigor used to evaluate the psychometric properties of motor function COA for adults with DM1. High-quality, methodologically robust studies are needed to strengthen the evidence base and support the appropriate selection of COA for clinical trials and longitudinal studies in this population. Will be updated before IDMC15.

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167 - Multi-omic profiling of stem cell-derived neurons

Haley Geertsma[1], Caroline Part[1, 2], Kaela O'Connor[1, 2], Sally Spendiff[1], Stephen Baird[1], Alex MacKenzie[1], Hanns Lochmuller[1, 3, 4, 5, 6]

[1]CHEO Research Institute, Ottawa, Canada, [2]Department of Cellular and Molecular Medicine, University of Ottawa, Canada, [3]Division of Neurology, Department of Medicine, The Ottawa Hospital, Canada, [4]University of Ottawa Brain and Mind Research Institute, Canada, [5]Department of Neuropediatrics and Muscle Disorders, Medical Centre, University of Frieburg, Faculty of Medicine, Germany, [6]Centro Nacional de Analisis Genomico, Spain

Myotonic dystrophy type 1 (DM1) affects several organs and organ systems including the brain and heart. It has been reported that excessive daytime sleepiness and cognitive dysfunction have the greatest impact on quality of life. DM1 is caused by a trinucleotide repeat expansion within *DMPK* leading to the sequestration of key RNA-binding proteins binding to the *DMPK* mRNA hairpin, resulting in global spliceopathy and altered DMPK function. Although the genetic cause of disease is known, there remain no disease-modifying treatments for DM1. I hypothesize that garnering a better understanding of the molecular mechanisms of disease will aid in

the discovery of disease-associated biomarkers and disease-modifying therapeutics. To address this hypothesis, I began by generating induced pluripotent stem cell (iPSC) lines from people with DM1 with varying degrees of CTG repeat expansion and symptom presentation. I used prime editing - which employs CRISPR/Cas9 to replace the CTG repeat expansion with a healthy 10 repeats - to generate isogenic control iPSC lines. I used lentivirus on both disease and isogenic control iPSC lines to generate stable doxycycline-inducible *NGN2* or *ASCL1* overexpression to differentiate glutamatergic or GABAergic neurons, respectively. I have begun characterizing general neuronal morphology and mitochondrial health and am working with a PhD student differentiating and characterizing iPSC-derived cardiomyocytes. Together, we have performed in-depth unbiased proteomics to identify common and cell-specific proteins that are altered in disease. We will also be performing ultra deep RNA sequencing to identify transciptomic changes across disease and cell type. These datasets will be cross-referenced to identify common disease-associated pathways that we can target for biomarker and drug discovery. Insights gleaned from this multi-omic analysis will guide our upcoming drug screen. Altogether, this research will bolster our understanding of the pathomechanism of DM1 and will pave the way to disease-modifying therapies.

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169 - Fibrosis, TGF beta and RNA Toxicity

Mani Mahadevan[1], Ramesh Yadava[1], Ranjit Sahu[1]

[1]University of Virginia

RNA toxicity in myotonic dystrophy eventually leads to dystrophic changes in the heart and skeletal muscles of individuals with DM1. We have evidence that RNA toxicity leads to dystrophic changes in mouse models of RNA toxicity. Our hypothesis is that i) fibro-adipogenic progenitor cells (FAPS) could be mediating these changes, and ii) that they are driven by increased TGF beta expression in the affected skeletal and cardiac muscles. Our goal is to study the contributions of FAP cells and TGF beta in the dystrophic process. We are using genetic and pharmacologic approaches to study this. We have generated mice with RNA toxicity (HSALR and DM200 models) in which the response to TGF beta has been abrogated in FAP cells. We have also worked with major pharmaceutical companies to obtain ASOs that target the toxic RNA, and highly specific anti-TGF beta therapeutics and have run blinded studies to see their effects on skeletal muscle fibrosis and fat infiltration as well as the same in cardiac muscles. We have utilized serial cardiac MRIs, EMGs, ECGs, grip strength, treadmill running and Barium Chloride induced muscle damage as phenotypic

assays. In addition, we have used extensive histologic staining and analyses, along with molecular (gene expression) analyses of relevant markers of adipogenesis, fibrosis, FAP cells, and TGF beta activity. Results from ongoing experiments will be presented from the trials that used HSALR as well as the DM200 model.

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170 - Engineered human myobundles as a proof-of-concept preclinical platform for therapeutic testing in Myotonic Dystrophy Type 1

Minh Ngoc Khong[1], Jérôme Polentes[1], Noémie Bérenger-Currias[1], Denis Furling[2], Cécile Martinat[1], Lise Morizur[1]

[1]I-STEM, CECS / Inserm UMR861 / UEVE - Corbeil-Essonnes (France), [2]Centre de Recherche en Myologie, Sorbonne Université, Inserm, Institut de Myologie, Paris (France)

Myotonic dystrophy type 1 (DM1) is the most common adult-onset muscular dystrophy. Despite identifying the causal mutation three decades ago, incomplete understanding of disease mechanisms hinders progress in treatment development. This underscores the need for innovative strategies and more predictive translational models. Recent advances in 3D cell culture techniques using human pluripotent stem cells (hPSCs) have enabled the development of functional human skeletal muscle constructs.

We implemented a transgene-free protocol to differentiate distinct hPSC lines into a homogeneous and expandable population of myogenic progenitor cells. In 2D culture, these progenitors fused to form myotubes with a high fusion index, well-organized sarcomeric architecture, and spontaneous contractile activity. Notably, a small fraction of cells expressed Pax7 adjacent to muscle fibers. To generate functional skeletal muscle tissue, progenitors were embedded within 3D hydrogel scaffolds anchored between flexible pillars. Myobundles derived from DM1 cells were subsequently used to evaluate multiple therapeutic strategies.

Engineered myobundles reproducibly formed cross-striated myotubes capable of generating active twitches in response to acetylcholine or electrical stimulation after 7 days. Contractile activity correlated with robust calcium transients after exposure to acetylcholine. We applied this 3D skeletal muscle platform to hPSCs carrying mutations in the DMPK gene. We validated the pathological relevance of the model by observing known molecular hallmarks of the disease, including nuclear RNA foci and splicing defects. DM1 myobundles also displayed functional impairments, with reduced contractile force at day 7 and day 14, and delayed relaxation kinetics. Notably, we observed reversal of key disease hallmarks following treatment with

multiple therapeutic modalities, including small molecules and gene therapy-based approaches.

We developed a robust 3D human skeletal muscle platform that recapitulates molecular and functional features of DM1. The model enables quantitative assessment of disease-associated contractile deficits alongside molecular hallmarks. It establishes a proof-of-concept functional preclinical platform to evaluate therapeutic candidates.

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171 - Somatic repeat expansion rate is higher in myotonic dystrophy type 1 patients with a more rapid progression of skeletal muscle weakness

Nemanja Radovanovic[1], Jovan Pesovic[1], Lana Radenkovic[1], Goran Brajuskovic[1], Vladimir M Jovanovic[2, 3], Vidosava Rakocevic Stojanovic[4, 5], Stojan Peric[4, 5], Dusanka Savic-Pavicevic[1]

[1]University of Belgrade-Faculty of Biology, Center for Human Molecular Genetics, Belgrade, Serbia, [2]Human Biology and Primate Evolution, Department of Biology, Chemistry, and Pharmacy, Freie Universität Berlin, Berlin, Germany, [3]Bioinformatics Solution Center, Department of Mathematics and Computer Science, Freie Universität Berlin, Berlin, Germany, [4]University of Belgrade-Faculty of Medicine, Belgrade, Serbia, [5]Neurology Clinic, University Clinical Center of Serbia, Belgrade, Serbia

The DMPK CTG repeat expansion undergoes a pronounced somatic expansion over time. We examined somatic expansion dynamics and their relation to the progression of skeletal muscle weakness in DM1 patients (N=39) followed up for 7.6±1.3 years, and blood-genotyped by the single-cell small-pool PCR. We used baseline 10th percentile allele length as the best estimate of the progenitor allele length (ePAL), the modal allele length (MAL) as a measure of somatic expansions, and the MAL increment as a measure of longitudinal increase in somatic expansion. Muscle strength was manually assessed with a maximal score of 20 points on MRC scale. Patients were classified as progressive based on a decrease of ≥2 points during the follow-up.

According to a linear mixed-effect model, MAL statistically significantly increased over time with larger ePAL, older baseline age and elapsed time, and slightly decreased due to ePAL and elapsed time interaction. The model explained 79.1% of the variance in MAL increase and additional 15.5% when accounting for baseline individual differences. Incorporating the interaction term between elapsed time and progression status in the model while accounting for baseline MRC score, we

observed a statistically significantly higher rate of MAL increase in the progressive group compared to non-progressive (21.8 vs. 13.8 repeats/year). Based on logistic regression adjusted for baseline age, each 10-repeat gain in MAL increment corresponded to a 15% increase in the odds of progression, while each additional year corresponded to an increase in odds by a factor of 2.39.

We demonstrate that the rate of somatic expansions is higher in blood cells of patients experiencing a faster decline in muscle strength, indicating that somatic expansions are an important therapeutic target; and emphasize the usefulness of MAL increment as a biomarker for disease progression.

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172 - Phenotype Specific Patterns of Mitochondrial Dysfunction in Skeletal Muscle of Women with Myotonic Dystrophy Type 1

Vincent Marcangeli[1, 2, 3], Laura Girard-Côté[4, 5, 6], Marie-Pier Roussel[6, 7], Maude Dulac[8], Guy Hajj-Boutros[8], José A Morais[8], Gilles Gouspillou[1, 2], Jean-Philippe Leduc[9], Elise Duchesne[4, 5, 6, 10]

[1]Department of Physical Activity Sciences, Université du Québec à Montréal, Montreal, Quebec, Canada, [2]Research Group for Adapted Physical Activity, Université du Québec à Montréal, Montréal, Quebec, Canada, [3]Department of Biological Sciences, Université du Québec à Montréal, Montreal, Quebec, Canada, [4]School of Rehabilitation Sciences, Faculty of Medicine, Université Laval, Quebec City, Quebec, Canada, [5]CHU de Québec-Université Laval Research Center, Quebec City, Quebec, Canada, [6]Groupe de recherche interdisciplinaire sur les maladies neuromusculaires (GRIMN), Saguenay-Lac-St-Jean Integrated University Health and Social Services Center, Saguenay, Quebec, Canada, [7]Department of Fundamental Sciences, Université du Québec à Chicoutimi, Chicoutimi, Québec, Canada, [8]Research Institute of the McGill University Health Center, Montreal, Québec, Canada, [9]Research Group in Cellular Signaling, Department of Medical Biology, Université du Québec À Trois-Rivières, Trois-Rivières, Quebec, Canada, [10]Center for Interdisciplinary Research in Rehabilitation and Social Integration (Cirris), Capitale-National Integrated University Health and Social Services Center, Quebec City, Quebec, Canada

Background. Myotonic dystrophy type 1 (DM1) is the most common muscular dystrophy in adults, but the exact mechanisms leading to skeletal muscle dysfunction remain poorly understood, largely due to the disease's clinical

heterogeneity. This heterogeneity is observed across five phenotypes: congenital, childhood/infantile, juvenile, adult/classic, and late-onset. While recent evidence points to mitochondrial dysfunction as a significant contributor to DM1 pathophysiology, a gap persists regarding the variation in these impairments across phenotypes. **Objective.** This study aimed to characterize skeletal muscle mitochondrial dysfunction in women with DM1 through a direct comparison with age-matched unaffected controls, focusing on identifying phenotype-dependent variations. **Methods.** Vastus lateralis muscle biopsies were obtained from unaffected women and with DM1. Mitochondrial respiration and hydrogen peroxide emission (an indicator of reactive oxygen species (ROS) production) were assessed in permeabilized myofibers with an Oroboros O2k high-resolution fluorespirometer. Oxidative phosphorylation (OXPHOS) protein abundance was quantified by immunoblotting. Participants with DM1 were categorized as juvenile or adult/late-onset. **Results.**Thirteen women with DM1 (juvenile: *n*=7, age range: 24-52 years); adult/late-onset: *n*=6, age range:30-59 years) and thirteen controls (age range: 22-63 years) were included. As a whole, the DM1 group did not differ from controls in total OXPHOS protein abundance (p=0.85). Juvenile participants exhibited reduced global OXPHOS content, with lower Complex II and IV (p=0.02) abundance. In contrast, the adult/late-onset group showed higher OXPHOS protein levels, including elevated Complex IV (p=0.01). Juvenile participants had lower absolute mitochondrial respiration than controls. In contrast, the adult/late-onset group showed decreased respiration relative to OXPHOS content, especially during ADP-stimulated respiration with Complex I and Complex I+II substrates. Normalized ROS production was surprisingly lower in the adult/late-onset group. **Conclusion.** These findings reveal phenotype-specific mitochondrial impairments in women with DM1, underscoring the importance of a phenotype-focused approach to accurately characterize disease mechanisms and guide the development of targeted therapies.

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173 - Methylation of CCG variant repeats is associated with heterogeneous methylation of CpG sites surrounding DMPK expansion in DM1 patients

Jovan Pesovic[1], Pavel Bashtrykov[2], Milica Poljicak[1], Lana Radenkovic[1], Igor Davidovic[3], Nemanja Radovanovic[1], Milos Brkusanin[1], Vidosava Rakocevic Stojanovic[4], Stojan Peric[4], Dusanka Savic-Pavicevic[1]

[1]Center for Human Molecular Genetics, University of Belgrade-Faculty of Biology, Belgrade, Serbia, [2]Department of Biochemistry, Institute of Biochemistry and Technical Biochemistry, University of Stuttgart, Stuttgart, Germany, [3]Center for

Genome Sequencing and Bioinformatics, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Belgrade, Serbia, [4]Neurology Clinic, Clinical Center of Serbia, University of Belgrade-School of Medicine, Belgrade, Serbia

Myotonic dystrophy type 1 (DM1) is among the most clinically variable monogenic diseases. We previously showed that variant repeats act as individual-specific genetic modifiers, delaying age-at-onset in DM1 patients by stabilizing CTG expansions within the *DMPK* gene in somatic cells. Since CCG variant repeats were most common, we aimed to investigate whether they were methylated themselves as well as associated with methylation of surrounding CpG sites, as observed with GC-rich repeats in other repeat expansion disorders.

Our study included 22 patients from 13 families with *DMPK* expansions carrying different patterns of CCG variant repeats. To examine methylation of CCG repeats, we designed methyl-specific repeat-primed PCR on bisulfite-converted genomic DNA using primers for both unmethylated and methylated CCG repeats. For confirmation, we performed repeat-primed PCR on genomic DNA digested with the methyl-sensitive *Ssi*I enzyme. We assessed methylation of CpG sites located 1.5 kb upstream and 1 kb downstream of the expansion using targeted Illumina and Oxford Nanopore bisulfite sequencing.

We discovered that CCG variant repeats were heterogeneously methylated in all patients. CpG sites both downstream and upstream of the repeat tract also showed heterogeneous methylation. Importantly, the extent and level of methylation, ranging 10-50%, depended on the structure of variant *DMPK* expansions. Patients with more CCG repeats generally had higher methylation in the downstream region. Moreover, upstream CpG sites also showed increased methylation in patients with the most abundant and complex CCG repeat patterns. These findings suggest that methylation initiates at the CCG repeats and spreads locally to adjacent CpG sites.

The discovery of methylation in variant CCG repeats raises questions about the role of epigenetic mechanisms in stabilizing the *DMPK* locus and their potential clinical relevance in DM1 patients beyond those with the congenital form.

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175 - The Role of Epigenetic Regulation in Congenital Myotonic Dystrophy

Julia Hartman[1], Omari McMichael[1], Karolina Aberg[2], Melissa Hale[1], Samuel Carrell[1], Nicholas Johnson[1]

[1]Center for Inherited Myology Research, Virginia Commonwealth University, Richmond, Virginia, 23298, USA, [2]Center for Biomarker Research and Precision Medicine, Virginia Commonwealth University, Richmond, Virginia, 23298, USA

Congenital myotonic dystrophy (CDM) is the most severe form of myotonic dystrophy type 1 (DM1). DNA methylation changes at the DMPK locus are present in CDM, but the specific role these epigenetic modifications play in CDM pathogenesis remains unclear.

DNA methylation patterns were evaluated in skeletal muscle biopsies and blood samples from 30 CDM patients, 10 adult DM1 patients, and 30 age-matched controls. Methyl-CpG binding domain sequencing (MBD-Seq) assessed genome-wide methylation patterns. Bisulfite sequencing was used to provide additional higher resolution of select genomic loci, including DMPK. Methylation changes were compared to RNA splicing patterns as well as long term outcomes.

Differing methylation patterns throughout specific regions of the DMPK locus, such as CpG island 43, are apparent when comparing muscle and blood samples from the same individuals. Results from methylation sequencing of the DMPK locus also demonstrates the utility of sampling across a range of developmental ages - our newborn and infant samples show 100% hypermethylation at the CTCF1 site (consistent with previously studies) but our samples from CDM individuals taken during adolescence show hypomethylation patterns at the CTCF1 site, more consistent with patterns from adult DM1 samples. Preliminary genome-wide methylation analyses reveal DMPK as being significantly methylated between CDM vs. controls/DM1 individuals. Preliminary analysis of case (CDM/DM1) vs. control (pediatric/adult) genome-wide methylation patterns reveals hits within the KCNQ1 and CNOT3 loci.

This study provides the first analysis of genome wide and targeted methylation patterns in DM1 and CDM individuals in multiple tissue types. Additionally, this is the first study that looks at developmental methylation patterns in CDM patients and how they change with age and disease severity. These findings also suggest that methylation changes in key regulatory regions of DMPK may correlate with disease progression in children with CDM.

178 - Neuropsychological outcomes in adults with childhood-onset myotonic dystrophy type 1

Isabelle Gaudet[1, 2], Yohann Savinsky[1, 2], Noémie Gilbert[1], Luc Laberge[2, 3], Cynthia Gagnon[2, 4, 5], Nathalie Angeard[6]

[1]Université du Québec à Chicoutimi, [2]Groupe de recherche interdîsciplinaire sur les maladies neuromusculaires (GRIMN), Center for Research and Innovation of the Saguenay-Lac-St-Jean Integrated University Health and Social Services Center, Saguenay, Quebec, Canada, [3]Groupe ECOBES, Cégep de Jonquière, [4]School of Rehabilitation, Faculty of Medicine and Health Sciences, Université de Sherboroke, Sherbrooke, Québec, Canada, [5]CHU de Sherbrooke-Université de Sherbrooke research center, Sherbrooke, Québec, Canada, [6]Memory, Brain and Cognition Unit (MC2 Lab, URP 7536) Université Paris Cité

Myotonic dystrophy type 1 (DM1) is a multisystemic neuromuscular disorder with prominent central nervous system involvement. The childhood-onset phenotype (ChDM1) is characterized by early neurodevelopmental difficulties, affecting cognition, behavior, social functioning, and fatigue, which persist into adulthood.

Despite the functional impact of these manifestations, adults with ChDM1 remain markedly underrepresented in research. As a result, their neuropsychological profile and its clinical implications remain insufficiently documented, limiting evidence-based care and readiness for therapeutic trials targeting central nervous system.

This prospective natural history study aims to characterize neuropsychological functioning in adults with ChDM1 through a comprehensive and standardized assessment protocol. Participants undergo evaluation of general intellectual functioning, attention, executive functions, working memory, and social cognition.

To situate the ChDM1 phenotype within the broader DM1 spectrum, outcomes will be compared with those of adults with the classic DM1 phenotype and with age- and sex-matched non-affected controls.

As data collection is ongoing, preliminary descriptive neuropsychological findings from the Quebec cohort will be reported. Based on previous work, we anticipate important heterogeneity among individuals, with frequent impairments in attention, executive functions, and social cognition. Early phases of the study are also expected to demonstrate the feasibility and tolerability of research protocol, despite disease-related fatigue and cognitive slowing.

Beyond cross-sectional characterization, this study is designed to support longitudinal follow-up and the identification of clinically meaningful cognitive endpoints. Future phases will examine short- and long-term cognitive trajectories and their associations with autonomy and social participation. Measures of fatigue and rest-activity cycles (actigraphy) will also be incorporated to clarify their contribution to neuropsychological functioning in adults with ChDM1.

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180 - Feasibility and tolerability of a tailored music and movement intervention for children with congenital myotonic dystrophy type 1 (DM1)

Tamara Burgess[1], Astrid Eisenkölbl[1, 2], Erin Parkes[3, 4], Olivia Adams[3], Lindsey Bryden[3], Gilles Comeau[4, 5], Jason Berard[6, 7], Mikael Swirp[4], Arian Sadeghi[4], Lisa A.S. Walker[6, 8, 9, 10], Angela Woollam[11], Heather Howley[1], Amanda Yaworski[12], Hugh McMillan[12], Hanns Lochmüller[1, 6, 10]

[1]Children's Hospital of Eastern Ontario Research Institute, Ottawa, Canada, [2]Kepler University Hospital, Austria, [3]Lotus Centre for Special Music Education, Ottawa, Canada, [4]University of Ottawa Music and Health Research Centre, Ottawa, Canada, [5]Institute of Mental Health Research at the Royal, Ottawa, Canada, [6]University of Ottawa Brain and Mind Research Institute, Faculty of Medicine, Ottawa, Canada, [7]Neuroscience, The Ottawa Hospital Research Institute, Ottawa, Canada, [8]Neuroscience, The Ottawa Hospital Research Institute, Canada, [9]School of Psychology, Faculty of Social Sciences, University of Ottawa, Canada, [10]Division of Neurology, Department of Medicine, The Ottawa Hospital, Canada, [11]Algonquin College - Pembroke Campus, Pembroke, Canada, [12]Department of Pediatrics, Children's Hospital of Eastern Ontario, University of Ottawa, Canada

Congenital DM1 (CDM) is associated with significant learning difficulties, cardiac conduction defects, gastrointestinal symptoms, and sleep disturbances, in addition to neuromuscular symptoms. There are currently no approved pharmacological therapies for CDM. Due to a desire to study holistic approaches that address outcomes beyond neuromuscular impairment, we identified music and movement as a novel intervention for CDM. Similar approaches are used in children with autism and cerebral palsy. To our knowledge, this study represents the first non-pharmacological therapy assessed in children with CDM.

This interventional study uses a convergent mixed-methods approach. The primary aim is to demonstrate the feasibility and tolerability of an adaptive music and movement intervention for children with CDM, including informing the use of wearable devices for future trials in this population.

Two cohorts of participants receive 10 weekly sessions of the 45-minute-long adaptive music and movement intervention. Pre- and post-intervention assessments evaluate physical and cognitive measures. Participants are fitted with wearable devices to monitor activity (Actigraph wGT3X-BT), single-lead ECG (Polar H10) and overnight EEG (Muse-S) over a 7-day period. Qualitative feedback is collected throughout the study via parent focus groups and questionnaires.

Results of the first group of 5 participants (4 male, 1 female) are presented. Mean age was 14.6 years old (range 13-18 years old). Attendance to music sessions was 78%. Parent-reported impacts on feasibility and tolerability included travel time to intervention, and adherence to wearable devices due to positioning and participant comfort. Post-session questionnaires found parents reported participants to be overall in positive moods following each music session.

These results indicate this accessible, holistic approach to CDM is overall feasible and tolerable to participants. Study limitations include a small sample size and recruitment from a single geographical area. Future directions may include expansion to other sites in a full-scale trial.

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181 - Design and Optimization of Antisense Oligonucleotides for Selective Suppression of the Mutant DMPK Allele

Mani Mahadevan[1], Ramesh Yadava[1]

[1]University of Virginia

Current investigational therapies for myotonic dystrophy lack specificity for the mutant DMPK allele. Given that DMPK is essential for muscle integrity, calcium homeostasis, and cardiac conduction, an effective therapeutic strategy should selectively reduce the mutant DMPK allele while preserving the wild-type allele. Such specificity could be achieved by directly targeting the expanded CTG repeat or by focusing on single-nucleotide polymorphisms (SNPs) associated with the CTG expansion. Several SNPs in DMPK have been identified in DM1 patients and are frequently linked to the CTG-expanded allele, making them promising candidates for allele-specific therapy. In this study, several human cell lines from both healthy individuals and DM1 patients were screened to identify these SNPs. The objective is to develop an antisense oligonucleotide (ASO) that selectively targets the mutant allele using high-frequency SNPs, while minimizing effects on the wild-type DMPK allele. Preliminary data supporting this approach will be presented.

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182 - Defining the Role of General Practitioners in Primary Care for Adults With Myotonic Dystrophy Type 1

Catherine Savard[1], Melissa Lavoie[1, 2], Maude Mousseau[3], Sara-Jeanne Gélinas[3], Félicia Harvey[1], Justine Brouillard[3], Salmah Abdul Rehman[3], Cynthia Gagnon[1, 3]

[1]Groupe de recherche interdisciplinaire sur les maladies neuromusculaires, [2]Université du Québec à Chicoutimi, [3]Université de Sherbrooke

Background: Myotonic dystrophy type 1 (DM1) is a multisystem, inherited neuromuscular disorder associated with progressive muscle weakness, cardiac conduction abnormalities, respiratory complications, endocrine involvement, cognitive impairment, and psychosocial challenges. Individuals with DM1 frequently experience diagnostic delays, fragmented care, and inconsistent follow-up. In Canada, general practitioners (GPs) are the cornerstone of primary care, providing first-contact, continuous, comprehensive, and coordinated care within the Patient Medical Home model. Despite this role, disease-specific guidance to support GPs in DM1 management remains limited nationally and internationally.

Objective: To develop clinical practice guidelines tailored to general practitioners for longitudinal management of adults with DM1, aligned with Canadian primary care principles and best practices in rare disease care.

Methods: The clinical practice guidelines are currently being develop using the Rare Knowledge Mining Framework to adapt existing guidelines. Furthermore, a scoping review of the literature was conducted to map the role of GP in rare diseases. Recommendations will be structured according to the Patient Medical Home framework, defining the GP role in accessibility, continuity, comprehensive team-based care, care coordination, patient- and family-partnered care, and quality improvement. Multidisciplinary experts and affected individuals and family's input will be collected to informed guideline development.

Results: Core recommendations will include aspects of proactive surveillance; structured follow-up schedules; coordination with neuromuscular specialists and rehabilitation services; and integration of psychosocial and caregiver support. Early results show that GP responsibilities include early recognition of red flags, facilitation of timely referrals, comorbidity management, and shared decision-making. Practical tools such as monitoring checklists, referral pathways, and communication templates to support implementation in routine primary care will be developed.

Conclusion: These clinical practice guidelines will clarify and operationalize the GP role in DM1 care within the Canadian primary care context and could be adapted to an international context.

184 - Longitudinal muscle-specific miRNAs as biomarkers of disease progression in myotonic dystrophy type 1

Andrie Koutsoulidou[1], Kristia Georgiou[1], Nikoletta Nikolenko[2], Maria Zanti[3], Kyriaki Michailidou[3], Marios Tomazou[4], Tassos C. Kyriakides[5], Grainne Gorman[6], Chris Turner[2], Hanns Lochmüller[7, 8, 9, 10], Leonidas A. Phylactou[1]

[1]Department of Molecular Genetics, Function & Therapy, The Cyprus Institute of Neurology & Genetics, Nicosia, Cyprus, [2]National Hospital for Neurology and Neurosurgery, Queen Square, University College London Hospitals NHS Foundation Trust, London, UK., [3]Biostatistics Unit, The Cyprus Institute of Neurology & Genetics, Nicosia, Cyprus, [4]Department of Bioinformatics, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus, [5]Department of Biostatistics, Yale School of Public Health, New Haven, Connecticut, USA, [6]Wellcome Trust Centre for Mitochondrial Research (Institute of Neuroscience), Newcastle University, Newcastle Upon Tyne, UK, [7]Children's Hospital of Eastern Ontario Research Institute; Division of Neurology, Department of Medicine, The Ottawa Hospital; and Brain and Mind Research Institute, University of Ottawa, Ottawa, Canada, [8]Division of Neurology, Department of Medicine, The Ottawa Hospital, Ottawa, Canada, [9]Brain and Mind Research Institute, University of Ottawa, Ottawa, Canada., [10]Centro Nacional de Análisis Genómico (CNAG), Barcelona, Spain

Myotonic dystrophy type 1 (DM1) is a progressive neuromuscular disorder characterized by variable muscle wasting, for which reliable and minimally invasive biomarkers to monitor disease progression are not yet available. We have previously reported that circulating muscle-specific miRNAs, miR-1, miR-133a, miR-133b, and miR-206, can assess the disease progression in cross-sectional analyses of DM1 patients. This study aimed to investigate the longitudinal behavior of these miRNAs in order to determine whether changes in their circulating levels reflect disease progression over time. Serum samples were collected from 90 DM1 patients enrolled in the PhenoDM1 study. Each patient provided yearly blood samples at two or three clinical visits. Patients were classified as stable or progressive based on their clinical examination. Circulating levels of the four muscle-specific miRNAs were quantified by real-time PCR and analyzed for their longitudinal association with clinical progression. Stable DM1 patients showed unchanged or decreased levels of the four muscle-specific miRNAs over time, whereas progressive patients demonstrated consistent increases. Analyses of within-patient changes confirmed that rising miRNA levels corresponded to clinical deterioration, while stable or declining levels

reflected clinical stability. These associations persisted across short- and mid-term follow-up intervals, with longitudinal profiling showing dynamic alignment between miRNA trajectories and clinical evolution. Our findings show that circulating muscle-specific miRNAs reflect longitudinal changes in disease activity in DM1. Their consistent patterns across multiple time points support their potential as sensitive, minimally invasive biomarkers for tracking disease progression and assessing therapeutic responses in clinical trials.

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185 - Patient-Reported Experiences and Preferences Regarding Palliative and End-of-Life Care in Myotonic Dystrophy: A UK Community Survey

Emma-Jayne Ashley[1], Nikoletta Nikolenko[2], Wendy Greenwood[1]

[1]Cure Myotonic Dystrophy UK Charity, UK, [2]National Hospital for Neurology and Neurosurgery, Queen Square, University College London Hospitals NHS Foundation Trust, London, UK

Myotonic Dystrophy (DM), particularly type 1 (DM1), is a progressive, currently incurable genetic disorder with significant morbidity, multisystem involvement and reduced life expectancy. DM1 presents with muscle weakness, myotonia, cardiac conduction abnormalities, respiratory compromise and other systemic manifestations, yielding complex care needs. Despite the progressive nature of the condition, palliative care services and Advance Care Planning (ACP) remain underutilised, with delayed referrals limiting comprehensive supportive care and potentially contributing to increased hospitalisations and suboptimal end-of-life experiences.

This study characterised the lived experience, service utilisation and preferences relating to palliative care and ACP among individuals affected by DM within the UK. Anonymised online questionnaires were disseminated to members of the UK DM community via CureDM UK charity networks. Respondents included DM1 patients or their caregivers. Data collected included demographic variables (year of birth, sex, residential location), clinical history (age at onset and diagnosis, recent illnesses, hospitalisations) and experiences with palliative services and ACP. Responses were analysed descriptively to identify patterns of service engagement and unmet needs.

Analysis identified marked differences between individuals who had received focused palliative care and those who had not. Respondents reporting palliative care involvement described fewer unplanned hospitalisations and greater access to hospice support. Conversely, many patients noted that discussions on end-of-life care were initiated “too late,” with deterioration signs frequently overlooked, resulting

in emergency hospital admissions and deaths in hospital settings rather than patients' preferred locations. Caregivers frequently reported avoidable adverse circumstances and gaps in coordinated care.

The survey highlights a significant need for earlier integration of palliative care and structured ACP in DM management. Charities and support groups are trusted conduits for collecting patient-reported data, offering vital insights into unmet needs. These findings underscore the importance of improving palliative care pathways to enhance patient-centered care and inform clinical trial design across the disease spectrum.

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186 - Development and Expert Evaluation of a Clinical Checklist for Adult Myotonic Dystrophy Type 1 Care

Cynthia Gagnon[1], Homira Osman[2], Charles Kassardjian[3]

[1]Universite Sherbrooke, [2]Muscular Dystrophy Canada, [3]University of Toronto

Objective: To develop and evaluate a pragmatic clinical checklist, with a corresponding patient-analog version, to support implementation of consensus-based DM1 care in adult neuromuscular clinics.

Methods: Adult DM1 care recommendations were compiled from the published consensus-based care recommendations and corroborated through a scoping review conducted in 2022, confirming their scope and supporting evidence. Checklist development began with an existing DM1 checklist developed by Dr. Charles Kassardjian, which was used as an initial structure and subsequently evaluated against the consensus-based care recommendations and expert review.

To assess implementation-relevant outcomes, a structured survey was completed by 26 DM1 clinical experts, all neurologists. Experts rated each recommendation on overall quality and suitability for use in their clinical context using a 7-point Likert scale. Consensus was defined a priori as ratings of 6 or 7. Quantitative ratings were summarized, and qualitative feedback was reviewed through expert focus groups. Recommendations with lower agreement or feasibility concerns were revised or clarified through a structured expert consensus process.

Results: Most recommendations achieved high expert consensus for both quality and suitability, particularly for diagnostic referral, cardiovascular and respiratory assessment, and anticipatory guidance. Recommendations with lower suitability ratings reflected contextual practice variability and were refined rather than excluded.

Recommendations were translated into a visual checklist organized into three domains: initial evaluation, follow-up assessment, and general management considerations. In parallel, a patient-analog checklist was developed using plain language and a mirrored structure to support patient understanding and care planning.

Conclusion: This consensus-informed, visual checklist and patient-analog companion addresses low awareness of existing DM1 care recommendations and provides a feasible, implementation-ready approach to supporting more standardized care and clinical readiness in an evolving therapeutic landscape.

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188 - Identification of novel blood-based biomarkers for Myotonic Dystrophy type 1 (DM1)

Charles Hurley[1], Nicholas Bradette[1], Ryan Joyce[1], Aymeric Ravel-Chapuis[1]

[1]University of Ottawa

Myotonic Dystrophy Type 1 (DM1) is a genetic neuromuscular disorder characterized by progressive muscle weakness and atrophy, often accompanied by a broad range of multisystemic symptoms including myotonia, cardiac conduction abnormalities, insulin resistance, and cognitive impairments. Despite improvements in understanding DM1 pathophysiology, clinically relevant biomarkers are still needed to improve disease monitoring and support therapeutic development. This study aims to identify novel circulating protein biomarkers for DM1. We used the muscle-specific HSA^{LR} transgenic mouse model of DM1. Serum samples from male and female HSA^{LR} and wild-type (WT) mice were analyzed using data-independent acquisition (DIA) global mass spectrometry. Protein identification and quantification were performed using MaxQuant and the UniProt database. This led to the identification of 1,561 proteins in male and 1,724 proteins in female serum samples, each present in at least 66% of either group (WT or HSA^{LR}). We identified 79 and 371 significantly differentially expressed proteins in the male and female samples, respectively. These proteins have been classified into biological processes using the REACTOME, PANTHER, Uniprot, and Entrez gene databases to prioritize candidate biomarkers that are not only differentially expressed but also mechanistically linked to key features of DM1 pathophysiology. These results provide a promising foundation for the identification of circulating biomarkers to support disease detection, monitoring, and therapeutic evaluation. Further validation in clinical samples is warranted to confirm translational potential and support the use of the HSA^{LR} model in biomarker discovery.

189 - Understanding the mechanisms of imbalance in Myotonic Dystrophy Type 1

Nikoletta Nikolenko[1], Matthew J. Bancroft[2], Gita Ramdharry[3], Chris Turner[1], Diego Kaski[1, 2]

[1]National Hospital for Neurology and Neurosurgery, Queen Square, University College London Hospitals NHS Foundation Trust, London, UK, [2]Department of Clinical and Movement Neurosciences, Institute of Neurology, University College London, London, UK, [3]Queen Square Centre for Neuromuscular Diseases, University College London, London, UK

Myotonic Dystrophy type 1 (DM1) is a progressive, multisystemic, autosomal dominant disorder and the most prevalent adult muscular dystrophy. A critical challenge for DM1 patients is imbalance and high risk of falls which leads to substantial morbidity, reduced quality of life and premature death. Despite the high prevalence of imbalance in DM1, the underlying mechanisms remain poorly characterised and standard functional assessments lack the specificity needed to isolate the sensory integration processes involved in postural control. The primary objective was to identify specific deficits in visual, proprioceptive and vestibular sensory channels that contribute to imbalance in DM1. This observational cohort study compared 12 DM1 participants with 12 age- and sex-matched healthy controls. The methodology utilized state-of-the-art 3D motion capture, force plates and surface electromyography to assess balance under normal conditions and in response to single-sensory-channel perturbations. These perturbations included: 1. Visual: Rotating dot screens to evoke sagittal plane sway; 2. Vestibular: Galvanic Vestibular Stimulation (GVS) delivered via mastoid electrodes. 3. Proprioceptive: High frequency vibration of Achilles and tibialis anterior tendons. Sway responses were quantified using force plates, 3D motion capture and electromyography. Direction, magnitude and response latency were quantified and response amplitudes were analysed within tasks in both groups to identify sensory-specific balance impairments in DM1 individuals relative to healthy controls. Statistically significant associations were identified between sway metrics and multiple domains, including functional assessments (6MWT, 10MWRT, 30SSST), muscle strength assessments (MRC, MIRS, hand-grip dynamometry), cardiac measures (ECG, echocardiography), respiratory spirometry and patient-reported outcome measures (DM1-ActivC, MDHI). By understanding how DM1 affects individual sensory channels, this study identifies specific elements of postural control that are impaired in DM1. These detailed insights provide a critical foundation for the development of targeted

DM1 interventions and novel therapies aimed at improving balance and preventing falls.

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190 - DM1 RAN Proteins Accumulate in Autopsy Brain Regions with Degenerative and Neuroinflammatory Changes and Promote Tau Aggregation in Neuronal Cells

Monica Banez-Coronel[1], Eduardo E. Rijos[1], John D. Cleary[1], Tao Zu[1], Anthony T. Yachnis[1], Laura P.W. Ranum[1]

[1]University of Florida

Repeat-associated non-AUG (RAN) proteins have been reported in 18 repeat-expansion disorders, including DM1 and DM2. In DM2, toxic LPAC and QAGR RAN proteins accumulate in human autopsy brains, with prominent LPAC RAN protein aggregation in regions showing organized necrosis and macrophage/microglia infiltration (Zu et al., *Neuron* 2017). Less is known about the role of RAN proteins in DM1. Although polyglutamine RAN proteins were reported in cardiomyocytes and leukocytes from DM1 patients and mice, due to the lack of suitable antibodies to detect RAN proteins in the brain, it has remained unclear if DM1 RAN proteins contribute to DM1 brain pathology.

Because the DM1 CTG·CAG expansion is bidirectionally transcribed, we developed and validated novel antibodies recognizing putative polyLeucine and polySerine RAN proteins expressed from sense (CUG reading frame) or antisense (AGC reading frame) expansion transcripts. These antibodies were used for immunohistochemical analyses of DM1 and control postmortem human brain tissue.

Our data show that sense (polyLeu) and antisense (polySer) RAN proteins accumulate in DM1 frontal cortex and hippocampus as large cytoplasmic neuronal aggregates or microaggregates in glial cells and axons (n=9 DM1; n=9 controls). White matter regions with intense RAN-positive staining show pathological features of disease, including activated microglia, increased GFAP staining and white-matter atrophy. Additionally, regions with prominent RAN protein accumulation also show robust Tau deposition and neurofibrillary tangles. Similar to a report showing polySer domains trigger tau aggregation, we show DM1 polySer RAN proteins promote neuronal p-Tau aggregation in a dose dependent manner.

Together, these results demonstrate that sense and antisense RAN protein aggregates accumulate in DM1 brain regions showing hallmark CNS features including, pTau aggregates, white matter-atrophy and neuroinflammation. Our data

identify RAN proteins as contributors to DM1 brain histopathology and highlight the need to fully understand the role of RAN proteins in disease.

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191 - Knowledge Mobilization for Neuromuscular Diseases: GRIMN's Multi Platform Strategy

Amélie Fournier[1], Elise Duchesne[1, 2, 3, 4], Cynthia Gagnon[1, 5, 6]

[1]Groupe de recherche interdisciplinaire sur les maladies neuromusculaires (GRIMN), Saguenay-Lac-St-Jean Integrated University Health and Social Services Center, Saguenay, Quebec, Canada, [2]School of Rehabilitation Sciences, Faculty of Medicine, Université Laval, Quebec City, Quebec, Canada, [3]Center for Interdisciplinary Research in Rehabilitation and Social Integration (Cirris), Capitale-National Integrated University Health and Social Services Center, Quebec City, Quebec, Canada, [4]CHU de Québec-Université Laval Research Center, Quebec City, Quebec, Canada, [5]School of Rehabilitation, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Sherbrooke, Québec, Canada, [6]CHU de Sherbrooke-Université de Sherbrooke research center, Sherbrooke, Québec, Canada

Background: Effective knowledge translation is essential in rare neuromuscular diseases to bridge gaps between research, clinical practice, patients, and decision-makers. Research teams must ensure that information is accessible, relevant, and responsive to the needs of diverse audiences. The *Groupe de recherche interdisciplinaire sur les maladies neuromusculaires* (GRIMN) has developed a multi-platform knowledge mobilization strategy to enhance the dissemination and uptake of neuromuscular research, particularly in myotonic dystrophy type 1.

Objective: To describe GRIMN's knowledge translation strategies and their contributions to supporting multidisciplinary clinical management, rehabilitation practices, and quality-of-life improvement in neuromuscular diseases.

Methods: GRIMN implemented a dissemination approach tailored to patients, clinicians, researchers, trainees, and community partners. The institutional website (grimn.ca) serves as a centralized knowledge hub, providing access to research projects, publications, biobank resources, and educational or rehabilitation materials. Facebook disseminates patient-oriented content including research updates, study recruitment, events, and accessible educational material, thereby fostering engagement with patients, caregivers, and community organizations. LinkedIn supports knowledge exchange among researchers, clinicians, trainees, and industry partners. Annual in-person knowledge-sharing days complement digital

activities by enabling direct presentation and discussion of research results and strengthening connections with the broader community.

Results: Since 2023, web analytics, social media indicators, and participation in in-person activities have documented engagement from 1,281 followers across diverse audiences, generating more than 10,000 interactions with GRIMN's knowledge translation content. Combined digital and in-person activities expanded the visibility of neuromuscular research, reaching approximately 134,000 individuals worldwide and accumulating about 265,000 views of knowledge translation materials. This integrated strategy enhanced the reach, accessibility, and relevance of research outputs, promoted bidirectional knowledge exchange, and strengthened engagement among patients, caregivers, clinicians, researchers, and stakeholders.

Conclusion: A coordinated digital and in-person knowledge mobilization strategy effectively supports the translation of neuromuscular research into clinical practice, reinforces multidisciplinary care, and contributes to improved quality of life.

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192 - Sense and antisense RAN protein aggregates accumulate in DM1 brain, muscle, and myotubes and are reduced in myotubes with metformin

Eduardo Rijos[1], Monica Banez-Coronel[1], Lisa Romano[1], Ramadan Ajredini[1], Tao Zu[1], Laura Ranum[1]

[1]University of Florida

Repeat associated non-AUG (RAN) proteins have been reported in 18 repeat expansion disorders, including DM1 and DM2. In DM2, sense and antisense LPAC and QAGR proteins are toxic to cells and accumulate in brain regions with necrosis and macrophage/microglia infiltration. In DM1, polyglutamine RAN proteins were previously reported in blood, however these initial studies were limited, and it remains unclear if RAN proteins contribute to DM1. We developed novel antibodies against the repeat motifs and unique C-terminal regions of all six predicted DM1 sense (polyLeu$_S$, polyCys$_S$, polyAla$_S$) and antisense (polyGln$_{AS}$, polySer$_{AS}$, polyAla$_{AS}$) RAN proteins. Antibody specificity was validated in cells expressing individual epitope tagged DM1 repeat or DM1 C-terminal specific proteins. Immunohistochemistry (IHC), immunofluorescence (IF) and western-blot experiments were performed on DM1 and control autopsy brains, autopsy skeletal muscle, and metformin treated and untreated patient-derived differentiated myotubes. IHC using both repeat and unique C-terminal antibodies show all six sense and antisense RAN proteins accumulate as neuronal and glial aggregates in DM1 (n=6) but not control (n=5) frontal cortex. IF studies show DM1 sense polyCys$_S$

and antisense polyGln$_{AS}$ RAN proteins accumulate in DM1 (n=4) but not in control (n=2) skeletal muscle (tibialis anterior). In skeletal muscle, the polyGln$_{AS}$ RAN proteins showed punctate aggregates with both the C-terminal and polyGln repeat antibodies. In contrast, both the polyCys$_s$ repeat and C-terminal antibodies showed a striking striatal pattern. PolyGln$_{AS}$ and polyCys$_s$ expression was also observed in DM1 patient-derived (n=4) but not control (n=4) myotubes by IF staining and western-blot. Finally, metformin treated DM1 myotubes showed decreased RAN PolyGln$_{AS}$ levels. In summary, we have developed a panel of novel DM1 anti-RAN protein antibody detection tools and show that sense and antisense RAN protein aggregates accumulate in DM1 frontal cortex, skeletal muscle, and myotubes. Additionally, we show that metformin reduces RAN proteins in DM1 myotubes.

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194 - Care for Scoliosis Complicating Congenital Myotonic Dystrophy

Minobu Shichiji[1], Yuki Kihara[1], Kumiko Ishiguro[1], Keiko Ishigaki[1], Satoru Nagata[1]

[1]Department of Pediatrics, Tokyo Women's Medical University School of Medicin, Tokyo, Japan

[Background] Congenital myotonic dystrophy (CDM) is a severe subtype of myotonic dystrophy (DM) characterized by generalized muscle weakness present at birth. Although scoliosis in DM1 is typically described as slowly progressive, a subset of patients with CDM shows rapid progression.

[Methods] We retrospectively reviewed 12 pediatric patients with CDM (3 males, 9 females; median age, 8 years [range, 5-13]) followed for spinal deformity at Tokyo Women’s Medical University. Clinical variables analyzed included scoliosis, brace treatment and age at initiation, and independent ambulation.

[Results] Scoliosis was present in 5 of 12 patients (42%), with rapid progression requiring bracing in 3. In one patient with marked truncal hypotonia, scoliosis developed at approximately 1 year of age, and bracing was initiated at 2 years. Gait training was started at 4 years following percutaneous Achilles tendon lengthening performed at 3 years of age. A second patient, who had post-hemorrhagic hydrocephalus treated with ventriculoperitoneal shunting, developed rapidly progressive scoliosis（Cobb angle 75）at around 6 years of age, necessitating brace treatment; surgical intervention is planned after completion of growth. The third patient, who had not achieved independent ambulation, required brace treatment at 5 years of age due to rapid scoliosis progression within one year.

[Discussion] In CDM, muscle strength and tone often improve with growth, and many patients achieve independent ambulation. However, some patients develop rapidly progressive severe scoliosis in early childhood despite ambulation. Early scoliosis progression was frequently associated with hydrocephalus, respiratory impairment due to laryngomalacia, and delayed ambulation related to congenital clubfoot. In several cases, bracing alone was insufficient to control progression, highlighting the need for further consideration of early intervention strategies.

[Conclusions] In CDM, scoliosis tended to occur more frequently in patients with multiple comorbidities and delayed motor development. Careful surveillance and early therapeutic intervention from early childhood are essential for optimal management.

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195 - Cardiorespiratory Assessment in Adults with Congenital Myotonic Dystrophy

Nikoletta Nikolenko[1], Mahalekshmi Desikan[1], Konstantinos Savvatis[1, 2], Nicoleta Spetea[1], Ronan Astin[1], Chris Turner[1]

[1]National Hospital for Neurology and Neurosurgery, Queen Square, University College London Hospitals NHS Foundation Trust, London, UK, [2]Inherited Cardiovascular Diseases Unit, Barts Heart Centre, Barts Health NHS Foundation Trust, London, UK

Congenital myotonic dystrophy (CDM) is the most severe form of myotonic dystrophy type 1 (DM1), typically manifesting at birth with respiratory insufficiency, hypotonia and feeding difficulties. While many infants do not survive their first year, those who do often stabilise but continue facing significant multisystemic challenges and premature death by their early 30s, primarily due to cardiorespiratory complications. Despite rapid development of targeted therapies for DM1, the adult CDM phenotype remains poorly characterised and these patients are often excluded from clinical trials because they lack capacity to consent or cannot comply with standard study assessments. The primary objective of this study was to assess the cardiorespiratory function of adult patients with CDM. Secondary objectives include investigating the relationship between motor, cardiac and respiratory functions to improve clinical surveillance and define reliable clinical endpoints for future therapeutic trials. This is an observational cohort study involving a comprehensive battery of assessments, including muscle strength tests and functional assessments (MRC scale, MIRS, handgrip dynamometry, 10meter walk test), cardiac evaluations (ECG, echocardiography, ambulatory cardiac monitoring), respiratory function tests (spirometry, sleep studies) and patient reported outcome measures (ccMDHI, MDHI,

DM1-Activ). In 20 adults with CDM, respiratory assessments highlighted considerable clinical burden. A substantial proportion of participants were unable to perform reliable spirometry due to cognitive or physical limitations. Sleep-disordered breathing was commonly observed and non-invasive ventilation (NIV) was associated with lower partial pressure of carbon dioxide (pCO_2) in those able to tolerate therapy. A subset of participants had permanent pacemakers, while only a few were classified as obese (BMI >30). This study provides some of the first deep-phenotyping data for this complex and historically underserved patient group. By identifying reliable and tolerable assessments this study may facilitate inclusion of adult CDM patients in emerging clinical trials and improve clinical care considerations in this patient cohort.

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196 - Spontaneous DNA damage response in myotonic dystrophy type 1: Sparing of CTG contraction individuals.

Shuqian Tang[1, 2], Vanessa Li[1, 2], Terence Gall-Duncan[1], Mahreen Khan[1, 2], Christopher Pearson[1, 2]

[1]Program of Genetics & Genome Biology, The Hospital for Sick Children., [2]Department of Molecular Genetics, University of Toronto.

Myotonic dystrophy type 1(DM1), caused by a CTG/CAG expansion in *DMPK*, is characterized by muscular dystrophy, muscle atrophy, and neurological, but not typically neurodegeneration. In other repeat expansion diseases, including Huntington's Disease (HD) and *C9orf7* expansion associated amyotrophic lateral sclerosis/frontotemporal dementia (*C9orf7*-ALS/FTD), cells spontaneously accumulate a burden of DNA damage, activating a persistent DNA damage response (DDR), thought to promote apoptosis and neurodegeneration. DNA damage and the DDR have not been characterized in DM1. Here, we assess DNA damage and the DDR in multiple DM1 families, including classical DM1, congenital DM1 (CDM1) families which exhibit large expansions between generations, and rare DM1 CTG contraction families, who have inherited large contractions from their parents. We show that DM1 patient-derived fibroblasts exhibit levels of double-strand DNA breaks, assessed by comet assay and γ-H2AX immunofluorescence. Interestingly, levels of DNA damage correlate with levels of intergenerational CTG instability rather than repeat size: CDM1 individuals, with the largest expansions, exhibit the highest levels of DNA damage, classic DM1 individuals exhibit moderate levels, while contraction individuals exhibit no elevation in DNA damage relative to cells of unaffected individuals.

197 - Transcriptomic characterization of Muscular Dystrophies using long-read direct RNA sequencing

Wendpingre Abdallah Hazaël SAWADOGO[1], Élise Duchesne[2], Nicolas Dumont[3], Marie-Claude Sincennes[1]

[1]Institut National de la Recherche Scientifique, [2]Université de Laval, [3]Université Québécoise de Montréal

Muscular dystrophies are a group of inherited neuromuscular disorders characterized by progressive muscle weakness, loss of motor function, and impaired muscle regeneration. Although these diseases share common clinical manifestations, their underlying molecular mechanisms differ across subtypes, reflecting the diversity of genetic alterations and biological pathways involved.

Importantly, several forms of muscular dystrophy are associated with defects in RNA biology, including disruptions in mRNA maturation, alternative splicing, polyadenylation, and gene expression regulation. However, conventional short-read sequencing technologies provide limited resolution for studying full-length transcripts and complex RNA processing events, thereby restricting our understanding of transcriptomic dysregulation in dystrophic cells.

The objective of this project is to perform a differential transcriptomic analysis between healthy and dystrophic muscle cells to identify molecular signatures associated with muscular dystrophies. We will perform these analyses on primary human myoblasts isolated from affected individuals and healthy controls. To achieve this, we will employ long-read direct RNA sequencing using Oxford Nanopore technology, followed by comprehensive bioinformatic analyses. This approach enables full-length transcript characterization, and precise detection of alternative splicing events of the mRNA. By capturing RNA processing events at single-molecule resolution, this study will provide deeper insight into the transcriptomic, molecular, and hereditary mechanisms underlying muscular dystrophies. Ultimately, this work aims to improve our understanding of RNA-based disease pathways and to support the development of improved molecular diagnostics and future translational strategies.

198 - CpG hypermethylation at the Dmpk locus correlates with CTG repeat length in a novel knock-in mouse model of Myotonic Dystrophy Type 1

HSIN YA HUANG[1], Samuel Mackenzie[1], Charles Thornton[1], Martha Susiarjo[1]

[1]UNIVERSITY OF ROCHESTER MEDICAL CENTER

Myotonic dystrophy type 1 (DM1) is caused by toxic RNA transcribed from an expanded CTG repeat at the *DMPK* locus. Prior studies indicate that large CTG expansions trigger increased CpG methylation flanking the repeat tract, implicating epigenetic remodeling as a potential driver of disease pathophysiology. Leveraging a knock-in mouse model harboring CTG repeats of various lengths at the endogenous *Dmpk* locus, we sought to determine the relationship between repeat length and methylation. Following bisulfite treatment, we quantified CpG methylation at sites located between the CTG repeat and a putative CTCF-binding region approximately 150 bp upstream. Methylation levels were compared across wild-type mice, HSA-LR mice, and three knock-in lines carrying 600, 1,700, or 5,000 repeats. Wildtype and HSA-LR mice exhibited negligible methylation at all sites (<1%). In contrast, knock-in mice showed repeat-length-dependent hypermethylation, reaching 30-35% in merged wildtype and expanded amplicons from the 5,000-repeat line. We also performed sequencing after allele-specific PCR amplification and observed near-complete methylation (90-100%) at all CpG sites in the 5,000-repeat line. These findings demonstrate that CpG methylation upstream of the *Dmpk* CTG repeat scales with repeat length, which is itself associated with more severe DM1 phenotypes. Though methylation is generally associated with reduced gene transcription, it may also reduce CTCF-mediated chromatin insulation; thus, its effect on *Dmpk* and adjacent gene transcription represents an active area of investigation. Additional future studies will examine methylation downstream of the repeat, integrate long-read sequencing to resolve allele-specific epigenetic signatures, and determine the impact of hypermethylation on DM1 phenotypes in knockin mice.

199 - Advancing motor function assessment across childhood in congenital and childhood-onset DM1

Michael Kiefer[1], Julia Hartman[1], Kiera Berggren[1], Amanda Butler[1], Aileen Jones[1], Melissa McIntyre[2], Man Hung[3], Samuel Carrell[1], Melissa Hale[1], Craig Campbell[4], Valeria Sansone[5], Nicholas Johnson[1]

[1]Center for Inherited Myology Research, Department of Neurology, Virginia Commonwealth University, Richmond, Virginia, USA, [2]Department of Pediatric Neurology, University of Utah, Salt Lake City, Utah, USA, [3]Roseman University, Salt Lake City, Utah, USA, [4]Department of Pediatrics, London Children's Hospital, University of Western Ontario, London, Ontario, Canada, [5]The NEuroMuscular Omnicentre (NEMO) Clinical Center, Milan, Italy

Therapeutic development in myotonic dystrophy has advanced rapidly, yet pediatric trials remain limited by the lack of feasible, sensitive, and clinically meaningful endpoints. Capturing motor function across a wide range of ages and abilities is essential to detect treatment effects and inform trial design.

Secondary analysis of previous natural history study of 138 observations from 42 children aged 3-15 years with CDM showed delayed walking in congenital myotonic dystrophy (CDM), with a median age of independent walking of 24 months (IQR 18-27). Age at independent walking was strongly correlated with [MBNL]inferred, a biomarker of splicing dysregulation (rho = −0.708, p = 0.001), and predicted later motor performance, including 10-meter walk/run velocity (R^2 = 0.31, β = 0.2, p = 0.003). These results highlight the need for endpoints that capture motor function in young children who have not achieved independent walking and demonstrate the value of early quantitative motor assessment to inform trial design across childhood.

Building on these insights, the TREAT-EXT and ASPIRE natural history studies were designed to establish feasible and sensitive outcome assessments in congenital and childhood-onset DM1. Data collection is ongoing and includes evaluation of the Gross Motor Function Measure (GMFM). The GMFM is validated in multiple neuromuscular conditions and captures motor abilities from infancy through adolescence. Interim analysis of five children aged 9-16 years with CDM demonstrated feasibility, with only 2.9% of items scored as "Not Tested." Item difficulty was consistent across GMFM-88 and the Rasch-derived GMFM-66, with lower scores in higher-level domains. GMFM-88 and GMFM-66 scores were strongly correlated (r = 0.95), supporting use of GMFM-66 in DM1. Scores ranged from 20.8-99.2 (GMFM-88) and 35.2-89.7 (GMFM-66).

Overall, these findings support the feasibility of GMFM to quantify motor function in pediatric DM1 and guide clinical trial design.

200 - Senescence-Driven Alterations in the Muscle Niche Impair Regeneration in Myotonic Dystrophy Type 1

Taeyeon Kim[1, 2], Tatiana Koike[1, 3], Zakaria Orfi[1], Charles-Antoine Dubois[1, 4], Inès Mokhtari[1, 3], Thomas Molina[1, 3], Elise Duchesne[5, 6], Nicolas Dumont[1, 7]

[1]CHU Sainte-Justine Research Center, Montréal, QC, CANADA, [2]Department of microbiology, infectiology and immunology, Faculty of Medicine, Université de Montréal, Montréal, QC, CANADA, [3]Department of pharmacology and physiology, Faculty of Medicine, Université de Montréal, Montréal, QC, CANADA, [4]Department of Biochemistry and Molecular Medicine, Faculty of Medicine, Université de Montréal, Montréal, QC, CANADA, [5]School of Rehabilitation Sciences, Faculty of Medicine, Université Laval, [6]Researcher at the Centre for Interdisciplinary Research in Rehabilitation and Social Integration (CIRRIS), QC, CANADA, [7]School of rehabilitation, Faculty of Medicine, Université de Montréal, Montréal, QC, CANADA

Myotonic dystrophy type 1 (DM1) is caused by CTG repeat expansion in the *DMPK* gene, leading to toxic RNA accumulation. Recent studies suggest that this RNA toxicity induces cellular senescence. Our group previously identified senescent myoblasts, muscle precursor cells essential for regeneration, in DM1 patients and provided a link between senescence and muscle weakness. In addition, senescent cells secrete a senescence-associated secretory phenotype (SASP) that can alter the muscle niche and influence the behavior of muscle stem cells. However, the muscle microenvironment in DM1 remains poorly understood. Therefore, we investigated how senescence affects the skeletal muscle microenvironment and regeneration in DM1.

We used the DMSXL mouse model, which carries large CTG repeats (over 1,000) from the human *DMPK* gene, to investigate skeletal muscle senescence and regeneration. Muscle weakness and senescence biomarkers were evaluated in DMSXL and wild-type mice. Alterations in the muscle microenvironment were analyzed using immunostaining and single-nucleus RNA sequencing (snRNA-seq) of skeletal muscle. Muscle regenerative capacity was assessed following cardiotoxin-induced injury by immunostaining for key myogenic markers across defined stages of the regeneration process.

DMSXL skeletal muscle exhibited increased expression of senescence markers and elevated SASP factors. Notably, DMSXL muscles displayed altered extracellular matrix organization, consistent with a pro-fibrotic microenvironment. Following injury, muscle regeneration was delayed in DMSXL mice, with persistently elevated numbers of myogenic committed cells at 7 days post-injury compared to WT. In

addition, DMSXL muscles showed increased necrotic myofibers, which were inefficiently cleared by macrophages exhibiting reduced phagocytic capacity.

This study demonstrates that cellular senescence in DM1 is associated with pathological remodeling of the muscle microenvironment and impaired regeneration. These findings provide new insights into the mechanisms underlying skeletal muscle weakness in DM1 and highlight senescence-associated niche dysfunction as a potential therapeutic target.

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201 - DMPK transcript metabolism underlies differential efficacy of DM1 therapeutics

Emma N. Shea[1], Eric T. Wang[1]

[1]University of Florida, USA

Although it may seem that the molecular pathomechanisms of Myotonic Dystrophy type 1 (DM1) are well understood--that disease is caused by sequestration of MBNL splicing factors on expanded *DMPK* transcripts leading to global splicing dysregulation, this is likely not the full story. There are still many unknowns about the metabolism and lifecycle of the expanded *DMPK* transcript including how expanded repeats affect the transcription, localization, and turnover of the *DMPK* transcript. This aspect of *DMPK* metabolism is highly relevant as it may affect patient response to oligonucleotide therapeutics. We developed and utilized SNP-containing primary DM1 myoblast cell lines in order to track the expanded *DMPK* transcript. We used cellular fractionation and a multiplexed targeted-sequencing approach to identify differences in wild type and expanded transcript composition, localization, and relative abundance. We supplemented sequencing methods with small molecule FISH to visualize transcript composition and localization. Since the success of therapeutics depends on how efficiently therapeutic molecules target the expanded *DMPK* transcript in muscle cells and current strategies target *DMPK* transcripts through distinct cellular mechanisms, we then combined our expanded transcript tracking techniques with ASO, siRNA, and PMO treatments. Ultimately, we show that understanding key elements of the expanded *DMPK* transcript life cycle allows us to leverage current oligonucleotide therapeutics to enhance rescue of DM1 phenotypes.

202 - Deciphering the mechanisms involved in the AMPK-induced therapeutic benefits in Myotonic Dystrophy type 1 skeletal muscle

Chimène Fahmi[1], Lola Lessard[2], Rémi Mounier[2], Aymeric Ravel-Chapuis[1], Bernard Jasmin[1]

[1]University of Ottawa, [2]Université de Lyon

Myotonic Dystrophy type 1 (DM1) is a multisystemic disease affecting skeletal muscles and other organs, for which no effective treatment currently exists. DM1 is caused by an abnormal expansion of CUG repeats in the 3'UTR of DMPK mRNAs, leading to a toxic gain-of-function of CUG-expanded transcripts. These transcripts accumulate in ribonuclear foci, disrupting splicing regulators, including MBNL1, CUGBP1 and Staufen1, causing a spliceopathy. Multiple signaling pathways are also impaired in DM1 muscle, contributing to the disease mechanism and offering potential therapeutic targets. Our lab previously demonstrated that AMPK signaling is repressed in DM1 skeletal muscles and that its activation through AICAR and exercise improves pathological features. However, conventional AMPK activators (AICAR and metformin) present some limitations and have AMPK-independent effects. To determine whether these therapeutic effects are indeed AMPK-mediated, we generated a DM1 AMPK-deficient mouse model by crossing DM1 mice with AMPK α-floxed mice and delivering AAV-Cre intramuscularly. Analysis of Cre-injected muscles revealed a 90% reduction in AMPK levels compared to saline-injected muscles. AMPK depletion aggravated several DM1 hallmarks, including increased toxic foci accumulation, exacerbated splicing defects, along with upregulation of MBNL1 and Staufen1. To test whether AICAR acts through AMPK, DM1 AMPK-floxed mice were injected with AAV-Cre or saline and subsequently treated with AICAR. AICAR improved splicing of DM1-relevant transcripts in AMPK-intact muscles but not in AMPK-deficient ones, confirming that its beneficial effects are AMPK-dependent. Interestingly, AMPK deletion resulted in increased protein levels of MBNL1, CUGBP1, and Staufen1, while AICAR had no effect on their expression. Ongoing experiments on treated mice include quantification of foci accumulation and assessment of muscle histology. Future studies will examine the effects of exercise on DM1 AMPK-deficient mice. Collectively, these investigations will clarify the role of AMPK in DM1 pathophysiology and further establish this pathway as a promising therapeutic target for the disease.

204 - Neuroanatomical changes in a Dmpk knock-in mouse model of myotonic dystrophy type 1 revealed by 9.4T magnetic resonance imaging

Dawling Dionisio Santos[1], Hsin Huang[2], Tanzil Arefin[2], Charles Thornton[1, 2, 3], Samuel Mackenzie[1, 2, 3, 4]

[1]Department of Neurology, University of Rochester, Rochester, NY, [2]Department of Neuroscience, University of Rochester, Rochester, NY, [3]Center for Health and Technology, University of Rochester, Rochester, NY, [4]Department of Pediatrics, University of Rochester, Rochester, NY

Progressive cognitive and neuropsychiatric symptoms are major drivers of morbidity in myotonic dystrophy type 1 (DM1). The lack of treatments for these symptoms reflects our incomplete understanding of DM1 pathophysiology in the central nervous system (CNS). Magnetic resonance imaging (MRI) studies in humans have shown that multifocal gray matter atrophy, white matter hyperintensities, and regional volumetric differences are common radiographic features of DM1. Leveraging knock-in mice in which expanded CTG repeats are inserted at the endogenous mouse *Dmpk* locus, we sought to evaluate structural differences in the brain using high-resolution 9.4T MRI. *In vivo* and *ex vivo* scans were performed on 1-year-old wild-type and *Dmpk* knock-in mice harboring 5,000 CTG repeats (N=4 per group). Our preliminary data indicate that *Dmpk* mice exhibit significantly decreased volume in several brain regions compared to controls. Establishing these neuroanatomical changes provides a critical baseline for future phenotyping and testing therapeutics that target DM1 pathology in the brain.

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205 - Characterization of Bitter Melon Natural Compounds that Activate AMPK Signaling as Novel Therapeutics for Myotonic Dystrophy Type 1 (DM1)

Shatha Atieh[1, 2, 3], Jia Liu[3, 4], Chun-Ping Tang[3, 4], Yang Yye[3, 4], Aymeric Ravel-Chapuis[1, 2, 3], Bernard J. Jasmin[1, 2, 3]

[1]University of Ottawa, [2]Eric J. Poulin Center for Neuromuscular Disease, [3]Joint Research Center on Systems and Personalized Pharmacology between The Shanghai Institute of Materia Medica (SIMM) and The University of Ottawa (UofO), [4]Chinese Academy of Sciences

Myotonic Dystrophy Type 1 (DM1) is a neuromuscular disease that is characterized by severe skeletal muscle dysfunction. Our lab was first to report that AMPK, a key

mediator of skeletal muscle plasticity, is repressed in DM1 and that pharmacological and/or physiological (exercise) activation of AMPK corrects key molecular and histopathological features of DM1. Current AMPK activators are either not FDA-approved or show mild improvements in DM1 patients. Of relevance, bitter melon natural compounds (BMC) were shown to activate AMPK in L6 myotubes. Here, we hypothesized that BMC would activate AMPK in DM1 muscle and ameliorate characteristic pathological features of DM1. Therefore, we characterized 26 BMC for their ability to activate AMPK in cultured muscle cells. Compared to the vehicle, BMC 23, 24, 25, 26 and 27 resulted in a ~ 1.5-to-2-fold increase in AMPK activation and maintained cell viability well over 92%. Due to the extensive investigation of BMC-25 in other disease contexts and its induction of AMPK in preclinical models, it was selected as our top candidate. Initially, DM1 (HSA^{LR}) mice were treated with BMC-25 for 30 minutes and 2 hours to determine its pattern of AMPK activation. Our results show that BMC-25 treatment activates AMPK levels in the tibialis anterior (TA) muscle of DM1 mice at these timepoints. Next, daily injections of BMC-25 for 6 weeks in DM1 mice reduced central nucleation in their TA muscles. We also observed a significant reduction in large hypertrophic fibers with a notable shift towards smaller cross-sectional areas, indicating an improvement in muscle morphology. Moreover, we observed a significant reduction in toxic RNA foci and a sex-specific rescue in the alternative splicing of *Serca1* and *Bin1* transcripts. Therefore, characterizing natural compounds like BMC-25 for their ability to activate AMPK could facilitate the rapid development of novel therapeutics for DM1 patients.

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206 - Apathy as a Distinct Executive Phenotype in Adult Myotonic Dystrophy Type 1

Melissa M. Dixon[1]

[1]University of Utah

Central nervous system (CNS) involvement in myotonic dystrophy type 1 (DM1) is well documented; however, adult studies have rarely distinguished apathy from depression, quantified real-world executive dysfunction using ecological measures, or integrated behavioral, cognitive, and genetic data to clarify mechanisms of functional impairment. To address these gaps, this study characterized behavioral executive dysfunction and apathy as distinct neurobehavioral features in adults with DM1 and examined their relationships with cognition and CTG repeat length. Adults with DM1 (n=22) completed the Behavior Rating Inventory of Executive Function-Adult (BRIEF-A), Apathy Evaluation Scale (AES), Beck Depression Inventory-II (BDI-II), Beck Anxiety Inventory (BAI), Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-

IV), and Wechsler Memory Scale-Fourth Edition (WMS-IV). Pairwise deletion addressed missing data. One-sample Wilcoxon signed-rank tests compared BRIEF-A T-scores and WAIS-IV/WMS-IV Index scores to normative reference values; associations were examined using Spearman correlations and partial Spearman correlations controlling for depressive symptoms. BRIEF-A scales were significantly elevated, most prominently Initiate, Working Memory, Metacognition Index (all p's <0.001), and Global Executive Composite ($p<0.01$), indicating a selective initiation-based dysexecutive profile. WAIS-IV revealed disproportionate reductions in Processing Speed ($p<0.00001$) and Working Memory ($p<0.0001$), with relatively preserved Verbal Comprehension ($p>0.05$) and a higher General Ability Index relative to FSIQ ($p<0.01$), consistent with cognitive inefficiency rather than global intellectual decline. WMS-IV demonstrated elevated Auditory Memory with reduced Visual Working Memory, supporting executive mediation of memory performance. AES scores significantly correlated with BRIEF-A GEC and Initiate; this association remained significant after controlling for depressive symptoms. CTG repeat length was not associated with executive or processing speed outcomes ($p>0.05$). These findings provide evidence that apathy in adult DM1 represents a distinct executive phenotype characterized by impaired initiation, independent of depression and global IQ, reframing CNS involvement as driven by real-world executive and processing inefficiency rather than affective or primary amnestic pathology.

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208 - Analysis of an AAV-Mediated Dual MBNL1 and RNAi Approach for DM1 Therapy

Darren Bisset[1], Stephanie Lee-Diaz[2], Joel Chamberlain[1]

[1]Division of Medical Genetics, Department of Medicine, University of Washington, [2]Department of Neurology, University of Washington

Introduction: DM1 is caused by expression of a trinucleotide repeat within the *DMPK* mRNA leading to sequestration of the nuclear splicing factor MBNL1 in focal accumulations. Release of MBNL1 from expanded repeat transcripts is known to reverse altered splicing events to restore cellular and molecular changes in cell and mouse models of DM1. We have pioneered an AAV-RNAi approach for restoration of functional levels of MBNL1 through RNAi pathway directed expanded repeat degradation by the cellular RNAi pathway. While this approach is in clinical trials, current methods are aimed at reducing the high AAV dose necessary for this treatment.

Methods: AAV vectors were engineered to express MBNL1 and RNAi sequences targeting the HSA mRNA in the HSALR mouse model to test a combination approach

aimed at reducing the need for high levels of RNAi activity by co-supplementation with MBNL1. After observing cardiotoxicity following MBNL1 heart expression a heart-specific miR208 binding site was included in the vectors. Systemic delivery of either AAV-MBNL1 or AAV-MBNL1-RNAi vectors, with a highly active or minimally active RNAi sequence, were compared to control vectors in HSALR mice.

Results: Myotropic vector systemic delivery resulted in a measurable shift by RT-PCR of TA mRNA splicing in *Atp2a1* exon 11 inclusion with injection of AAV-MBNL1 compared to the control vector. Exon 11 inclusion increased with the AAV-MBNL1-RNAi combined vector containing the active RNA-targeting sequence. As anticipated, the combined vector with little RNAi activity showed a minimal splicing change. Experiments to test vector activity with local administration are underway to assess the potential for greater potency in systemic applications.

Conclusions: Methods to reduce AAV burden in clinical applications, such as providing a dual disease modifying approach with myotropic vectors, or other delivery strategies, have the potential to provide safe and effective therapeutic options for individuals living with DM.

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209 - Venous Thromboembolism and Hemodynamic Events in Myotonic Dystrophy type 1 and type 2

Eleanor Stanton[1], Brianna Brun[1], Johanna I Hamel[1]

[1]University of Rochester Medical Center

Myotonic dystrophy type 1 (DM1) and type 2 (DM2) are multisystem disorders with effects on skeletal and smooth muscle. Effects on vascular smooth muscle can lead to low blood pressure, particularly in DM1, which is associated with greater mortality. Venous thromboembolic and hemodynamic complications have been reported but remain understudied, with immobility as a potential contributing risk factor.

To study the prevalence of venous thromboembolic and hemodynamic events in a large US-based cohort, we will evaluate the prevalence in the National Registry, comprising 1300 patients with DM1 and 250 patients with DM2, and compare results with Registry members with FSHD (n=500). FSHD causes mobility limitations but is not expected to affect smooth muscle or liver synthesis. For a feasibility analysis, we utilized TriNetX, a federated electronic health record research network, to compare individuals with DM and FSHD. Due to limitations in the data structure, individuals with DM1 and DM2 were analyzed as a single cohort. Outcomes included pulmonary

embolism (PE), deep vein thrombosis (DVT), hypotension, and syncope. Analyses were stratified by age. Group differences were assessed using chi-square tests.

Among adults aged 18 years and older, PE was observed in 4.16% in DM (n=12,390, mean age 53 years) compared with 2.07% in FSHD (n=4,196, mean age 55 years), and DVT in 3.20% versus 1.98%, respectively (all $p<0.001$). Hypotension (12.92% vs 6.86%) and syncope (9.60 vs 7.70%) were also more prevalent in the DM cohort ($p<0.001$). Differences were most pronounced among adults aged 50 years and older. In pediatric patients, event prevalence was low across cohorts, limiting analysis.

Preliminary data suggest that individuals with DM experience a greater burden of venous thromboembolic and hemodynamic events than patients with FSHD, supporting the feasibility of a Registry-based study (data to be presented), to characterize provoked versus unprovoked events and explore disease-specific mechanisms.

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210 - Proteogenomic Discovery of Splice-Junction Peptides as Novel Biomarkers in Cerebrospinal Fluid of Myotonic Dystrophy Type 1 (DM1)

Marwa Zafarullah[1], Eric Wang[2], Glendon Parker[3], Jacinda B. Sampson[1], John W. Day[1]

[1]Department of Neurology and Neurological Sciences, Stanford School of Medicine, Stanford, CA, [2]Department of Molecular Genetics & Microbiology, University of Florida, Gainesville, FL, USA., [3]Department of Environmental Toxicology, University of California Davis, One Shields Ave., Davis, CA 95616, USA

Myotonic Dystrophy Type 1 (DM1), caused by expanded CTG repeats in the *DMPK* gene, is a multisystemic disorder characterized by widespread RNA mis-splicing and protein dysfunction. While aberrant splicing is a key pathogenic mechanism, its detection at the protein level in accessible biofluids remains largely unexplored, limiting biomarker development and therapeutic monitoring capabilities. This study employed an innovative multi-omics approach integrating cerebrospinal fluid (CSF) proteomics with RNA sequencing data from DM1 post-mortem brain tissue to identify protein biomarkers and splice-junction peptides. We analyzed CSF samples from DM1 patients (n=5) and healthy controls (n=4) using high-resolution mass spectrometry (TIMS-TOF Ultra coupled with nanoElute 2), followed by spectral analysis using Spectronaut. A novel bioinformatics workflow was developed to detect splice-junction peptides corresponding to previously identified brain mis-splicing events. We quantified 2,056 proteins, identifying 14 with differential expression between DM1 patients and controls. Five proteins were upregulated (LAMA2, ANTXR2, FCER2, TCTN3, FREM2), while nine were downregulated (TAGLN, CALB2,

NTNG2, IGHV3-38, OLR1, FAM177A1, SLITRK6, RPS10, NCAM1). Pathway enrichment analysis revealed alterations in key biological processes relevant to DM1 pathophysiology. Critically, splice-junction peptide analysis revealed differential expression of Prosaposin (PSAP) isoforms, with Exon 7/9 showing elevated peptide area in DM1 samples. This provides proof-of-concept for detecting aberrant splice variants at the protein level in CSF. This pioneering approach successfully translates RNA-level splicing defects into detectable protein biomarkers, establishing a framework applicable across neuromuscular disorders characterized by splicing dysregulation. These splice-junction peptides offer unprecedented potential as pharmacodynamic markers for clinical trials, providing direct molecular evidence of therapeutic correction of splicing defects. Ongoing enrichment strategies for low-abundance proteins will further expand biomarker discovery, potentially transforming treatment monitoring in DM1 and related neuromuscular diseases.

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211 - Genetic block of Cav1.1 conductance rescues muscle weakness in a severe DM1 mouse model.

Sakura Hamazaki[1], Lily Cisco[1], Matthew Sipple[1], Rachel Knebel[1], Katherine Lupia[1], John Lueck[1]

[1]University of Rochester, USA

While the pathogenesis underlying DM1 is well-defined, the molecular mechanism driving muscle weakness and wasting remains unresolved. Efforts by the Lueck Lab have shown that expression of the gain-of-function fetal isoform of Cav1.1, a voltage-gated L-type calcium channel, aggravates respiratory muscle weakness in a mild DM1 mouse model. Conversely, we hypothesize that blocking Cav1.1 conductance may be protective against progressive myopathy in mouse models with a severe DM1 phenotype. Additionally, recent studies in the lab have also revealed that FDA approved L-type calcium channel blockers can significantly alleviate myopathy in severe DM1 mouse models. However, potential off-target effects limit our ability to make direct links between pharmacological block of Cav1.1 and improved muscle function. Therefore, to directly evaluate whether Cav1.1 conductance alone is a therapeutic target for improving DM1 myopathy, we utilized a non-conducting Cav1.1 (termed ncDHPR) mouse model and crossed it with an established severe DM1 mouse model (*HSA*^{LR}/Mbnl1$^{-/-}$) to generate ncDHPR/*HSA*^{LR}/Mbnl1$^{-/-}$ mice. We then characterized survival, growth, muscle function (*in vitro, in vivo* muscle contraction, and EMG recordings), and histopathology to determine if genetic block of Cav1.1 conductance is sufficient to eliminate or reduce the progressive myopathy. We found

that ncDHPR/*HSA*^{LR}/Mbnl1$^{-/-}$ mice demonstrate a significant rescue in both survival and muscle function compared to *HSA*^{LR}/Mbnl1$^{-/-}$ mice. These studies directly corroborate the role of Cav1.1 in driving DM1 myopathy, which in turn provides confidence in the future pursuit of calcium channel blockers as a novel therapeutic approach to improve DM1 patient outcomes.

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212 - Brain Structure, Cognitive Function, and Fluid Biomarkers in DM2: A Multi-Modal Study

Araya Puwanant[1], Diana A. Madrid Fuentes[1], Laura A. Flashman[1], Joseph Rigdon[1], M Constance Linville[1], Michelle M Mielke[1], Suzanne Craft[1], Peggy Nopoulos[2]

[1]Wake Forest University School of Medicine, USA, [2]University of Iowa, USA

Background: Nearly 70% of individuals with myotonic dystrophy type 2 (DM2) report cognitive symptoms as a major source of disability. Limited brain imaging studies suggest cerebral white matter (WM) is predominantly affected in DM2; however, mechanisms underlying cognitive dysfunction remain poorly understood.

Method: 3T brain MRIs were acquired from 38 adults with DM2 and 24 age-and sex-matched healthy controls (HC). Brain morphometry and WM integrity were assessed using T1-MPRAGE and diffusion tensor imaging (DTI). DTI metrics (fractional anisotropy [FA], radial, axial, and mean diffusivity [RD, AD, MD]) and gray matter (GM) volumes were compared between groups. Comprehensive cognitive measures and fluid biomarkers were evaluated and correlated with imaging findings.

Results: Among 62 participants (55% female), there were no group difference in age (DM2=57.5 vs. HC=60.2 years) or education (DM2=16.2 vs. HC=17.0 years). Compared to controls, DM2 participants demonstrated widespread disruption in WM microstructural abnormalities, characterized by lower FA and higher RD (mean differences: FA=0.035; P-val<0.0001 and RD=0.00005; P-val<0.0001). Cortical GM loss was observed across multiple lobes (*t*-value=4.46; P-val<0.0001). DM2 participants demonstrated significant deficits in executive function (p<0.003), working memory (p<0.05), and episodic memory (p<0.017). We found strong correlations between superior frontal FA vs. executive function (r=0.44, P-val=0.008), and between superior frontal and parietal GM volume vs. working memory (r=-0.41, P-val=0.015). 18 plasma biomarkers were significantly elevated in DM2, including P-tau181 (log_{FC}=1.03, P-val_{FDR}=0.006), P-tau231(log_{FC}=0.8, P-val_{FDR}=0.016), total-tau (log_{FC}=0.56, P-val_{FDR}=0.03), and NfL (log_{FC}=0.63, P-val_{FDR}=0.02).

Conclusion: Our study demonstrates strong associations between measures of WM microstructure, regional GM volume, and cognitive dysfunction in DM2. Elevated plasma biomarkers support tau-related disease mechanisms secondary to RNA splicing abnormalities. Longitudinal studies and validation of fluid biomarkers are required to better understand disease mechanisms and progression in the DM2 brain. Additional subjects and CSF biomarker analyses will be updated at the IDMC meeting.

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213 - First Canadian Data from the DM-Scope Registry: Clinical and epidemiological profile of Myotonic dystrophy type 1

Marianne Nury[1, 2], Lola Lessard[3, 4], Xavier Rodrigue[1, 2], Isabelle Côté[5], Rachel Thompson[6], Justine Dolbec[5], Tamara Burgess[6], Mariem Blel[7], Dalil Hamroum[8], Stéphanie Belliveau[9], Dhouha Meftah[7], Joaquin Machado[9], Helene Simard[5], Melinda Gyenge[7], Hanns Lochmuller[6, 10, 11], Cynthia Gagnon[5], Guillaume Bassez[7]

[1]Department of Medicine, Faculty of Medicine, Université Laval, Quebec City, Canada, [2]Centre intégré universitaire de santé et de services sociaux de la Capitale-Nationale, Québec, QC, Canada, [3]Service Troubles du Mouvement et Pathologies Neuromusculaires, Hôpital Neurologique, Hospices Civils de Lyon, Lyon, France, [4]Institut NeuroMyoGène, Laboratoire Physiopathologie et Génétique du Neurone et du Muscle, CNRS UMR 5261 -INSERM U1315Université Claude Bernard Lyon 1, Lyon, France, [5]Groupe de recherche interdisciplinaire sur les maladies neuromusculaires, Centre de recherche et d'innovation du CIUSSS Saguenay-Lac-St-Jean, [6]Children's Hospital of Eastern Ontario Research Institute, [7]Institute of Myology, Paris, France, [8]CHRU de Montpellier, Direction de la Recherche et de l'Innovation, Hôpital La Colombière - Pavillon 3239 avenue Charles Flahault, 34295. Montpellier, France, [9]Neuroscience Program, Ottawa Hospital Research Institute, [10]Division of Neurology, Department of Medicine, The Ottawa Hospital, [11]Brain and Mind Research Institute, University of Ottawa, Ottawa, Canada

The DM-Scope registry, initiated in France in 2008, recently expanded to Canada to form the International DM-Scope (iDM-Scope), a multicenter database collecting standardized real-world data from individuals with myotonic dystrophy type 1 (DM1).

Sociodemographic, clinical, and genetic data from Canadians with DM1 enrolled in iDM-Scope who had ≥1 visit between 2019 and 2025 were collected retrospectively and prospectively. Analyses were cross-sectional and based on the most recent visit. Missing or unavailable data were excluded. Results are reported using available-case denominators and summarized as median [IQR] or percentages.

A total of 341 individuals with DM1 from seven Canadian centers were included (53.0% female). Age at inclusion was 48 [35-59] years; 6.0% were <18 years. Clinical phenotypes (n=331) included congenital (6.3%), childhood-onset form (16.0%), juvenile (25.0%), adult (34.3%), late-onset (16.3%), and asymptomatic (2.1%). CTG repeat length was 400 [169-919] repeats (n=248). Median BMI was 24.7 [20.5-30.1] kg/m^2 (n=200); 14.5% were underweight and 26.0% obese. Diabetes mellitus was present in 12.5%. Cataract surgery was reported in 33.3%, and cardiac device implantation in 26.3% (pacemaker) and 3.0% (defibrillator). Non-invasive ventilation was used by 33.3%. Loss of unassisted ambulation occurred in 12.0% at a median age of 51 [44-60] years. Death was reported in 6.5% at a median age of 59 [52-68] years, most commonly due to cardiac causes and aspiration pneumonia.

This first Canadian iDM-Scope analysis demonstrates marked heterogeneity in DM1 expression, with multisystem complications contributing variably to individual disease burden beyond genetics alone. These findings support a personalized, life-course approach to DM1 care integrating early screening, multidisciplinary management, and individual risk profiling. iDM-Scope provides a robust platform for personalized risk stratification and longitudinal outcome assessment, while international harmonization enables the generation of comparative data to better inform clinicians, researchers, and other stakeholders.

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214 - Uncovering DMPK-Dependent Mitochondrial Defects in Myotonic Dystrophy Type 1 Muscle Stem Cells

Pauline Garcia[1, 2], Maya Sottolichio[3], Floriane Dumont Du Plessis[3], Inès Mokhtari[2, 3], José Carlos Rivera[1], Jean-Sébastien Joyal[1], Elise Duchesne[4, 5], Nicolas Dumont[1, 6]

[1]CHU Sainte Justine, [2]Département de Physiologie et Pharmacologie, Université de Montréal, [3]Université de Montréal, [4]Groupe de Recherche Interdisciplinaire sur les Maladies Neuromusculaires (GRIMN), [5]Centre Interdisciplinaire de Recherche en Réadaptation et Intégration Sociale (Cirris), [6]Faculté de Médecine, Université de Montréal

Myotonic Dystrophy type 1 (DM1) is a multisystemic disorder caused by CTG trinucleotide repeat expansion in the *DMPK* gene, leading to the accumulation of toxic RNA and widespread splicing defects. In skeletal muscle, these alterations compromise muscle stem cells (MuSCs), driving senescence and impairing regeneration. Emerging evidence implicates mitochondrial dysfunction in this process, yet the underlying mechanisms remain poorly understood.

Here, we investigated mitochondrial function in human DM1 MuSCs. Transcript and protein analyses revealed no major defects in mitochondrial gene expression; however, functional assays demonstrated respiration defects and elevated reactive oxygen species (ROS) levels during proliferation and early differentiation. Furthermore, we observed increased mitochondrial membrane permeability, as well as abnormalities in mitochondrial length and positioning relative to the nucleus, suggesting cytoskeletal and organelle organization defects. Given the established role of *DMPK* isoforms at the mitochondrial membrane, we examined DMPK protein localization. In control MuSCs, DMPK was distributed between the cytoplasm, nucleus, and mitochondria. Strikingly, in DM1 MuSCs, DMPK was predominantly nuclear, with reduced mitochondrial localization. To test whether DMPK loss contributes to these abnormalities, we silenced *DMPK* using siRNA and assessed mitochondrial organization *via* TOM20 immunostaining. DMPK depletion recapitulated mitochondrial mislocalization, supporting a direct role for DMPK in mitochondrial dynamics.

Our findings indicate that mitochondrial defects are an early and intrinsic feature of DM1 MuSCs, driven in part by altered DMPK localization. Understanding the interplay between DMPK, mitochondrial impairment, and oxidative stress may reveal novel therapeutic targets to restore muscle regeneration in DM1.

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215 - Integrated functional and multi-omic profiling of DM1 iPSC-derived cardiomyocytes

Caroline Part[1, 2], Haley Geertsma[1], Stephen Baird[1], Alex MacKenzie[1], Sally Spendiff[1], Hanns Lochmuller[1, 3, 4, 5, 6]

[1]CHEO Research Institute, Ottawa, ON, Canada, [2]Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, ON, Canada, [3]Division of Neurology, Department of Medicine, The Ottawa Hospital, Ottawa, ON, Canada, [4] Department of Neuropediatrics and Muscle Disorders, [5] Centro Nacional de Análisis Genómico, Barcelona, Spain, [6] University of Ottawa Brain and Mind Research Institute, Ottawa, ON, Canada

Myotonic Dystrophy Type 1 (DM1) is the most common adult-onset muscular dystrophy with the highest global prevalence of 1:500 found in Northeastern Quebec. While muscle weakness and wasting are hallmark features, DM1 is a multisystemic disorder with widespread clinical manifestations. Notably, cardiac abnormalities occur in 80% of patients and are the second leading cause of death. DM1 is caused by a trinucleotide repeat expansion in the DMPK gene and individuals with greater

than 50 repeats manifest the disease. Mutant *DMPK* mRNA forms stable secondary structures that accumulate in the nucleus as RNA foci and disrupt splicing proteins. This results in a global spliceopathy in which tissue-specific mis-splicing events drive cellular dysfunction and disease pathology. Despite the severity of cardiac involvement, no disease-modifying treatments currently exist. The objective of this study is to define cell type-specific functional and molecular mechanisms underlying DM1 cardiac pathology. To address this gap, I generated ventricular, atrial, and sinoatrial nodal cardiomyocytes derived from DM1 patient induced pluripotent stem cells (iPSCs) using established protocols. I am quantifying repeat length and nuclear foci to assess cell type-specific repeat instability. Additionally, live-cell imaging of action potentials and calcium signaling is being used to assess electrophysiological dysfunction and its contribution to arrhythmias in DM1. Pilot proteomic analyses identified differential expression of proteins implicated in cardiac disease that have not previously been associated with DM1. Notably, subtype-specific proteomic differences were observed across DM1 iPSC-derived cardiomyocytes, with sinoatrial nodal cells exhibiting perturbations in calcium-handling proteins. RNA sequencing will further be performed to identify transcriptomic changes between cardiomyocyte subtypes in disease and assess concordance with proteomic alterations. Altogether, this work aims to define subtype-specific molecular and functional vulnerabilities in DM1 cardiomyocytes, discover novel biomarkers and therapeutic targets to inform future drug-screening efforts to improve clinical outcomes for patients with DM1.

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216 - Cancer Risk in Myotonic Dystrophy

Martin Payne[1]

[1] Dr Martin Payne (retired toxicologist), Ilkley, West Yorkshire, UK

The 2018 “Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type 1” state: “Recent epidemiological studies comparing the risks of malignancies in DM1 patients with the general population have shown that DM1 patients are at increased risk of certain cancers, especially those arising in the ovary, colon, endometrium, brain and thyroid gland.”

However, they also make clear that “Studies have shown that cancer is a distant third among cause of death in DM1 patients, after respiratory and cardiovascular complications.” It is the purpose of this contribution to review the basis of these conclusions and illustrate how an understanding of the strengths and limitations of statistical parameters produced such as SIRs (Standardized Incidence Ratios) in the assessment of cancer “risk” may assist in the interpretation of the results.

The present work looks afresh at the published studies, clarifying the meaning of "increased risk" in that context, which may have wrongly been taken to represent changes in lifetime risk of cancer, that in practice is much reduced due to frequently early death (< 60 years) by competing causes of mortality.

A shift of cancer onset for some cancer types to younger ages, has been reported, as is found in many familial cancers with a genetic component. However, the overall contribution of cancer to lifetime morbidity and mortality of myotonic dystrophy although significant (about 10% and 6% respectively) is small compared with the lifetime experiences of the general population of e.g. USA, Canada and Europe (roughly 50% and 25% respectively).

The likely mechanisms of age-specific changes in cancer incidence in myotonic dystrophy have been considered in this work: a significant role of mis-splicing of key "players" defending against malignancy is likely. However, variability between cancer types is evident.

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217 - Dosage of neurodegeneration biomarkers in the blood of myotonic dystrophy type I patients with or without type II Diabetes

Nicolas SERGEANT[1], Coraille FORMENTIN[1], Sabiha EDDARKAOUI[1], Ophelie RABATEL[1], Camille CHIVE[1], Marguaux LEQUEUX[2], Jean-baptiste DAVION[2], Gregory KUCHCINSKI[2], Marie-Christine VANTYGHEM[2], David DEVOS[2], Luc BUEE[1], Susanna SCHRAEN-MASCHKE[1], Thibault LEBOUVIER[1], Amelie BONNEFOND[3], Charlotte CORDONNIER[2], Celine TARD[2]

[1]Inserm UMRS1172, Univ. Lille, CHRU of Lille, Lille Neuroscience Research Center, Lille Neuro & Chemistry, [2]Inserm UMRS1172, Univ. Lille, CHRU of Lille, Lille Neuroscience Research Center, Degenerative and Vascular Cognitive Disorders, [3]University Lille, CNRS, INSERM, UMR8199-1283, EGID, Institut Pasteur de Lille, EGID, Lille University Hospital, 59000 Lille, France; Department of Metabolism, Imperial College London, Hammersmith Hospital, London W12 ONN, UK.

Introduction: Myotonic dystrophy type I affects the cognitive functions and presents neuropathological lesions, the so-called neurofibrillary degeneration. Yet, no biomarkers correlate with brain impairment and could also serve as theragnostic biomarkers. We herein quantified central nervous system biomarkers, including Abpeptides, Neurofilaments, Glial fibrillary acidic protein, Tau, and phospho-tau, in blood collected from three patient cohorts. The DM1 cohort includes more than 60 DM1 individuals with or without type I diabetes, a confounding risk of cognitive

impairment, and an age-matched cohort of controls (n=30) and patients with type II diabetes. All DM1 patients underwent cognitive evaluation and brain MRI.

Methods: Central nervous system blood biomarkers were quantified using SIMOA Technology (Quanterix) Neurology 4-PLEX E (Ab40, Ab42, GFAP, and NfL) and the BD-Tau and P-Tau231 SIMOA assay kits. Measured concentrations were recovered, and statistical analyses were performed using the Prism 10 GraphPad Software.

Results: Among all biomarkers, NfL and GFAP were correlated with the Montreal Cognitive Assessment (MoCA). In DM1 cohort A, peptide concentrations were significantly higher than in the PRECIDIAB control and type II diabetes cohorts. Statistical analyses with cognitive assessments and brain imaging are ongoing, and results will be presented.

Conclusion: As shown in a previous DM1 cohort study, we reproducibly demonstrate that Ab peptide blood concentrations are increased in DM1 patients, and that other biomarkers, such as GFAP and NfL, are associated with type II diabetes-related cognitive impairments.

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218 - Integrating proteomics and structure prediction to determine the interactome of proteins involved in muscular dystrophies and myopathies

Yasmine Amina Bachir[1], Marie-Claude Sincennes[1], Martine Tétreault[2], Lekha Sleno[3]

[1]INRS - Centre Armand-Frappier - Santé Biotechnologie, Unité mixte de recherche (UMR) INRS- UQAC en santé durable, [2]Université de Montréal, [3]Université du Québec à Montréal (UQAM)

Muscular dystrophies and myopathies are a heterogeneous group of neuromuscular disorders characterized by progressive muscle weakness, muscle wasting, impaired regeneration, and, in some cases, cardiac and respiratory involvement. Many of these conditions are monogenic, including myotonic dystrophy type 1, oculopharyngeal muscular dystrophy, Duchenne muscular dystrophy, as well as several rare inherited myopathies. Despite extensive efforts to develop effective treatments, most of these diseases remain incurable, highlighting the need for alternative therapeutic strategies.

One promising approach is to target protein-protein interactions, as disease-causing mutations may alter the interactome of a protein, leading to the loss of physiological interactions or the formation of aberrant ones that contribute to disease progression. In this project, we aim to develop an integrated proteomics- and bioinformatics-based pipeline to predict and identify protein-protein interactions that are

maintained, lost, or newly formed when disease-associated proteins are mutated in muscle tissue.

To elucidate interactomes in vitro, we are developing a BioID2-based proximity labeling system directly in myogenic cells rather than fibroblasts, which are commonly used but do not accurately reflect muscle biology. This system is being optimized in C2C12 cells, enabling the characterization of interactomes in both proliferating myoblasts and differentiated myotubes. High-confidence candidate interactors will be identified by LC-MS/MS and validated using co-immunoprecipitation assays. In parallel, in silico analyses based on AlphaFold3 structural predictions are used to prioritize potential interaction interfaces and generate mechanistic hypotheses relevant to disease pathogenesis.

Using Muscle LMNA-Interacting Protein (MLIP), a protein associated with a rare distal myopathy, as a proof of concept, this study aims to define its interactome to better elucidate its biological function. By integrating proteomic and structural approaches, this strategy may be broadly applicable to other muscular dystrophies and myopathies, including myotonic dystrophy type 1.

219 - Cognitive and social decision-making skills in adult-onset Myotonic Dystrophy type 1

Maria Carolina Fontana Antunes de Oliveira[1], Amandine Dervy[1], Ana Ferreiro[2], Stefan Winblad[3], Nathalie Angeard[1]

[1] Université Paris Cité - Memory, Brain and Cognition Laboratory (MC2 Lab),[2] Neuro-Myology Department, Institute of Myology - Pitié-Salpétrière Hospital,[3] University of Gothenburg

Decision-making integrates cognitive, emotional, and social processes to guide goal-directed behavior. In DM1, Decision-making impairments have been reported but remain insufficiently characterized. Cognitive and/or social deficits may contribute to less adaptive decisions; however, the underlying mechanisms have not yet been clearly elucidated.

This pilot study aims to investigate decision-making processes in adult-onset DM1 compared with matched healthy controls. It will explore patients' sensitivity to social cues and examine the contributions of executive functions and social cognition to decision-making performance.

The study will include 24 participants aged 20 to 50 years: 12 adults with DM1 and 12 healthy controls matched for age, sex, and education. All participants will

undergo a comprehensive neuropsychological assessment including: (1) a short, validated form of the WAIS-IV adapted for DM1 to assess general intellectual ability; (2) one version of the Iowa Gambling Task (Standard or Social) to evaluate decision-making processes, with the social version specifically designed to assess sensitivity to positive or negative social cues; and (3) additional measures of executive functions, social cognition, and visuoconstructive abilities to analyze their contribution to decision-making performance. Performance will be compared across social and non-social decision-making paradigms. Within the social IGT, congruent and incongruent conditions will be contrasted. Learning trajectories will also be examined using block-by-block performance indices to characterize learning processes over time.

We hypothesize that adults with DM1 will demonstrate less adaptive decision-making—especially in socially cued conditions—and that task performance will be associated with executive functioning and social cognitive abilities. We further expect individuals with DM1 to exhibit a distinct learning trajectory compared to controls, particularly under incongruent conditions.

These preliminary findings will contribute to a better understanding of the cognitive, emotional, and social mechanisms underlying decision-making in adults with DM1 and may help elucidate everyday challenges related to personal, medical, and social decisions in this population.