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SAVOIR & COMPRENDRE
AVANCÉES DE LA RECHERCHE

# Advances 2024 in congenital muscular dystrophies

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This document, published to coincide with the AFM-Téléthon General Meeting 2024, presents congenital muscular dystrophy research news from the past year (ongoing observational studies and clinical trials, scientific and medical publications, etc.).

AFMTÉLÉTHON
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# Congenital muscular dystrophies CMD

Apparent at birth or in the first few months of life, congenital muscular dystrophies (CMD) are a group of very diverse, rare diseases characterised by progressive muscle weakness in the trunk and limbs. They may also affect other organs such as the heart, brain and eyes.

## Common symptoms

- **Muscle weakness** with hypotonia (low muscle tone) causing impaired motor skills and often associated with breathing and/or feeding problems.
- **Orthopaedic deformities** such as contractures (shortening of muscles and their tendons) causing skeletal deformities.
- **These symptoms vary** from one type of CMD to another and from patient to patient, even within the same family.

## Management and treatment

- **Multidisciplinary** (particularly orthopaedic) treatment of symptoms at specialist centres.
- **Preventing complications**, particularly muscle, joint, respiratory system, digestive tract and heart problems.
- **Improving quality of life.**

## Diagnosis

**Clinical diagnosis**

Clinical examination by a doctor to characterise and quantify the muscle weakness

**Genetic diagnosis**

Blood or muscle (less often) sample taken to identify the causative gene

## In numbers

CMD affect **0.6 to 0.9** people in every 100,000

**52** scientific articles published between May 2023 and May 2024 *(PubMed®)*

**8** observational studies including **2** in France *(ClinicalTrials.gov 31/05/2024)*

# What causes congenital muscular dystrophies?

- **Over 30 genes coding for proteins needed for muscle fibres to work properly.**
- An **autosomal recessive** mode of inheritance in the vast majority of cases.
- To date, **six groups of CMD** have been distinguished based on the genes or proteins involved.

## CMD linked to abnormalities in the extracellular matrix

| Disease | Gene |
|---|---|
| Ullrich CMD (UCMD) | *COL6A1, A2, A3* |
| Merosin-deficient CMD (MDC1A) or LAMA2-CMD | *LAMA2* |
| CMD with collagen XII deficiency | *COL12A1* |
| CMD with integrin alpha-7 deficiency | *ITGA7* |
| CMD with integrin alpha-9 deficiency | *ITGA9* |

## Dystroglycanopathies (also called alpha-dystroglycanopathies)

| | |
|---|---|
| Fukuyama CMD | *FKTN* |
| CMD type 1B (MDC1B) | *Gene still unknown* |
| CMD type 1C | *FKRP* |
| Muscle-eye-brain disease (MEB) | *LARGE1* *B3GALNT2; B4GAT1; CRPPA; DAG1; DPM1; DPM2; DPM3; FKRP; FKTN; GMPPB; ISPD; LARGE1; POMK; POMT1; POMT2; POMGNT1; POMGNT2; TMEM5* |
| Walker-Warburg syndrome (WWS) | *B3GALNT2; B4GAT1; CRPPA; DAG1; DPM1; DPM2; FKRP; FKTN; GMPPB; ISPD; LARGE1; POMK; POMT1; POMT2; POMGNT1; POMGNT2; TMEM5 (RXYLT1)* |

## CMD linked to membrane trafficking defects

| | |
|---|---|
| *TRAPPC11*-related CMD | *TRAPPC11* |
| *TRAPPC2L*-related CMD | *TRAPPC2L* |
| CMD with or without seizures (MYOS) | *GOSR2* |
| CMD with rapid progression (MDRP) | *BET1* |

## CMD linked to abnormalities in the nuclear envelope

| | |
|---|---|
| *LMNA*-related CMD (L-CMD) | *LMNA* |
| *SYNE1*-related CMD | *SYNE1* |
| Davignon-Chauveau-type CMD (MDCDC) | *TRIP4* |

## CMD linked to abnormalities in endoplasmic reticulum proteins

| | |
|---|---|
| *SEPN1*-related myopathy (rigid spine muscular dystrophy) | *SEPN1 (SELENON)* |

## Other CMD (cytosol protein defect, etc.)

| | |
|---|---|
| Megaconial-type CMD | *CHKB* |
| CMD with cataracts and intellectual disability (MDCCAID) | *INPP5K* |
| Muscular dystrophy, congenital hearing loss, and ovarian insufficiency syndrome (MDHLO) | *GGPS1* |

**For more information on CMD, please visit:**
www.afm-telethon.fr/fr/fiches-maladies/dystrophies-musculaires-congenitales [page in French]

# 4 highlights from the past 12 months

## A natural history study of *LAMA2*-related CMD in France

▪ This year, AFM-Téléthon, the LAMA2 France association and clinicians from the FILNEMUS rare neuromuscular diseases healthcare network and the Institut de Myologie collaborated in order to launch the first ever French national prospective natural history study of merosinopathy (*LAMA2*-related CMD).

## A new causative gene in CMD

▪ Following the identification of *SNUPN* as a causative gene, a new type of recessive CMD was discovered this year. This new form marks the introduction of "snurportinopathies" into the realm of neuromuscular diseases. It is characterised by being caused by RNA splicing (maturation) abnormalities and inducing, among other things, myofibrillar structural abnormalities.

## Collagenopathies - treatment avenues being studied

▪ New biological therapies continue to be developed in collagen VI (COL6)-related dystrophies (including UCMD). In the United States, the feasibility and efficacy of two approaches that involve inactivating the pathological copy of the *COL6* gene were evaluated in cell models in 2024. More "traditional" methods have not been ignored, however. An Italian team confirmed the relevance of evaluating spermidine, a compound that induces autophagy (a process which is impaired in COL6-related dystrophies).

## Our understanding of CMD continues to improve

▪ Descriptions of Iranian, Dutch, and Indian patients, descriptions of new symptoms, the study of pathological mechanisms - our knowledge of CMD continues to grow and our understanding of their mechanisms is becoming more refined.

## Medical and scientific CMD conferences

### The MDA Clinical & Scientific Conference 2024

▪ The MDA (Muscular Dystrophy Association) Clinical & Scientific Conference 2024 took place in Orlando, Florida (United States) and online between 3 and 6 March 2024. Once again, the event proved to be very popular. Nearly 1,700 participants attended in person and almost 390 took part online with over 370 posters and 43 oral presentations delivered across more than 32 sessions.

▪ This conference presents the latest advances in preclinical, translational and clinical research and continues to draw a large audience. Several pharmaceutical companies attended including Biogen, Edgewise Therapeutics, ML Bio Solutions, Pfizer, Sanofi and Sarepta Therapeutics, some of which are directly involved in clinical development for several types of CMD.

www.mdaconference.org

### Meeting of the French network for nuclear envelope-related diseases

▪ The **22nd annual meeting of the French network "Dystrophie Musculaire d'Emery-Dreifuss et autres pathologies de l'enveloppe nucléaire"** [Emery-Dreifuss muscular dystrophy and other nuclear envelope-related diseases] took place on Friday 10 November 2023 at the Institut de Myologie (Paris, France) and online. This meeting featured presentations on basic and clinical research in laminopathies. An update on DNA damage observed in L-CMD was presented by Marine Leconte, a researcher at the Institut de Myologie.

www.institut-myologie.org/wp-content/uploads/2023/11/Programme-22eme-reunion-reseau-EDMD-Final.pdf [page in French]

### LAMA2-CMD consortium meetings

**Flashback**
In March 2023, the **second international *LAMA2*-related congenital muscular dystrophy (LAMA2-CMD) conference** took place in Barcelona, Spain. Funded by the EJP-RD, this event was an opportunity for researchers, clinicians and patient representatives to come together to discuss and establish an international collaboration network.

▪ One of the tangible outcomes of this **second international LAMA2-CMD conference** was the creation of the "LAMA2-CMD consortium meetings". First held in September 2023, these monthly meetings aim to advance scientific collaborations and research efforts in LAMA2-CMD. The meetings are recorded and can be accessed by members of the LAMA2 consortium. Patients and their organisations can attend the meetings after registering on the LAMA2 Europe website.

www.maastrichtuniversity.nl/news/lama2-cmd-conference-barcelona
lama2.com/news/lama2-consortium-meetings/

*The **EJP-RD** (European Joint Programme on Rare Diseases) is a project aiming to create an effective rare diseases research ecosystem which facilitates progress and innovation for the benefit of patients. Over 130 institutions across more than 35 countries are involved.*

### Iowa Wellstone dystroglycanopathy conference 2023

▪ The **13th Dystroglycanopathies Patient & Family Conference** took place in Iowa City (United States) on 23 and 24 June 2023. This annual event is dedicated to Walker-Warburg syndrome (WWS), muscle-eye-brain disease (MEB), Fukuyama CMD, MDC1C and MDC1D, as well as certain limb-girdle muscular dystrophy (LGMD) subtypes.
Organised for over 10 years by the Iowa Wellstone Center, this conference is open to all and enables patients and their families, patient organisations and healthcare professionals to meet other members of the community and learn more about the diseases (advances in research, daily disease management, etc.).
The next conference will be held in Iowa City on 12 and 13 July 2024.
wellstone.medicine.uiowa.edu/news-and-events

## Observational studies

### What is an observational study?

▪ Unlike interventional studies such as clinical trials, observational studies simply watch participants for certain outcomes without changing their usual care.

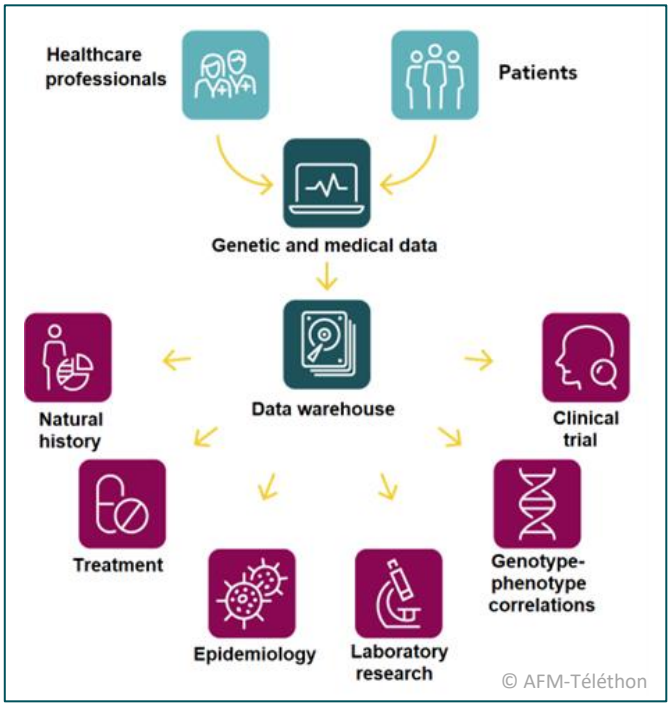
**Different types of observational studies**
▪ **Cross-sectional:** a type of study that collects data from subjects at a single point in time (frequency, morbidity, risk factors, etc.).
▪ **Prospective:** a type of study that follows participants over a period of time, like in natural history studies.
▪ **Retrospective:** a type of study that examines past data from patient records.
▪ **Registry:** a system that uses observational methods to collect data indefinitely.

*The so-called **natural history** of a disease, as doctors refer to it, is the description of the different manifestations of a disease and their progression over time without treatment (drugs, physiotherapy, surgery, etc.).*

▪ These studies help us to **better understand and describe diseases**, and to identify better diagnostic and follow-up tools. They are essential for understanding the epidemiology of diseases, improving treatment and management and preparing future clinical trials.

### CMD patient registries

▪ Medical data warehouses and patient registries typically **collect information on patients** and/or help to quickly identify possible candidates for clinical trials. Registries can be national, however, given the rareness of certain diseases, more and more are now international in order to be able to collect data from a greater number of patients.




***Medical databases*** *and* ***data warehouses*** *collect and store medical data on people with the same disease, often without a time limit. Analysing this data helps to determine the natural history of the disease, establish genotype-phenotype correlations and recruit participants to clinical trials.*

## Congenital Muscle Disease International Registry (CMDIR)

- The **CMDIR** aims to carry out a census of the global congenital muscle disease community. Anyone with a congenital muscle disease, whether or not they have had genetic confirmation, can register their data and, most importantly, contribute towards a better understanding of the natural history of these diseases, facilitate recruitment in clinical studies and increase awareness of congenital muscle diseases.
- This registry was created in 2009 and is sponsored by the American patient organisation Cure CMD. The information available on the CMDIR has been provided with the help, advice and approval of a group of experts in congenital muscular dystrophies.

**CMDIR – CMDPROS1 study (all congenital muscle diseases)**

**International** | **4,000 participants** | **Recruiting** | **20-year follow-up period**

NCT01403402

www.cmdir.org/

## Global FKRP Registry

- Set up in 2011 and sponsored by Newcastle University (United Kingdom), the **Global FKRP Registry** is a healthcare data warehouse which collects data from people with diseases caused by mutations in the *FKRP* gene. These include several types of CMD such as MDC1C, MEB, WWS, and, by extension, LGMD R9.

**A better understanding of *FKRP*-related conditions**

▪ The Global FKRP Registry aims to enhance the understanding of the natural history and frequency of *FKRP*-related conditions, and to facilitate the identification of potential candidates for future clinical trials.

▪ Patients enter their data onto a secure portal (age of onset of the disease, initial symptoms, family history, motor function and muscle strength, heart and lung function, medication, quality of life and pain).

▪ This data is updated annually and can be deleted upon request.

**Global FKRP Registry (MDC1C, MEB, WWS, LGMD R9)**

**International**

**1,000 participants (all ages)**

**Recruiting**

**Nov 2013 – Dec 2025**
**10 years of follow-up**

NCT04001595

www.fkrp-registry.org

## Registry of Muscular Dystrophy (Remudy)

▪ The **Remudy** was developed in 2009 in Japan in collaboration with TREAT-NMD. This national database collects information on the natural history, epidemiology and treatment of Japanese patients with muscular dystrophies, including CMD. Remudy has also been collecting a subset of data from patients with Fukuyama CMD since 2011.

**Fukuyama CMD** is the second most common type of muscular dystrophy in Japan. It is a dystroglycanopathy caused by mutations in the *FKTN* gene which codes for fukutin.

*Nakamura, H. et al. Orphanet J Rare Dis. 2013*
*Ishigaki, K. et al. Neuromuscul Disord. 2018*

***TREAT-NMD** is an international network for neuromuscular diseases which brings together scientists, clinicians and patient groups. It was created in 2012 and initially funded by the European Commission. One of its objectives is to accelerate the development of potential treatments.*

*treat-nmd.org/*

## Observatory for Patients with Laminopathies and Emerinopathies (OPALE)

▪ The **OPALE** registry is supported by AFM-Téléthon and aims to register all of the laminopathy and emerinopathy patients in France. It should therefore enable the natural history of these diseases to be better understood, links to be made between genetic mutations and their clinical manifestations, and patients to be identified for research and future clinical trials.

**OPALE (L-CMD, other laminopathies, emerinopathies)**

**France**

**800 patients**

**Recruiting**

**July 2013 – July 2033**
**10-year follow-up**

NCT03058185

www.afm-telethon.fr/fr/essais/laminopathie-ou-demerinopathie-lobservatoire-opale [page in French]

### A genetic database for laminopathies

In addition to the OPALE registry, the **UMD-LMNA** (Universal Mutation Database for Laminopathies), supported by AFM-Téléthon, has been collecting and sharing genetic information from people with *LMNA* gene mutations published in scientific literature or identified in a French laboratory since 2000.
www.umd.be/LMNA/

## Global Registry for COL6-related Dystrophies

- The Global Registry for COL6-related Dystrophies, sponsored by Newcastle University (United Kingdom), collects medical data from patients and clinicians. This healthcare data warehouse for collagen VI (COL6)-related CMD aims to identify and characterise the population of patients who have been diagnosed with UCMD, Bethlem myopathy (LGMD R22 and LGMD D5) or their intermediate forms, and describe the natural history of these diseases.
- It is funded by the Collagen VI Alliance (which is supported by AFM-Téléthon) and is part of the TREAT-NMD Alliance global network of registries.

**Global Registry for COL6-related Dystrophies**

| International | 1,000 participants (all ages) | Recruiting | August 2018 – Oct 2024<br>5 years of follow-up |
|---|---|---|---|

NCT04020159

www.collagen6.org

## Swiss Registry for Neuromuscular Disorders (Swiss-Reg-NMD)

- The **Swiss-Reg-NMD** collects medical data from Swiss neuromuscular disease patients in order to facilitate their access to therapeutic studies. The registry also enables questions to be answered about this population in areas such as epidemiology and quality of life. Currently, the registry contains data on **merosin-deficient CMD (MDC1A), COL6-related dystrophies** and other neuromuscular diseases such as spinal muscular atrophy (SMA), Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD).

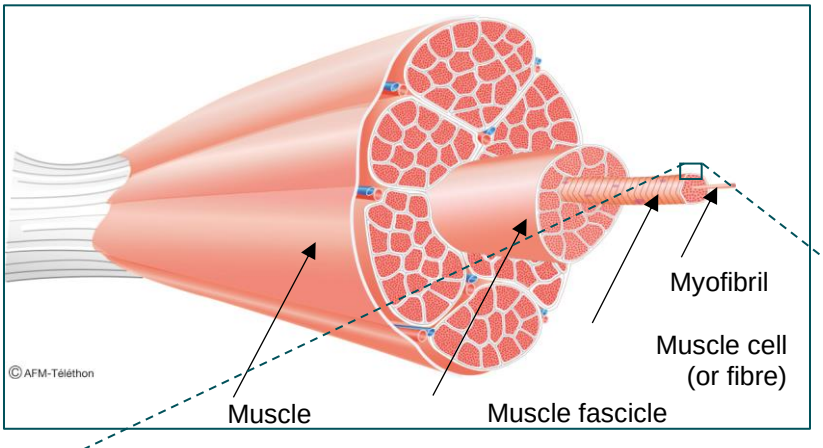
**Swiss-Reg-NMD (all neuromuscular diseases)**

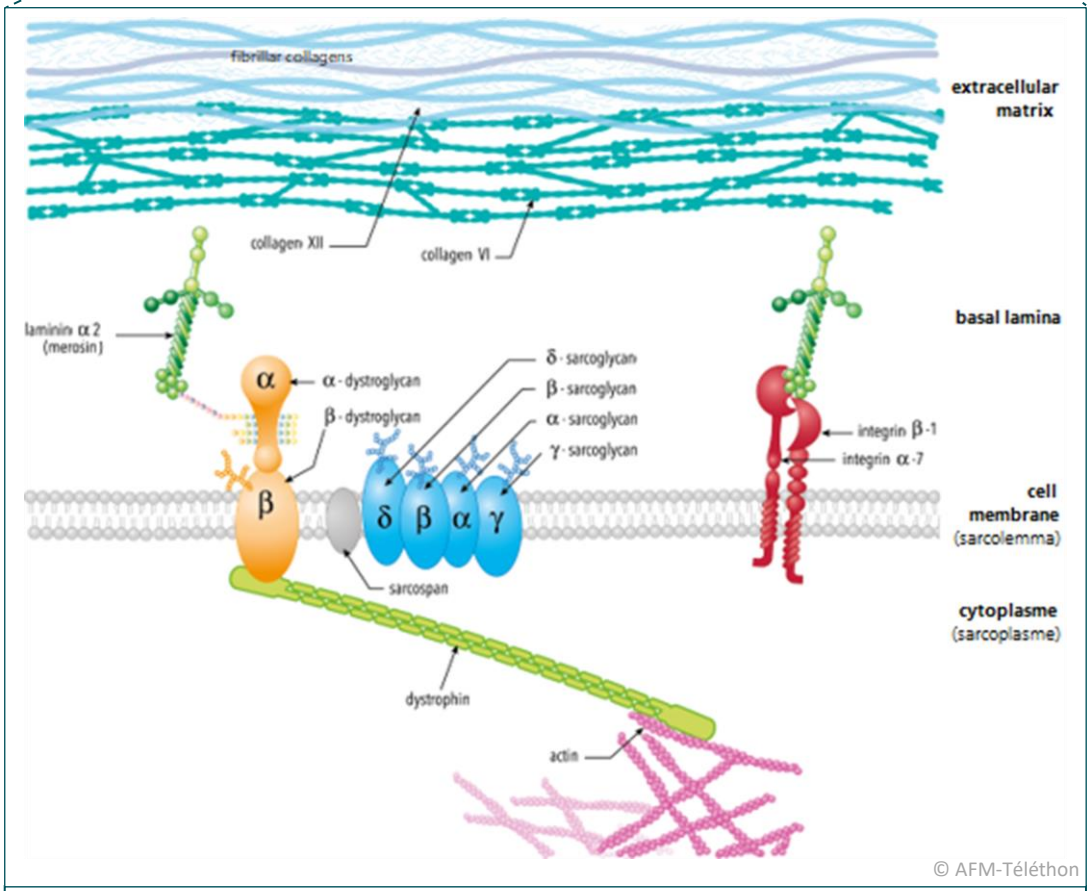
| Abroad | 2,000 participants (all ages) | Recruiting | June 2018 – Jan 2071<br>Up to 80 years of follow-up |
|---|---|---|---|

NCT05102916

www.swiss-reg-nmd.ch/en/about-the-registry

*The **TREAT-NMD Alliance** is an international network for neuromuscular diseases which brings together scientists, clinicians and patient groups. It was originally supported by the European Commission as an EU Network of Excellence. Since 2012, the TREAT-NMD Alliance's objective has been to maintain an infrastructure which ensures that the most promising research reaches patients quickly. It also seeks international recognition of the best current care practices for people with neuromuscular diseases. With this dual aim, the TREAT-NMD Alliance has developed tools that are essential for clinicians and treatment developers such as global patient registries and the TACT (TREAT-NMD Advisory Committee for Therapeutics), an independent evaluation platform for preclinical projects.*
www.treat-nmd.eu




***Proteins that form connections between muscle cells and their surroundings (extracellular matrix).***

*The contact area between muscle fibres and the connective tissue that surrounds them is very important for cohesion between the muscle fibres which make up muscle. In CMD, this connection is impaired, causing muscle to weaken.*

***Laminin alpha 2***, ***collagen VI***, ***collagen XII***, ***integrin alpha 7*** *and* ***alpha-dystroglycan*** *all help to maintain a connection between the inside and outside of cells. This docking system between the two environments allows muscle cells to adapt to mechanical stress, particularly the deformations they undergo during muscle contraction, and to exchange signals that are essential for the function and survival of muscle cells.*

## Observational studies in CMD

### Respiratory function in *SEPN1*-related myopathy and *LAMA2*-related CMD

- A natural history study conducted over a year and a half in 11 patients with *SEPN1*-related myopathy and 26 patients with *LAMA2*-related CMD showed that respiratory impairment was common in both diseases.
- Respiratory function was **worse in the *SEPN1*-related myopathy patients** than in the *LAMA2*-related CMD patients, with more frequent use of mechanical ventilation and more severe diaphragmatic dysfunction.
- Spirometry and respiratory muscle strength tests stood out as appropriate clinical outcome measures for future studies in these diseases, even in very young patients (from the age of five).

*Bouman, K. et al. Eur J Paediatr Neurol. 2024*

### Bone fragility in *SEPN1*-related myopathy and *LAMA2*-related CMD

**Fragility fractures**

Fragility fractures usually occur in people who have osteoporosis (a condition characterised by reduced bone mass or bone mineral density that weakens bones). This type of fracture is frequently reported in neuromuscular diseases. It is important to identify at-risk populations, particularly people who have already sustained a fragility fracture and are at risk of experiencing another.

*Thériault, G. et al. CMAJ. 2023.* [article in French]

- A team of Dutch clinicians conducted a one-year prospective natural history study in 10 *SEPN1*-related myopathy patients and 21 *LAMA2*-related CMD patients in order to assess their bone quality and determine their fracture history.
- The results showed that **90% of the patients had low bone quality.** Nearly 40% of the *LAMA2*-related CMD patients and 50% of the *SEPN1*-related myopathy patients had a history of long-bone (e.g. humerus, femur, tibia) fragility fractures.
- The authors reported that they found no differences in bone mineral density between the start and end of the study. Based on international guidelines for the management and treatment of osteoporosis, adequate calcium and vitamin D intake as well as standardised clinical monitoring using DEXA scans or BHI (bone health index) are recommended in all patients with these diseases.

*Bouman, K. et al. Neuromuscul Disord. 2024*

### Natural history of Dutch patients

- **Dutch** clinicians reported laboratory and clinical data from 27 *LAMA2*-related congenital muscular dystrophy patients with an average age of 21. The investigators found that:

• 12 had a very early age of onset but survived into adulthood;
• the MFM-20 and -32 and accelerometry proved to be the most suitable tools for measuring disease progression;
• cardiac involvement was uncommon but not rare.

**The MFM - an essential tool**

▪ The MFM (Mesure de la Fonction Motrice [Motor Function Measure]) is a scale that measures motor function in adults and children with a neuromuscular disease.
▪ It is reproducible, easy to use (35 minutes) and can be used for any disease severity (patient able or unable to walk).
▪ It comprises 32 items (MFM-32) classified into three domains - D1: standing and transfers, D2: axial and proximal motor function and D3: distal motor function. It was approved in 2004 for patients aged six to 60 years old.
▪ A paediatric version, which comprises 20 items (MFM-20), was approved in 2009 for children under seven years old.
mfm-nmd.org/

▪ This data provides important information on the natural history of this disease, particularly in the context of future therapeutic trials.
*Bouman, K. et al. Neurol Genet. 2023*

## Outcome measures in *SEPN1*-related myopathy and *LAMA2*-related CMD

▪ The above results are from the "**LAST STRONG**" natural history study (NL64269.091.17) which was launched in the Netherlands in 2020 and included 38 Dutch patients with *SEPN1*-related myopathy or *LAMA2*-related CMD. The study, which ended this year, was sponsored by the Radboud University Medical Center (RUMC) and the investigators were attempting to determine the most appropriate outcome measures for future clinical trials in these diseases.

**LAST STRONG study (natural history) – *SEPN1*-related myopathy and *LAMA2*-related CMD**

| Netherlands | 38 participants (all ages) | Analysis in progress | Aug 2020 – March 2024<br>1.5 years of follow-up |
|---|---|---|---|

NCT04478981

▪ In order to expand the dataset collected during the "LAST STRONG" study and analyse it in more detail, the RUMC launched a new natural history study at the end of 2023 (the **"extended LAST STRONG"** study) which will follow 40 patients with *SEPN1*-related myopathy or *LAMA2*-related CMD.

**Extended LAST STRONG study (natural history) – *SEPN1*-related myopathy and *LAMA2*-related CMD**

| Netherlands | 40 participants (all ages) | Recruiting | Oct 2023 – Sept 2026<br>1.5 years of follow-up |
|---|---|---|---|

NCT06132750

*The **National Institutes of Health** (NIH) is the United States government institution responsible for medical and biomedical research. The French equivalent of the NIH is the INSERM (Institut National de la Santé et de la Recherche Médicale [French National Institute of Health and Medical Research]).*

## Clinical characterisation of dystroglycanopathies

▪ Since 2006, an American study sponsored by the National Institute of Neurological Disorders and Stroke (NINDS), a branch of the NIH, has been collecting clinical data on dystroglycanopathies, including Walker-Warburg syndrome, muscle-eye-brain disease, Fukuyama CMD, MDC1C and MDC1D. The study investigators are particularly interested in early signs and

symptoms of these diseases, motor and lung function, and quality of life. The data collected will be used to set standards for future clinical trials. Any individual with a confirmed mutation in one of the genes known to be involved in dystroglycanopathies (*B3GALNT2, B4GAT1, CRPPA, DAG1, DPM1, DPM2, FKRP, FKTN, GMPPB, ISPD, LARGE1, POMK, POMT1, POMT2, POMGNT1, POMGNT2* and *TMEM5 (RXYLT1)* for CMD) can participate in the study.

**Clinical trial readiness for dystroglycanopathies**

**United States**

**190 (all ages)**

**Recruiting**

**April 2006 – July 2026 Collection of biological samples and data**

NCT00313677

### Natural history of COL6- and *LAMA2*-related dystrophies

▪ A team from the NINDS in the United States is collecting natural history data **from children** with COL6- and *LAMA2*-related dystrophies from infancy up to the age of five. This study consists of gathering medical histories and performing clinical examinations, muscle ultrasounds, motor assessments and blood and urine tests (not mandatory) on the children involved.

This natural history study will help to contribute to readiness for future clinical trials.

research.ninds.nih.gov/bonnemann-lab

## COL6-related dystrophy - extracellular matrix

### Increase in collagen VI expression

▪ In Italy, **69 patients** with COL6-related dystrophies were examined in order to identify innovative clinical data to better prepare future clinical trials.

▪ For the first time, the four known phenotypes of COL6-related dystrophies were analysed together in a single study. Thirty three patients had Bethlem myopathy, 24 had UCMD, seven had an intermediate phenotype and five had myosclerosis.

▪ Analyses revealed a correlation between collagen VI defects and the severity of the clinical phenotype. They also showed a **gradual increase in collagen VI expression with age.** This time-dependent modulation of collagen VI has never been reported before. Even though this phenomenon has not been explained yet, the authors encourage others to take this finding into consideration in genetic correction clinical trials in COL6-related dystrophies.

*Merlini, L. et al. Int J Mol Sci. 2023*

***Phenotype** refers to the physical characteristics of an individual (hair colour, eye colour, manifestations of a disease, etc.).*

### Clinical course of Bethlem myopathy

▪ A group of American doctors retrospectively studied **23 patients** with Bethlem myopathy (ages ranging from three to 19 years old with an average age of 11.65) in order to characterise the manifestation of the disease, potential management strategies and patient outcomes.

▪ The average age at **initial presentation of symptoms was just over four years old.** Muscle weakness was the most common manifestation (65%) and the average age at diagnosis was just over eight years old.

Nearly 74% of the patients required assistive devices, especially for walking. **Orthopaedic manifestations** (scoliosis, foot and ankle deformities, etc.) were observed in nearly all of the patients, and almost 87% had contractures, most often in the ankles (55%) and elbows (40%).

- This study showed that even though Bethlem myopathy is less severe than other myopathies such as Duchenne muscular dystrophy, it does lead to progressive deformity of the musculoskeletal system and often requires the use of mobility aids and/or surgical procedures.

*Silverstein, R. S. et al. J Pediatr Orthop. 2023*

## *LAMA2*-related CMD - extracellular matrix

### Launch of a new natural history study in France

- Funded by AFM-Téléthon, a study created by LAMA2 France and clinicians and researchers from the FILNEMUS network and the Institut de Myologie will start this year in children and adolescents with *LAMA2*-related CMD.
- With only around 200 patients recorded in France, *LAMA2*-related CMD is an extremely rare disease and is also relatively poorly understood. This new study therefore aims to enhance our understanding of it. It is the first French prospective study of paediatric patients with this disease.

#### A huge national collaboration

- Sponsored by the Institut de Myologie, this study will be conducted at four investigator sites in France: the Institut I-Motion [I-Motion Institute] in Paris, CHU de Montpellier [Montpellier University Hospital], Hôpital Raymond-Poincaré [Raymond-Poincaré Hospital] in Garches and Hospices Civils de Lyon [Lyon University Hospital]. More than 20 healthcare professionals (paediatric neurologists, physiotherapists, radiologists, etc.) will be involved.
- This **three-year study** will include 40 young people (who may or may not be monitored at one of the four investigator sites) between the ages of two and 15 years old who have *LAMA2*-related CMD which has been confirmed genetically and by a muscle biopsy. It will focus on determining the characteristics of the disease and its progression over time.
- The participants will attend a **study visit every six months** for two years during which the investigators will assess muscle impairment (strength, motor function, respiratory function, imaging, blood tests, etc.) but also their cognitive abilities. Their quality of life and burden of care on themselves and their families will also be studied.
- The investigators also hope that this work will help to identify reliable **outcome measures** and **biomarkers** that can be used to determine the efficacy of potential future treatments in *LAMA2*-related CMD.

**NatHis LAMA2 (natural history) – *LAMA2*-related CMD**

| France | 40 (2 to 15 years old) | Not yet recruiting | June 2024 – June 2027 2 years of follow-up |
|---|---|---|---|

NCT06354790

## Is there a correlation between muscle and brain defects?

- Brazilian clinicians compiled clinical data and brain imaging results from patients with *LAMA2*-related CMD in order to identify a potential correlation between muscle and brain defects.
- The vast majority of the 52 patients included in the study were unable to walk (85%). Nearly 20% had significant malformations, around 20% had epilepsy and 15% had intellectual disability.
- The presence of **cortical malformations was significantly correlated with the severity of the motor phenotype.**
- The authors also noted the possible existence of a founder effect in this group of patients.

*Camelo, C. G. et al. J Neuromuscul Dis. 2023*

## Nerve damage in merosinopathy

- **In Japan**, researchers examined three children (all under two years old) with MDC1A with the aim of characterising possible structural and **nerve conduction** changes in their intramuscular nerves.

**Did you know?**

**MDC1A - effects on nerves rarely studied**

Merosin is a protein found in the extracellular matrix of muscle fibres, but also in certain regions of central and peripheral nervous system tissue. Given the prominence of muscle symptoms in MDC1A and research efforts being concentrated in this area, the impact of merosin deficiency on the nervous system has received little attention so far.

- They observed that the **myelin sheaths were significantly thinner** in MDC1A patients than in the control group, however, the analyses did not show any evidence of demyelination.

This study showed that myelin formation may be disrupted in MDC1A and suggested that merosin may be involved in myelin maturation.

*Saito, Y. et al. Muscle Nerve. 2024*

***Demyelination** refers to the loss of or damage to the myelin sheath, the protective membrane that wraps arounds nerves.*

## Deregulation of autophagy in MDC1A

- Autophagy is increased in several muscular dystrophies and has been demonstrated in a mouse model of MDC1A. An Italian team attempted to confirm the existence of this phenomenon in humans using muscle biopsies from newborns with merosinopathy.
- Tests confirmed what had been observed in the **animal model**, with the presence of markers (accumulation of autophagosomes, overexpression of LC3B and ATG5, etc.) indicating **hyperactivation of autophagy** in this disease. This deregulation of autophagy could be characteristic of the pathophysiology of merosinopathy.

*Mastrapasqua, M. et al. Eur J Transl Myol. 2023*

***Autophagy** is a process by which a cell breaks down part of its contents. Autophagosomes are vacuoles that contain cellular constituents to be broken down. They fuse with lysosomes (**autophagolysosome**) which "digest" these cellular constituents.*

## *FKRP*-related conditions – dystroglycanopathy

### Phenotype and genotype of Indian patients

▪ A team from the National Institute of Mental Health and Neurosciences in Bangalore, **India**, retrospectively analysed the **medical records** of Indian patients with a muscular dystrophy and *FKRP* gene mutation.

▪ From 418 cases of muscular dystrophy, the researchers identified nine patients with *FKRP* mutations: six with limb-girdle muscular dystrophy R9 (LGMD R9) and three with CMD, with onset between the ages of 18 months and seven years old. Examination of the CMD patients found:

• delayed acquisition of gross motor developmental milestones, facial muscle weakness and calf hypertrophy in all of the patients;

• low muscle tone (hypotonia), speech delay and knee and ankle contractures in two of the patients.

▪ Muscle biopsies from the CMD patients exhibited a dystrophic pattern. Creatine kinase (CK) levels in the blood ranged from 3,800 to 7,000 U/L. Finally, two out of the three patients had never been able to walk independently, while the other patient was still able to walk at the most recent examination.

*Unnikrishnan, G. et al. J Neuromuscul Dis. 2023*

***Creatine kinase (CK)** is a muscle enzyme that is abundant in muscle cells which is released into the bloodstream in the event of muscle damage.*

## L-CMD - nuclear envelope

### Modulators of clinical expression in laminopathies

▪ A French **observational study** of L-CMD is currently underway. The study is funded by the INSERM and is collecting biological samples and phenotypic information from patients with *LMNA* gene mutations. The objective of the investigators is to explain the **clinical variability** observed in laminopathies and identify factors that affect disease severity, particularly "modifier" genes likely to modulate clinical manifestations.

**LMNAModifier study**

**France**

**40 (all ages)**

**Recruiting**

**June 2022 – June 2027**
**5 years of follow-up**

NCT05394506

## MDCDC - nuclear envelope

### Expanding the spectrum of phenotypes in *TRIP4*-related myopathies

▪ *TRIP4* gene mutations have been reported in 16 families to date: 12 whose disease was identified as a congenital myopathy, and four with a phenotype resembling spinal muscular atrophy (SMA).

▪ An Italian team recently reported **two new cases** involving a five-year-old Pakistani girl and her five-month-old brother. The pathogenic homozygous p.Arg46* (c.136C>T) *TRIP4* gene mutation was identified in both siblings. This genetic variant had already been reported previously in a two-month-old Russian baby who had been diagnosed with MDCDC.

▪ Unlike this previous case, the newly-identified patients had **mixed sensory-motor polyneuropathy.** This was also the first time a demyelinating neuropathy had been associated with a *TRIP4* gene variant.

▪ This study therefore makes it possible to expand the spectrum of phenotypes associated with *TRIP4*-related myopathies.

*Frongia, I. et al. J Neuromuscul Dis. 2024*
*Kozhanova, T. et al. Neuromuscular Diseases. 2021*
*Knierim, E. et al. Am J Hum Genet. 2016*

## Megaconial-type CMD – cytosol

### Characterisation of Iranian patients

▪ Researchers reported laboratory and clinical data from **13 Iranian patients** who had been diagnosed with megaconial-type CMD in Iran in the past few years. Analysis of this data revealed:

• that the 13 patients came from 11 consanguineous families;
• motor impairment of varying severity and cognitive impairment in all 13 patients, with behavioural problems in some;
• large mitochondria on muscle biopsies;
• 11 pathological *CHKB* variants, six of which had never been described before.

This type of work helps improve our understanding of the natural history of this extremely rare disease.

*Zemorshidi, F. et al. Neuromuscul Disord. 2023*

## MDHLO – cytosol

### A new patient identified

▪ Muscular dystrophy, congenital hearing loss, and ovarian insufficiency syndrome (MDHLO) is a disease that was only discovered very recently (2020), with **just 26 cases described to date.** It generally affects the muscles, inner ear and function of ovarian cells.

▪ A new team of clinicians identified the **27th patient** in 2024 - an eight-year-old girl with proximal muscle weakness and elevated liver transaminase levels. Her hearing ability, however, was not affected, unlike 70% of the patients described previously.

▪ **Hepatic involvement is a new addition** to the spectrum of clinical manifestations of this disease. Also, unlike in previous cases, this patient's motor function was initially unaffected, with impairment only starting at the age of three.

- The authors identified a **homozygous mutation in the *GGPS1* gene** in this patient which had previously only ever been reported as a compound heterozygous mutation in other patients.
- This new description extends the phenotypic and genetic variability of this extremely rare disease.

*Altassan, R. et al. Am J Med Genet A. 2024*
*Kaiyrzhanov, R. et al. Ann Clin Transl Neurol. 2022* *Foley, A. R. et al. Ann Neurol. 2020*

## MDCCAID - cytosol/endoplasmic reticulum

### *INPPK5* and brain development

- The pathological mechanisms involved in congenital muscular dystrophy with cataracts and intellectual disability (**MDCCAID**) are still poorly understood. Previous studies have shown that *INPP5K* is highly expressed in the developing and adult human brain, eyes, and skeletal muscle.
- A team from Friedrich Schiller University Jena in Germany used **neuroblastoma cell lines** to study the effects of reduced *INPP5K* expression in nerve tissue *in vitro*.
- The investigators were able to show that **deactivating the *INPP5K* gene** in this cell model **impaired neuronal-like differentiation** (in particular the development and maintenance of dendrites), which may explain the neurological manifestations observed in MDCCAID patients, particularly cerebral and cerebellar atrophy.
- Finally, protein glycosylation was also affected in this cell model which is consistent with the hypoglycosylation of alpha-dystroglycan seen in patients.

*Manzolillo, A. et al. Front Mol Neurosci. 2024*

***Skeletal muscles** (also known as voluntary muscles) are muscles that are attached to bones. They are under voluntary control and move different parts of the body by contracting. They are sometimes called striated muscles due to their striped appearance under a microscope.*

*Initially cultured in the 1940s to diagnose cancers, **neuroblastoma cell lines** are now often used as cell models in the study of various diseases. They are mainly used to investigate their effects on the differentiation of nerve tissue in response to biological changes caused by the disease.*
Harenza, J. L. et al. Sci Data. 2017; Thiele, C. J. J. Human Cell Culture. Lancaster, UK: Kluwer Academic Publishers. 1998.

***Glycosylation** is a process in which glycans (large carbohydrate molecules containing many small sugar molecules) are attached to proteins. It takes place in the endoplasmic reticulum and Golgi apparatus, two cell structures where glycoproteins are formed.*

## *SNUPN*-related CMD – cytosol/nucleus

### A new type of CMD

- Two international studies have suggested that the ***SNUPN* gene** may be the cause of various diseases ranging from CMD to limb-girdle muscular dystrophy (LGMD).
- A review of data from **23 patients** (12 female and 11 male aged three to 36 years old) spread across three continents, all with a *SNUPN* gene mutation, revealed the following:

• **childhood onset** in all cases, before the age of two in most;
• **progressive proximal limb muscle weakness** in all of the patients, often associated with distal limb muscle weakness;
• severe **respiratory insufficiency** and significant diffuse **contractures** in the majority of the patients;
• **extramuscular manifestations** such as central nervous system and eye symptoms in several patients.

- Each patient studied had a homozygous mutation in the *SNUPN* gene which codes for snurportin-1, a protein involved in RNA maturation.

Studies conducted in animals (fruit flies) have confirmed the deleterious effects of *SNUPN* mutations, particularly on motor function and life expectancy.

*Iruzubieta, P. et al. Brain. 2024* *Nashabat, M. et al. Nat Commun. 2024*

# Basic and preclinical research

## What is basic and preclinical research?

▪ The INSERM defines basic research as **exploratory research** which can reveal novel concepts. Its main objective is to produce knowledge and understanding of natural phenomena. In health sciences, it sheds light on how the human body functions, as well as factors and pathological processes that cause diseases.
Basic research is therefore usually the first essential step in the development of new treatments. **It precedes preclinical and clinical research** and produces a bank of knowledge on which these two later stages can be based.

▪ Preclinical studies involve exploring the safety and/or efficacy of a drug candidate, treatment or procedure using animal models (*in vivo*) or cell cultures (*in vitro*). If the results are conclusive, clinical trials in humans can be considered and planned for the product in question.

www.inserm.fr/en/our-research/fundamental-research

*__Zebrafish__ are animal models used frequently in developmental biology. Their lifecycle makes them ideal for laboratory research work and their embryos are completely transparent which allows researchers to observe their organ development without having to resort to complex or time-consuming techniques.*

## COL6-related dystrophy - extracellular matrix

### CRISPR or siRNA - "switching off" the dominant pathological allele

▪ Certain COL6-related dystrophies are **dominant-negative disorders**, meaning that the presence of just one mutant allele is enough to cause muscle symptoms. However, in healthy individuals, collagen genes are **"haplosufficient"**, meaning that in the absence of a pathological mutation, just one copy of the gene is enough to produce functional collagen (which is essential for the maintenance of the extracellular matrix).

▪ This year, Carsten Bönneman from the NINDS in the United States and his team published the results of their evaluations of two therapeutic approaches (CRISPR/Cas9 and siRNA) that **inactivate pathological alleles** in COL6-related dystrophies. This research drew on the haplosufficiency of the *COL6A1* gene. By inactivating the mutant copy of the gene, they hoped to be able to enable the healthy copy of the gene to synthesise a functional COL6 protein in order to prevent the onset of the disease.

*The same gene can exist in several different forms called __alleles__. Different alleles of the same gene are composed of a DNA sequence that has small variations. They are located at the same place on the chromosome and have the same function. For every gene, each individual has two alleles, one from each parent.*
*In genetic diseases, one allele is composed of the correct DNA sequence while the other is composed of a DNA sequence with a genetic mutation which causes the symptoms of the disease.*

**CRISPR/Cas9** and **siRNA** are two different approaches used to stop a deleterious protein from being produced.
**CRISPR/Cas9** permanently modifies DNA and prevents the genetic message from being recognised by cellular machinery, meaning that transcription of the pathological gene does not take place. The modified cell then transmits and spreads this correction during cell proliferation.
**siRNA** enables transcription to take place but stops the next step (translation) from happening by disrupting messenger RNA (mRNA), the template used to create proteins. It is a shorter-term solution with generally incomplete gene inactivation, however, it is often less complicated to implement than the CRISPR approach and is reversible therefore potentially safer.

### The CRISPR/Cas9 approach is effective

- In the first study, they corrected a mutation (c.868G>A; G290R) which is common in COL6-related dystrophy patients by using the **CRISPR/Cas9** approach in **fibroblasts** taken from patients with the disease.
- The method worked - analyses showed that the genome editing was successful, specific inactivation of the mutant allele and an **improvement in the collagen extracellular matrix** in the fibroblasts taken from patients.

*__Fibroblasts__ are connective tissue cells. They produce extracellular matrix components (laminin, collagen, etc.).*

**The CRISPR/Cas9 system**
This technique enables changes to be made to the genome (a method known as genome editing). The principle consists of targeting a DNA sequence or gene in a cell in order to modify, repair or remove it.

### And so is the siRNA approach

- In the second study, Carsten Bönneman's team inactivated another genetic mutation (c.877G>A; G293R) which is commonly involved in UCMD using **siRNA**.
- The treatment of fibroblasts taken from patients **successfully reduced the number of mutant transcripts** while maintaining normal levels of healthy transcripts. These healthy transcripts were able to rescue the secretion and assembly of the collagen matrix by reducing the dominant-negative effect.

*When talking about heterozygous mutations, we use the term __dominant-negative effect__ when the protein coded for by a mutant allele not only loses function, but also interferes with that of the normal allele, with the normal allele being unable to compensate for this loss of function.*
Hanna, N. et al. Med Sci (Paris). 2005. www.academie-medecine.fr [page in French]

### Research to continue *in vivo*

- CRISPR/Cas9 and siRNA are therefore promising therapeutic approaches for deactivating a dominant pathological allele (present in over 65% of pathological *COL6* variants), however, more research is needed in order to ensure that the healthy allele is not unintentionally targeted and altered. Researchers are preparing to test these molecular tools on mouse models of UCMD.

*Bolduc, V. et al. bioRxiv. 2024* *Brull, A. et al. Mol Ther Nucleic Acids. 2024*

## Spermidine - the nutraceutical being studied

- One of the characteristics of COL6-related dystrophies, such as UCMD, is defective autophagy. Spermidine, a nutraceutical that induces autophagy, is a compound whose safety and numerous benefits have been demonstrated in humans and various animal models.

**What are nutraceuticals?**
A combination of the words "nutrient" and "pharmaceutical", **nutraceuticals** or "**functional foods**" are substances derived from food products which have physiological properties and provide protection against certain diseases. They are therefore a subset of **dietary supplements** that are **therapeutic** as well as nutritional, although they also seek to improve health (**ginseng**, **echinacea** and **omega-3** are some examples). **Spermidine** is a nutraceutical which has anticancer properties. It is found in several foods such as soya and wheat germ. It is also found in sperm where it was identified for the first time, hence its name.
Unlike pharmaceutical molecules, nutraceuticals are not protected by patents and do not fall under the authority of health and/or regulatory agencies.

- The administration of **spermidine** for one month in mouse models whose *COL6A1* gene had been inactivated reactivated autophagy and led to a reduction in muscle fibre abnormalities. However, it did not induce any functional improvements.

- A new study by the same team showed that more than **three months** of spermidine treatment can **restore muscle strength** in mice and also positively impact other structures disrupted by the disease, such as mitochondria and the neuromuscular junction, without significant side effects.
- This study provides evidence that supports the notion of spermidine being evaluated in future clinical trials for COL6-related myopathies.

*Gambarotto, L. et al. Autophagy. 2023*

## *LAMA2*-related CMD - extracellular matrix

### LAMA1 as a compensatory modifier for LAMA2 deficiency

- Laminin 1 (LAMA1) is a protein that shares many similarities with laminin 2 (LAMA2). The use of LAMA1 as a compensatory modifier for LAMA2 deficiency, as observed in merosinopathy patients, is a therapeutic approach currently being studied.
- This year, a team from Modalis Therapeutics published the results of the use of their CRISPR-GNDM® technology in a mouse model of MDC1A which compensates for LAMA2 deficiency by activating the expression of the *LAMA1* gene.

**CRISPR-GNDM®** (CRISPR-Guide Nucleotide Directed Modulation) technology uses the CRISPR/Cas9 system to deliver a regulatory element to a specific location in the genome that activates the expression of a target gene. This is therefore called "epigenetic" editing as it enables the expression of the genome to be regulated by introducing a control factor without altering the genetic information.

The study showed long-lasting expression of *LAMA1*, significantly prolonged survival and improved muscle strength in the animals treated.

- The *LAMA1* gene can also be activated by directly modifying the host DNA sequence using the CRISPR/Cas9 approach. A Chinese team looked at the effectiveness of this method in mice with a severe form of MDC1A. They observed a nearly doubled median survival as well as improvements in the weight and grip strength of the mice treated.
- These studies show that LAMA2 deficiency can be compensated for by activating *LAMA1* expression, although its longer-term safety and efficacy need to be confirmed.

*Liu, Y. et al. J Genet Genomics. 2024* *Qin, Y. et al. bioRxiv. 2024*

## *SEPN1*-related myopathy - endoplasmic reticulum

### TUDCA - a possible treatment avenue

*The **endoplasmic reticulum** is a complex network of cavities in the cytoplasm of a cell where proteins and lipids are created. The muscle cell equivalent is called the sarcoplasmic reticulum. The sarcoplasmic reticulum releases and reabsorbs calcium, playing an essential role in muscle contraction.*

***Endoplasmic reticulum (ER) stress** is caused by the accumulation of unfolded or misfolded proteins in the ER and activates a regulatory system called the unfolded protein response (UPR).*

▪ *SEPN1*-related myopathy is caused by selenoprotein (SEPN1) deficiency. SEPN1 is a protein localised to the **endoplasmic reticulum** (ER) membrane which is involved in the regulation of calcium flux between the interior of the ER and the cytosol of the cell. The absence of SEPN1 makes cells more sensitive to **endoplasmic reticulum stress** (ERS) which can lead to cell dysfunction (misfolded proteins, etc.) and even cell death.

▪ Overexpression of the ERO1 protein, a major contributor to ERS, has previously been observed in animal models of *SEPN1*-related myopathy. A European research team showed that inactivating the *ERO1* gene in a mouse model of the disease can attenuate ERS and improve diaphragm muscle function.

**Protein-folding molecules**

**Chaperones** are proteins that help proteins being synthesised attain their properly-folded three-dimensional structure, thus preventing the formation of aggregates. Many chaperones are "heat shock proteins" (Hsp), proteins that are expressed in response to temperature changes. The structure of proteins is in fact heat-sensitive (they denature and lose their biological function). The role of chaperones is to prevent potential protein structure damage caused by heat or other types of cellular "stress".

**Chemical chaperones** are able to bind to these defective proteins and stabilise them in order to restore their shape and functionality.

#### Drug repurposing

Following this discovery, the researchers opted to pursue ERS reduction as a treatment avenue and turned their attention to **TUDCA** (tauroursodeoxycholic acid), a **chemical chaperone** that helps fold proteins properly in the ER. They showed that TUDCA administered for three weeks in SEPN1-deficient mice **restored the calcium transport capacities** of muscle fibres and improved diaphragm muscle function.

This study therefore highlights the role of *ERO1* in the pathogenesis of *SEPN1*-related myopathy and its relevance as a potential therapeutic target. The results also showed the value of considering TUDCA, a molecule which has already been tested and approved for the treatment of primary biliary cholangitis (PBC), as a drug candidate in *SEPN1*-related myopathy and evaluating it in a clinical trial.

*Germani, S. et al. Cell Rep Med. 2024*

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Keep up to date with congenital muscular dystrophy research news throughout the year on the AFM-Téléthon website:
**www.afm-telethon.fr/en/latest-news**