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SAVOIR & COMPRENDRE
AVANCÉES DE LA RECHERCHE

Advances 2024 in limb-girdle muscular dystrophies

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

AFMTÉLÉTHON
INNOVER POUR GUÉRIR

Table of contents

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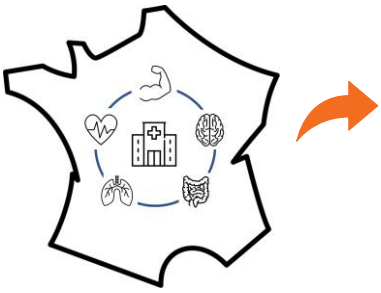
Limb-girdle muscular dystrophies LGMD

As the name suggests, limb girdle muscular dystrophies (LGMD) affect the "limb girdle" muscles. Symptoms generally appear before the age of 30, with slow progression and no facial muscle involvement.

Common symptoms

- **Wasting and weakness of the limb girdle muscles:** shoulder muscles (shoulder girdle) and hip muscles (pelvic girdle) as well as the surrounding muscles (upper arms and thighs).
- Symptoms **vary greatly**, ranging from muscle fatigability to loss of ambulation.
- Possible respiratory and/or cardiac involvement.

Management and treatment



- **Multidisciplinary** (particularly orthopaedic) treatment of symptoms at specialist neuromuscular disease centres.
- **Innovative therapies** such as gene therapy are currently being developed.

Diagnosis

Clinical diagnosis

Clinical examination by a doctor to determine the pattern of muscle involvement (limb girdle muscles)

Genetic diagnosis

Blood test and muscle biopsy to identify the causative gene

In numbers

1 to 3 people in every 100,000 have LGMD

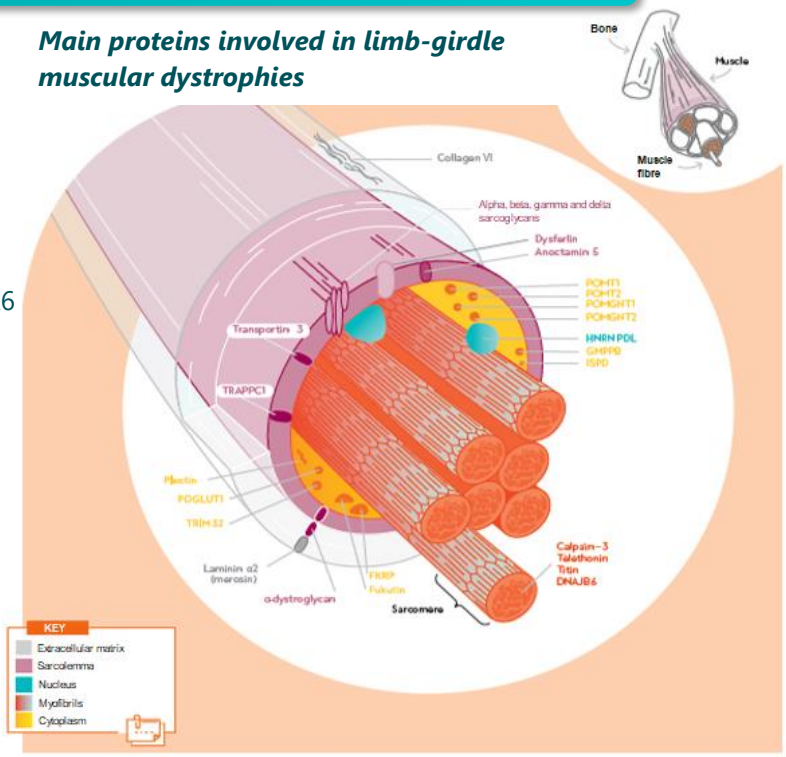
148 scientific articles published between June 2023 and May 2024 *(PubMed)*

11 clinical trials including **6** gene therapy trials *(ClinicalTrials.gov 31/05/2024)*

Mode of inheritance

- **27 autosomal recessive subtypes**
  From LGMD R1 to LGMD R27
  including five groups:
  - Calpainopathies: LGMD R1
  - Dysferlinopathies: LGMD R2
  - Anoctaminopathies: LGMD R12
  - Sarcoglycanopathies: LGMD R3, R4, R5 and R6
  - Dystroglycanopathies: LGMD R9, R11, R13, R14, R15, R16, R19, R20 and R24
- **5 autosomal dominant subtypes (much rarer)**
  From LGMD D1 to LGMD D5

Main proteins involved in limb-girdle muscular dystrophies



A new naming system since 2018

AUTOSOMAL RECESSIVE

Name	Gene	Protein
LGMD R1 (formerly LGMD2A)	*CAPN3*	Calpain-3
LGMD R2 (formerly LGMD2B)	*DYSF*	Dysferlin
LGMD R3 (formerly LGMD2D)	*SGCA*	α-sarcoglycan
LGMD R4 (formerly LGMD2E)	*SGCB*	β-sarcoglycan
LGMD R5 (formerly LGMD2C)	*SGCG*	γ-sarcoglycan
LGMD R6 (formerly LGMD2F)	*SGCD*	δ-sarcoglycan
LGMD R7 (formerly LGMD2G)	*TCAP*	Telethonin
LGMD R8 (formerly LGMD2H)	*TRIM32*	TRIM32
LGMD R9 (formerly LGMD2I)	*FKRP*	FKRP
LGMD R10 (formerly LGMD2J)	*TTN*	Titin
LGMD R11 (formerly LGMD2K)	*POMT1*	POMT1
LGMD R12 (formerly LGMD2L)	*ANO5*	Anoctamin 5
LGMD R13 (formerly LGMD2M)	*FKTN*	Fukutin
LGMD R14 (formerly LGMD2N)	*POMT2*	POMT2
LGMD R15 (formerly LGMD2O)	*POMGNT1*	POMGnT1
LGMD R16 (formerly LGMD2P)	*DAG1*	α and β dystroglycans
LGMD R17 (formerly LGMD2Q)	*PLEC*	Plectin
LGMD R18 (formerly LGMD2S)	*TRAPPC11*	TRAPPC11
LGMD R19 (formerly LGMD2T)	*GMPPB*	GMPPB
LGMD R20 (formerly LGMD2U)	*ISPD*	ISPD
LGMD R21 (formerly LGMD2Z)	*POGLUT1*	Protein O-glucosyltransferase 1
LGMD R22	*COL6A1, -A2, -A3*	Collagen VI
LGMD R23	*LAMA2*	Laminin α2 (merosin)
LGMD R24	*POMGNT2*	POMGNT2
LGMD R25 (formerly LGMD2X)	*BVES*	POPDC1
LGMD R26	*POPDC3*	POPDC3
LGMD R27	*JAG2*	Jagged-2
LGMD R28	*HMGCR*	HMG-CoA reductase

AUTOSOMAL DOMINANT

Name	Gene	Protein
LGMD D1 (formerly LGMD1D)	*DNAJB6*	DNAJB6
LGMD D2 (formerly LGMD1F)	*TNPO3*	Transportin 3
LGMD D3 (formerly LGMD1G)	*HNRNPDL*	hnRNPDL
LGMD D4 (formerly LGMD1I)	*CAPN3*	Calpain-3
LGMD D5 (formerly LGMD2A)	*COL6A1, -A2, -A3*	Collagen α1, 2, 3(VI) chain

For more information on LGMD, please visit:
www.afm-telethon.fr/fr/fiches-maladies/myopathie-des-ceintures
[page in French]

5 Highlights from the past 12 months

LGMD R9 (*FKRP*) - more and more treatment avenues

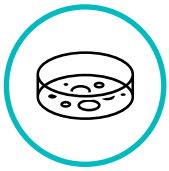
- This past year (2023-2024), the spotlight has been on LGMD R9. Atamyo Therapeutics launched its own gene therapy clinical trial in Europe and also became the second pharmaceutical company, after the American company AskBio, to evaluate a therapeutic gene for this disease in humans.
- In the field of pharmacology, **ribitol**, developed by ML Bio Solutions, continues to prove its efficacy in humans and is currently being evaluated in a phase III trial. Additionally, studies in animals have shown that ribitol may even be able to increase the efficacy of gene therapy, demonstrating a synergy which comes at the right time given the trials currently taking place.

Sarcoglycanopathies and gene therapy - it's France's turn

- Tested by Généthon almost 15 years ago in LGMD R5 (*SGCG*), gene therapy will be tested once again from 2024 with **ATA-200**, a product developed by Atamyo Therapeutics (a spin-off of Généthon), representing a tangible hope for the implementation of gene therapy in this disease.

LGMD R2 (*DYSF*) - gene therapy is possible

- Gene therapy is a very complex technique, and even more so when large genes such as *DYSF* are involved. A possible solution to this is the dual vector approach which was successfully tested this year in mice. The results confirm those obtained by Généthon over 10 years ago.



Cell therapy trial in humans delayed

- The **bASKet** trial in Germany, which was due to evaluate the transplantation of patient stem cells that had been genetically corrected by CRISPR/Cas9 in humans, was highly anticipated last year. The medical journal Nature Medicine named it as one of 11 clinical trials to watch in 2023. It was due to start in July 2023 but has been postponed until 2024.
- The biggest disappointment comes from **VT-100** developed by Vita Therapeutics. Its trial, based on the same therapeutic principal but in LGMD R1 specifically, was cancelled following a re-evaluation of the company's programme development strategy.

The list of LGMD subtypes continues to grow

- Following the identification of *SNUPN* as a causative gene, the **29th recessive subtype of LGMD** was discovered by two independent research teams just a few weeks apart. This new form marks the introduction of "snurportinopathies" into the realm of neuromuscular diseases. It is characterised by being caused by RNA splicing abnormalities and inducing, among other things, myofibrillar structural abnormalities.

LGMD news

A new emergency medical information form for LGMD patients

▪ In order to improve LGMD patient care in France, the AFM-Téléthon LGMD peer support group (Groupe d'Intérêt) with the help of Prof. Léonard Féasson (Saint-Étienne), created an LGMD-specific **emergency medical information form**.

▪ This form provides **emergency medicine doctors and paramedics** with crucial information for when emergency care needs to be administered (cardiac or respiratory conditions, medications and procedures to avoid, what to do in the event of a fracture, etc.).

▪ Patients can download the form and fill in their personal information (their name, LGMD subtype, GP, etc.), the characteristics of their disease and their medical history.

It is included in a "kit d'urgence" [emergency kit] which is also available to those concerned and will help to reassure patients and their families.

www.lgmd.afm-telethon.fr/fiche-durgence-medicale-lgmd/ [page in French]

The MDA Clinical & Scientific Conference 2024

▪ The **MDA Clinical & Scientific Conference 2024**, organised by the Muscular Dystrophy Association (MDA), 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.

www.mdaconference.org

The 2024 LGMD Scientific Workshop

▪ On 8 February 2024, the Speak Foundation held the **2024 LGMD Scientific Workshop** in Rockville, Maryland in the United States. This event, inspired by the Externally-Led Patient-Focused Drug Development (EL-PFDD) meeting in 2022, brought together patients, medical experts, associations, regulatory authorities and biotechnology companies in order to discuss the needs of patients and ways to optimise and accelerate the development of new therapies. The workshop focused on LGMD R1-R5 and R9 and was attended by over 20 experts on these diseases including Jerry Mendell, Lindsay Alfano, Douglas Sproule, Louise Rodino-Klapac and Peter Kang.

www.thespeakfoundation.com/scientific-workshop

The first European LGMD R9 conference

▪ A European conference dedicated to patients with LGMD R9 was held in Amsterdam on 25 May 2024. Organised by the John Walton Muscular Dystrophy Research Centre in collaboration with the AFM-Téléthon Groupe d'Intérêt LGMD, among others, this unprecedented event brought together patients, their families, and expert clinicians and researchers from the United States and Europe to share their experiences and discuss progress made in research and clinical trials.

www.lgmd.afm-telethon.fr/conference-europeenne-lgmdr9-2i-fkrp-le-25-mai-2024-a-amsterdam/ [page in French]

__Translational research__ bridges the gap between basic research (understanding the mechanisms that cause diseases) and clinical research (evaluating a drug candidate in humans).
It involves a great deal of collaboration between researchers and clinicians, going from basic research to application in patients, but also from patient observations back to basic research.

The __Speak Foundation__ was founded in 2008 by Kathryn Bryant-Knudson following her diagnosis of LGMD R9 two years earlier. The mission of this foundation is to improve the quality of life of muscular dystrophy patients and to be a voice for those living with rare diseases.

www.thespeakfoundation.com

*The **European Neuromuscular Centre (ENMC)** is an international organisation which aims to support research in the field of neuromuscular diseases. It regularly organises meetings on a given topic which bring together scientists and clinicians from around the world.*
www.enmc.org/

***TREAT-NMD** is an international network for neuromuscular diseases which brings together scientists, clinicians and patient groups. Created in 2012 at the request of AFM-Téléthon and initially funded by the European Commission, TREAT-NMD aims to accelerate the development of potential treatments.*
www.treat-nmd.org/

***Basic** (studying muscle physiology, identifying immunological/genetic causes and exploring the mechanisms of each type of neuromuscular disease, etc.), **preclinical** (experimentation/exploration of possible therapeutic approaches using biological models) and **clinical** (natural history of the disease, improving diagnosis and treatment, trials of potential treatments, etc.) **research** are all used to study neuromuscular diseases.*

The 2023 International LGMD Conference

▪ After being held in Chicago in 2019 and online in 2021, the third **International LGMD Conference** took place in Washington D.C. (USA) from 27 to 29 October 2023.

▪ Organised by the Speak Foundation, it brought together experts such as Dr Carsten Bönneman and Dr Volker Straub, but also representatives from associations (MDA, etc.) and biotechnology companies (ML Bio Solutions, Sarepta Therapeutics, etc.). This conference was mainly aimed at patients and the LGMD community, with sessions on the status of trials currently underway on in preparation, preclinical developments regarding innovative treatments and practical advice. The sessions were also made available to stream online for those who were unable to attend in person.
www.lgmd-info.org/event/international-lgmd-conference-2023/

A conference on dysferlinopathies

▪ The **2024 Dysferlin Conference** was held in Houston, Texas (USA) between 8 and 11 May 2024. This one-of-a-kind conference organised by the Jain Foundation is dedicated to dysferlin and its associated diseases, which include LGMD R2 (*DYSF*). In the first conference held in almost a decade, international experts in the field (Volker Straub, Harmen Reyngoudt, Ana Topf, Noah Weisleder, etc.) were invited to present the studies and trials currently taking place in these diseases, and to discuss possible collaborations and the challenges faced in treatment development.
www.jain-foundation.org/research/conferences/dysferlin-conference/

Upcoming events

The International TREAT-NMD Conference

▪ The **8th International TREAT-NMD Conference** will take place from 6 to 8 February 2025 in Dubai (UAE). It will bring together researchers, patients, patient organisations, clinicians and representatives from the pharmaceutical industry where they will discuss challenges in the development of treatments for neuromuscular diseases, present the latest advances in care as well as outcome measures and innovative treatment avenues currently being studied or trialled, and exchange ideas on translational research. Registration for this event is not open yet, but you can fill in an online form to register your interest.
www.treat-nmd.org/event/the-8th-international-treat-nmd-conference/

Clinical trials

▪ Clinical trials consist of **assessing a potential treatment in humans** (drug candidate, medical device, etc.) in order to ensure that it is well tolerated and effective in treating a disease. The product is tested during **successive phases (I, II, III, IV)** which each answer specific questions. Is it well tolerated? What is the optimal dose? Is it effective and according to what criteria (walking ability, motor function, respiratory function, cardiac function, etc.)? Even if the product receives Marketing Authorisation (MA), it will continue to be monitored when being used in real life in order to refine knowledge of the product and identify any unexpected serious or non-serious side effects that may occur.

www.afm-telethon.fr/fr/vivre-avec-la-maladie/mon-parcours-de-soins/les-essais-cliniques-en-pratique [page in French]

Ongoing clinical trials in LGMD

TRIAL TITLE	LGMD SUBTYPE	THERAPEUTIC APPROACH	CLINICAL DEVELOPMENT
			PHASE I / PHASE II / PHASE III
SRP-9003-101 *(Sarepta Therapeutics, United States)*	**LGMD R4 (*SGCB*)**	**Gene therapy**	**SRP-9003** Not recruiting
SRP-9003-102 (VOYAGENE) *(Sarepta Therapeutics, United States)*	**LGMD R4 (*SGCB*)**	**Gene therapy**	**SRP-9003** Not recruiting
SRP-9003-301 (EMERGENE) *(Sarepta Therapeutics, multinational)*	**LGMD R4 (*SGCB*)**	**Gene therapy**	**SRP-9003** Recruiting
ATA-003-GSAR *(Généthon – Atamyo Therapeutics, France)*	**LGMD R5 (*SGCG*)**	**Gene therapy**	**ATA-200 (GNT0007)** Not yet recruiting
ATA-001-FKRP *(Généthon – Atamyo Therapeutics, France)*	**LGMD R9 (*FKRP*)**	**Gene therapy**	**ATA-100 (GNT0006)** Recruiting
LION-CS101 *(AskBio, United States)*	**LGMD R9 (*FKRP*)**	**Gene therapy**	**LION-101 (AB-1003)** Recruiting
MLB-01-003 *(ML Bio Solutions, United States)*	**LGMD R9 (*FKRP*)**	**Pharmacotherapy**	**BBP-418 (ribitol)** Not recruiting
MLB-01-005 (FORTIFY) *(ML Bio Solutions, United States)*	**LGMD R9 (*FKRP*)**	**Pharmacotherapy**	**BBP-418 (ribitol)** Recruiting
DUNE Phase 2 Exercise Challenge *(Edgewise Therapeutics, United States)*	**LGMD R9 (*FKRP*)**	**Pharmacotherapy**	**EDG-5506 (sevasemten)** Not recruiting
bASKet *(Myopax, Germany)*	**LGMD**	**Cell therapy**	**GenPHSats** Not yet recruiting

Clinical trials covering multiple LGMD subtypes

Cell therapy: stem cell transplantation

- The **bASKet** trial, which was due to start in 2023, has unfortunately been postponed to July 2024.
- The objective of the cell therapy that will be evaluated in this phase I/IIa trial is to regenerate healthy muscle by **taking muscle stem cells** (or "GenPHSats" (gene edited primary human satellite cells)) from patients and correcting them *in vitro* using the CRISPR/Cas9 genome editing tool before injecting them back into the patients (autologous transplantation). This approach is based on research carried out by a team led by Simone Spuler, cofounder of the biotechnology company Myopax.
- Six adolescents and/or adults with LGMD (any subtype) are expected to be included in the study. They are due to be monitored for a year in order to evaluate the treatment's impact on muscle strength and structure.

Müthel, S. et al. Mol Ther Nucleic Acids. 2023 *Arnold, C. et al. Nat Med. 2022.*

Phase I
Safety/tolerability

Phase II
Dose/effect

bASKet trial

Germany	6 (over 14 years old)	Not yet recruiting	July 2024 – July 2025 1 year of follow-up

NCT05588401

Medical device: Abilitech™ exoskeleton

- Funded by the Schulze Family Foundation and Abilitech Medical, the American **Schulze** study tested use of the Abilitech™ Assist **wearable orthotic device** in neuromuscular disease patients over one year.

Did you know?

Founded in 2016, Abilitech is one of many companies (such as Myomo, Orthopus and Maxon) which have been trying for several years to democratise the use of new technologies, such as exoskeletons, intended to improve the lives of neuromuscular disease patients who have reduced mobility in their upper limbs.

*An **exoskeleton** is a wearable robotic device designed to compensate for muscle weakness and thus increase autonomy. They can be used during rehabilitation sessions or on a daily basis to assist movement.*

- This study included 35 participants, some of whom had LGMD among other neuromuscular diseases (DMD, FSHD, etc.), and evaluated the efficacy and scope of the assistance provided by the Abilitech™ device in the recovery of certain motor functions in the arms during activities of daily living. The study started in 2022 and was due to be completed in June 2023.

www.clinicaltrials.gov/ct2/show/NCT05409079

LGMD R1 (*CAPN3*– calpainopathy)

The VTA-100 clinical trial will not take place

- **VTA-100** is a therapy that **combines genome editing and stem cells**. Genetic mutations in cells collected from patients are corrected *in vitro*, then the modified cells are readministered to the patients (autologous transplantation) in order to enable the development of functional muscle fibres.

▪ Despite obtaining positive results in a mouse model of LGMD R1, the VTA-100 clinical trial planned for 2025 by Vita Therapeutics was **abandoned due to financial reasons.** The company has decided to focus on developing its more universal allogenic approach (VTA-200) rather than its autologous stem cell therapy.
Vita Therapeutics. Letter to the Community. 2024.

LGMD R2 (*DYSF* - dysferlinopathy)

Gene therapy: SRP-6004

▪ Evaluation of the effects of **SRP-6004** (rAAVrh74.MHCK7.DYSF.DV), a gene therapy product designed to express the dysferlin protein, started in humans in 2016 with the **IRB15-00669** clinical trial (NCT02710500) sponsored by Sarepta Therapeutics. This trial, which has since been completed, aimed to evaluate the safety and tolerability of SRP-6004 in LGMD R2 (dysferlinopathy). Two patients received an intramuscular injection of the product as part of the trial and did not experience any notable adverse drug reactions.

*In its early days, **gene therapy** consisted solely of replacing a defective gene by delivering a normal gene into the body. Since then, gene therapy techniques have progressed, including those that introduce genetic material such as DNA or RNA (therapeutic genes, antisense oligonucleotides, etc.) into the body for therapeutic purposes.*
www.inserm.fr [website in French]

The evaluation continues with NAVIGENE

▪ Based on data from the IRB15-00669 trial, Sarepta Therapeutics launched the open-label **SRP-6004-102** (or NAVIGENE) trial in the United States in May 2023. Its main objective is to evaluate the safety and efficacy (phase I trial) of SRP-6004 administered by systemic IV infusion in two ambulatory patients with LGMD R2 (dysferlinopathy). In August 2023, Sarepta Therapeutics announced that the first patient had received an infusion of the gene therapy product in the second quarter of 2023. The results are yet to be published.
Sarepta Therapeutics. Sarepta. Press release. 2023 *Pozsgai, E. et al. Neurodegener Dis Manag. 2021.*

SRP-6004-102 (NAVIGENE) trial – LGMD R2

Phase I
Safety/tolerability

United States	2 (over 18 years old)	Not recruiting	May 2023 – August 2028 5 years of follow-up

LGMD R4 (*SGCB* – beta-sarcoglycanopathy)

Gene therapy: SRP-9003

▪ Launched in 2018, the phase I/II **SRP-9003-101** trial (ongoing) is aiming to evaluate the safety and tolerability of **SRP-9003** (rAAVrh74.MHCK7.SGCB), a gene therapy product that delivers the *SGCB* gene (which codes for the beta-sarcoglycan protein) into the cells of LGMD R4 patients.

Phase I
Safety/tolerability

Phase II
Dose/effect

SRP-9003-101 trial – LGMD R4

United States | **6 (4 to 13 years old)** | **Not recruiting** | **Oct 2018 – Feb 2025 5 years of follow-up**

NCT03652259

- A publication reported the effects of SRP-9003 two years after six patients received a low- or high-dose IV infusion of the product (three patients for each dose).

A reasonably well tolerated product

- The therapy proved to be relatively well tolerated by the majority of the patients (four out of six) who only experienced mild side effects (vomiting, gastrointestinal pain, loss of appetite, etc.). The other two patients experienced more severe adverse drug reactions (hepatitis and significant dehydration) which resolved after a few days with appropriate treatment. These side effects did not lead to the clinical trial being suspended or terminated.

Lasting effects two years after initial infusion

- SGCB protein levels measured in the muscles of the patients before treatment were less than 10% of normal, however, 60 days after receiving the treatment at the highest dose, these levels had increased to nearly 62% of levels found in healthy subjects. The authors also noted a restoration of the sarcoglycan protein complex at the muscle fibre membrane, a mark of its stability.
- Creatine kinase (CK) levels in the blood were reduced by nearly 90%, indicating a significant reduction in muscle fibre breakdown.

These improvements were maintained at similar levels two years after the initial infusion.

Improved motor performance

- During the same observation period, motor assessments performed using the NSAD scale (walking, squats, climbing stairs, etc.) indicated improved motor function in both groups (almost three more points on average). By comparison, a control group made up of five LGMD R4 patients who did not receive the treatment recorded on average about four points less on the same scale.

A proven measuring tool

The North Star Assessment for limb-girdle type muscular dystrophies (NSAD) is a scale that measures motor performance in ambulatory and non-ambulatory individuals. It was initially developed for use in LGMD R2 from another scale (the North Star Ambulatory Assessment or NSAA) used in Duchenne muscular dystrophy.

Confirmed with VOYAGENE

- Sarepta Therapeutics also launched **SRP-9003-102** (or VOYAGENE), a phase I open-label trial conducted in five children (non-ambulatory) and adults (ambulatory or non-ambulatory), in order to obtain more data on the product.

SRP-9003-102 (VOYAGENE) trial – LGMD R4

Phase I
Safety/tolerability

United States

5 participants

Not recruiting

Feb 2023 - Feb 2028
Follow-up period not specified

NCT05876780

The next phase is in preparation

At the beginning of 2024, Sarepta Therapeutics announced that candidate selection for a new phase III trial (EMERGENE) had already started. The trial will include 15 ambulatory or non-ambulatory patients over the age of four and will continue to test the efficacy of SRP-9003 in LGMD R4.

SRP-9003 (EMERGENE) trial – LGMD R4

Phase III
Efficacy

International

15
(over 4 years old)

Recruiting

Dates to be determined
Follow-up period not specified

NCT06246513

Mendell, J. R. et al. Nat Med. 2024 *Sarepta Therapeutics. Press release. 2024* *Sarepta Therapeutics. Press release. 2023.*

www.genesislgmd.com/study/voyagene

www.sarepta.com/community-letter-community-update-lgmd-programs-development

LGMD R5 (*SGCG* – gamma-sarcoglycanopathy)

Gene therapy: clinical trial in humans due to start soon

▪ Atamyo Therapeutics, a spin-off of Généthon (a pharmaceutical company created by AFM-Téléthon), has just obtained the regulatory approval needed to test the safety and efficacy of **ATA-200**, an AAV vector carrying the *SGCG* gene. This gene therapy product, born out of research carried out by Isabelle Richard, LGMD expert at Généthon, will be evaluated in six ambulatory LGMD R5 patients between the ages of six and 12 years old.

Proven feasibility

▪ This is not the first time that gene therapy has been tested in LGMD R5. In 2006, Généthon launched its first phase I gene therapy trial in humans. The results were published in 2012 and showed that the product was well tolerated. In 2019, Isabelle Richard and her team observed the dose-dependent efficacy of another product with a more effective vector (which would become ATA-200) in mice, thus paving the way for a human trial.

A European trial

▪ A new multicentre phase I/II trial has received approval to be conducted **in France and Italy** and is due to start this year. Two doses of ATA-200 (one low dose and one three times higher) administered via systemic IV injection will be tested. The safety of the product will be evaluated during the first six months and the patients will continue to be monitored for four and a half years.

Phase I
Safety/tolerability

Phase II
Dose/effect

ATA-003-GSAR trial – LGMD R5

France and abroad	6 (6 to 12 years old)	Not yet recruiting	May 2024 – Dec 2030 5 years of follow-up

NCT05973630

LGMD R9 (*FKRP*– dystroglycanopathy)

Gene therapy: encouraging initial results for ATA-100

▪ **GNT0006 (ATA-100)** is an intravenously-administered gene therapy product which aims to restore production of the FKRP protein in LGMD R9 patients.

▪ A phase I/II clinical trial called **ATA-001-FKRP** was launched in 2022 in order to test the safety and efficacy of this product. This trial is sponsored by Atamyo Therapeutics and is being conducted in **Denmark, France and the United Kingdom.** Recruitment of the second group of patients is still taking place.

Did you know?

A product of Généthon research

ATA-100 was developed using research carried out by Généthon researcher Isabelle Richard and her team. In 2017, they published an article reporting that functional and histological manifestations of the disease had been corrected in mouse models following injection of an rAAV2/9 vector expressing a functional version of the FKRP protein.

Positive preliminary results

▪ Intermediary data from the trial was presented at the International LGMD Conference in October 2023 in the United States as well as at Myology 2024, a conference organised by AFM-Téléthon held between 22 and 25 April 2024 in Paris, France. Analyses conducted on the first cohort treated (three patients) showed:

• evidence of transgene expression three months after treatment;
• no unexpected adverse drug reactions;
• sustained improvements in walking speed;
• disappearance of cramps and muscle pain, and better quality of life;
• a marked decrease in CK levels;
• correction of intracellular abnormalities (centronucleation) usually seen in dystrophic muscle fibres.

The effects of a higher dose will be evaluated in a second group of patients.

Atamyo Therapeutics. Press release. 2023 *Gicquel, E. et al. Hum Mol Genet. 2017.*

www.afm-telethon.fr/fr/essai-fkrp-gnt0006 [page in French]

Phase I
Safety/tolerability

Phase II
Dose/effect

ATA-001-FKRP trial – LGMD R9

France and abroad	39 (over 16 years old)	Recruiting	August 2022 – Oct 2030 5 years of follow-up

NCT05224505

Gene therapy: first patient receives LION-101 in the United States

▪ **LION-101** (or AB-1003) is an intravenously-administered gene therapy product which aims to restore production of the FKRP protein in LGMD R9 (*FKRP*) patients. Mouse models of the disease have already yielded positive results in terms of the product's safety, tolerability and dose-dependent efficacy.

▪ A phase I/II multicentre clinical trial called **LION-CS101**, launched by Asklepios BioPharmaceutical (AskBio), is currently taking place in the United States. It will include a total of 10 adults and adolescents with LGMD R9. The pharmaceutical company announced last August that the first patient had received a dose of the gene therapy product. The intermediary results are yet to be released.

Asklepios BioPharmaceutical. Press release. 2023.

LION-CS101 trial – LGMD R9

United States

10
(18 to 65 years old)

Recruiting

March 2023 – Dec 2028
1 year of follow-up

NCT05230459

Phase I
Safety/tolerability

Phase II
Dose/effect

Pharmacotherapy: ribitol's efficacy is confirmed

▪ Ribitol or BBP-418 (a substrate of the FKRP protein in glycosylation) is an orally administered medication that compensates for the abnormal hypoglycosylation of alpha-dystroglycan seen in LGMD R9. A sufficient supply of ribitol stimulates glycosylation. The efficacy of ribitol, particularly on motor function and life expectancy, has been demonstrated in mouse models of the disease.

▪ The efficacy of ribitol is currently being evaluated in humans in a phase II trial **(MLB-01-003)** launched in February 2021 by ML Bio Solutions (a BridgeBio Pharma company).

***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.*

MLB-01-003 trial
LGMD R9 - Ribitol

United States

14
(12 to 55 years old)

Not recruiting

Feb 2021 – Nov 2026
5 years of follow-up

NCT04800874

Phase II
Dose/effect

Positive long-term results

▪ In 2022 and at the start of 2023, intermediary results were already showing that the product was well tolerated when taken daily, significantly improved alpha-dystroglycan glycosylation and motor function in patients and did not cause any serious adverse drug reactions. In September 2023, ML Bio Solutions revealed 21-month results which confirmed these previous findings:

- long-term treatment well tolerated;
- no toxicity;
- significant reduction (over 80%) in serum CK levels;
- stabilisation of walking test results and NSAD scores.

Phase III already underway

▪ Following these results, a phase III trial of ribitol (**MLB-01-005** or **"FORTIFY"**) was launched in 2023 with participating centres in the United States, Europe (Denmark, Italy, Norway, the Netherlands and the United Kingdom) and Australia, enabling the safety and efficacy of long-term oral ribitol to be evaluated on a larger scale (81 participants). The first patient was dosed in August 2023. An analysis of the effects of the product after 12 months of treatment is due to be released soon. Recruitment for this trial is still taking place.

BridgeBio Pharma. Press release. Oct 2023 *Wu, B. et al. PLoS One. 2022.*
BridgeBio Pharma. Press release. Mar 2023

Phase III
Efficacy

MLB-01-005 (FORTIFY) trial
LGMD R9 - Ribitol

International	81 (12 to 55 years old)	Recruiting	April 2023 – July 2027 3 years of follow-up

NCT05775848

Pharmacotherapy: the clinical efficacy of ribose is yet to be demonstrated

An alternative to ribitol

Ribose is another molecule currently being studied to help stimulate FKRP protein activity. This sugar molecule, which is a precursor of ribitol, has already had its safety proven and is available over the counter.
Studies have shown that the addition of ribose in cell models of another dystroglycanopathy (LGMD R20) increases ribitol levels and restores alpha-dystroglycan glycosylation.
Ortiz-Cordero, C. et al. Elife. 2021 *van Tol, W. et al. Clin Chem. 2019* *Gerin, I. et al. Nat Commun. 2016.*

▪ A ribose supplementation trial conducted for six months in one LGMD R9 patient showed that the product was well tolerated at doses of 9 or 18 g a day, with the higher dose leading to a 70% decrease in CK levels and a significant increase in ribitol levels in certain cells. Although clinical improvements were not able to be demonstrated by analysing objective clinical data, the patient did report improvements in their pain, fatigue and muscle strength.
Thewissen, R. M. J. et al. JIMD Rep. 2024.

*A **biological marker** (or **biomarker** for short) is a measurable characteristic that indicates a normal or pathological biological process. The identification of new biological markers for a disease is very important in monitoring the progression of the disease and the efficacy of new treatments. These markers are physiological (change in blood pressure, blood sugar levels, heart rate, etc.) or molecular (change in the expression of a protein, etc.).*

Pharmacotherapy: EDG-5506 unconvincing in LGMD R9

▪ **EDG-5506** (or **sevasemten**) is an orally administered small molecule developed by Edgewise Therapeutics to combat muscle wasting and fibrosis.
It inhibits an ATPase that targets the myosin in fast-twitch muscle fibres. This limits the recruitment of fast-twitch muscle fibres, which are particularly affected in dystrophies, thus preventing their degradation.
▪ Launched by Edgewise Therapeutics in February 2023, the phase II "DUNE" trial is evaluating the effect of EDG-5506 on biomarkers of muscle damage following exercise in nine patients with LGMD R9, nine patients with Becker muscular dystrophy (BMD) and three patients with McArdle disease.

Analysis still ongoing

▪ Although sevasemten was shown to be well tolerated and effective in reducing exercise-induced muscle damage in BMD, **the results were statistically inconclusive** for the **LGMD R9** patients. A larger number of participants may be needed to better understand the treatment response. The investigators are continuing to compile and analyse the data.

Edgewise Therapeutics. Press release. 2023 *Edgewise Therapeutics. Press release. 2024.*

www.edgewisetx.com/science/211

DUNE trial
LGMD R9 - EDG-5506

Phase II
Dose/effect

United States | **21 participants** | **Not recruiting** | **Feb 2023 – August 2024**
Follow-up period not specified

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.

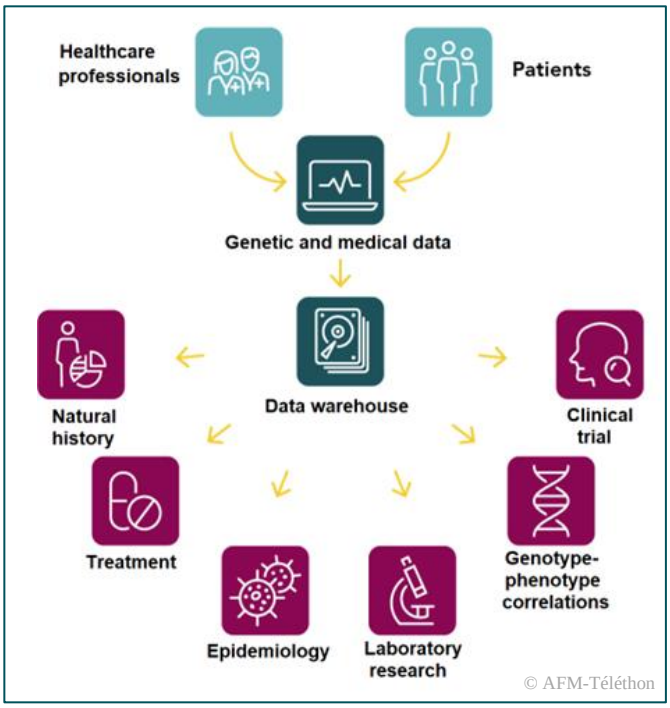
▪ These studies help us to better understand and describe diseases, and to identify better diagnostic and follow-up tools. They are essential for understanding the epidemiology of diseases, improving treatment and management and preparing future clinical trials.

*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.).*

LGMD 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.

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.*



Two French national LGMD registries

Patient registries *are centralised and comprehensive collections of medical data from patients with the same disease for a specific geographical region.*

Two French LGMD registries supported by AFM-Téléthon are about to be launched:

- A registry for **calpainopathies** coordinated by Prof. Edoardo Malfatti (Centre de Référence de Pathologie Neuromusculaire [specialist neuromuscular disease centre], Hôpital Henri Mondor [Henri Mondor Hospital], Paris, France) and Isabelle Richard (researcher at Généthon, Évry, France).
- A registry for **sarcoglycanopathies** coordinated by Prof. Pascal Laforêt (Centre de Référence de Pathologie Neuromusculaire Nord/Est/Ile-de-France [North/East/Ile-de-France specialist neuromuscular disease centre], Hôpital Raymond Poincaré [Raymond Poincaré Hospital], Garches, France).

Ten international LGMD registries

- The AFM-Téléthon LGMD peer support group (Groupe d'Intérêt) and the LGMD Awareness Foundation identified **10 LGMD patient registries** from around the world.

www.lgmd.afm-telethon.fr/registres-internationaux-lgmd/ [page in French]
www.lgmd-info.org/knowledge-base/navigating-lgmd/for-patients/international-lgmd-patient-registries/

Disease(s)	*Gene(s)*	*Registry (coordinating country)*
LGMD D1	*DNAJB6*	*LGMD-1D DNAJB6 Foundation and International Registry (USA)*
LGMD D4, R1	*CAPN3*	*LGMD2A/Calpainopathy Registry (USA)*
LGMD D5, R22	*COL6A1-3*	*Global Registry for COL6-related dystrophies (UK)*
LGMD R2	*DYSF*	*The Dysferlin Registry (USA)*
LGMD R3	*SGCA*	*LGMD2D Foundation Registry (USA)*
LGMD R4	*SGCB*	*GFB Registry (Italy)*
LGMD R5	*SGCG*	*Kurt+Peter Foundation Registry (USA)*

LGMD R9	*FKRP*	*Global FKRP Registry (UK)*
LGMD R12	*ANO5*	*LGMD2L Foundation Registry (USA)*
LGMD D1, LGMD D5, LGMD R7-11, LGMD R13-20, LGMD R22-24	*COL6A1, COL6A2, COL6A3, CRPPA (ISPD), DAG1, DNAJB6, FKRP, FKTN, GMPPB, LAMA2, PLEC (PLEC1), POMGNT1, POMGNT2, POMT1, POMT2, TCAP, TRAPPC11, TRIM32, TTN*	*Congenital Muscle Disease International Registry (CMDIR) (USA)*

Observational studies in LGMD

Respiratory problems in LGMD

▪ An international consortium of specialists attempted to characterise the prevalence and progression of respiratory problems in LGMD patients. These researchers reviewed nearly 20 years' worth (2002-2020) of lung function tests (spirometry) from **156 patients** representing seven LGMD subtypes (LGMD R1-R5, R9 and R12).

Respiratory problems are relatively common

▪ Over 37% of the patients had a forced vital capacity percentage predicted below 80%, while nearly 9% had an ineffective cough (peak cough flow value below 270 l/min).

▪ These two parameters **declined gradually over time**, regardless of age, wheelchair use or LGMD subtype, although the patients with LGMD R9 and R3-5 (sarcoglycanopathies) appeared to have a quicker decline in their forced vital capacities compared to the other patients.

Muni-Lofra, R. et al. Neurol Genet. 2023.

A better understanding of underrepresented populations

▪ An international partnership undertook a large-scale study which endeavoured to record the genetic and clinical characteristics of neuromuscular disease patients from geographical areas that had previously been poorly represented in reference medical databases.

Did you know?

Skewed data

Even though most neuromuscular disease patients live in developing countries, the overwhelming majority (86%) of genetic data collected on these diseases comes from individuals of European descent.

A large-scale study

▪ Eighteen centres in seven countries (South Africa, Brazil, India, Turkey, Zambia, the Netherlands and the United Kingdom) recruited 6,001 participants, 82% of whom were of non-European descent, over four years. The majority of the 3,600 patients studied in more detail belonged to four neuromuscular disease groups: **limb-girdle muscular dystrophies (18%)**, inherited peripheral neuropathies (16%), muscular dystrophies and congenital myopathies (9%), and Duchenne and Becker muscular dystrophy (9%). These groups were in line with those observed elsewhere in the world.

Diagnostic yield could be improved in LGMD genotyping

▪ Out of more than 800 patients genetically analysed during the study, just over 50% were able to receive a definitive or conditional genetic diagnosis. In the four groups of neuromuscular diseases mentioned above, this number went up to 72% (just under 45% for LGMD).

Unequal opportunities to receive a diagnosis

▪ The small number of specialist neuromuscular disease centres and professionals specialising in this field means that opportunities are limited in developing countries when it comes to receiving a genetic diagnosis. Over 90% of the participants genetically analysed in this study had never been tested before.

Wilson, L. A. et al. Brain. 2023.

Clinical progression in recessive LGMD

▪ The clinical course of recessive LGMD is extremely variable. A group of researchers wanted to more accurately estimate the frequency of loss of ambulation and progression to cardiac and/or respiratory involvement in certain subtypes (LGMD R1, R2, R3-R6, R9 and R12).

▪ Following a systematic literature review and after screening nearly 3,000 scientific publications concerning over 1,800 patients, the investigators identified **418 patients** whose ambulatory status had been provided, 57% (142) of which also had information on their respiratory and cardiac function.

LGMD R9 and sarcoglycanopathies - severity confirmed

▪ Over 63% (265) of the 418 patients were non-ambulant or wheelchair dependent. The authors noted that loss of ambulation was more common in the LGMD R1 and R2 patients, and was even more common and occurred earlier (generally before the age of 20) in the sarcoglycanopathy patients. The LGMD R12 patients analysed experienced loss of ambulation less often compared to the other patients, and none of those who did lose their ability to walk had cardiac or respiratory manifestations.

▪ Among the 142 patients for whom cardiac and/or respiratory function was reported, cardiac involvement was most common (73%) in the LGMD R9 patients, while respiratory involvement occurred most often (74%) in the patients with a sarcoglycanopathy (LGMD R3-R6).

▪ Cardiac and/or respiratory involvement were less common in the ambulatory patients, except for in the LGMD R9 patients, 71% and 52% of whom had respiratory and cardiac problems respectively.

Cheung, A. et al. J Clin Neuromuscul Dis. 2023.

A move towards better molecular diagnosis in LGMD

▪ To this day, LGMD is still very hard to diagnose, in particular because of the clinical and genetic heterogeneity of the different subtypes and how they mimic other muscular dystrophies.

A more comprehensive gene panel

▪ In order to improve efficacy and optimise the cost of genetic diagnosis, American researchers launched the “Lantern Project”, a national genotyping programme. They developed the “Lantern Focused Neuromuscular Panel”, a new gene panel that can for the first time simultaneously detect genetic variants in a sequence of DNA, but also copy number variations (CNV).

Did you know?

Another type of genetic diversity

CNV (copy number variations) are when certain sections of the genome in an individual are repeated. This number of repeats varies from person to person and can be particularly affected by a person's health or past exposure to certain factors (electromagnetic radiation for example). CNV contribute to the diversity of humankind. They can have no consequences, cause morphological variations or even be the source of (often rare) diseases. *Pös, O. et al. Biomed J. 2021*.

▪ A total of **66 genes** (compared to 35 previously) in nearly **6,500 patients** with clinically suspected LGMD or a muscular dystrophy similar to it were analysed. The investigators reported:

• that a molecular diagnosis was established in nearly 20% of the patients;

• that the majority of the LGMD patients had *CAPN3*, *DYSF*, *ANO5* and *FKRP* gene mutations;

• that several patients had mutations in genes associated with other muscular dystrophies (*PABPN1*, *MYOT*, *FLNC,* etc.);

• CNV of varying sizes including exons and introns but also whole genes (*DMD*, *CAPN3*, *ANO5*, *SGCG*, *LAMA2,* etc.).

▪ Widespread deployment of this more comprehensive genetic test has the potential to ensure earlier and more accurate diagnoses in LGMD and other phenotypically-similar myopathies.

Nallamilli, B. R. R. et al. Ann Clin Transl Neurol. 2023.

A look at the Czech LGMD population

▪ Genetic testing conducted by a team of researchers in **226 Czech LGMD patients** identified **157 different mutations**, including 54 which have only ever been identified in the Czech LGMD population to date.

▪ LGMD R1 was the most common subtype (53% of the patients), followed by LGMD R9 (11%) and LGMD R12 (7%). In contrast to its distribution in other populations around the world, this study showed that LGMD R2 is one of the least common subtypes in Czechia.

Zídková, J. et al. Clin Genet. 2023.

Characterisation of recessive LGMD in southern Brazil

▪ A nine-gene sequencing panel was used to analyse the DNA of **36 Brazilian LGMD patients** in order to determine the proportion of different LGMD subtypes in this part of the world. All of the patients were monitored at a neuromuscular disease centre in the city of Curitiba and had a recessive subtype of LGMD.

Consistent results

▪ Sequencing revealed a total of **27 pathogenic variants** in 64% of the participants, and it identified calpainopathy (LGMD R1) in 26%, dysferlinopathy (LGMD R2) in 26%, telethoninopathy (LGMD R7) in 18%, sarcoglycanopathies (LGMD R3-R5) in 13%, dystroglycanopathy (LGMD R9) in 13%, and anoctaminopathy (LGMD R12) in 4%.

▪ Although limited by the small number of patients, the study showed that the frequencies of LGMD subtypes were similar to those reported in other groups of Brazilian patients, particularly from the Southeast and Central-West regions of the country. The high proportion of patients with

telethoninopathy found in this study differs from observations made in Europe and North America, probably due to a **founder effect** in this region. *Lorenzoni, P. J. et al. Arq Neuropsiquiatr. 2023.*

*The **founder effect** refers to the establishment of a new population from a small number of individuals (the "founders"). These founders have only a fraction of the genetic diversity of the original population. The founder effect therefore results in a newly established population that is genetically impoverished and one that has an increased occurrence of specific alleles which may lead to an increased prevalence of certain rare diseases.*

Kivisild, T. (2013). Brenner's Encyclopedia of Genetics (Second Edition). In S. Maloy et al. (pp. 100-101). San Diego: Academic Press.

LGMD in China

- In China, data from **81 patients** clinically suspected of having LGMD were screened in order to better understand the genetic and clinical specificities of the disease in the south east of the country.
- Among the 50 patients screened with genetically-confirmed LGMD (62% or 41 families):

• the most common subtypes were LGMD R2 (37%) and LGMD R1 (29%).
• the most common childhood-onset subtypes in the group (12% of the families) were dystroglycanopathies (LGMD R9, R11, R14 and R20);
• nearly 15% of the families had LGMD R7;
• nearly 2% of the families had LGMD R10;
• one patient had LGMD R18.

- A total of 22% of the patients had cardiac abnormalities and 15% had restrictive respiratory insufficiency.

Lin, F. et al. Orphanet J Rare Dis. 2023.

Mobility and pulmonary function in sarcoglycanopathies

- A prospective natural history study of sarcoglycanopathies (LGMD R3-R5) called **SRP-LGMD-501-NHS** began in April 2021 in the United States.
- Sponsored by Sarepta Therapeutics, this study's objective is to monitor the clinical course of ambulatory and non-ambulatory patients for three years by evaluating their forced vital capacities, and NSAD and PUL (Performance of the Upper Limb) scores.

SRP-LGMD-501-NHS study
LGMD R3, R4 and R5 - Mobility and pulmonary function

United States

160 (over 4 years old)

Recruiting

April 2021 – Dec 2025
3 years of follow-up

NCT04475926

Natural history of LGMD R1 and R4

- A single-centre natural history study (sponsored by the Nationwide Children's Hospital) taking place in the United States is aiming to characterise the clinical progression and functional impact of LGMD R1 and R4 on patients. Muscle strength and walking speed are measured every six months for three years. Originally due to end in 2022, the study will now continue until 2025.

Prospective observational study (natural history)
LGMD R1 and R4 - Motor function

United States

100 (all ages)

Recruiting

Jan 2018 – June 2025
3 years of follow-up

NCT03488784

Clinical characteristics of dystroglycanopathies

▪ In order to help prepare for future clinical trials, an American study sponsored by the National Institute of Neurological Disorders and Stroke (NINDS) has been collecting clinical data (early signs, motor and pulmonary function, quality of life, etc.) on dystroglycanopathies (*CRPPA/ISPD*, *DAG1*, *FKRP*, *FKTN*, *GMPPB*, *POMGNT1*, *POMGNT2*, *POMT1* and *POMT2*-related limb-girdle muscular dystrophies) since 2006.

*The **NINDS** is part of the NIH (National Institute of Health), the primary biomedical research agency in the United States. The NINDS funds and conducts research on diseases of the brain and nervous system.*

First analysis in LGMD R9

▪ Using the PROMIS (Patient-Reported Outcomes Measurement Information System) self-assessment questionnaire, researchers were able to determine the prevalence of pain and fatigue in **77 LGMD R9 patients** (54 adults and 23 children) included in this study. The patients were required to evaluate their symptoms annually (for up to six years for some).

Not necessarily more painful

▪ The results indicated that **pain interference** (the extent to which pain hinders engagement in physical, cognitive and recreational activities in daily life, sleep and enjoyment in life) levels were **not greater** than in the general population.

▪ However, around 60% of the patients recorded pain interference levels greater than in the general population on at least one assessment during the study.

The results suggest that pain is often variable and episodic in LGMD R9 patients, with a generally limited impact on daily life.

A cumulative effect

▪ In the study, fatigue scores were elevated in the adult patients but not the children. The investigators also observed that fatigue and pain interference were positively correlated and that both **increased over time** but were not linked to sex or ambulation status.

Reelfs, A. M. et al. Neuromuscul Disord. 2023.

Prospective observational study (natural history)
Dystroglycanopathies

United States

160 (all ages)

Recruiting

April 2006 – July 2026
Collection of biological samples and data

NCT00313677

GRASP-LGMD - outcome measures in LGMD

▪ A prospective natural history study (**GRASP-01-001**) of LGMD D1, R1-R6, R9 and R12 coordinated by the GRASP-LGMD (Genetic Resolution and Assessments Solving Phenotypes in LGMD) consortium is evaluating the usefulness of a set of clinical outcome measures on a wide range of LGMD

*The **GRASP-LGMD** (Genetic Resolution and Assessments Solving Phenotypes in LGMD) **consortium** brings together an international team of neuromuscular disease specialists, scientists, rehabilitation workers, geneticists, computer scientists and patient representatives with the aim of accelerating the translation of research into therapies.*

www.mdcrn.com/grasp/network-information

phenotypes in order to determine whether these measures are reliable and able to be used in individuals with different phenotypes.

- The study will include **188 patients** from 11 sites in the United States and two in Europe. It will be the largest consortium to date to validate outcome measures and help prepare for and plan future LGMD trials.
- Two other GRASP-LGMD consortium studies with the same goal of preparing for future clinical trials are also currently underway (**GRASP-01-005** - all LGMD subtypes, and **GRASP-01-003** - LGMD R1).

Doody, A. et al. BMC Neurol. 2024.

GRASP-01-001 study
LGMD D1, R1, R2, R3, R4, R5, R6, R9, R12

United States and United Kingdom	188 (4 to 65 years old)	Recruiting	June 2019 – June 2024 1 year of follow-up	NCT03981289

GRASP-01-003 study
LGMD R1

United States	100 (12 to 50 years	Recruiting	Jan 2024 – May 2028 2 years of follow-up	NCT05618080

GRASP-01-005 study
LGMD (all subtypes), myotonic dystrophy type 2, late-onset Pompe disease

United States	1,000 (6 to 50 years old)	Recruiting	Oct 2023 – May 2029 2 years of follow-up	NCT05989620

Biomarkers in fragile sarcolemmal muscular dystrophies

- An American study aiming to **identify biomarkers** in fragile sarcolemmal muscular dystrophies (including LGMD R2, LGMD R3-R6, LGMD R9 and LGMD R12) is currently underway.

Prospective observational study – LGMD R2, R3, R4, R5, R6, R9, R12

United States	11 (over 18 years old)	Not recruiting	Nov 2014 – Dec 2024 1 year of follow-up	NCT01851447

Clinical course of motor function in LGMD

- A French prospective natural history study (**EIDY**) conducted by the Laboratoire d'Analyse du Mouvement [Laboratory of Movement Analysis] at Hôpital Raymond Poincaré in Garches (Assistance Publique-Hôpitaux de Paris [Greater Paris University Hospitals], also known as AP-HP) is monitoring motor parameters in **40 ambulatory LGMD patients** for two years.
- The investigators are evaluating muscle strength, joint range of motion while walking, upper limb spatial exploration and manual dexterity. The participants will also complete questionnaires regarding their day-to-day activities, quality of life and fatigue during each six-monthly visit.

EIDY study (natural history) - all LGMD subtypes

France	80 (18 to 70 years old)	Recruiting	April 2021 – Jan 2025 2 years of follow-up

NCT04772027

Diagnosis and disease progression in China

- A Chinese study sponsored by Huashan Hospital in Shanghai is collecting clinical (motor function, etc.), genetic, physiological and histological (muscle biopsies) data on 450 LGMD patients over a three-year period. The initial results are expected to be published in July 2024.

KY2019-409 study (natural history) – all LGMD subtypes

China	450 (over 10 years old)	Enrolling by invitation	July 2021 – Dec 2024 3 years of follow-up

NCT04989751

LGMD D4 (*CAPN3* – calpainopathy, autosomal dominant)

Clinical characteristics of dominant calpainopathies

- **In Italy**, a retrospective study was launched by IRCCS San Camillo (Venice) in September 2023 to review clinical and biomarker information in a cohort of 50 patients with LGMD D4 in order to improve the diagnostic strategy for this disease. The investigators will analyse the patients' medical records and laboratory test results obtained from centres participating in the study.

Retrospective observational study – LGMD D4

Italy	50 (children and adults)	Enrolling by invitation	Sept 2023 – June 2025 No follow-up (retrospective study)

NCT05956132

p.Lys 254del mutation: necessary but not enough

- The **p.Lys 254del mutation** (c.759_761del) in the *CAPN3* gene has been previously detected in two families with LGMD D4, the autosomal dominant form of calpainopathy. It was therefore assumed that the presence of this mutation in just one of the two *CAPN3* alleles was enough to cause the disease.
- Spanish researchers discover two families in which the calpainopathy had been inherited recessively (LGMD R1). Genetic testing revealed that some family members had the p.Lys 254del mutation in the *CAPN3* gene but did not exhibit any of the myopathic features (including camptocormia) described in dominant patients.
- The link between the presence of the p.Lys 254del (c.759_761del) mutation in the *CAPN3* gene and the manifestation of clinical muscle symptoms in an individual is therefore not as straightforward as initially thought. The variant is clearly **not the only factor responsible for the phenotype** of dominant patients.

Valls, A. et al. Muscle Nerve. 2024.

LGMD R1 (*CAPN3* – calpainopathy, autosomal recessive)

CALNATHIS - clinical course of muscle function

- This year, the Assistance Publique – Hôpitaux de Paris (AP-HP) **in France** launched a new natural history study involving **25 adults** with LGMD R1 monitored by the specialist neuromuscular disease centre at Henri Mondor hospital.
- Its objective is to **quantify loss of strength** in the arms and legs over a period of two years, mainly using the NSAD scale.
- The investigators are also hoping to determine the most relevant clinical outcome measures for future clinical trials and assessing responses to treatment.

www.lgmd.afm-telethon.fr/calnathis-etude-francaise-dhistoire-naturelle-lgmdr1-2a-calpainopathie/ [page in French]

CALNATHIS (natural history) – LGMD R1

France

25 (over 18 years old)

Recruiting

April 2024 – April 2026 2 years of follow-up

NCT06390566

Alternatives to muscle biopsies

- An **Italian study** attempted to identify new biomarkers in order to help diagnose LGMD. When analysing the RNA and protein content of various biological samples from **60 patients** with LGMD R1, the researchers observed the presence of the *CAPN3* full-length transcript in urine and skin samples (fibroblasts) for the first time. CAPN3 protein levels in the skin samples were also comparable to those found in muscle.
- These results suggest that **skin biopsy** and **urine samples** could serve as less invasive methods for evaluating calpain levels as a complement to molecular diagnosis, especially when the latter is inconclusive.

Aguti, S. et al. Cells. 2024.

Preparing for future clinical trials is becoming urgent
The speed of treatment development in LGMD R1 requires future clinical trials in the disease to be prepared.
This preparation involves identifying biomarkers and clinical outcome measures in order to monitor the progression of the disease and measure therapeutic efficacy.

LGMD R2 (*DYSF* - dysferlinopathy)

COS2: natural history of dysferlinopathies

- The international **COS2** (Clinical Outcome Study for Dysferlinopathy) study sponsored by the Jain Foundation aimed to confirm and refine the results of the **Jain COS study** (completed in 2018), identify the most relevant outcome measures (biomarkers, tools, tests, etc.) for future clinical trials in dysferlinopathies (including LGMD R2) and characterise the progression of the disease.
- The study is being conducted in nine countries: Chile, Denmark, Spain, the United States, France, Italy, Japan, South Korea and the United Kingdom. The investigator site in France is the Institute of Myology (Paris).

www.jain-foundation.org/patients-clinicians/how-to-take-action/clinical-trials-studies-and-surveys/cos2

COS2 study – LGMD R2

France and abroad	200 (over 18 years old)	Not recruiting	Sept 2012 – March 2024 2 years of follow-up

NCT01676077

Detecting dysferlinopathy using MRI

- The first Jain COS study identified eight diagnostic criteria which made it possible to detect dysferlinopathy (LGMD R2) using MRI. An international study attempted to confirm the usefulness of these criteria in distinguishing dysferlinopathy from other genetic myopathies.

__MRI__ (magnetic resonance imaging) is a medical imaging technique which can obtain cross-sectional or volumetric images of an organ or area of the human body. MRI scans are painless. They involve lying still on a bed which slides into a cylindrical machine that contains a very powerful magnet.

Distinguishing LGMD R2 from 10 other diseases

- The investigators applied these criteria to MRI scans performed on 182 patients with LGMD R2, and 1,000 patients with LGMD R1, R3-R5, R9, R12, Duchenne muscular dystrophy (DMD), *LMNA*-related congenital muscular dystrophy (L-CMD), facioscapulohumeral muscular dystrophy type 1 (FSHD1), Pompe disease, inclusion body myopathy with Paget disease of bone and frontotemporal dementia (IBMPFD) or oculopharyngeal muscular dystrophy (OPMD).

Five criteria found more often in LGMD R2

- Five of the criteria were met more frequently by the dysferlinopathy patients. The authors therefore suggested a model (decision tree) using these five criteria to help diagnose dysferlinopathy, with a sensitivity of nearly 96%, specificity of 46% and accuracy of 67%.

A useful model for ruling out LGMD R2 but not for confirming it

- Given the high sensitivity of this model, a negative result meant that LGMD R2 could be confidently ruled out. Conversely, a positive result was not very informative as its low specificity did not make it discriminatory; it did not therefore necessarily indicate dysferlinopathy.
- This study shows the relevance of using MRI to diagnose dysferlinopathy.

Bolano-Diaz, C. et al. Neuromuscul Disord. 2024.

A Russian study

- The Russian biotechnology company Human Stem Cells Institute is sponsoring a natural history study in LGMD R2 patients from different parts of Russia, recruited from the national dysferlinopathy registry (DYSF Russian registry). The study is looking at several variables (phenotype, genotype, motor and cardiac function, etc.) and aims to describe the characteristics of the disease within the Russian population.

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

***Genotype** refers to the genetic characteristics of a living thing. In a way, it's the genetic ID card of an individual.*

Prospective observational study (natural history) – LGMD R2

Russia	100 (18 to 85 years old)	Enrolling by invitation	Jan 2020 – July 2024 2 years of follow-up

NCT04824040

LGMD R4 (*SGCB* – beta-sarcoglycanopathy)

A founder effect identified in India

- Indian clinicians recently identified an area in **southern India** (the states of Karnataka, Tamil Nadu and Andhra Pradesh) with a high number of LGMD R4 cases - 14 patients from 13 unrelated families have been diagnosed with the disease.
- All of the patients had the same c.544 T > G (p.Thr182Pro) mutation. Further genetic testing conducted in the 14 patients and 150 healthy subjects confirmed the very likely existence of a founder effect in this region. These results could have positive implications for when gene therapy trials are being set up for this subtype of LGMD.

Sanga, S. et al. Sci Rep. 2023.

A study prior to a future gene therapy trial

- The Nationwide Children's Hospital (UK) and Myonexus Therapeutics (since acquired by Sarepta Therapeutics) are currently sponsoring a **preinclusion study** which is aiming to recruit LGMD R4 patients who are potentially eligible for a gene therapy trial and describe the clinical course of the disease over two years. It was due to end in March 2023 but appears to still be ongoing.

A preinclusion natural history study – LGMD R4

United States

25
(3 to 15 years old)

Recruiting

March 2018 – March 2023
2 years of follow-up

NCT03492346

LGMD R9 (*FKRP*– dystroglycanopathy)

Sleep and quality of life in Norwegian patients

- In LGMD R9, sleep can be impacted by symptoms of the disease, muscle pain or even sleep disordered breathing (SDB) such as sleep apnoea.
- Two studies assessed fatigue, **the frequency of insomnia and SDB,** and their impact in a group of **90 Norwegian LGMD R9 patients** using a questionnaire evaluating sleep quality, fatigue and quality of life.

Sleep disorders and fatigue are common

- At least one third of the patients, regardless of whether or not they used non-invasive ventilation (NIV), suffered from insomnia. The more severe their insomnia, the more their health-related quality of life was reduced.

Out of the 26 patients not using NIV for SDB, over 60% met the criteria for obstructive sleep apnoea/hypopnoea syndrome (apnoea-hypopnoea index (AHI) greater than or equal to 5). Older age and an ejection fraction of under 50% negatively affected AHI scores.

The impact of genetic mutations

- Out of the 84 patients who assessed their daily disease burden, questionnaire responses showed a greater perceived worsening of muscle fatigue and quality of life in patients with homozygous mutations than in patients with compound heterozygous mutations, although the latter reported more dysphagia and physical difficulties.
- This study shows that **sleep problems are often overlooked in LGMD R9.** Nearly one in two patients in the group studied reported poor sleep. Testing for sleep disorders is therefore essential, especially in cases of extreme fatigue.

Jensen, S. et al. J Neurol. 2023 *Jensen, S. M. et al. J Neuromuscul Dis. 2023.*

Endpoints for future LGMD R9 trials

- Généthon is sponsoring **GNT-015-FKRP**, an international prospective natural history study of LGMD R9. Taking place in France, Denmark and the United Kingdom, the aim of this study is to gain a better understanding of the mechanisms of the disease and to characterise the disease course using standardised evaluations. Another one of its objectives is to determine the best endpoints for future clinical trials. The study is still underway despite being initially scheduled to end in December 2023.

GNT-015-FKRP study – LGMD R9

France

52
(16 to 99 years old)

Not recruiting

Feb 2020 – Dec 2023
2 years of follow-up

NCT03842878

LGMD R12 (*ANO5* – anoctaminopathy)

Characterisation of muscle involvement using MRI

▪ A retrospective study of **200 medical records** from LGMD R12 patients from multiple countries around the world was launched in 2021 by teams at Rigshospitalet in Denmark. Its objective is to characterise the muscle involvement (symmetry, difference in severity between men and women, whether there is a correlation with the causative genetic mutation, etc.) in LGMD R12 using **MRI**. Data collected by health centres from all over the world is shared with Copenhagen Neuromuscular Center via the electronic platform MyoShare.

Retrospective observational study (natural history) – LGMD R12

Denmark

200
(all ages)

Recruiting

April 2021 – August 2025
Review of patient records

NCT05102799

Progression of the disease over time

▪ Rigshospitalet has also been funding another natural history study in LGMD R12 (*ANO5*) since 2018. Its objectives are to describe the progression of the disease (fatigue, quality of life, motor function, etc.) and identify reliable clinical outcome measures. The end of the study has been pushed back to 2025.

▪ The intermediary results (2021) from the study were consistent with observations made previously in this disease (calf muscle atrophy, relatively preserved back muscles, milder phenotype in women, ability to walk generally retained, etc.).

Khawajazada, T. et al. Eur J Neurol. 2021.

Prospective observational study (natural history) – LGMD R12

Denmark

17
(over 18 years old)

Not recruiting

Jan 2018 – Nov 2025
3 years of follow-up

NCT05206617

LGMD R18 (*TRAPPC11*)

A founder effect in the traveller population

▪ A consortium of Spanish clinicians reported laboratory and clinical data from a group of **25 LGMD R18 patients** from the **traveller community**. Analyses found:

• a homozygous genetic variant (c.1287+5G>A) in the *TRAPPC11* gene;

• never before reported clinical manifestations, including microcephaly (in almost every patient in this cohort), psychomotor regression and epilepsy;

• mitochondrial defects.

These results suggest a **founder effect**, a phenomenon that is seen often in the traveller community.

Justel, M. et al. J Med Genet. 2023.

LGMD R29 (*SNUPM*)

A new subtype of LGMD

▪ Two international studies have suggested that the ***SNUPN* gene** is the cause of various diseases ranging from congenital muscular dystrophy (CMD) to 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.

A gene with no associated diseases until these studies

▪ Each patient studied had a homozygous mutation in the *SNUPN* gene which codes for snurportin-1, a protein involved in RNA maturation. Snurportin-1 interacts with protein complexes containing the SMN protein (involved in spinal muscular atrophy or "SMA") to ensure the nucleocytoplasmic transport of small nuclear ribonucleoproteins.

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

Distinguishing features

▪ This new LGMD subtype is the **29th recessive subtype (LGMD R29)** discovered to date. It has certain similarities with other LGMD subtypes (particularly LGMD R16 and LGMD R3) and myofibrillar structural abnormalities similar to those seen in myofibrillar myopathies.

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

Preclinical studies - treatment avenues

Did you know?

Preclinical research

▪ Preclinical studies constitute the first step in exploring or demonstrating the safety and/or efficacy of a drug candidate or treatment in animal models (*in vivo*) or cell cultures (*in vitro*).

▪ Only in the event of conclusive preclinical results can clinical trials of a drug candidate in humans be considered.

In vitro *(Latin for "in glass") studies are carried out in laboratory containers (formerly made of glass) - cell models.*

In vivo *(Latin for "in the living") studies are performed in living organisms - animal models.*

LGMD R1 (*CAPN3* – calpainopathy)

Feasibility of genome editing using CRISPR/Cas9

▪ Research carried out by Simone Spuler, Stefanie Müthel and their team published at the start of 2023 showed that the most common mutation causing LGMD R1 could be corrected precisely and in a way that is not toxic to cells using the **CRISPR/Cas9 system.** They managed to use this tool to cut and **correct DNA** at the mutation site in induced pluripotent stem cells (iPSC) and primary human satellite cell-derived muscle stem cells (PHSats) from LGMD R1 patients.

*Like a pair of molecular scissors, the **CRISPR/Cas9 system** is an approach that is able to remove, repair or modify a DNA sequence or gene by cutting at specific locations in the genome in any cell.*
It uses guide RNA to locate target regions. The number of treatment strategies using this approach has increased. They make it possible for a piece of DNA to be removed, a mutation to be corrected, the reading frame of a gene to be modified, a splicing site to be changed in order to induce exon skipping, and even a piece of DNA to be added to a gene.

Corrected stem cells for muscle regeneration

▪ At the end of 2023, it was the turn of another German team to demonstrate the possibility of using the CRIPSR/Cas9 approach in LGMD R1, this time on cells from a patient with a compound heterozygous mutation (in exon 3 and 4 of the *CAPN3* gene). The researchers managed to obtain iPSC and muscle stem cells from the patient and correct the two mutations.

▪ The ability to successfully correct muscle stem cells, which are used to repair muscle, confirms the feasibility of using this approach for therapeutic purposes, meaning the clinical trial currently in preparation resulting from this work is all the more anticipated.

Mavrommatis, L. et al. Stem Cells Int. 2023 *Müthel, S. et al. Mol Ther Nucleic Acids. 2023.*

LGMD R2 (*DYSF* - dysferlinopathy)

Proof of concept - dual vector approach in gene therapy

What is ATL1102?

ATL1102 is an antisense oligonucleotide designed to target and inhibit the expression of the *CD49d* gene which is involved in the inflammation process, particularly in muscle.

▪ After obtained positive results in 2022, Percheron Therapeutics (formerly Antisense Therapeutics) announced the start of the second phase of its programme to study the effects of its antisense therapy product **ATL1102** in a mouse model of LGMD R2 in February 2023.

▪ This second **preclinical stage**, carried out in collaboration with Murdoch Children's Research Institute (MCRI) in Australia and the Jain Foundation in the United States, aims to assess the effects of the treatment over a longer period of time (four months) and will evaluate key indicators (muscle fat fraction) of disease progression.

In September 2023, the biotechnology company shared **positive results** from this research, stating that ATL1102 had restored normal function and physiology of the calf muscles in **a mouse model** of LGMD R2.
Antisense Therapeutics. Press release. 2023 (Sept) *Antisense Therapeutics. Press release. 2023 (Feb)* *Antisense Therapeutics. Press release. 2022 (June).*

LGMD R9 (*FKRP*– dystroglycanopathy)

Gene therapy and pharmacology - the winning combination

- Pharmacological and gene therapy approaches are currently being tested in LGMD R9 and are each producing positive results. But what about combining the two?
- American researchers tested **adding ribitol** (a substrate of the FKRP protein) to the drinking water of five-week-old mouse models of LGMD R9, then administering them with a dose of gene therapy (at low or high doses) four weeks later to provide their cells with a working copy of the *FKRP* gene.

A synergistic pairing

- The results demonstrated **the effectiveness of the combined strategy** with no significant side effects observed in the animals. Average life expectancy increased more (+50% minimum) than with a low dose of gene therapy alone (+47%).
- This **synergistic effect was comprehensive** at tissue level. The mice treated with both methods had a more intense and homogeneous increase in alpha-dystroglycan glycosylation levels in the heart, limb muscles and diaphragm, a 10% greater reduction in muscle fibrosis, and a more homogeneous distribution of muscle fibre size than those treated with gene therapy or ribitol alone.
- Invariably, the mice treated with both methods had better or identical results (muscle function, diffusion of the gene therapy viral vector, etc.) to those obtained by the most effective treatment for a given parameter.

The stabilising effect of ribitol

- The investigators concluded that the best results were obtained by combining a high dose of gene therapy with ribitol. Ribitol helps stabilise disease progression before starting gene therapy, and fosters the maintenance and prolongation of the efficacy of the therapeutic gene after injection.
- This synergistic dual approach provides a working gene and its protein substrate for increased therapeutic efficacy.

Cataldi, M. P. et al. Mol Ther. 2023.

LGMD R21 (*POGLUT1*)

Mutation correction using CRISPR/Cas9 and the role of *POGLUT1*

▪ An international research team used cell (iPSC) and animal (mouse) models of *POGLUT1*-related LGMD R21 to study the pathological mechanisms of the disease and the feasibility of using CRISPR/Cas9 gene correction for therapeutic purposes.

*The **Notch signalling pathway** is a form of communication between cells. It is involved in cell differentiation and the development of several tissues.* Zhou, B. et al. Signal Transduct Target Ther. 2022 ; Cormier, S. et al. Med Sci (Paris). 2007

***POGLUT1* is involved in muscle development**

▪ Analysis of the iPSC indicated dysregulation of cell communication (Notch signalling pathway) and muscle development. POGLUT1 enzyme activity was reduced and myogenesis was defective. Muscle stem cell formation and PAX7 protein (involved in the differentiation of muscle stem cells) expression were also reduced.

***Induced pluripotent stem cells** (iPSC) are cells that can self-renew indefinitely in a culture and differentiate into any specialised cell in the body.*

Gene correction is effective

▪ By using the CRISPR/Cas9 tool, the investigators were able to successfully correct the *POGLUT1* gene mutation in iPSC taken from patients. Functional normalisation was observed in these cells (interactions with the extracellular matrix, migration potential, etc.).

▪ These results were confirmed in mice where transplantations of genetically-corrected muscle progenitor cell showed improved muscle regeneration potential.

Ortiz-Vitali, J. L. et al. Mol Ther Nucleic Acids. 2023
Malfatti, E. cahiers-myologie.org. 2020 *[article in French]*
Servián-Morilla, E. et al. Acta Neuropathol. 2020.

Basic research

What is basic research?

- INSERM (Institut National de la Santé et de la Recherche Médicale [French National Institute of Health and Medical Research]) 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 mechanisms that cause diseases.
- Basic research is usually the **first 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.

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

LGMD R1 (*CAPN3* – calpainopathy)

Calpain and store-operated calcium entry (SOCE)

Did you know?

Calcium - a key player in muscle contraction.

A muscle cannot contract without the calcium balance in the cytoplasm of muscle fibres changing. This is achieved by calcium ions being exchanged between the cytoplasm, extracellular environment and sarcoplasmic reticulum.

- Calpain, the protein whose deficiency causes LGMD R1, is a protease (an enzyme that breaks down other proteins) activated by calcium. Its localisation in structures (in particular the sarcoplasmic reticulum) that regulate intracellular calcium entry suggests that it too is involved in this regulation. This involvement was studied by an international team using a mouse model of LGMD R1.

*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.*

Altered SOCE activity

- Their analyses conducted in resting mice showed that the loss of calpain caused a change in the distribution of the calcium normally found in muscle fibre cytosol and the sarcoplasmic reticulum. After a period of physical exertion, muscle calcium levels depleted more quickly, and diminished force production was exhibited in certain muscles after repeated bouts of exercise. The muscle fibre calcium ion entry mechanisms had clearly been impaired.
- These results show that SOCE dysregulation is involved in LGMD R1 and that calpain is an essential regulator of SOCE.

Villani, K. R. et al. bioRxiv. 2024.

LGMD R4 (*SGCB*), R6 (*SGCD*)

A new zebrafish model in sarcoglycanopathies

Did you know?

Essential experimental models

While they are not perfect (milder symptoms, additional disorders, etc.), cell (*in vitro*) and animal (*in vivo*) models of diseases are essential for understanding the mechanisms of a disease and evaluating possible treatment options.

▪ A multinational research team, which included Isabelle Richard from Généthon, used the CRISPR/Cas9 genome editing tool to generate **novel zebrafish lines** of LGMD R4 (*SGCB*) and LGMD R6 (*SGCG*). The animals presented a disease phenotype that worsened between the larval and adult stages with myopathic features seen in the adult fish.

▪ With the new zebrafish model of LGMD R6, the researchers were able to show that the mutated gamma-sarcoglycan protein is the target of the endoplasmic reticulum-associated protein degradation system, indicating premature degradation of the protein caused by protein folding defects.

Dalla Barba, F. et al. Int J Mol Sci. 2023.

LGMD R9 (*FKRP*– dystroglycanopathy)

A new cell model for assessing gene therapies

Efficacy to be demonstrated before clinical trials

Gene therapy is finally being evaluated in humans in LGMD R9; preclinical studies have paved the way for two ongoing phase I-II clinical trials. Before moving on to this stage, and to demonstrate the efficacy of the treatment, regulatory authorities require several quality controls, including a potency assay to quantify the intended biological effect of the gene therapy product.

▪ Researchers from **Généthon** and the **Institut de Myologie** have developed a **new cell line** in which the *FKRP* gene (the causative gene in LGMD R9) has been inactivated using CRISPR/Cas9 technology. This makes it possible to determine the biological activity of the transgene in the treated cells, in particular by measuring the restoration of alpha-dystroglycan glycosylation levels.

These new muscle cells and this technique which is specific to them are additional tools that will enable **the effects of other gene therapies to be assessed** in LGMD R9.

Geoffroy, M. et al. Cells. 2023.

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Keep up to date on limb-girdle muscular dystrophy research news throughout the year on the AFM-Téléthon website:

www.afm-telethon.fr/en