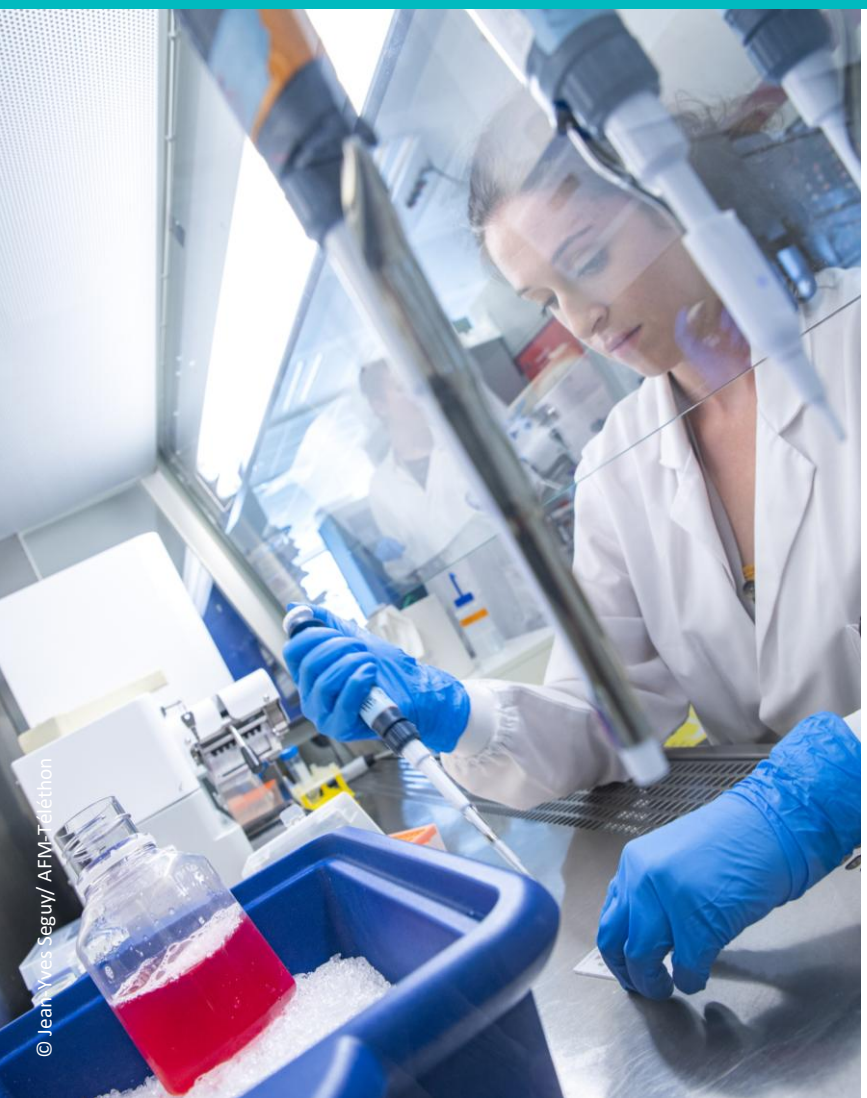
JUNE 2025

SAVOIR & COMPRENDRE
AVANCÉES DE LA RECHERCHE

Advances 2025 in limb-girdle muscular dystrophies



This document, published to coincide with the AFM-Téléthon General Meeting 2025, presents a selection of limb-girdle muscular dystrophy research news stories from the past year (ongoing observational studies and clinical trials, scientific publications, events, etc.).

AFMTÉLÉTHON
INNOVER POUR GUÉRIR

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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 simple muscle fatigability to loss of ambulation.
- Possible respiratory and/or cardiac involvement.

Management and treatment

- **Multidisciplinary treatment** of symptoms at specialist 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 (if necessary) to identify the causative gene

In numbers

1 to 3 people in every 100,000 have LGMD

154 scientific articles published between June 2024 and May 2025 *(PubMed)*

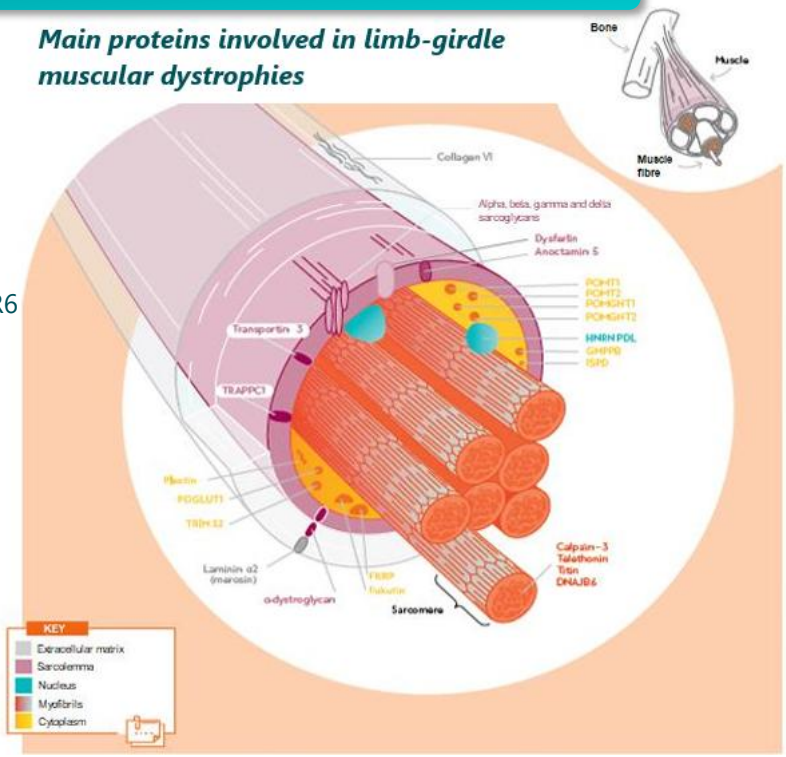
11 clinical trials including **9** gene therapy trials *(ClinicalTrials.gov 31/05/2025)*

Mode of inheritance

- **27 autosomal recessive subtypes**
  From LGMD R1 to LGMD R28
  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]

4 highlights from the past 12 months

Two French national registries launched in 2025

▪ After years of waiting, they're finally here! French registries for calpainopathies and sarcoglycanopathies started collecting data in January 2025. Funded and hosted by AFM-Téléthon, these two registries will collect valuable medical and genetic information that will help research projects, all in the interest of patients.

LGMD R2 - an abundance of treatment avenues

▪ Treatment research in LGMD R2 is in full swing this year, with projects taking place involving techniques such as exon skipping, drug repurposing, gene therapy and genome editing. But this research boom has not just been limited to innovative therapies, with projects focusing on topics such as the effects of corticosteroids, screening for respiratory problems, etc. Dysferlinopathy has been the subject of numerous research projects and advances in recent months.

LGMD R5 - gene therapy products being evaluated

▪ The evaluation of ATA-200 started in the United States this year with two patients treated in a trial sponsored by Atamyo Therapeutics. The American pharmaceutical company Sarepta Therapeutics is preparing to move to the clinical trial stage with its gene therapy product SRP 9005. These trials represent a real hope for patients. LGMD R5 therefore joins LGMD R3 and R4 in the list of sarcoglycanopathies in which gene therapy can be implemented.

LGMD R9 - preclinical studies and clinical trials

▪ Pharmacotherapy and gene therapy are both being studied in LGMD R9. In France, Atamyo Therapeutics completed a phase I/II clinical trial of the gene therapy product ATA-100, whose positive results are to be confirmed in a pivotal trial (phase III). The American pharmaceutical company Askbio, after having completed the dose escalation phase of its LION-CS101 clinical trial, is now expected to move on to the next stage of evaluation for its gene therapy drug candidate. Preclinical research is also ongoing in LGMD R9, and this year another American team demonstrated the feasibility of a gene therapy product that constitutes a vector containing two genes, namely the *FKRP* gene to compensate for the genetic mutation and the *FST* gene which codes for follistatin to promote muscle growth.

Clinical trials

▪ Clinical trials consist of assessing **a potential treatment** 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)** to answer specific questions. Is it well tolerated? What is the optimal dose? Is it effective and according to what criteria (walking ability, motor function, cardiac function, etc.)? After a treatment has received regulatory approval, it is then used in real life and continues to be monitored in order to identify any side effects that may occur.

Les essais cliniques en pratique [Clinical trials explained]

Ongoing clinical trials in LGMD

TRIAL TITLE	LGMD SUBTYPE	THERAPEUTIC APPROACH	CLINICAL DEVELOPMENT
			PHASE I / PHASE II / PHASE III
SRP-6004-102 (NAVIGENE) *(Sarepta Therapeutics, United States)*	**LGMD R2 (*DYSF*)**	**Gene therapy**	**SRP-6004**
SRP-9004-102 (DISCOVERY) *(Sarepta Therapeutics, United States)*	**LGMD R3 (*SGCA*)**	**Gene therapy**	**SRP-9004**
SRP-9003-101 *(Sarepta Therapeutics, United States)*	**LGMD R4 (*SGCB*)**	**Gene therapy**	**SRP-9003**
SRP-9003-102 (VOYAGENE) *(Sarepta Therapeutics, United States)*	**LGMD R4 (*SGCB*)**	**Gene therapy**	**SRP-9003**
SRP-9003-301 (EMERGENE) *(Sarepta Therapeutics, multiple countries)*	**LGMD R4 (*SGCB*)**	**Gene therapy**	**SRP-9003**
ATA-003-GSAR *(Généthon – Atamyo Therapeutics, multiple countries including France)*	**LGMD R5 (*SGCG*)**	**Gene therapy**	**ATA-200 (GNT0007)**
SRP-9005-101 (COMPASS) *(Sarepta Therapeutics, United States)*	**LGMD R5 (*SGCG*)**	**Gene therapy**	**SRP-9005**
ATA-001-FKRP *(Généthon – Atamyo Therapeutics, multiple countries including France)*	**LGMD R9 (*FKRP*)**	**Gene therapy**	**ATA-100 (GNT0006)**
LION-CS101 *(AskBio, United States)*	**LGMD R9 (*FKRP*)**	**Gene therapy**	**LION-101 (AB-1003)**
MLB-01-003 *(ML Bio Solutions, United States)*	**LGMD R9 (*FKRP*)**	**Pharmacotherapy**	**BBP-418 (ribitol)**
MLB-01-005 (FORTIFY) *(ML Bio Solutions, multiple countries)*	**LGMD R9 (*FKRP*)**	**Pharmacotherapy**	**BBP-418 (ribitol)**

DUNE Phase 2 Exercise Challenge *(Edgewise Therapeutics, United States)*	**LGMD R9 (*FKRP*)**	**Pharmacotherapy**	**EDG-5506 (sevasemten)**
bASKet *(Myopax, Germany)*	**LGMD**	**Cell therapy**	**GenPHSats**

Clinical trials covering multiple LGMD subtypes

The effects of prednisone - identifying biomarkers

*A **biological marker** (or **biomarker** for short) is a measurable characteristic that indicates a normal or pathological biological process. Identifying new biomarkers for a disease is very important for monitoring the course of the disease and measuring the efficacy of new treatments. These markers can be physiological, histological or molecular.*

- From 2019 to 2022, the North American clinical trial Weekly Steroids in Muscular Dystrophy, or WSiMD (NCT04054375), evaluated the effects of low-dose (once a week) corticosteroid treatment (prednisone) administered for six months in 19 adults aged 18 to 60 years old with LGMD R1, R2, R4-R6, R9 or R12 (and one patient with Becker muscular dystrophy (BMD)).
- Corticosteroids at this dose were well tolerated, did not cause any significant side effects, and seemed to protect muscle. The patients showed improvements in their grip strength and timed walk/run test scores.

Biomarkers of its effect

- Two years later, the clinical trial investigators published the results from the analysis of blood samples taken from the trial participants. Before treatment, the researchers noted an increase in muscle protein levels in the patients' blood related to the muscle damage observed in muscular dystrophies. After treatment, of the 6,411 proteins detected by the analysis, 24 proteins had increased and 132 had decreased.
- The proteins whose levels had decreased were associated with immune system function, but also muscle structural constituents. Amongst the proteins whose levels had increased, several were involved in changes (growth, repair, etc.) in the extracellular matrix and muscle development.

This data shows that it would be possible to design biomarkers to better personalise steroid use, optimise their efficacy and limit side effects.

Willis, A. B. et al. Sci Rep. 2024

Cell therapy - stem cell transplantation

- The **bASKet** trial was due to start in 2023 but still has not started. 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 was developed by a German team led by Simone Spuler, cofounder of the biotechnology company Myopax.

***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.*

- Six adolescents and/or adults with LGMD 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*

bASKet trial

Germany

6 (over 14 years old)

Not yet recruiting

Start date unknown
1 year of follow-up

NCT05588401

Phase I
Safety/tolerability

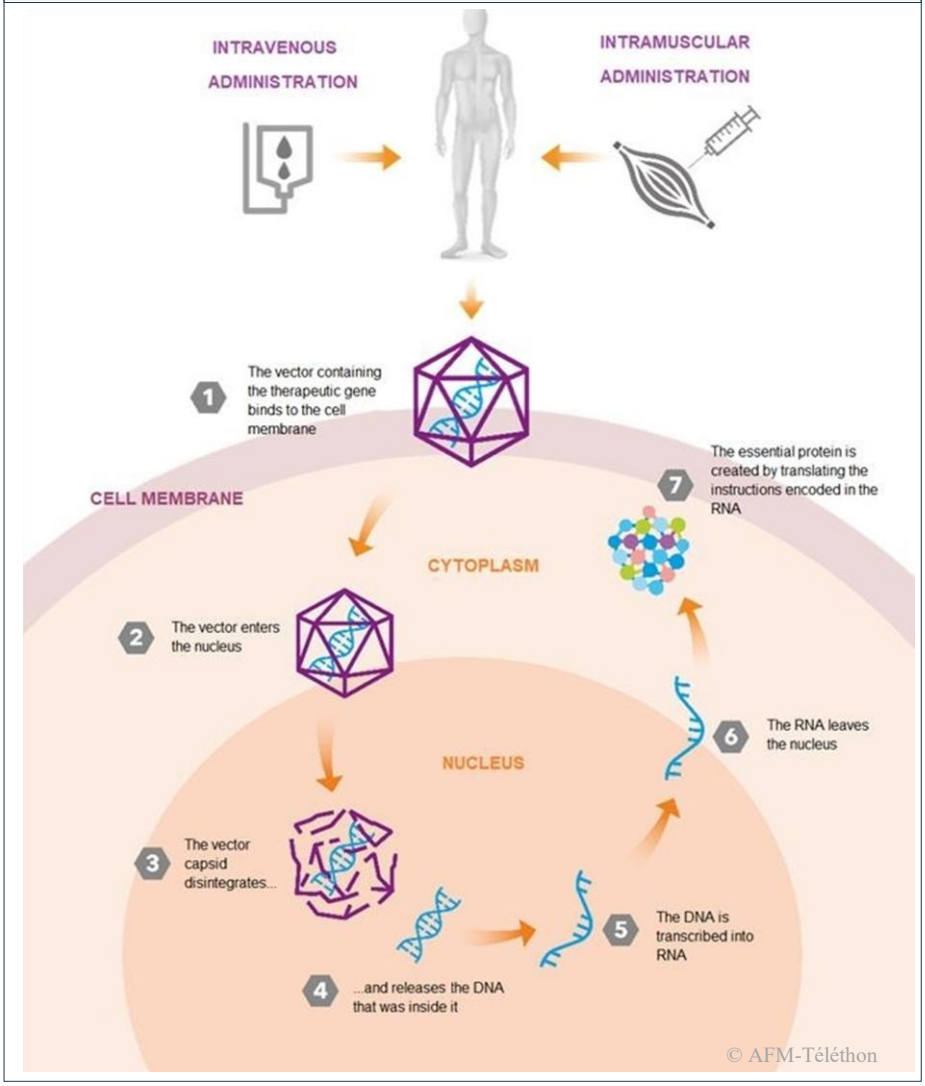
Phase II
Dose/effect

LGMD R1 (*CAPN3* – calpainopathy)

Gene therapy - a clinical trial on the horizon?

▪ Généthon is currently developing a gene therapy drug candidate (GNT0008/ATA-300) to replace the defective *CAPN3* gene in LGMD R1. So far, the later phases of preclinical development have been completed with very encouraging results in terms of the efficacy and safety of the product.
https://www.youtube.com/watch?v=1y-doAySl80 [video in French]

What is gene therapy?



*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.afm-telethon.fr/fr/termes/therapie-genique [page in French]

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 dysferlin, began in 2016 in two patients as part of the **IRB15-00669** clinical trial (NCT02710500) sponsored by Sarepta Therapeutics. The product was administered via intramuscular injection and did not cause any notable adverse drug reactions.

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 of SRP-6004 administered by systemic IV infusion in two ambulatory patients with LGMD R2 (dysferlinopathy).

*An **open-label trial** is a clinical trial in which the doctors and participants know what treatment is being administered.*

Phase I
Safety/tolerability

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

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

NCT05906251

LGMD R3 (*SGCA* - alpha-sarcoglycanopathy)

Gene therapy - SRP-9004

▪ In 2019, the results of the **SRP-9004-101 trial** conducted in six patients demonstrated that **SRP-9004** (scAAVrh74.tMCK.hSGCA), a gene therapy product developed by Sarepta Therapeutics, was well tolerated, restored alpha-sarcoglycan expression in muscle, and brought about a mild clinical improvement in some of the participants.

The evaluation continues

The **DISCOVERY (SRP-9004-102)** clinical trial was launched in the United States in 2025 with the primary objective of collecting more information on the safety and efficacy of SRP-9004 administered intravenously in four LGMD R3 patients.

Phase I
Safety/tolerability

SRP-9004-102 trial – LGMD R3

United States	4 (over 4 years old)	Not recruiting	Jan 2025 – March 2030 5 years of follow-up

NCT06747273

LGMD R4 (*SGCB* – beta-sarcoglycanopathy)

Gene therapy - SRP-9003

▪ Launched in 2018, the **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.

SRP-9003-101 trial – LGMD R4

Phase I
Safety/tolerability

Phase II
Dose/effect

United States	6 (4 to 15 years old)	Not recruiting	Oct 2018 – Feb 2027 7 years of follow-up

NCT03652259

▪ Interim results reported so far have shown that the therapy has been relatively well tolerated by the majority of the patients with mild side effects (vomiting, gastrointestinal pain, loss of appetite, etc.). A small number of patients have experienced more severe adverse drug reactions (hepatitis and significant dehydration) but these resolved after a few days with appropriate treatment.

Improvements in motor function and laboratory test results

▪ A few weeks after the treatment was injected, creatine kinase (CK) levels in the patients' blood decreased 10-fold, and beta-sarcoglycan (SGCB) levels measured in their muscles increased six-fold. The sarcoglycan protein complex was restored at the muscle fibre membrane. Motor assessments (NSAD) showed significant functional improvements (nearly three points more on average).

A proven outcome measure

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.

Confirmation with VOYAGENE

▪ Sarepta Therapeutics also launched **SRP-9003-102** (or VOYAGENE), an open-label trial conducted in six 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	6 participants (4 to 50 years old)	Not recruiting	Dec 2022 – Aug 2028 5 years of follow-up

NCT05876780

Moving to the next stage with EMERGENE

Sarepta Therapeutics also launched a phase III clinical trial in 2024 **(SRP-9003-301 or EMERGENE)** which is continuing to evaluate the efficacy of SRP-9003 in LGMD R4. The trial is no longer recruiting and is currently being conducted in 17 patients (ambulatory or non-ambulatory) over the age of four. Sarepta Therapeutics announced that it is on track to submit a marketing authorisation application to the US health authorities (Food and Drug Administration or FDA) in the second half of 2025.

Phase III
Efficacy

SRP-9003 (EMERGENE) trial – LGMD R4

Abroad (outside France)	17 (over 4 years old)	Not recruiting	Jan 2024 – Nov 2029 5 years of follow-up

NCT06246513

Sarepta Therapeutics. Press release 15 April 2025
Mendell, J. R. et al. Nat Med. 2024
Sarepta Therapeutics. Press release 16 January 2024
www.genesislgmd.com
www.lgmd.afm-telethon.fr/sarepta-programmes-lgmd-en-developpement/ [page in French]

LGMD R5 (*SGCG* – gamma-sarcoglycanopathy)

Gene therapy trial

▪ In early 2025, Atamyo Therapeutics, a spin-off of Généthon (a pharmaceutical company created by AFM-Téléthon), launched a new phase I/II clinical trial to test the safety and efficacy of **ATA-200**, an adeno-associated viral (AAV) vector carrying the *SGCG* gene (which is defective in LGMD R5). This gene therapy product, born out of research carried out by a team led by Isabelle Richard, LGMD expert at Généthon, is due to be evaluated in six ambulatory LGMD R5 patients (six and 12 years old) who will be monitored for five years.
Atamyo Therapeutics. Press release 12 November 2024

▪ This new multicentre trial has received approval to be conducted **in France, Italy and the United States.** In April and May 2025, two American patients were able to be treated with the drug candidate at the University of Florida (United States) thanks to funding from the DION Foundation. The trial has yet to start in Europe.

Phase I
Safety/tolerability

Phase II
Dose/effect

ATA-003-GSAR trial – LGMD R5

France and abroad	6 (6 to 12 years	Feb 2025 - Jan 2032 5 years of follow-up

NCT05973630

Gene therapy - the USA follows suit

▪ In 2025, the FDA gave Sarepta Therapeutics permission to launch **COMPASS** (SRP-9005-101), a new first-in-human phase I/II/III clinical trial that will evaluate the effects of a gene therapy product called **SRP 9005** in LGMD R5. This American multicentre trial will include 15 children and adults with the disease (ambulatory or non-ambulatory) and will be made up of two parts: a safety evaluation part, and an efficacy evaluation part. The patients will receive a single dose of the drug candidate and will be monitored for five years.
Sarepta Therapeutics. Press release 15 April 2025

COMPASS trial – LGMD R5

Phase III
Efficacy

United States

15
(over 4 years old)

Recruiting

May 2025 – March 2032
5 years of follow-up

NCT06952686

LGMD R9 (*FKRP*– dystroglycanopathy)

Gene therapy - first part of phase I/II completed 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. Sponsored by Atamyo Therapeutics, the trial is taking place **in France, Denmark and the United Kingdom**, and so far only the six patients included in the first part of the trial have received the treatment.

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.

The best dose - less is more

▪ After having evaluated the effects of two doses of the drug candidate (injection) in two different patient cohorts, Atamyo announced in April 2025 that it had completed the dose escalation phase of the trial and had determined the dose that gave the best results.

While both doses tested were well tolerated, a marked efficacy was observed in the patients treated with the lower dose. Improvements in functional and histological endpoints were noted in all of the patients, as well as a reversal of the decline usually observed in the natural history of the disease. At twelve months post-treatment, the patients':

- forced vital capacities (FVCs) had increased by 5% on average;
- NSAD scores had stabilised, and improved at 18 months;
- walking speeds had improved by 19% on average (10-metre walk test).

These improvements were maintained beyond 12 months. The lower dose was therefore selected for the further clinical development of ATA-100.

Rare Pediatric Disease Designation in the United States

The Rare Pediatric Disease Designation is granted by the FDA to a drug being developed if it can show that it can **prevent or treat a rare paediatric disease**, that is, a disease that is mainly found in children from birth to the age of 18, severely reduces life expectancy, and affects fewer than 1 in 200,000 people in the United States.

Obtaining this designation for ATA-100 in 2025 confirms its potential to provide a previously non-existent treatment option for children and adolescents with LGMD R9.

Mease, C. et al. Orphanet J Rare Dis. 2024.

Atamyo Therapeutics. Press release 3 April 2025

Atamyo Therapeutics. Press release 12 November 2024

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)

Aug 2022 – Oct 2030
5 years of follow-up

NCT05224505

Gene therapy - LION-101 to be evaluated in a second cohort

- **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 (a subsidiary of Bayer also known as AskBio), is currently taking place in the United States. It will include a total of 10 adults with LGMD R9.

In March 2025, after obtaining positive results regarding the safety and tolerability of the gene therapy product in the first cohort, the pharmaceutical company announced that it had received approval from the DSMB to continue its evaluation of LION-101 and determine its effects at a higher dose in a second cohort. Recruitment for this second cohort has already started.

Asklepios BioPharmaceutical. Press release 7 March 2025.

A **DSMB** (data safety monitoring board) is a group of experts, independent of the sponsor and investigators, who periodically examine the interim results of a clinical trial once it is underway.

They ensure the integrity of the trial and that the benefit/risk ratio for the participants remains favourable to the continuation of the trial throughout its duration.

Brun-Buisson, C. M/S : médecine sciences. 2005. [article in French]

LION-CS101 trial – LGMD R9

Phase I
Safety/tolerability

Phase II
Dose/effect

United States	10 (18 to 65 years old)	Recruiting	May 2023 – Dec 2028 1 year of follow-up

NCT05230459

Pharmacotherapy - ribitol continues its journey

- 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.*

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.

MLB-01-003 trial
LGMD R9 - Ribitol

Phase II
Dose/effect

United States	14 (12 to 55 years old)	Not recruiting	Feb 2021 – Nov 2026 5 years of follow-up

NCT04800874

Ribitol now in phase III

- Following positive and durable interim results (favourable safety and tolerability, decrease in serum CK levels, improvements in motor function) from this phase II trial, an international, phase III, multicentre trial of ribitol (**MLB-01-005** or **"FORTIFY"**) was launched in 2023, enabling the safety and efficacy of long-term oral ribitol to be evaluated on a larger scale (112 participants). Recruitment has now been completed and the results of the interim analysis are due to be released this year.

BridgeBio. Press release 20 February 2025
www.lgmd.afm-telethon.fr/nouvelles-de-mlbio-solutions-sur-le-bbp-418-ribitol/ [page in French]

Phase III
Efficacy

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

Abroad (outside France)	112 (12 to 55 years old)	Not recruiting	April 2023 – July 2027 3 years of follow-up

NCT05775848

Pharmacotherapy - an uncertain future for sevasemten

▪ **Sevasemten** (or **EDG-5506**) is an orally-administered small molecule developed by Edgewise Therapeutics to prevent muscle wasting and fibrosis.

It limits the recruitment of fast-twitch muscle fibres, which are particularly affected in dystrophies, thus preventing their degradation. It is being tested primarily in Duchenne muscular dystrophy but is also undergoing trials in other myopathies, including LGMD.

▪ In late 2022, Edgewise Therapeutics launched the phase II **"DUNE" trial** in Denmark to evaluate the effect of EDG-5506 on biomarkers of muscle damage following exercise in nine patients with LGMD R9, nine patients with BMD and three patients with McArdle disease.

▪ In early 2024, the pharmaceutical company reported that although sevasemten had been 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. Further analyses were due to be carried out, but the results have not yet been released.

Edgewise Therapeutics. Press release 9 May 2024

www.edgewisetx.com/science/211

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.

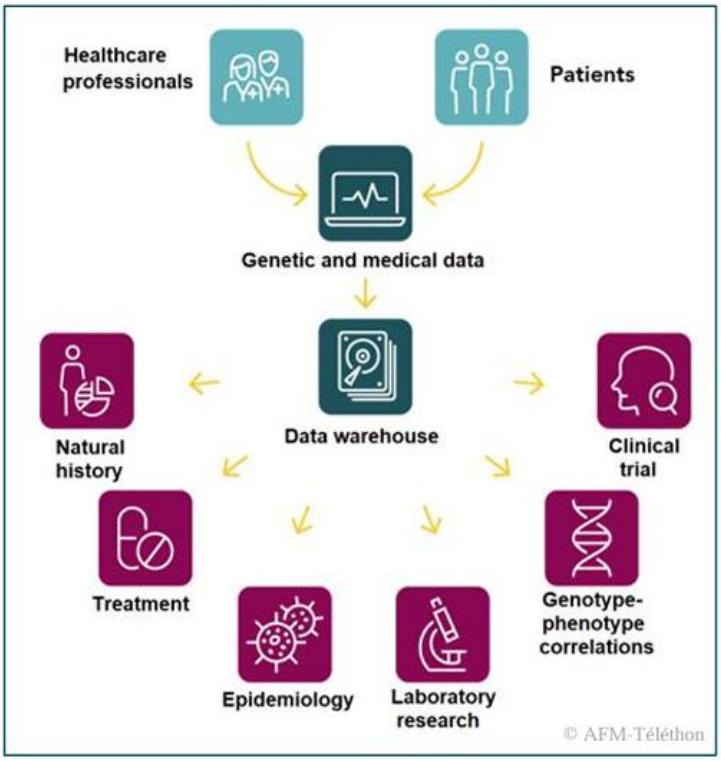
Different types of observational studies
▪ **Cross-sectional:** a type of study that collects data from subjects at a single point in time (frequency, morbidity, risk factors, etc.).
▪ **Prospective:** a type of study that follows participants over a period of time, like in natural history studies.
▪ **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.

LGMD patient registries

▪ Medical data warehouses and 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 were launched in January 2025:

- 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).

www.afm-telethon.fr/fr/vivre-avec-la-maladie/l-entrepot-de-donnees-de-sante/la-collecte-de-donnees-sur-les-calpainopathies [page in French]

- 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).

www.afm-telethon.fr/fr/vivre-avec-la-maladie/l-entrepot-de-donnees-de-sante/la-collecte-de-donnees-sur-les-0 [page in French]

Ten international LGMD registries

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

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)*

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/

Observational studies in LGMD

A better understanding of the prevalence of LGMD subtypes

- Next-generation sequencing (NGS) conducted between 2017 and 2018 in 2,372 patients from 21 countries outside Europe (Latin America, Asia, Middle East, South Africa) with limb-girdle muscle weakness revealed that 225 of them (9%) had LGMD.

▪ LGMD R2 was the most common subtype (27%), followed by LGMD R1 (23%), LGMD R3 and R9 (9%), LGMD R7 (6%), and LGMD R4, R5 and R12 (4%). LGMD R6 was the least common subtype (just one case in Brazil).
Amongst the 261 patients with limb-girdle muscle weakness who were able to be diagnosed by NGS, 86.4% had LGMD and 13.8% had Pompe disease (caused by mutations in the *GAA* gene). These results advance current knowledge on the prevalence of the various LGMD subtypes around the world, but also highlight the benefit of including the *GAA* gene in NGS panels in the event of limb-girdle muscle weakness.
Bevilacqua, J. A. et al. Front Genet. 2024.

An LGMD-specific PROM

What is a PROM?
Patient-Reported Outcome Measures, or PROMs, evaluate quality of care from the **perspective of patients.** Unlike clinical evaluations conducted by healthcare professionals, PROMs record experiences and opinions directly from patients regarding their health using **questionnaires**, enabling the collection of important information that cannot be collected by traditional clinical measures. They can also be used to evaluate the impact of potential therapies in clinical trials.
www.has-sante.fr [website in French]

▪ There are currently no widely-used PROMs that are specific to LGMD. The **LGMD Health Index** (LGMD-HI) is a measure recently developed by researchers from the GRASP-LGMD consortium that aims to meet this need.
▪ It was developed from a study involving 163 participants and is comprised of 97 items split into 15 categories, including ambulation, hand function, fatigue and emotional health. It shows significant differences in scores amongst patients based on their ambulation status, but not on their sex, employment status or LGMD subtype. It provides information on disease severity and takes approximately 15 minutes to complete.
The researchers concluded that this disease-specific PROM was able to account for the diversity seen in LGMD; it reliably measures disease burden across the multiple subtypes. However, the overrepresentation of *FKRP* mutations (57%) and Caucasian patients (92%) in the cohort used to evaluate the LGMD-HI could limit its applicability to the entire LGMD population.
Stouffer, J. A. et al. Neuromuscul Disord. 2024.

Sarcoglycanopathies in Russia

▪ Genetic and clinical data from 49 Russian patients with sarcoglycanopathies was retrospectively analysed in order to determine the spectrum of mutations and the prevalence of these diseases in Russia.
▪ The analyses found that 35 of these patients (71%) had genetic variants in the *SGCA* gene (LGMD R3), 6 (12%) had genetic variants in the *SGCB* gene (LGMD R4), 6 (12%) had genetic variants in the *SGCG* gene (LGMD R5) and 4% had genetic variants in the *SGCD* gene (LGMD R6). Over 30 variants were identified, including six that had never been reported before. The researchers estimated the incidence of sarcoglycanopathies in Russia to be one in 4,115,039, which is lower than elsewhere in the world.
Bulakh, M. et al. Gene. 2024.

This is not DMD

▪ Duchenne muscular dystrophy (DMD) is the most common type of muscular dystrophy and is typically clinically diagnosed in boys and men by the presence of calf hypertrophy, Achilles tendon contractures in early childhood, leg muscle weakness, and difficulties in walking, standing or sitting. Depending on their subtype, LGMD patients can also present with these clinical manifestations and may be misdiagnosed with DMD as a result.

▪ Researchers in India demonstrated this by conducting genetic testing in 961 boys and men (two to 35 years old) with clinically suspected DMD.

LGMD detected in most of the misdiagnosed patients

▪ The results indicated that 816 of these patients did indeed have DMD, but the remaining 145 patients had other types of muscular dystrophy. Over 75% of these 145 patients had LGMD (D5, R1-R6, R17 and R22), with LGMD R4 being the most common subtype (28%). Other diseases such as Emery-Dreifuss muscular dystrophy and *LAMA2*-related congenital muscular dystrophy (4%) were also detected.

▪ The researchers also identified 44 new variants in the non-DMD patients, including six in LGMD R2 and six in LGMD R17.

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

▪ This study highlighted the degree of phenotypical proximity between some DMD and LGMD patients, and the importance of genetic testing (including NGS) to be able to make the correct diagnosis and implement the right care.

Karthikeyan, P. et al. Mol Genet Genomic Med. 2024.

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 (natural history)
LGMD R3, R4 and R5

Abroad (outside France)	241 (over 4 years old)	Recruiting	April 2021 – April 2030 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

United States

100 (all ages)

Not 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.

Data collected on 77 LGMD R9 patients was the subject of an initial analysis conducted in 2023 which showed that pain interference (the extent to which pain hinders engagement in activities in daily life, sleep and enjoyment in life) levels in these patient were generally not greater than in the general population. The investigators also observed that fatigue and pain interference were positively correlated and that both increased over time. Further analyses are pending.

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

*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.*

Prospective observational study
Dystroglycanopathies

United States

190 (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 (including for decision-making in clinical trials) on a wide range of LGMD phenotypes in order to determine whether these measures are reliable and able to be used in individuals with different phenotypes. The study is being conducted in **80 patients** from nine sites in the United States and one in Europe.

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

United States and United Kingdom	80 (4 to 65 years old)	Not recruiting	June 2019 – June 2025 1 year of follow-up

NCT03981289

- Two other GRASP-LGMD consortium studies with the same goal of preparing for future clinical trials are also currently underway (**GRASP-01-003** - LGMD R1, and **GRASP-01-005** - all LGMD subtypes).

GRASP-01-003 study (natural history)
LGMD R1

United States and Europe	100 (12 to 50 years old)	Recruiting	Jan 2024 – Aug 2028 2 years of follow-up

NCT05618080

GRASP-01-005 study (natural history)
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 2025 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 **80 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. The study is still ongoing and is still recruiting patients.

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.

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

China	450 (over 10 years old)	Enrolling by invitation	July 2021 – Dec 2026 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

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

CALNATHIS - clinical course of muscle function

- In 2024, the AP-HP **in France** launched a natural history study involving **25 adults** with LGMD R1 monitored by the specialist neuromuscular disease centre at Hôpital Henri Mondor.
- 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

The value of quantitative MRI

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.

Quantitative MRI (qMRI) is a relatively new, non-invasive technique that is able to evaluate muscles in great detail (fat percentage, water content, etc.), including damage, inflammation and degeneration in neuromuscular diseases.

- German researchers evaluated the ability of qMRI to identify muscle changes in **LGMD R1** patients over time. They collected clinical data (muscle strength, walking ability, performance of activities of daily living, etc.) from **13 patients** and performed MRI scans of their leg muscles.
- The qMRI data collected at the initial assessment and 12 months later was significantly different, particularly for the fat fraction of certain muscles (biggest increase observed 10% to 50%). Muscle degeneration was also observed in the second clinical assessment, with some results significantly correlating with the qMRI values.

Forsting, J. et al. NMR Biomed. 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, is aiming to confirm and refine the results of the **Jain COS study** (completed in 2018), identify the most relevant outcome measures (biomarkers, scales, tests, etc.) for future clinical trials in dysferlinopathies (including LGMD R2) and characterise the progression of the disease.
- The study is taking place in France at the Institut de Myologie (Paris) and 15 other locations around the world.
- Its target of 200 participants has been reached. The results of the study, which was due to be completed in 2024, have yet to be released.

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

COS2 study (natural history) – LGMD R2

France and abroad	200 (over 10 years old)	Not recruiting	Sept 2012 – March 2024 2 years of follow-up

NCT01676077

An alternative way of screening for respiratory problems

▪ Dysferlinopathy can cause respiratory muscle weakness. However, the monitoring of respiratory function is sometimes made difficult by a lack of access to a spirometer and/or respiratory specialists.

A team of researchers and healthcare professionals looked at the possibility of using an alternative method (the **PUL scale**) to indirectly evaluate respiratory function in dysferlinopathy.

The PUL (Performance of the Upper Limb) scale measures upper limb function in people with muscular dystrophies.

Composed of 22 items that measure the performance of everyday tasks (picking up an object, pressing a switch, etc.) and evaluate all moving parts of the arm (shoulder, elbow, wrist, fingers), **the PUL scale assesses motor function (muscle strength, dexterity, etc.) over time**, from children who are still able to walk to adults with very limited mobility.

A strong correlation

▪ Using data from 193 LGMD R2 patients participating in the Jain COS study, the investigators were able to observe a strong correlation between the PUL test and reduced respiratory function (FVC), which was present regardless of walking ability, age or sex.

▪ This test can be added to the list of predictors of reduced respiratory function (aging, weight gain, low NSAD scores).

Borland, H. et al. Neuromuscul Disord. 2024.

Chronic pain - a sign of the disease

▪ A team from the Institut de Myologie (Paris) reported the case of a **52-year-old woman** who had been suffering from permanent, generalised muscle pain for four years. This pain was aggravated by exercise and associated with joint pain. She also reported fatigability in her arms, which she struggled to keep raised in the air.

▪ A muscle biopsy revealed a significant decrease in dysferlin expression, and a complete lack thereof in some fibres. Genetic testing confirmed the diagnosis of dysferlinopathy.

This late-onset, painful and unusual form of dysferlinopathy further increases the clinical heterogeneity seen in these diseases.

Sanchez-Casado, L. et al. Neuromuscul Disord. 2025.

LGMD R5 (*SGCG* – gamma-sarcoglycanopathy)

A new natural history study preparing to start in France

▪ Sponsored by Atamyo Therapeutics, an observational study of LGMD R5 (**ATA-002-GSAR**) taking place in France (Garches) and Tunisia is due to start soon. It will include **50 ambulatory children and adults** (six to 35 years old). The study's objectives are to characterise the course of the disease over two years and to determine the best outcome measures.
The follow-up will include assessments of respiratory and motor function (walking, going up and down stairs, etc.), and imaging (MRI) of the lower limb muscles. Recruitment has not started yet.

ATA-002-GSAR study (natural history) – LGMD R5

France and Tunisia	50 (6 to 35 years old)	Not yet recruiting	Nov 2024 – May 2027 2 years of follow-up

NCT06210672

Characteristics of LGMD R5 in Bulgaria

▪ LGMD R5 is the most common myopathy amongst the Romani people of Bulgaria, with a prevalence higher than that of DMD. A team analysed the clinical and genetic characteristics of the largest group of Bulgarian LGMD R5 patients (**57 patients**, including 29 men and 28 women), all of whom had the same C283Y mutation in the *SGCG* gene.

Great clinical variability

▪ The natural history of the disease in these patients was similar to that of another group of travellers previously observed with the same mutation (onset of symptoms between the age of two and 13 years old or six years old on average, difficulty walking and climbing stairs, frequent falls, tendency to walk on their tiptoes).
▪ Their arm and thigh muscles were affected before their torso and neck muscles. Distal muscle strength (forearms, hands, calves and feet) was preserved even in advanced stages of the disease.
▪ Despite them all having the same genetic mutation, the researchers noted significant variations in the course of the disease between the families studied, but also within the same families, including between siblings of the same sex.

Differences between sexes

However, the disease appeared earlier in the men, with a more rapid progression and an earlier onset of walking difficulties.
This study provides further data to support the existence of epigenetics factors that modify the severity of the disease.
Taneva, A. et al. Genes (Basel). 2024.

LGMD R7 (*TCAP*)

Brazilian patients under the magnifying glass

▪ A Brazilian team studied the cases of 41 patients monitored at 13 Brazilian health centres who all had the same mutation in the *TCAP* gene (c.157C>T/(p.Gln53*)). After performing a literature review, they found 119 more patients from around the world with this mutation. Their analyses found that the disease was more severe in men. Furthermore, the highest numbers of LGMD R7 patients were found in Brazil (39 families), China (35 families) and Bulgaria (12 families), suggesting founder effects in these populations.

Gaviraghi, T. et al. Clin Genet. 2024.

*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 R9 (*FKRP*– dystroglycanopathy)

Reliability of clinical outcome measures

▪ In collaboration with the GRASP-LGMD consortium, ML Bio Solutions launched a natural history study (**MLB-01-001**) at the end of 2019 prior to their BBP-418 trial involving 101 LGMD R9 patients aged 10 to 64 years old. The results of this study (which took place in the United States and Denmark) were published this year.

A validation of existing outcome measures

▪ The objective of this study, conducted in 101 LGMD R9 patients (ambulatory or non-ambulatory) aged 10 to 64 years old, was to evaluate the validity and reliability of eight standard clinical outcome measures (NSAD, PUL, TUG, 9HPT, etc.) in order to help monitor the progression of the disease, guide patients in their choice to be included in clinical trials, and measure the effects of candidate drugs in trials.

Every measure has its uses

▪ The results indicated that all of the outcome measures tested were highly correlated (except 9HPT) and had excellent repeatability. The investigators also showed that no single outcome measure was able to provide a representative measurement of a patient's motor function across all abilities and ages.

NSAD and PUL in particular confirmed their sensitivity and suitability for measuring motor function in patients across the disease progression spectrum.

Medical decision support

▪ By quantifying the motor function of patients at different ages and stages of the disease, clinical outcome measures also provide objective data to support the implementation of certain medical interventions. For example, the use of technology to support safe transfers should be discussed when a patient starts to take longer than seven seconds to complete the timed 10-metre walk test.

Alfano, L. N. et al. Ann Clin Transl Neurol. 2025.

Endpoints for future 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.
www.institut-myologie.org/en/recherche-clinique/essais-en-cours/limb-girdle-muscular-dystrophies/

GNT-015-FKRP study (natural history) – LGMD R9

France and abroad	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 imaging

▪ 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 – Aug 2026 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.

▪ In 2021, intermediary results from the study confirmed 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 2026 3 years of follow-up

NCT05206617

LGMD R27 (*JAG2*)

New patients identified

▪ Three years after it was first described in 23 patients from 13 families (including one French patient) in 2021, LGMD R27 was detected in five new individuals aged five to 14 years old (three from Australia and two from Russia). Those from Australia were of European or Pakistani descent, and those from Russia were of Tajikistani descent. Their clinical manifestations and disease characteristics were similar to those of other LGMD R27 patients previously described:

- early childhood onset;
- rapid disease progression;
- facial, neck and proximal limb muscle weakness;
- loss of independent ambulation between the ages of six and eight years old;
- contractures of the elbows, wrists, knees and/or ankles.

Four of the genetic variants identified had never been reported before.

Dofash, L. et al. Neuromuscul Disord. 2024; Nikitin, S. et al. Front Pediatr. 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.

LGMD R2 (*DYSF* - dysferlinopathy)

Exon skipping works *in silico*

▪ A Franco-Canadian team explored the applicability of exon skipping induced by antisense oligonucleotides in dysferlinopathies.

Exon skipping is a treatment approach which encourages the cellular machinery to "skip over" one or several exons with a pathogenic mutation and ignore them when producing the protein coded for by the gene. The resulting protein is shorter but functional.

Using data from the Universal Mutation Database for Dysferlin (UMD-DYSF), researchers evaluated the theoretical possibility of excluding genetic mutations from the *DYSF* gene for all pathogenic variants reported in dysferlinopathy patients, all while preserving the gene's reading frame and therefore its ability to produce a functional protein.

*An **antisense oligonucleotide (ASO)** is a fragment of RNA that is usually synthesised in a laboratory which can bind specifically to naturally-produced messenger RNA molecules. The nucleotide sequence of antisense oligonucleotides is complementary to that of the messenger RNA molecules which it targets. They can therefore modify messenger RNA (skip or incorporate exons by intervening during its maturation stage (splicing)).*

Dozens of possible configurations

▪ They identified 61 theoretically applicable exon skipping strategies which have the potential to address 90% of reported variants. However, the dysferlin protein produced would be truncated, therefore an improvement in its function would not be guaranteed.

▪ This *in silico* study showed that exon skipping could be a potential treatment option in dysferlinopathies, however, its efficacy remains to be demonstrated in animal models and in humans.

Leckie, J. et al. Cells. 2025.

Exon 27 - a new target for antisense therapy

- Antisense oligonucleotides have been successfully used in several *in vitro* models of LGMD R2 to induce exon skipping (namely exon 8, 9, 19, 21, 25, 28-30, 34 and 38 skipping).
- In another study, the same Canadian team that had demonstrated the possibility of using this method for exons 28 and 29 attempted to prove its feasibility for exon 27, and its ability to restore the disrupted reading frame.
- They therefore created an antisense oligonucleotide targeting exon 27 in patient-derived muscle cells with a mutation that led to exon 26 exclusion, a frameshift in the *DYSF* gene and no detectable levels of the dysferlin protein.

Partial dysferlin restoration

- Analysis of the cells treated showed up to 92% exon 27 skipping and dysferlin levels between 39 and 51% of normal expression. The researchers also noted functional membrane repair, improved myotube fusion and better cellular metabolism (increased activity, reduced cell death, etc.).
- This study was the first to demonstrate the efficacy of exon 27 skipping in restoring a functional dysferlin protein in cells taken from LGMD R2 patients. It was also the first to report the positive effects of antisense therapy on cytotoxicity, cell vitality and apoptosis in these cells.

__Apoptosis__ is a form of programmed cell death. It is an orderly process with several stages which culminate in the whole cell and its contents being disposed of without the surrounding cells being damaged. Apoptosis is in constant balance with cell multiplication in order to ensure cell renewal.

The prospect of mini-dysferlin

- These results, which need to be confirmed in *in vivo* models, suggest that the regions of the dysferlin protein coded for by exons 26 and 27 are not essential for cell repair, or that their function can be compensated for by other domains of the protein. This information could help guide the development of exon skipping strategies which, like micro-dystrophin in DMD, would preserve the essential functions of dysferlin in a shorter form, all while bypassing various pathogenic mutations.

Did you know?

Proof of concept established by Généthon

In 2010, a team from Généthon, with the support of AFM-Téléthon, demonstrated the possibility of using a truncated version of the *DYSF* gene to produce a partially functional **mini-dysferlin** in mouse models of dysferlinopathy. The animals treated recovered the ability to repair muscle cell membranes.

Krahn, M. et al. Sci Transl Med. 2010.

https://www.genethon.fr [document in French]

Anwar, S. et al. Mol Ther Nucleic Acids. 2025.

Drug repurposing - the potential of bazedoxifene

What is bazedoxifene?
Bazedoxifene is a selective oestrogen receptor modulator. It binds to oestrogen receptors and is used as a hormonal treatment for oestrogen deficiency symptoms associated with menopause.

▪ Teams from I-Stem and Généthon led by Xavier Nissan and Isabelle Richard, in collaboration with the Institut de Myologie, set out to determine whether drugs that are already known to be beneficial in other diseases could relocate defective dysferlin in the membrane and therefore improve the resistance of muscle cell models of LGMD R2.

A more resistant cell membrane

▪ The researchers therefore evaluated the effects of over 2,200 compounds. Only two (**saracatinib** and **bazedoxifene)** significantly reduced cell death.

Saracatinib is an experimental drug initially developed to treat cancer. It inhibits certain proteins from the kinase family.

▪ While saracatinib appeared to be effective in cells in which dysferlin was expressed but was absent from the sarcolemma, bazedoxifene also seemed to be effective in cells not producing the protein. The results suggested that saracatinib had an effect on protein folding, while bazedoxifene seemed to induce autophagy (the process by which a cell breaks down unwanted substances in its cytoplasm). In both cases, these changes seemed to make cell membranes more resistant to mechanical stress, notably through improved repair abilities and cell survival.

A new area of research

▪ These discoveries provide therapeutic alternatives to other techniques being studied in LGMD R2 (gene therapy and exon skipping). Furthermore, the idea of compensating for dysferlin deficiency by pharmacological means has already shown its relevance in LGMD R2 with the use of galectin-1. I-Stem and Généthon have also demonstrated the efficacy of small molecules givinostat and bortezomib in LGMD R3.

▪ These avenues are worth exploring, especially since drugs like bazedoxifene could improve the efficacy of gene therapy by inducing autophagy.

Bruge, C. et al. British Journal of Pharmacology. 2025.

Drug repurposing *refers to the process of discovering new therapeutic uses for existing drugs (usually ones that have already been granted marketing authorisation).*
Martinat, C. et al. Médecine/sciences. 2018. [article in French]

Genome editing - *in vitro* proof of concept

▪ In Germany, a team led by Simone Spuler (principal investigator of the bASKet trial which has not yet started) attempted to demonstrate the feasibility and efficacy of genome editing in dysferlinopathies.

Focus on a particular mutation

▪ They focused specifically on correcting a mutation in exon 44 in the *DYSF* gene (c.4872_4876delinsCCCC) which shifts the reading frame and prematurely stops the synthesis of dysferlin, resulting in a non-functional protein.

*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.

▪ By using the CRISPR/Cas9 system on muscle stem cells taken from two LGMD R2 patients with the mutation in question, the researchers managed to insert an additional nucleotide upstream of the mutated genetic sequence in the *DYSF* gene.

Functional dysferlin produced

▪ Analyses showed that this insertion led to the restoration of the gene's reading frame and the production of a full-length dysferlin protein. Although it had four amino acids that differ from its usual structure, the protein produced appeared to be functional with a distribution in the cell identical to that of the non-mutated version.

Effective in muscle

▪ In order to test the therapeutical potential of gene editing, the researchers used the same method on muscle stem cells taken from mouse models of LGMD R2 with the c.4872_4876delinsCCCC mutation. Transplantation of the cells corrected *in vitro* back into the muscle of these mice (autologous transplantation) restored dysferlin expression and muscle regeneration.

▪ Although this therapeutic approach is not feasible for all *DYSF* gene mutations, it is justified in the event of frequent founder mutations, where many patients could benefit from targeted genome editing.

▪ These results confirm the feasibility of this method in LGMD and underpin the importance of the upcoming bASKet clinical trial which is based on this research.

Escobar, H. et al. Nat Commun. 2025.

LGMD R3 (*SGCA* - alpha-sarcoglycanopathy)

Pharmacological profile of C17

▪ LGMD R3 is usually caused by missense mutations that produce a characteristic, misfolded, defective alpha-sarcoglycan protein which is detected and destroyed by certain cellular enzymes.

▪ In 2022, a team led by Dorianna Sandonà at the University of Padua in Italy (with the support of AFM-Téléthon) demonstrated the potential of repurposing C17 to treat LGMD R3. C17 is a small molecule used to correct folding defects in the CFTR protein in cystic fibrosis. They observed that injecting C17 into mouse models of LGMD R3 restored the sarcoglycan complex and improved sarcolemma integrity. Muscle strength in the mice treated returned to a level that was almost identical to that of the healthy controls.

Did you know?

Drug repurposing

Repurposing a drug that has already been approved for use in another disease can help accelerate the development of treatments.

- This year, the same team (supported once again by AFM-Téléthon) conducted a detailed study of C17's pharmacological properties, in particular its absorption, distribution, metabolism and excretion.
- Data from mouse models of LGMD R3 treated with C17 for five weeks (intraperitoneal injections) showed that the molecule:

- was safe;
- reached the most vascularised organs first (liver, kidneys, spleen) before being redistributed to the whole body via the bloodstream;
- was still detectable in skeletal muscle and the heart 48 hours after injection;
- seemed to be metabolised in the small intestine;
- was excreted through urine and faeces.

- The researchers also confirmed the results obtained in 2022, with restoration of the sarcoglycan complex and muscle strength in the mice treated.

Benetollo, A. et al. Biochem Pharmacol. 2025.

LGMD R7 (*TCAP*)

Proof of concept for gene therapy

- One of the characteristics of LGMD R7 patients is the abnormal distribution of their mitochondria in their cells. The cause of this phenomenon is still unknown, although it is also observed in other LGMD subtypes.
- Chinese researchers, whose previous research had highlighted defective mitophagy in cells taken from a fish model of LGMD R7, attempted to confirm these results, determine the pathological mechanisms of the disease and evaluate the effects of gene therapy.

***Mitochondria** are the powerhouses of the cell. Their respiratory chain provides energy for the cell to use. The number of mitochondria in a cell is variable and depends on the cell's energy needs, with numbers ranging from a few hundred to nearly a million. Muscle fibres, which have a high energy demand, contain several thousand mitochondria.*

Disorganisation of the cytoskeleton

- Their results indicated that telethonin (a protein coded for by the *TCAP* gene) combines with desmin and maintains its stability. The absence of telethonin leads to the collapse of the desmin cytoskeleton. This in turn causes disorganisation of the mitochondrial network, leading to mitochondrial dysfunction and dislocation.

Positive effects of gene therapy

- By using gene therapy, the researchers were able to introduce a non-mutated copy of the *TCAP* gene into the muscle cells of mouse models of LGMD R7. The mice treated showed evidence of restored telethonin expression, improved mitochondrial organisation, and a rebalancing of proteins associated with cellular respiration. Physical tests revealed an increase in endurance in the mice. Gene therapy is therefore well tolerated and induces durable physiological and functional improvements in animals models.
- Although this study is the first to publish results showing the potential of gene therapy in LGMD R7, this approach is also being explored by a team from the Nationwide Children's Hospital in the United States.

Gushchina, L. et al. Proceedings from Muscular Dystrophy Association Clinical & Scientific Conference 2025 *Lv, X. et al. Brain. 2024.*

LGMD R9 (*FKRP*– dystroglycanopathy)

Ribose and ribitol - effect on metabolism

▪ A team led by Marcela Cataldi in the United States was the first to demonstrate the effectiveness of ribitol in restoring alpha-dystroglycan function in mice. They also investigated the effect of ribitol and ribose (a precursor of ribitol) on the metabolism of muscle cells in a mouse model of LGMD R9.

Comparable efficacies, different impacts

▪ Even though both of the molecules showed that they were able to restore the synthesis of matriglycan, a polysaccharide that links alpha-dystroglycan to extracellular matrix proteins (particularly laminin), they did not have the same effect on metabolism.

While ribitol increased lipid metabolism levels (which were reduced in the untreated mice), ribose significantly increased levels of advanced glycation end products (proteins or lipids that become impaired after exposure to sugars and potentially toxic).

▪ These results suggest that ribitol is more effective at restoring normal metabolism and that glycation status should be monitored with long-term ribose use in clinical trials.

Did you know?

Two potential treatments

Ribitol is a drug candidate **currently undergoing trials** for LGMD R9 whose interim results have been positive. Its use in combination with gene therapy has even shown a synergistic effect in animals which increases its therapeutic efficacy.

▪ **Ribose**, on the other hand, has been tested in one patient with LGMD R9 and was well tolerated. It led to a decease in CK levels and a significant increase in the amount of ribitol in some 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.

Cataldi, M. P. et al. Sci Rep. 2025 *Thewissen, R. M. J. et al. JIMD Rep. 2024*

Gene therapy - two is better than one

▪ Researchers from the Nationwide Children's Hospital in the United States looked into the possibility of using gene therapy to not only prevent muscle damage in patients with muscular dystrophy, but to reverse disease and rebuild muscle mass too, particularly in those with more advance stages of disease.

Two genes, two actions

▪ The researchers intramuscularly injected one-month-old mouse models of LGMD R9 with a gene therapy product that constituted an AAV vector containing two genes, namely the ***FKRP*** gene to compensate for the genetic mutation and to prevent further muscle damage, and the ***FST*** gene (the **follistatin** gene) to promote muscle growth and reverse the loss in strength.

Did you know?

A muscle growth regulator

Follistatin is a protein that induces muscle growth. It binds to and inhibits myostatin (another protein that causes a decrease in muscle growth and strength) so that it can no longer interact with its receptors on the surface of muscle cells.

Muscle gains

▪ The results of tests completed six months post-injection showed that the mice treated were able to develop muscle mass and strength that exceeded that of the healthy controls. And while the untreated mice with the disease had a 60% average decrease in endurance on walking tests, the endurance of the treated mice was similar to that observed in the healthy controls.

▪ Furthermore, the two genes seemed to act **synergistically** (the expression of each of the therapeutic genes appeared to be amplified compared to when they were administered separately).

These results show that dual *FKRP/FST* gene therapy can overcome loss of ambulation by simultaneously stopping the progression of the disease and improving muscle strength.

Advantageous in more ways than one

▪ Follistatin gene therapy is not new. It has already obtained encouraging results in other neuromuscular diseases (BMD, inclusion body myositis, etc.). The combination of its safety and beneficial effects with those of a gene therapy targeting the pathogenic mutation is therefore particularly attractive. The *FST* gene is also relatively small, making it a good candidate for a dual gene therapy approach.

Lam, P. et al. Mol Ther. 2024.

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 R2 (*DYSF* - dysferlinopathy)

Better understanding the effects of corticosteroids

▪ Dysferlinopathies are characterised, among other things, by a pronounced inflammatory phenotype, which includes the infiltration of immune cells into certain muscles. For this reason, glucocorticoids (anti-inflammatory drugs) have been used in the past to treat LGMD R2. However, despite their positive effects on muscle in patients with DMD and other myopathies, these drugs have been shown to worsen symptoms in some LGMD R2 patients.

▪ A team from the University of Western Australia wanted to understand the mechanisms involved in the response to glucocorticoids in dysferlinopathies. The researchers evaluated the effects of dexamethasone administered for four to five weeks in mouse models of LGMD R2.

The complement system *is a part of the immune system that helps defend the body against pathogens via activation of a local inflammatory response.* Daugan, M. et al. Medecine Sciences: M/S. 2017. [article in French]
www.msdmanuals.com

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.

▪ Analysis of the muscle fibres of the mice treated showed prolonged activation of genes involved in the immune response, including the impaired expression of complement- and inflammasome-related genes, and increased lipid and glycogen deposition in the muscles analysed. These cellular changes have the potential to damage muscles, possibly through the pathological swelling of cells that can lead to cell death (oncosis).

▪ These findings provide new directions for research which may eventually enable dysferlinopathy patients to benefit from effective corticosteroid therapy, a treatment that has already been shown to be beneficial in several other neuromuscular diseases.

Lloyd, E. M. et al. Skelet Muscle. 2024.

Inflammasomes *are protein complexes of the innate immune system which are responsible for regulating inflammatory responses and cell death induced by the detection of pathogens/injury.* Jamilloux, Y. et al. médecine/sciences. 2013. [article in French]
www.insb.cnrs.fr [page in French]

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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/latest-news