Vol 2 / Issue 1

LGMD News

Uniting the Limb-Girdle Muscular Dystrophy Community

What's on the Horizon for LGMD2A/R1?

Coalition to Cure Calpain 3 is Actively Pursuing Innovative Approaches to Curing LGMD2A/R1

JOHN WALTON MUSCULAR DYSTROPHY RESEARCH CENTRE
A Leader for LGMD

AFM-TÉLÉTHON AND GÉNÉTHON
Two Major Players in an Ongoing Medical Revolution

JOURNEY

We welcome you to join our Journey...

Journey is a clinical outcomes assessment study, also referred to as a natural history study. Journey studies the natural progression of the disease and how it affects the muscles, lungs, and heart over a period of time (~3 years). The study does not involve the use of an investigational study drug. Individuals affected with Sarcoglycan Limb-girdle muscular dystrophy are invited to participate.

The Journey to uncover your potential treatment options

Currently there are no therapies for individuals with Limb-girdle muscular dystrophy. Participation will provide you access to highly experienced clinical trial physicians and clinicians with expertise in your condition and knowledge about future drug therapy research. Your participation in Journey will not hinder your ability to participate in future clinical studies, including those with investigational study drugs.

Who may be eligible

- Male or Female
- Age 4 years and older
- Genetic diagnosis of LGMD2E/R4, LGMD 2D/R3, or LGMD2C/R5

*Other inclusion/exclusion may apply and will be discussed with a study doctor at screening.

Journey Participation

Study participants will undergo medical and functional procedures during the screening visit, and at scheduled study visits throughout the lifetime of the study.

On-site visits: For screening and every 6-month visit:
- meet with the study doctor and research team
- complete motor assessments.

In between on-site visits: For every 3-month visit:
- study research team will contact you every 3 months by phone
- ask you questions on your health and wellbeing.

Journey Locations

The Journey study is currently enrolling at research centers in the United States and is planned to be active in Canada, Europe, and parts of South America and Asia.

To learn more about the study and how you can join the Journey, go to journeyLGMD.com

You can also find more information about this study and participating locations, by visiting ClinicalTrials.gov and searching NCT04475926.

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LGMD News

Editorial

Editor In Chief
Kathryn Bryant Knudson

Medical Editor
Peter B. Kang, MD
University of Minnesota Medical School

Contributors
Carol Abraham
Christopher Anselmo
Kelly Brazzo
Jessica Evans, PsyD
Mary Fiance
Debra Frankel, MS OTR
Rebecca Lucas Gregg
Emmanuelle Guiraud
Heather Hilsden
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Jennifer Levy, PhD
Nathan Peck
Kaitlyn Reilly
Rachel Sapp
Jeffrey M. Statland, MD
Volker Straub, MD, PhD
Thierry Toursel, PhD
Brad Williams, PhD
Tamara Wyzanski

Design + Production

Design Director
Jonathan Price

Advertising

Advertising Coordinator
Jessica Evans, PsyD
ContactUs@TheSpeakFoundation.com

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Thank you for your support!

The Speak Foundation

Uniting the entire LGMD community to make a difference together in future treatments for this rare disease.

The origin of The Speak Foundation's name comes from Proverbs 31:8. It is: "Speak up for those who have no voice." Living with a rare disease means many of us wait years to have a voice in areas that impact our daily lives personally. The Speak Foundation helps our voices to be heard.

About the Cover

CRISPR/Cas9 molecular structure—system for editing, regulating and targeting genomes. The Cas9 protein uses a gRNA (guide RNA) sequence to cut DNA at a complementary site. RNA in red, DNA in yellow.

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Advocacy Opportunities for 2022

You are not going to believe the things coming in 2022!

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TheSpeakFoundation.com/PFDD

TheSpeakFoundation.com/Global-Advocacy-Summit

It is my great pleasure to wish you a Happy New Year, as I believe 2022 will be monumental for the limb-girdle community. I am excited to write our first editorial for Volume 2 of *LGMD News*, meaning we already have one year of publications under our belts! Through this endeavor, we have been able to connect with thousands of individuals living globally with LGMD. We were able to connect with even more at our 2021 International LGMD Conference, which was livestreamed around the world this past September with record numbers tuning into the programming. You are not going to believe the things coming in 2022!

On May 20, 2022, The Speak Foundation will be hosting a virtual Global Advocacy Summit, a first for our community, where you, as the patient, will have the opportunity to interact directly with the pharmaceutical companies that are designing clinical trials and developing treatment drugs for LGMD. You will hear about new trials, learn more about the companies' drug development process, and share your voice on what matters to you most. During the summit, there will also be a unique roundtable discussion featuring 8 individuals living with LGMD from around the globe. These selected delegates will share what matters most to them in drug development. Would you like to apply to be one of those chosen delegates? You can apply when you sign up to participate at **TheSpeakFoundation.com/Global-Advocacy-Summit**.

Additionally for 2022, I am elated to announce that the first group of LGMDs have been approved to meet with the FDA and other stakeholders for an Externally-Led Patient-Focused Drug Development (EL-PFDD) meeting on September 23, 2022. Many organizations have worked together to make this happen for the subtypes of 2a, 2c, 2d, 2e, 2f, and 2i. To get involved with this monumental event, go to **TheSpeakFoundation.com/PFDD**.

The Speak Foundation has a few other projects in the works that will be unveiled in future issues of *LGMD News*. We cannot wait for you to learn more. 2022 is sure to be a groundbreaking year! ■

Kat Bryant Knudson

Kathryn Bryant Knudson
Editor In Chief

Our Mission

The Speak Foundation was based on the principle of "Speak up for those who have no voice."

Speak up for those who cannot speak for themselves. — Proverbs 31:8

International Consortium of LGMD Organizations

United States

The Speak Foundation
Uniting the entire LGMD community
TheSpeakFoundation.com

Beyond Labels & Limitations
Funding research for LGMD 2A/R1 and educating on its disease course
BeyondLabelsLimitations.com

Breathe with MD
Educating and raising awareness about breathing muscle weakness in neuromuscular disease
BreatheWithMD.org

CamronsCure
Funding research for LGMD 2S/R18
CamronsCure.com

Coalition to Cure Calpain 3
Funding research for LGMD 2A/R1
CureCalpain3.org

Cure LGMD2I
Funding research for LGMD 2I/R9
CureLGMD2I.org

Kurt + Peter Foundation
Funding research for LGMD 2C/R5
KurtPeterFoundation.org

LGMD Awareness Foundation
Join us for LGMD Awareness Day
LGMD-Info.org

LGMD-1D DNAJB6 Foundation
Representing LGMD 1D/D1 and DNAJB6 subgroup
LGMD1D.org

LGMD2D Foundation
Funding research for LGMD 2D/R3 and educating patients and physicians
LGMD2D.org

LGMD2I Research Fund
Funding research for LGMD 2I/R9 and educating the patient community
LGMD2IFund.org

LGMD2L Foundation
Representing the LGMD 2L/R12 Anoctamin5-related community
LGMD2L-Foundation.org

Team Titin
A consortium of scientists and affected community members for LGMD2J/R10 Titin-related
TitinMyopathy.com

The Jain Foundation
Funding research for LGMD 2B/R2 and educating the patient community
Jain-Foundation.org

Argentina

ADM Argentina Muscular Dystrophy LGMD Group
Funding research for neuromuscular diseases
ADM.org.ar

France

"GI LGMD"/LGMD Patient Group of AFM-Telethon
Focusing on all subtypes of LGMD, supporting research and educating the patient community
LGMD.AFM-Telethon.fr

Italy

Conquistando Escalones Association
Funding research for LGMD 1F/D2
ConquistandoEscalones.org

"GFB ONLUS"/ Family Group of Beta-Sarcoglycanopathy
Representing the LGMD 2C/R5 Gamma Sarcoglycan-related, LGMD 2D/R3 Alpha Sarcoglycan-related, LGMD 2E/R4 Bèta-Sarcoglycan-related, and LGMD 2F/R6 Delta-Sarcoglycanrelated communities
Beta-Sarcoglicanopathy.org

Italian Association Calpain 3
Funding research for the LGMD 2A/R1 Calpain3-related community
AICA3.org

Japan

Patients' Association for Dysferlinopathy Japan
Representing the Japanese and International LGMD 2B/R2 Dysferlin-related and Miyoshi Muscular Dystrophy 1 (MMD) communities
PADJ.jp/index.html

Netherlands

Stichting Spierkracht
Raising awareness and supporting the LGMD2D/R3 Alpha Sarcoglycan-related community
StichtingSpierkracht.com

Spain

Conquistando Escalones Association
Funding research for LGMD 1F/D2
ConquistandoEscalones.org

Proyecto Alpha
Funding research for LGMD 2C/R5 Gamma Sarcoglycan-related, LGMD 2D/R3 Alpha Sarcoglycan-related, LGMD 2E/R4 Bèta-Sarcoglycan-related, and LGMD 2F/R6 Delta-Sarcoglycanrelated
ProyectoAlpha.org

Volker Straub, MD, PhD

Director, John Walton Muscular Dystrophy Research Centre
Newcastle University
Newcastle upon Tyne, England, UK

Meet the Expert

Volker Straub, MD, PhD is the Director at John Walton Muscular Dystrophy Research Centre in Newcastle University, Newcastle upon Tyne, England. He has a long-standing interest in the pathogenesis of genetic muscle diseases. His current research also involves the application of magnetic resonance imaging, next generation sequencing, and other technologies for the characterization of primary neuromuscular disorders. One of Volker's main interests in muscle diseases is translational research.

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CureCalpain3.org
ClinicalTrials.gov

Q

What is the current status of LGMD2D research?

A

LGMD2D, now also called LGMD R3, is one of the two most common forms of sarcoglycanopathy, and a current natural history study is collecting data to better understand the disease. The next step is to consider gene therapy, which is extremely exciting, but trials have not yet started.

Q

I suffer from muscle fatigue, especially in my legs. What exactly is it and what causes it? Also, do people with LGMD suffer more from it? If so, why?

A

Pain and fatigue are common symptoms in neuromuscular disorders, with a frequency of 30–90%, present in all types of muscle diseases, including LGMD, both in adults and in children. Fatigue has been defined as a lack of energy or the existence of weakness or exhaustion. Most often fatigue is activity-related, as your affected muscles are challenged more when they are used. It is still important to be active, but do not push yourself beyond your limits. It is also important to make sure that both your respiratory and your cardiac function is monitored, as poor respiratory or cardiac function can contribute to fatigability.

Q

Is it possible to have more than one neuromuscular disease (specifically, centronuclear myopathy and LGMD)?

A

Yes, it is possible to be affected by more than one neuromuscular disease, although this is very rare, as all neuromuscular diseases are rare diseases, and you would unfortunately be affected by two rare diseases. In a cohort of about 2,000 patients with LGMD, we identified that around 1% of patients were affected by a second genetic neuromuscular disease. This number will increase in populations where you have high rates of consanguinity, but it might be a lot less in other populations.

Q

In the future, when a patient has undergone gene therapy for repair of his/her muscular dystrophy, will this mean the patient will no longer pass the defective gene on to their offspring?

A

This is an excellent question. The gene therapy approaches that are currently explored do not necessarily reduce the recurrence risk of passing on a faulty gene to the next generation. My advice for patients with a genetic muscle disease who want to start a family is to first get genetic counseling, whether they had gene therapy or not!

Q

I have LGMD2B/R2 and I am puzzled by the disease's progression. I have assumed that my body's declining inclination to produce dysferlin changes slowly but incrementally, and that this is a function somehow related to increasingly inaccurate replications of DNA—and so increasing malfunctions. By this logic, my production of dysferlin started off weakly and has simply declined more sharply than my non-affected peers, whose musculature is also weakening with age, just more slowly. When I was a teenager, I was quite athletic and there was no obvious sign of muscle weakness. It seems there may be other, more subtle timing switches at play. Can you tell me more about this apparent conundrum?

A

In almost all patients with this disease, the dysferlin protein is absent from birth, despite the fact that patients will only experience weakness in their late teenage years or later. Many patients with dysferlinopathy are very good at sports when they are younger and the absence of dysferlin might even contribute to this. We do not have a clear understanding why patients can be asymptomatic for twenty years and then start to develop symptoms, often quite rapidly. It is indeed puzzling!

Q

Will the Pfizer vaccine affect my potential for future treatment if there is one available via AAV gene therapy? If yes, is there another COVID vaccine that is recommended instead?

A

No, neither the Pfizer nor any of the other COVID-19 vaccines are AAV-based and therefore they do not induce the production of anti-AAV antibodies. I would strongly recommend getting your vaccination with one of the approved COVID-19 vaccines, as there is no need to worry about the eligibility for future gene therapy trials.

Q

How can I keep myself updated about the gene therapies or treatments for LGMD Type 2A (Calpainopathy)?

A

I would always suggest checking out the websites of the relevant patient advocacy groups. In the case of LGMD2A/R1, I would look into the websites of Coalition to Cure Calpain 3 (**CureCalpain3.org**) and The Speak Foundation (**TheSpeakFoundation.com**). There is also a government website that lists all the relevant clinical trials for limb-girdle muscular dystrophies at **ClinicalTrials.gov**. The website is easy to use!

> *Pain and fatigue are common symptoms in neuromuscular disorders with a frequency of 30–90%, present in all types of muscle diseases, including LGMD, both in adults and in children.*

Q

I have a son diagnosed with LGMD2A. He intermittently has discrete toe walking and effort cramps. Will he struggle with these issues for a long time, and can I do anything to slow the progression of his disease?

A

Toe walking and cramping is something we frequently see in patients with limb-girdle muscular dystrophies, including LGMD2A/R1. Continuous toe walking can lead to the tightening and shortening of the Achilles tendons, and it is therefore very important that this is assessed by an experienced physiotherapist or clinician. There are specific exercises but also orthotic devices (splints) that can help to prevent the development of ankle contractures. Unfortunately, we currently do not have any therapeutic approaches that can slow down the progression of the disease.

Q

I have Bethlem myopathy but do not usually see it grouped with other LGMD disorders. Is this because of the current naming convention, and if so, do you think the naming convention will change anytime soon?

A

Patients with Bethlem myopathy, caused by genetic changes in the genes responsible for collagen VI, can indeed present with signs and symptoms of limb-girdle muscular dystrophy. In the most recent classification for LGMD, we therefore also assigned forms of LGMD to collagen VI-related diseases, namely LGMDD5 and LGMDR22.

Q

It seems clinical trials to treat dystrophies are progressing rapidly. The treatment approach varies, from addressing the genetic cause with different gene therapies to treating stem cells for tissue regeneration. For trials of new therapies, inclusion criteria related to age and disease stage are generally requested. People with advanced dystrophy are not being tested in the trials. Having narrowed the inclusion criteria for trials and tested treatments to a certain age range, many of us are excluded. Why, and will it change to include patients with varying degrees of progression?

A

You are correct to observe that most of the clinical trials we have seen in patients with muscular dystrophy over the past 15 years (mainly in Duchenne muscular dystrophy), have focused on younger patients with less advanced stages of their disease. This is frustrating for patients with more advanced stages of muscular dystrophy, who also have an interest in clinical trials and the development of potential therapeutic approaches. Less advanced patients have normally more muscle tissue left, which is important for the efficacy of drugs that target skeletal muscle. In patients with more advanced stages of the disease, we also see less change over time, which means the efficacy of a drug is more difficult to measure. Nevertheless, companies and clinical researchers are aware of the unmet needs of patients with advanced stages of muscular dystrophy, and we now see more drug development programs for those patients. ■

Companies and clinical researchers are aware of the unmet needs of patients with advanced stages of muscular dystrophy, and we now see more drug development programs for those patients.

Have a Question for Our Experts?

Send Questions To:
ContactUs@TheSpeakFoundation.com

John Walton Muscular Dystrophy Research Centre: A Leader for LGMD

Above: The Centre for Life, Newcastle upon Tyne, home of the John Walton Muscular Dystrophy Research Centre.

Newcastle University's John Walton Muscular Dystrophy Research Centre (JWMDRC) is a collaboration of hospital and university staff in Newcastle upon Tyne, UK, directed by Professor Volker Straub. The JWMDRC proudly bears the name of Lord Walton of Detchant, who first established a dedicated and integrated neuromuscular clinical and research unit at Newcastle in the 1950s. In 1954 it was Sir John Walton, together with mentor Professor Frederick Nattrass, who first coined the term limb-girdle muscular dystrophy in a seminal article published in Brain.

Dr. Volker Straub, Director, John Walton Muscular Dystrophy Research Centre

Dr. Chiara Marini-Bettolo, Lead for the UK Specialised Service for LGMD

The center is commissioned by the National Health Service (NHS) England to provide expert clinical and diagnostic advice for patients with LGMD. This service is led by Dr. Chiara Marini-Bettolo and composed of three arms: the clinic, the molecular laboratory, and the muscle immunoanalysis unit. The service accepts patient referrals and patient samples for comprehensive diagnostic testing from all over the UK. The approach is very much patient-centered and when visiting clinics, patients are assessed by an experienced multidisciplinary team. The physiotherapy team has longstanding expertise in the management of LGMD with the approach of "measurement for management"—utilizing the most appropriate assessments to measure the impact of the disease on muscle strength and daily functions such as standing and walking. Individualized management plans are then developed, tailored to current functional abilities, including advice on exercise, joint mobility, orthoses, walking aids, wheelchair use, pain management, and chest physiotherapy as required.

The LGMD service runs weekly meetings to provide comprehensive advice on all referrals. As advanced sequencing techniques are now being integrated in the diagnostic workup, these are increasingly complex. Staff collaborate closely with university colleagues, including Dr. Ana Topf, who coordinates diagnostic research projects. For example,

JWMDRC has implemented Next Generation Sequencing (NGS) to gain better understanding of LGMD genetic origins, as part of international initiatives such as NeurOmics and SeqNMD. Further to these projects, MYO-SEQ was established in 2014 as a collaboration between academia (Newcastle University and the Broad Institute, USA), patient organizations (LGMD2i Fund, LGMD2D Foundation, Kurt+Peter Foundation, CureLGMD2i Foundation, and Coalition to Cure Calpain 3) and industry (Sanofi Genzyme and Ultragenyx) to exome sequence a large cohort of patients with unexplained limb-girdle weakness to contribute to their diagnostic pathway. Using networks previously created by TREAT-NMD, JWMDRC enrolled over 50 specialized NMD centers from Europe and the Middle East and recruited a total of >2,000 undiagnosed patients. Through whole exome sequencing (WES) analysis, a genetic diagnosis was proposed for 55% of the cohort. WES also provided scope both for novel gene discovery and research into genotype-phenotype correlations. The current follow-up project focuses on investigating the prevalence of regulatory and non-coding genetic variants and their effect on splicing as a pathomechanism in LGMD.

As well as diagnostic research projects, JWMDRC is active in clinical research studies for patients with LGMD. Our physiotherapists are critical to the delivery of clinical trials for neuromuscular diseases, assessing the impact of treatments using clinical outcome measures. JWMDRC is one of the world's leading centers for the development and evaluation of outcome measures, and much of the current focus is on developing appropriate measures for the LGMD patient population. In partnership with Jain Foundation, JWMDRC is the coordinating center for the largest natural history study in LGMD, the Clinical Outcome Study for Dysferlinopathy (COS). The center also collaborates closely with colleagues in the GRASP and LGMD 2i consortia as the lead UK site. Meredith James, the lead research physiotherapist says, "Through COS we have learned so much about the importance of good natural history data using clinically meaningful outcome measures that reflect the patient experience. One of the main outputs of COS is the first LGMD-specific, functional assessment called the North Star Assessment for limb-girdle-type muscular dystrophies (NSAD). We are very pleased to see the NSAD being used in the current LGMD gene therapy trials. We continue to learn and evolve our outcome measures but can only do this together with the global LGMD community and, specifically, your participation in natural history studies. With a greater depth of understanding of how assessments perform in patients with LGMD, we can drive trial readiness forward with informed, data-driven guidance for future clinical trial design and selection of appropriate assessment methods to measure drug effectiveness."

Investigators at JWMDRC are also performing basic research to better understand LGMD.

Left: Meredith James and Jono Whitehead at a COS Study visit. Jono says, "I've been participating in the COS Study for over a year now. It's useful to be able to check in with professionals at Newcastle who already understand the condition and can give context to how my body has changed and is working at the moment."

We continue to learn and evolve our outcome measures but can only do this together with the global LGMD community and, specifically, your participation in natural history studies.

The group, led by Prof. Jordi Díaz-Manera, is interested in characterizing the role of fibroadipogenic precursor cells (FAPs) in different genetic muscle diseases, including Duchenne muscular dystrophy (DMD), dysferlinopathies, sarcoglycanopathies, and Pompe disease. Cutting-edge technology is being used to study the gene profile of muscle biopsies of controls and patients with these diseases to the single cell level. These studies will provide valuable information to understand the molecular pathways leading to muscle degeneration in these diseases and to identify treatment strategies to slow disease progression. The group has now developed a cell-based protocol using immortalized FAPs to test compounds in a high drug screening protocol that could serve to identify new therapeutic approaches. First drugs have been characterized that target the reduction of connective tissue (fibrosis), such as nintedanib, which is being tested in murine models of sarcoglycanopathies.

Prof. Jordi Diaz Manera **(right)** and Ana Topf **(second right)** with the JWMDRC lab team

One of the main challenges facing scientists in their study of rare diseases is access to patient samples.

One of the main challenges facing scientists in their study of rare diseases is access to patient samples. Biobanks aim to address this issue by collecting and curating tissue and blood donations from patients. The Newcastle MRC Centre Biobank for Rare & Neuromuscular Disease was established in 2008 and has since become an integral part of JWMDRC. The bank is also member of a large network of rare disease biobanks called EuroBioBank. Samples stored at JWMDRC have been used to identify new, promising biomarkers in serum of patients with dysferlinopathy that correlate with disease progression.

Dan Cox, Biobank Manager at JWMDRC, says, "Natural history studies such as COS can also be a great opportunity for those who wish to donate biomaterial. Collecting samples in line with natural history data gives added value to researchers who can request functional data as well as biobank samples through the study governance structures. We have been delighted to enable 16 requests for over 1100 samples from the COS study to the benefit of research into the dysferlinopathies. We are always pleased to hear from researchers internationally, and hopefully support their research."

Dr. Michela Guglieri is the lead for clinical research at JWMDRC.

Dr. Michela Guglieri is the lead for clinical research at JWMDRC and is excited to be working with the team to set up the first LGMD gene therapy trial in the UK. Michela is determined that the LGMD community learns lessons from DMD. "It is so important that we all use every opportunity to harmonize our research efforts so we can accelerate the planning of trials and initiatives to improve care and to develop care standards. To this end, Volker and I organized a meeting through TREAT-NMD, a global network for translational research in neuromuscular diseases, in Amsterdam in 2019, to bring all our colleagues who were planning or delivering natural history studies in patients with LGMD together, to align and collectively identify and address gaps in our research portfolios."

Over the course of 2020, JWMDRC successfully drove collaborations forward despite COVID-19. Prof. Jordi Diaz Manera and Michela Guglieri established the TREAT NMD Global LGMD Task Force and delivered two projects. For one, Jordi worked with international colleagues on the task force to develop an educational program of activities to increase recognition and improve care. To date, three LGMD masterclasses for medical and allied health professionals have been delivered. A total of 328 professionals from 51 countries attended with a further masterclass in development. For the second project, expert colleagues and patient advocacy groups generously gave their time to work with Michela to define the first agreed, disease-specific data set for patient registries. This is now at a pilot stage with international patient registries trialling a common data set for LGMD.

Two LGMD registries are coordinated from Newcastle: the Global FKRP Registry and the Registry for Collagen 6-related dystrophies. The Global FKRP Registry is for individuals with conditions caused by genetic changes in the Fukutin-Related Protein gene (FKRP), the majority of whom have LGMD R9, dystroglycan-related (also known as LGMD 2i). The registry is generously supported by the LGMD2iFund and CureLGMD2i. The international registry for collagen 6-related dystrophies collects data from individuals with genetic changes in the collagen 6 genes, some of which have recently been re-classified as forms of LGMD (LGMD R22 and LGMD D5) and has been supported by funding from the Collagen VI Alliance through Muscular Dystrophy UK.

Over the past 30 years that Volker has worked in the field of muscular dystrophies, he has learned that "for patients with these rare genetic diseases, it is absolutely important that we work together internationally to improve their diagnoses, care, and treatment opportunities. With our translational research approach at the JWMDRC, including basic research, genetic testing, muscle biopsy analysis, biomarker and outcome measure studies, patient registries, and clinical trials, we hope to contribute to the international efforts to improve the quality of life and life expectancy of patients with LGMD around the world." ■

Written by Heather Hilsden
Senior Project Manager
Jain COS Study

Above: Dan Cox, Biobank Manager, at work in the Newcastle MRC Centre Biobank for Rare & Neuromuscular Disease.

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Global FKRP Registry
FKRP-Registry.org

Global Registry for COL-Related Dystrophies
Collagen6.org

Newcastle-Muscle.org
TREAT-NMD.org
MYO-SEQ.org

AFM-Téléthon and Généthon: Two Major Players in an Ongoing Medical Revolution

AFM-Téléthon is behind a whole host of world firsts in the field.

Many of the gene therapy drugs currently on the market derive from research or technologies kick-started or supported by AFM-Téléthon, the French Muscular Dystrophy Association, including research led at Généthon, the association's gene therapy lab. Ten products resulting from Généthon's research are currently in clinical trials, and five further products will enter trials over the next five years, notably for limb-girdle muscular dystrophy (LGMD).

Over the past 30 years, AFM-Téléthon — an association set up in 1958 for patients and families affected by neuromuscular diseases — has become a major player in biomedical research into *all* rare diseases, thanks to the success of the French Telethon. In 1990, AFM-Téléthon founded Généthon in Évry, France. Généthon, a nonprofit R&D organization, went on to provide the scientific community with the first genome maps just two years later. This offered an incredible boost to the Human Genome Project, which paved the way for the identification of hundreds of genes involved in diseases, as well as gene therapy.

AFM-Téléthon is behind a whole host of world firsts in the field. It supported Professors Fischer, Cavazzana-Calvo, and Hacein-Bey-Abina of Necker–Enfants Malades Hospital, Paris, who used gene therapy in

1999 to treat the first "bubble babies"—children with X-linked Severe Combined Immunodeficiency (X-SCID). In 2002, in collaboration with Italy's Telethon, it began funding the work of Maria Grazzia Roncarolo, MD at San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), Italy. This work resulted in GlaxoSmithKline's Strimvelis,™ the first gene therapy to be granted a marketing authorization in Europe, for another immunodeficiency, in 2016. The Association also supported the development of many gene therapies (for example, X-linked adrenoleukodystrophy, beta thalassemia, Leber hereditary optic neuropathy, and other rare diseases).

Despite accounting for approximately 40% of a person's body weight, muscles have long appeared inaccessible to gene therapy. But

AFM-Téléthon has supported pioneers in this field, too. And the results are incredible! For Type 1 spinal muscular atrophy (SMA)—the most severe form of the disease, which was likely fatal for children before the age of two years—gene therapy (Zolgensma® from Novartis) can now save lives. This treatment owes a great deal to research conducted in

Above: Thanks to the success of the French Telethon, AFM-Téléthon has become a major player in biomedical research into *all* rare diseases.

Opposite: Isabelle Richard and the Généthon Team.

Today, it is the turn of limb-girdle muscular dystrophy (LGMD) to enter the era of gene therapy.

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AFM-Telethon.com
Genethon.com

France and instigated by AFM. In 1995, French researcher Judith Melki identified the SMN1 gene based on DNA collected in 1988 from families belonging to AFM. Then, between 2004 and 2011, Martine Barkats' team at Généthon developed a viral vector that enabled the therapeutic gene developed by the American company AveXis, Inc. (a Novartis company) to be delivered to motor neurons. The same process resulted in a gene therapy for myotubular myopathy, currently being evaluated in a clinical trial. In 1996, French researchers supported by AFM-Téléthon discovered the gene responsible for the disease, then Ana Buj-Bello developed the treatment at Généthon. The results in terms of the respiratory and motor capacities of the treated children are highly encouraging.

Today, it is the turn of limb-girdle muscular dystrophy (LGMD) to enter the era of gene therapy. In the 1990s, Généthon launched an ambitious program focused on LGMD, led by Dr. Isabelle Richard, CNRS Research Director and head of the progressive muscular dystrophies team at Généthon. Richard helped identify the gene responsible for calpainopathy in 1995, the gene for dysferlinopathy in 1998, and the FKRP gene in 2001. Her team then developed gene therapy approaches, for which she established the proof-of-principle of efficacy, for calpainopathy (2006), alpha-sarcoglycanopathy (2007), dysferlinopathy (2010), FKRP myopathy (2017), and gamma-sarcoglycanopathy (2019). Work on FKRP-related LGMD (LGMD2i/R9) is the most advanced. In preclinical mice models, Richard's gene therapy was found to correct the symptoms and biomarkers of the disease at particularly low doses for an intravenous gene therapy designed to treat muscular disease. These results enabled Atamyo Therapeutics, a spin-off of Généthon, to submit authorization applications for a clinical trial in France, Denmark, and England, which could begin in 2022. Another world first is on its way!

For more information, please visit **AFM-Telethon.com** and **Genethon.com**. ■

Written by Emmanuelle Guiraud
Director of Communications
AFM-Téléthon

Atamyo Therapeutics: A Biotech Company Dedicated to LGMD

Created in 2020 by Généthon, Atamyo Therapeutics develops gene therapies for various limb-girdle muscular dystrophies. A clinical trial into FKRP-related LGMD (LGMD2i/R9) should get underway in 2022. Four other clinical trials are planned, for gamma-sarcoglycanopathy (LGMD2C/R5), calpainopathy (LGMD2A/R1), dysferlinopathy (LGMD2B/R2), and alpha-sarcoglycanopathy (LGMD2D/R3). "The creation of Atamyo by Généthon reflects our ambition to create a gene therapy champion for LGMD, one that will benefit from all our progress in these fields and whose mission will be to develop these treatments for the benefit of as many patients as possible—patients who currently have no curative treatment," explains Frédéric Revah, CEO of Généthon. "Atamyo will have the necessary financial resources to accelerate the clinical development of LGMD programs up to the marketing phase."

Atamyo.com

Potential Therapy for LGMD2i/R9 Receives FDA Fast Track Designation

ML Bio Solutions and **BridgeBio Pharma** announced that its investigational therapy for limb-girdle muscular dystrophy type 2i/R9 (LGMD2i/R9), BBP-418, was granted Fast Track Designation by the U.S. Food & Drug Administration (FDA). LGMD2i/R9 is an inherited form of LGMD caused by a mutation in the FKRP gene, which causes patients to experience muscle degeneration that can ultimately lead to cardiac and respiratory impairment.

BBP-418 is a drug candidate in development to treat LGMD2i/R9 at its source, through an oral medication that is designed to provide additional substrate to the affected enzyme in LGMD2i/R9, with the potential to improve muscle strength and function.

Fast Track Designation is granted to accelerate delivery of potentially life-changing medicines to patients who have limited treatment options. Now that ML Bio Solutions has received Fast Track Designation for BBP-418, the FDA will provide more frequent communication to discuss the BBP-418 development plan and ensure collection of appropriate data and design of the proposed clinical trial needed to support approval.

"We were thrilled to hear that ML Bio Solutions and BridgeBio received Fast Track Designation from the FDA for the development of BBP-418. Our LGMD2i community has been anxiously awaiting a potential treatment for this disease. This announcement brings hope and excitement for our patients and families who are affected by limb-girdle muscular dystrophy type 2i/R9," said Kelly Brazzo, Co-Founder and CEO of CureLGMD2i Foundation. "If this therapy becomes approved by the FDA, it will likely be the first treatment made available to our LGMD2i patients, which will hopefully slow or even reverse the progressive effects of this devastating condition."

ML Bio Solutions has completed a Phase 1 study (testing BBP-418 on healthy volunteers) and has an ongoing Phase 2 study (testing for dosing and safety) that is closed to enrollment. We will work to complete Phase 2 to assess the treatment's safety and efficacy in a small group of patients. A Phase 3 pivotal trial (evaluating the efficacy of BBP-418 on a larger cohort of patients) is in development. We are hopeful the designation will allow us to address this unmet medical need by allowing us to potentially deliver our medicine to patients more quickly. Please monitor **ClinicalTrials.gov** and **MLBioSolutions.com** for more information. ■

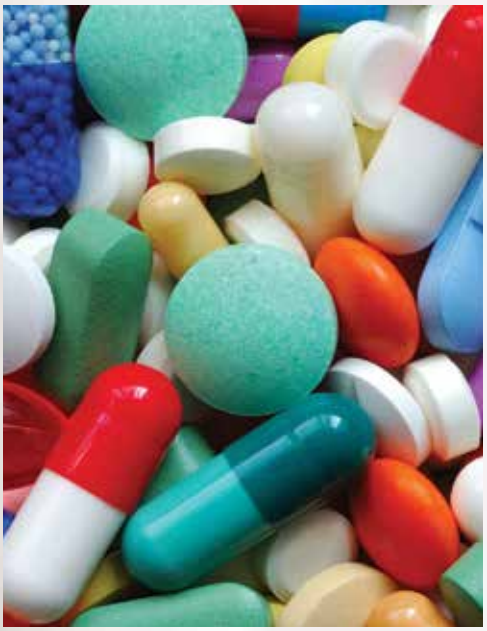
Written by Kaitlyn Reilly
Senior Manager, Communications
ML Bio Solutions

Above: Mobility and strength assessments are important elements of BBP-418 studies.

> *This announcement brings hope and excitement for our patients and families who are affected by limb-girdle muscular dystrophy type 2i/R9.*

Connect with Us

MLBioSolutions.com
BridgeBio.com
ClinicalTrials.gov



Overcoming Drug Development Barriers

One of the missions of the GRASP-LGMD Consortium is to advance bench to bedside research for inherited disorders of muscle, which includes collaborating with basic scientists, developing tools and infrastructure for high quality clinical trials, and advancing clinical trials of new, genetically targeted drugs. These are rare and underserved disorders which require a comprehensive approach involving all key stakeholders, especially at a time when new molecular targeted therapies are being approved.

This is an exciting time in the LGMD community! There is more interest in the field than ever before, and companies are ready to come into the space and start their first, in-human drug trials. However, a barrier still exists. We still have not identified the best measures for seeing change in LGMD over time, determined how large a change would be clinically meaningful, or decided the best biomarkers for proof of concept or dosing studies. Overcoming these barriers to drug development is the mission of the GRASP-LGMD network and succeeding is a group effort. We need the LGMD community's help by participating in natural history studies — studies where LGMD participants are followed over time — so we can determine which of these measures are best and should be used in future trials. We cannot advance the field without the help and participation of those living with LGMD. For more information about LGMD clinical trials, or to find a LGMD study near you, go to **ClinicalTrials.gov**. ■

We cannot advance the field without the help and participation of those living with LGMD.

Written by Dr. Jeffrey M. Statland
Professor of Neurology
University of Kansas Medical Center

UPDATED: DECEMBER 1, 2021

Active GRASP-LGMD Clinical Trials

RECRUITING: Defining Clinical Endpoints in Limb-Girdle Muscular Dystrophy (LGMD) (GRASP)

Inclusion Criteria:

- Age between 4–65 at enrollment
- Clinically affected (defined as weakness on bedside evaluation in either a limb-girdle pattern, or in a distal extremity)
- A genetically or functionally confirmed mutation in ANO5, CAPN3, DYSF, DNAJB6, or SGCA-G
- Ambulatory

Exclusion Criteria:

- Non-ambulatory at the time of enrollment
- Any other illness that would interfere with the ability to undergo safe testing or would interfere with interpretation of the results in the opinion of the site investigator

Subtypes:

- CAPN3 (LGMD 2A/R1)
- DYSF (LGMD 2B/R2)
- ANO5 (LGMD 2L/R12)
- DNAJB6 (LGMD 1D/D1)
- Sarcoglycan (LGMD 2D/R3, LGMD 2E/R4, LGMD 2C/R5, LGMD 2F/R6)

NOT RECRUITING: Biomarker Development in LGMD 2I/R9 (MLB-01-001)

Inclusion Criteria:

- Age between 10–65 at enrollment
- Clinically affected (defined as weakness on bedside evaluation in either a limb-girdle pattern, or in a distal extremity)
- A genetically confirmed mutation in FKRP (LGMD 2I/R9)
- Up to 60 participants will complete the10-meter walk test in greater than 4 seconds
- Up to 40 participants will complete the 10-meter walk test in over 12 seconds
- Up to 20 participants may be non-ambulatory

Exclusion Criteria:

- Any other illness that would interfere with the ability to undergo safe testing or would interfere with interpretation of the results in the opinion of the site investigator
- History of a bleeding disorder, platelet count <50,000, current use of an anticoagulant
- Positive pregnancy test at start or at any time during the trial

Subtype:

- FKRP (LGMD 2I/R9)

Contact: **Brittney Holmberg** | Project Manager, Grasp-LGMD Consortium | (804) 997-9384 | *Brittney.Holmberg@vcuhealth.org*

GRASP-LGMD Consortium Members


Vijay Ganesh, MD, PhD
Brigham and Women's Hospital


Conrad "Chris" Weihl, MD, PhD
Washington University in St. Louis


Doris Leung, MD, PhD
Hugo W. Moser Research Institute at Kennedy Krieger


Jeffrey M. Statland, MD
University of Kansas Medical Center Research Institute, Inc.


John Vissing, MD
University of Copenhagen


Katherine Mathews, MD
University of Iowa


Linda Lowes, PT, PhD
The Research Institute at Nationwide Children's Hospital


Matthew Wicklund, MD
University of Colorado Denver


Nicholas Johnson, MD, MSci, FAAN
Virginia Commonwealth University


Peter B. Kang, MD
University of Minnesota Medical School


Tahseen Mozaffar, MD, FAAN
University of California Irvine


Urvi Desai, MD
Atrium Health


Volker Straub, MD, PhD
Newcastle University


Monkol Lek, PhD
Yale University, Non-Clinical Site

GRASP-LGMD Researcher Spotlight

Dr. Jeffrey M. Statland | University of Kansas Medical Center

Dr. Jeffrey M. Statland is Professor of Neurology at University of Kansas Medical Center in Kansas City, Kansas. His research background has centered primarily on describing the natural history of and response to therapy for inherited neuromuscular diseases. He completed a neuromuscular fellowship in Experimental Therapeutics of Neurological Diseases at University of Rochester Medical Center and currently serves as a principal investigator or co-investigator for research studies in limb-girdle muscular dystrophy (LGMD), facioscapulohumeral muscular dystrophy (FSHD), Duchenne muscular dystrophy, spinal muscular atrophy, and myotonic dystrophy. His specific research interest over the last six years has been preparing for clinical trials in muscular dystrophy. He has worked with collaborators to develop new, disease-relevant outcome measures to assess patient-reported disease burden, functional impairment, and physiological changes in muscle, as well as piloting studies in blood and muscle-based biomarkers. He currently is Director of the KUMC Muscular Dystrophy Association clinics, co-director for the FSHD Clinical Trials Research Network, and PI and Clinical Liaison for the GRASP-LGMD research network.

Sarepta Opens Gene Therapy Center in Ohio: Excellent News for the LGMD Community

Right: Sarepta's Chief Scientific Officer, Dr. Louise Rodino-Klapac, cuts the ribbon during a grand opening event Oct. 4 for the opening of their new research facility in Ohio.

Jessica Evans

Pat Furlong

Columbus, Ohio continues to emerge as a hub for gene therapy progress. The city is home to the Abigail Wexner Research Institute at Nationwide Children's Hospital, known by many in the LGMD community for its gene therapy research focused on various neuromuscular diseases.

October 4th marked a significant day for both the LGMD community and the city of Columbus, as Sarepta Therapeutics hosted a ribbon-cutting ceremony for the grand opening of their Genetic Therapies Center of Excellence at Easton Commons.

Sarepta's team invited advocacy leaders and patients from the LGMD and Duchenne communities, leaders from Columbus' growing biotechnology sector, as well as several of Ohio's politicians, legislators, and policy makers to join them for the celebration.

Doug Ingram, Sarepta's President & CEO, set a hopeful tone for the event as he opened by sharing the company's vision and mission "to treat and transform lives otherwise diminished and stolen by rare genetic disease" through precision genetic medicine. Dr. Louise Rodino-Klapac, Executive Vice President, Head of R&D, and Chief Scientific Officer with Sarepta, went on to speak about the promising results of their early clinical trials as well as the goal of advancing their pipeline, which includes six LGMD gene therapy programs (for LGMD2E, LGMD2D, LGMD2C, LGMD2B, LGMD2L and LGMD2A).

The Speak Foundation was honored to be invited to share on behalf of the LGMD community during Sarepta's ceremony. Speak's Assistant Director and resident of Ohio, Jessica Evans, was present to highlight the urgent, unmet need for effective treatments for LGMDs that will extend and enhance lives. Evans stressed to all in attendance, "There are forms of LGMD that have devastating effects on respiratory and cardiac health." Ohio native Pat Furlong, who is the Founding President and CEO of Parent Project Muscular Dystrophy (PPMD), was also in attendance to advocate for the Duchenne community.

The event concluded with a tour of Sarepta's state-of-the-art facility, which boasts 85,000 square feet of space, but far more impressive and exciting are the scientific research and development efforts that will continue to take place within its walls.

The Speak Foundation continues to partner with biotech companies like Sarepta Therapeutics because, as Evans shared during the ceremony, we are "on a mission to help find treatments for all forms of LGMD and we will not give up. This family of diseases is complex, with over 30 forms, so we are working to unite the entire LGMD community because we believe we can make a greater impact this way as we advocate for effective treatments. Gene therapy is the potential treatment that our community is so hopeful to see come to fruition."

We are closer than ever to seeing a major breakthrough. Join us in believing there is hope for a cure. ▪

Connect with Us

TheSpeakFoundation.com
ParentProjectMD.org
Sarepta.com

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Team Titin

Variants in the massive gene titin (TTN) can cause a spectrum of muscle and heart disorders including LGMD 2J, also known as LGMD R10 Titin-related.

Team Titin is a consortium of scientists and affected community members aimed at making a worldwide difference in Titin-related muscle and heart disorders by: collaborating with other organizations, raising awareness, connecting with families, providing education, and supporting research. Our goal is to serve as a catalyst for stakeholders to develop a better understanding of Titin-related disorders, leading ultimately to a cure.

To learn more visit titinmyopathy.com

EMAIL:
CureMyopathy@gmail.com

FACEBOOK:
facebook.com/groups/teamtitin

REGISTRY:
Congenital Muscle Disease International Registry (cmdir.com)

Team Titin

"Brrr ... I Am Cold!"

Thankfully, there are a variety of products on the market that can be used to help keep warm.

Regardless of the season, many individuals living with LGMD struggle with feeling cold. The problem is often related to being immobile or less physically active, and the fact that our muscles are not contracting as much. Thankfully, there are a variety of products on the market that can be used to help keep warm. Below are some products for you to consider. ▪



Keep Warm this Winter with these Helpful Products

Heat Packs — Warmers

- **Disposable hand, toe, and foot warmers** are very handy and easy to use. Common brands include Grabber and Hot Hands. These are found in many retail stores.
- **OCOOPA USB Rechargeable Hand Warmer** provides a quick source of heat for warming your hands with 3 heat settings.
  It is recommended to keep the hand warmer in a carrying pouch when in use.
- **Microwaveable Heat Pack:** Bed Buddy® is one commercial brand available, but many people make their own using rice or other grains, in a bag or sock that is sewn shut.
- **Venture Heat™ Infared Deluxe Heating Pad:** Its large surface provides therapeutic heat.

Clothing — Apparel

- **Battery-Operated Clothing:** Heated vests, shirts, socks, mittens, etc. offer lightweight, heated warmth without the bulk of heavy clothing. Popular websites for these items include **CozyWinters.com** and **VentureHeat.com**.
- **Lightweight Long Underwear and Clothes** provide warmth without limiting movement and allow layering without bulkiness. Cuddl Duds® is a popular brand offering products for both adults and children.
- **Flannel-Lined Satin Pajamas** improve bed mobility while keeping you warm.

Bedding — Blankets

- **Sunbeam Heated Throw:** This is a staple item for many! A 12-volt, heated version is also available for use when traveling in a car.
- **Electric Mattress Pad and/or Blankets** are available in most stores where bedding is sold.
- **Serta's Electric Foot Warmer** can be used in or out of bed to warm cold feet.
- **Flannel Bed Sheets** provide added warmth in bed, although the fabric can impact bed mobility.
  It is highly recommended to wear silky fabric pajamas to improve bed mobility when using flannel sheets.
- **Cocoon® CoolMax Travel Blanket:** Ultra compact and lightweight, it is easy to tuck away in a backpack, purse, or wheelchair pouch. It offers just enough warmth to provide comfort!

Other Heating Products

- **The QMark Radiant Heat Desk Panel** provides lower extremity warmth while working at a desk. The unit can rest on the floor or attach discreetly to the inside panel of a desk.
- **Gas or Electric Indoor Fireplace:** When finances and house design allow, a remote control-operated fireplace is great for on-demand heat throughout the year.

Written by **Carol Abraham**, *Retired OTR; Director of Community Outreach, Coalition to Cure Calpain 3; Founder, LGMD Awareness Foundation*

Remember! Heated products should always be used with caution and in following with the manufacturers' instructions.

By Jennifer Levy, PhD
Scientific Director, Coalition to Cure Calpain 3

What's on the Horizon for LGMD2A/R1?

Limb-girdle muscular dystrophy type 2A/R1 (LGMD2A/R1, also called LGMDR1 calpain3-related, or calpainopathy) is the most common form of LGMD. The gene associated with LGMD2A/R1, the calpain 3 gene, was the first to be linked to an LGMD. This leaves patients and their loved ones wondering — when will there be a cure for LGMD2A/R1?

A Nonprofit Dedicated to LGMD2A/R1

Coalition to Cure Calpain 3 (C3) was founded in 2010 by Kristine Kurnit and Michele Wrubel, two women living with LGMD2A/R1. They recognized that there was no organization dedicated specifically to understanding and curing this disease. In the 11 years since C3's founding, they have awarded nearly $2 million in grants to international leaders in the muscular dystrophy field, putting more money into LGMD2A/R1 research in the last decade than any other United States-based nonprofit organization. C3 also hosts scientific meetings, maintains a patient registry, and raises global awareness of LGMD2A/R1.

Molecular Scissors

Mutations in the calpain 3 gene cause LGMD2A/R1. This slowly progressive muscular dystrophy affects skeletal muscles but typically not the heart or lungs. Onset of weakness usually occurs in childhood or early adulthood and first affects the upper leg muscles. Toe walking and protrusion of the shoulder blades (scapular winging) are common, and patients typically lose their ability to walk within 10 to 30 years from the first onset of symptoms.

Calpain 3 is a protease, meaning it has the ability to cut other proteins in the cell. Mutations associated with LGMD2A/R1 can lead to either absence of calpain 3 or to expression of inactive or partially-active calpain 3. A substantial amount of effort has gone into understanding the cellular role for calpain 3 and why defects in its function lead to this disease. Experiments show that when calpain 3 cuts muscle proteins, remodeling of muscle is facilitated in response to exercise. This means that calpain 3 helps muscles to adapt and change in response to different types of exercise. Calpain 3 also appears to have a structural role that is distinct from its proteolytic role. In this role, it binds to and stabilizes a protein complex that is critical for muscle signaling. Loss of calpain 3 expression or activity leads to a variety of changes in muscle, including abnormal growth, irregular mitochondria, and metabolism abnormalities. Of calpain 3's many cellular functions, it is unclear if the loss of one or a subset of these is the primary driver of LGMD2A/R1 disease progression.

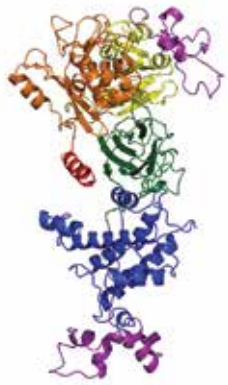


Illustration depicting the structure of calpain 3. Calpain 3 deficiency causes LGMD2A/R1.

Gene Replacement

The most direct way to treat LGMD2A/R1 would involve replacing the defective calpain 3 gene with a healthy copy. Gene replacement strategies, often simply referred to as gene therapy, are being tested in several muscular dystrophies, including Duchenne Muscular Dystrophy and other LGMDs. This approach most commonly uses a viral vector such as adeno-associated virus (AAV) to deliver the replacement gene to target cells and tissues. In the case of LGMD2A/R1, an AAV vector (transportation vehicle for a gene) is selected that can deliver the calpain 3 gene to muscle. A small DNA sequence called the promoter functions to ensure that only the intended tissues express the gene. A single administration of gene therapy is expected to last for years, and some researchers think it may even last a lifetime.

Dr. Melissa Spencer, Chair of the C3 Scientific Advisory Board and Professor, University of California, Los Angeles

The first LGMD2A/R1 gene therapy study, led by Dr. Isabelle Richard of Généthon, used AAV gene replacement in a mouse model of the disease. This was toxic to the heart muscles and illuminated the need for calpain 3 to be very specifically expressed in skeletal muscle. Indeed, subsequent studies from Dr. Richard, as well as from Dr. Zarife Sahenk of Nationwide Children's Hospital, demonstrate that if heart muscle expression is suppressed, then delivery of the calpain 3 gene improves muscle in an LGMD2A/R1 mouse model. These approaches, each funded in part by C3 research grants, are currently being advanced by biotechnology companies. Dr. Richard's LGMD2A/R1 gene therapy program is now a part of Atamyo Therapeutics' pipeline. Dr. Sahenk's program was recently incorporated in Sarepta Therapeutics' pipeline. Both companies are completing studies to demonstrate that LGMD2A/R1 gene therapy is safe and effective in animals before initiating human clinical trials.

C3, along with the National Institutes of Health, recently funded C3 Scientific Advisory Board Chair Dr. Melissa Spencer (University of California, Los Angeles) and Dr. Jeffrey Chamberlain (University of Washington)

> ***"Sarepta's commitment and research investment in limb-girdle muscular dystrophy (LGMD) is unparalleled, with investigational approaches in development for six LGMD subtypes, including LGMD2A/R1. We are working with urgency to advance innovative treatment options that will bring clinically meaningful improvement in the prognosis and quality of life for individuals with LGMD. Sarepta's program for LGMD2A/R1 is currently in the preclinical stage. As the LGMD programs advance through the stages of development, there are important things the patient community can do now to help, including joining a disease registry or natural history study and taking advantage of genetic testing options, activities that help advance our scientific understanding of LGMD and its subtypes."***

Louise Rodino-Klapac, PhD
Executive Vice President,
Head of R&D and Chief Scientific Officer,
Sarepta Therapeutics, Inc.

to develop additional safeguards that ensure calpain 3 gene therapy is targeted to skeletal muscle and excluded from the heart.

Gene Editing

Recently, technologies have been developed that can directly edit the DNA inside a cell. Rather than replacing the calpain 3 gene with a normal copy, as described above for gene therapy, gene editing fixes the mutations in the calpain 3 gene. This can be accomplished using an *in vivo* approach, in which gene editing technologies are delivered systemically to the affected tissues, or an *ex vivo* approach, in which the genes in cells outside of the body are edited. These gene-edited cells are then transplanted into the patient's body.

There are significant challenges to developing *in vivo* gene editing for muscular dystrophies due to the nature of muscle cells. However, at least two groups are dedicated to applying *ex vivo* gene editing technologies to LGMD2A/R1. Dr. Rita Perlingeiro of The University of Minnesota has tested the feasibility of using CRISPR-Cas9-mediated editing to correct mutations in the calpain 3 gene in stem cells derived from LGMD2A/R1 patients. These cells were then delivered to a mouse model of LGMD2A/R1. Vita Therapeutics, an early-stage cell engineering company, recently announced their plans to use gene correction to develop a treatment for LGMD2A/R1. They anticipate that the technology will help repair and replace muscle cells with cells that express corrected calpain 3. Vita recently completed enrolling five patients for a lead-in study to generate gene-edited stem cells from a blood draw. Recruitment for this study occurred through the LGMD2A/R1 Patient Registry. If results are promising, Vita hopes to initiate a first-in-human trial to deliver stem cells into the patients via a series of intramuscular injections.

Importantly, while the above groups are developing gene-edited stem cells to treat LGMD2A/R1, there are currently no approved stem cell treatments for this disease. Any clinics selling stem cell treatment as a therapy are making unsubstantiated claims about the safety and efficacy of this approach. These clinics put patients at risk for harm, and C3 urges patients not to seek this type of treatment.

Can Small Molecule Drugs Make a Big Impact?

Gene therapy and gene editing will hopefully lead to a cure for LGMD2A/R1 by replacing or fixing the calpain 3 gene. These cutting-edge technologies are relatively new. In addition to a cure being sought, some researchers are exploring small molecule drugs that target the cellular pathways with which calpain 3 interacts. If these drugs can compensate for the loss of functional calpain 3, then they might be beneficial in LGMD2A/R1 patients. These drugs could be taken on their own, or in combination with gene therapy, should they get approved.

One promising small molecule has recently been identified by Dr. Spencer. Work from her lab shows that loss of calpain 3 activity is associated with improper signaling of a chemical messenger called CaMK. CaMK is known to play a critical role in muscle's response to exercise, and therefore, altered CaMK might be at the center of LGMD2A/R1 symptoms. Dr. Spencer used a chemical screen to identify AMBMP, a chemical that activates CaMK messaging. When administered to mice, muscle structure improved and running ability was increased compared to animals given a placebo. These results suggest that targeting CaMK or a related protein could be beneficial for patients. The researchers are currently exploring similar compounds that they anticipate will be suitable for human use.

Muscle biopsies from patients show abnormalities in the structure of mitochondria, the parts of the cell that are responsible for generating energy that the cell can utilize to perform its functions. Dr. Kanneboyina Nagaraju (Binghamton University) and colleagues recently demonstrated that treatment of an LGMD2A/R1 mouse with a mitochondria-targeting chemical improves mitochondrial function and muscle repair. These experiments suggest that drugs that target mitochondria could be beneficial to LGMD2A/R1 patients.

Dr. Amets Sáenz (Biodonostia Health Research Institute) and colleagues discovered that patient cells are defective in components of signaling pathways called Wnt and mTOR, which mediate cell regulation. The scientists successfully restored these pathways in patient cells by administering small molecules that inhibit a protein called GSK-3beta. It is possible that this approach could lead to a treatment that helps LGMD2A/R1 patients.

Joining the C3 Registry benefits both patients and the scientific community.

"Your experience counts! A robust registry is a prerequisite to attract the attention of the scientific world to take up our cause and search for a cure. Join C3's registry today to help researchers, and all of us, better understand the number of people living with LGMD2A/R1 and the many ways it manifests and progresses. Participants will be kept up-to-date about C3 news and clinical trial opportunities."

Jennifer Levy, PhD
Scientific Director,
Coalition to Cure Calpain 3

Masters of Science student Anthonia Anowai (above left) and lab manager Daniel Young (above right) research calpain 3 in the laboratory of Dr. Antoine Dufour, University of Calgary.

What is Next?

C3 is actively pursuing innovative approaches to curing LGMD2A/R1. Dr. Antoine Dufour, a research grant recipient from the University of Calgary, is currently probing the biological role of calpain 3 through a proteomic approach. This project could lead to the identification of new approaches for treating the disease.

There also may be future therapies that improve muscle strength and function, which have the potential to slow progression of muscular dystrophies. Some of these are being developed for other similar diseases and could be effective in treating LGMD2A/R1.

There has never been so much activity in the LGMD2A/R1 field! While C3 is eager for these possible treatments to reach the global patient community, the experimental approaches described above have only been tested in cells and mice. Research remains to be done to demonstrate that the therapies are safe and effective in human patients. Through their Research Grant Program, C3 funds these types of studies as well as the development and testing of new therapeutic approaches.

How the LGMD2A/R1 Community Can Drive Research Forward

C3 encourages all patients to join their Global Patient Registry at **LGMD2A.org**. A major challenge in the development of treatments for rare diseases, such as LGMD2A/R1, is understanding disease symptoms and progression. The registry collects information directly from people living with LGMD2A/R1 about how the disease affects them. When the registry data is used for research purposes, all personalized data is removed to maintain privacy. The knowledge gained from this research helps scientists learn about the disease, design effective clinical trials, and identify where patients are so they can be contacted for trials.

C3 is committed to keeping the LGMD2A/R1 community informed. Patients who join their registry receive research news and are notified when there are clinical research studies such as trials of investigational drugs. C3 is excited about all the work being done to develop cures and treatments for LGMD2A/R1. They pledge to share updates as research progresses and opportunities arise. ■

Patients Who Have Gone Into Science Series

PART 2 Andrea Lane, PhD Candidate

LGMD2A/R1

Written By Rebecca Lucas Gregg

By Brad Williams, PhD
Director of Research, Jain Foundation

A Diagnosis Turned Into a Mission

Individuals living with LGMD often look to science, but Andrea Lane, a PhD candidate at Emory University who is living with LGMD2A/R1, has taken her interest in science a step further. Lane is currently studying biostatistics, which is the application of statistics to medical and public, health-related issues.

Biostatisticians work in several different areas. Perhaps most notably, many biostatisticians have been involved in assessing the data from the COVID-19 vaccine clinical trials to determine vaccine effectiveness. Lane says, "The great thing about biostatistics is that we can use our skills in several different health research areas. For example, most recently, I have conducted statistical analyses on projects related to diabetes, pediatric heart transplants, and COVID-19 immunoresponse."

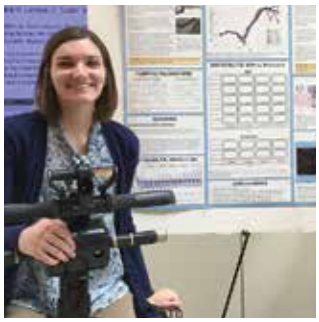
Biostatisticians develop new statistical methodology when needed. Recent technological innovations have spurred new types of data generation, triggering cutting-edge research questions, and supplementing traditional statistical methods which can be inadequate. Lane's dissertation project develops statistical methods for analyzing genetic and epigenetic data to better understand causal relationships between an exposure (e.g., smoking), our genetic material, and an outcome (e.g., cancer). Lane shares, "I felt like it provided a path for me to use my quantitative abilities to effect meaningful change in the community."

> **"I felt like it provided a path for me to use my quantitative abilities to effect meaningful change in the community."**

For Lane, living with LGMD has played an influential role in her career choice in a very practical way. She states, "I always enjoyed and excelled in math growing up. I decided to major in Math in college because I liked it and thought it could lead to a stable and fairly lucrative career." Later, Lane became fascinated by genetics when she took a genetics course in college. "Although I have not felt motivated to research LGMD specifically, I imagine my diagnosis influenced my interest in public health and genetic/genomic data. Now that I am in my mid-20s and

Right: Andrea presents her dissertation proposal titled, "Detecting Cell Type-specific Mediation Effects in DNA Methylation Data."

"Living with LGMD often requires creative problem-solving and the ability to adapt to change. These skills translate very well to a career in science."



my LGMD continues to progress, I see how expensive it is to have a disability. I think it is important for me to have a marketable skill that offers flexibility and financial support. As a biostatistician, I have a lot of flexibility in terms of where I can work, the ability to work from home with flexible hours, and I should be able to cover disability-related costs as they arise."

Lane recommends a career in science to those with LGMD. "Practically, careers in science offer flexibility and financial support that are great for people with LGMD. Moreover, any area of science is always growing and moving forward in new and exciting directions. The scientific community is so diverse and offers so many opportunities to pursue curiosity. Because it is a fast-paced and evolving field, curiosity and adaptability are important traits to have. Living with LGMD often requires creative problem-solving and the ability to adapt to change. These skills translate very well to a career in science."

If you are considering a scientific career, Lane recommends researching fellowships and grants, attending conferences, and participating in other programs that support students with disabilities. She says,"I was awarded an NSF Graduate Research Fellowship (a program that specifically prioritizes underrepresented groups, including persons with disabilities), and this fellowship gave me the necessary financial support to live independently in Atlanta while I pursue my PhD. In addition, I have attended multiple conferences for underrepresented students and students with disabilities in my field. These are funded opportunities to travel to new places and meet other students and researchers with disabilities."

"Don't be afraid of pursuing a career in science and pursuing a PhD," Lane encourages. "These things can sound daunting, but if you are interested in a particular area, you should pursue it! Perhaps most people picture a lab coat and chemicals when they hear the word 'science,' but the opportunities go far beyond that traditional image."

Lane's passion for science led her to pursue a career as a biostatistician. Where will your passions lead you? ▪

Do You Know Your Subtype

By Donavon Decker

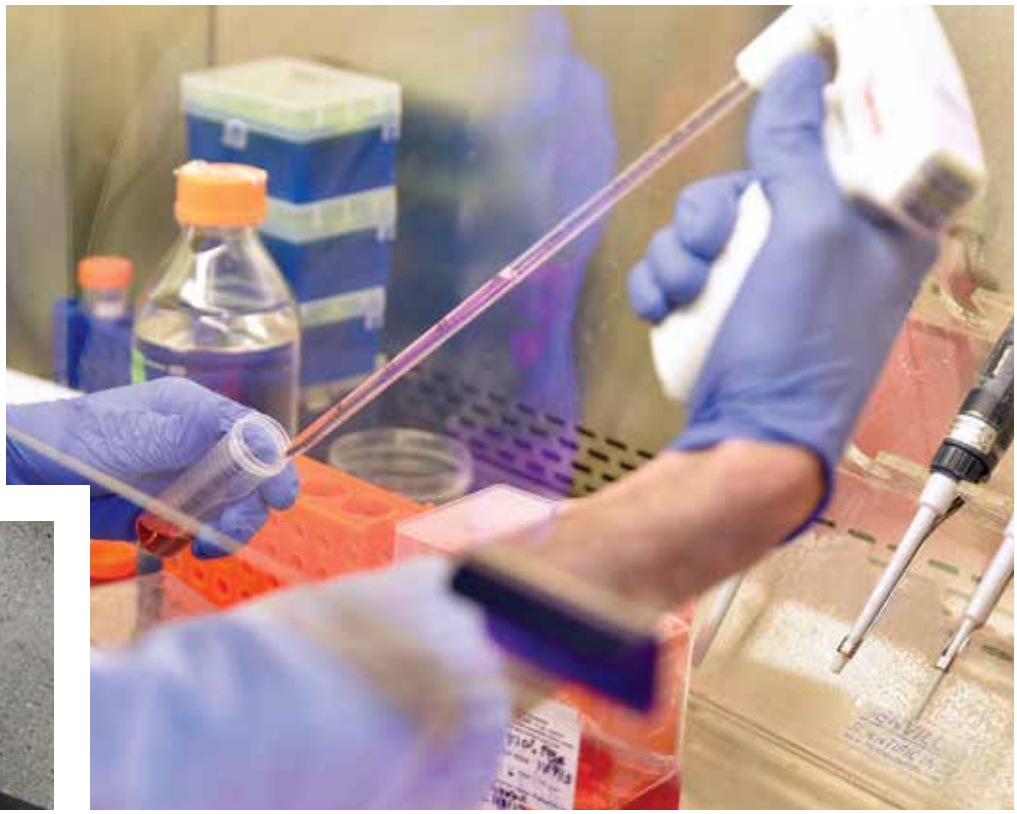
As an individual with LGMD, you may have wondered what you can do to support progress on the path to a cure. Testing that reveals which gene is connected to your specific subtype is an invaluable piece of LGMD research. Accurate and early gene identification of affected individuals allows for improved clinical outcomes and the opportunity to participate in clinical trials. The table below highlights three, free options for testing. Please visit each project's website for more detailed information. ▪

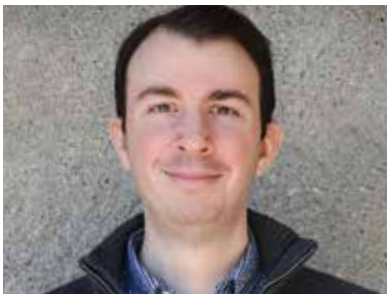
	1 Detect Muscular Dystrophy	2 The Lantern Project
Company	Invitae	PerkinElmer Genomics Sponsored by Sanofi Genzyme
URL Address	**Invitae.com/en/detect-muscular-dystrophy**	**LanternProjectDX.com**
Phone Number	1-800-436-3037	1-866-354-2910
Name of Test	Detect MD Program	Focused Neuromuscular Disease Panel
Genes Covered	211 genes including those causative of LGMD	66 genes including those causative of LGMD
Sample Requirements	3mL whole blood; saliva, assisted saliva, buccal swab and gDNA acceptable	Dried blood spots preferred; whole blood or saliva acceptable
Turnaround Time	10–21 calendar days (average 14 days) after specimen received	3 weeks
Genetic Counseling	Available to those tested in the U.S. or Canada, no charge	Not part of program currently
Eligibility Criteria	Individuals in eligible countries suspected of having muscular dystrophy as defined by symptoms listed on the website or having a family history of muscular dystrophy or evidence for muscular dystrophy through a muscle biopsy	1. Symptoms suggestive of LGMD or 2. Clinical diagnosis of unspecified LGMD requiring genetic confirmation
Test Ordering	By your doctor, or individuals with LGMD can schedule a genetic counseling session with an expert who can place the order.	By your doctor only
Availability Outside US	Canada, Australia, Argentina, Brazil, Chile, Colombia, Mexico	None
Notes	This program is not intended for carrier screening. Other tests available for inherited muscular dystrophies and neuromuscular conditions other than LGMD.	This program is not appropriate for carrier testing. No age restriction for panel. Panel includes genes causative of Pompe disease, Duchenne muscular dystrophy, and other myopathies and myasthenic syndromes.

3 The Rare Genomes Project

The Rare Genomes Project at the Broad Institute is another no-charge option available for those who have had prior genetic testing that was negative or did not provide a full genetic explanation. It is a research study using whole-genome sequencing (WGS) to try to find the genetic cause of rare diseases, including LGMD. You must have a suspected genetic condition, currently be under the care of a clinician, and live in the U.S. Eligible individuals will be asked to donate a blood sample and medical records. If a result is identified, it will be returned through your doctor. Visit **RareGenomes.org/limb-girdle-muscular-dystrophy** to learn more about this study.

This is not an exhaustive list of testing options for LGMD | **Other commercially available testing options through insurance or self-pay methods can be found at ConcertGenetics.com or NCBI.NLM.NIH.gov/gtr.**





Below: Christopher Anselmo, once grieved by his LGMD2B diagnosis, now works at MDA to strengthen others living with LGMDs.

Strength through Connection

The sooner you connect with people and organizations that understand what you are going through, the sooner you will feel empowered to fight back.

One of the greatest ironies of my life is that I now work for the Muscular Dystrophy Association (MDA), an organization I actively sought to avoid for three years.

When I first started experiencing symptoms of limb-girdle muscular dystrophy type 2B (LGMD2B) at age 21, I knew my life was about to change in significant ways. I needed to preserve my remaining strength and get ahead of my weakness. However, I was unprepared for the magnitude of the changes to come. No amount of planning prepared me for the trauma of losing the ability to run or experiencing my first fall. When I had to move out of the apartment that I shared with my college friends because it had too many stairs, I was mad at the world. My goals and dreams felt unattainable. Instead of seeking support, I internalized my struggles, even pushing away those closest to me.

I knew there were nonprofit organizations such as MDA and Jain Foundation that were researching my disease and could provide resources to navigate my new reality, but I wanted no part of them. To me, reaching out in this way felt like the disease had won. It took three years of needless suffering before I finally sought help.

In 2011, unable to shoulder this burden alone any longer, I finally opened up to my parents and sister. Although they knew I had this disease, they lived out-of-state, so they were not aware of just how much it was truly affecting me. I also talked to my closest friends and coworkers. Everyone was supportive and wanted to help in any way they

could. I couldn't help but wonder why I had waited so long to share about it.

With this foundation of support, I felt empowered to seek other resources and make additional connections. I reached out to Jain Foundation, whose mission is to find a cure for LGMD2B/dysferlinopathy, and MDA. Both organizations were instrumental, connecting me with information and support to help manage my disease. They really understood my struggles. I soon enrolled in Jain Foundation's natural history study for dysferlinopathy, eager to do my part to help researchers better understand the progression of my disease. Additionally, MDA opened me up to the wider neuromuscular disease community. I attended local events and blogged about my journey, which enabled me to befriend others who understood life with a neuromuscular disease. I was also connected to a neurologist through their MDA Care Center Network.

In 2014, I made the decision to leave my job at a tech company in Boston and enroll full-time in business school. I wanted to make a career change and work in the healthcare space for a company or organization working on muscular dystrophy.

Four years later, I joined MDA's Healthcare Partnerships Team in a market research and account management role, building relationships with biotech and pharma companies developing treatments for muscle diseases. Today, I am on the National Marketing Team in a research role. It is difficult but rewarding work.

It was not until I joined the MDA team, however, that I learned just how active MDA is in the limb-girdle space. On the research side, MDA helped to establish the Limb-Girdle Muscular Dystrophy Clinical Research Network, supporting seven sites that are building the tools and resources necessary to conduct therapeutic trials and bring treatments to the LGMD population. In addition, MDA has seven active grants, totaling nearly $900,000, and has invested $61 million into high-impact LGMD research since MDA's inception. MDA also supports LGMD education. Every year, MDA hosts the LGMD Engage Symposium, a one-day, virtual event which provides information to the community on the latest in research, standards of care, genetic testing, and lifestyle issues. From a policy standpoint, MDA's Advocacy Team has been active on issues affecting the LGMD community, including making sure air travel is accessible, modernizing FDA practices to speed up potential therapies, ending workplace discrimination, and ensuring that those with LGMD have access to affordable and quality healthcare. MDA has also worked closely alongside other LGMD organizations to urge the CDC to assign specific diagnostic codes for those diagnosed with LGMD, instead of the currently used "Other Muscular Dystrophy" code. This change would potentially shorten the diagnosis timeline patients face, deliver precise medical care, and improve clinical trials and future access to targeted treatments.

Above: As part of the MDA Advocacy Team, Christopher is active in raising awareness for important issues facing the LGMD community today.

Dealing with a life-altering disease is difficult. But as I have learned the hard way, the sooner you connect with people and organizations that understand what you are going through, the sooner you will feel empowered to fight back. Your struggle might even become your career. ■

Written by Christopher Anselmo
Market Intelligence Manager
Muscular Dystrophy Association

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MDA.org/Care/Request-Services

ResourceCenter@mdausa.org

1-833-ASK-MDA1

An Urgent Mission


Nathan Peck

Patients have to tell their story. Otherwise, no one will understand the burden of your disease.

Connect with Us

CureVCP.org

Four of Nathan Peck's family members were diagnosed with LGMD in the 1990s, but it was not until a researcher discovered the valosin-containing protein (VCP) gene mutation a decade later that his family truly understood their familial health struggles. In early stages of diseases, it is not uncommon for many to mimic one another. As they progress, more characteristics become apparent to differentiate other diseases from LGMDs. Genetic testing is crucial, as new discoveries are happening all the time. VCP disease is an ultra-rare, hereditary, adult-onset disease that can affect any combination of a patient's muscles, bones, and brain. About 90% of patients develop inclusion body myopathy (IBM) in their late 30s to early 40s, which very much resembles LGMD symptoms. Patients can also develop Paget disease of the bone (PDB) and frontotemporal dementia (FTD) (now called IBMPFD), and/or amyotrophic lateral sclerosis (ALS).

Nathan witnessed his mother's struggle with the debilitating symptoms of the disease over a twenty-year period prior to her passing away in 2014, at the age of 65. During that time, he and his wife, Allison, were determined to make the most of life, rather than worry about the potential that he may develop the disease as well. However, in time, Nathan began to experience muscle weakness, which led him to pursue genetic testing, confirming a diagnosis of VCP disease.

Nathan's diagnosis inspired him to start a nonprofit, Cure VCP Disease, Inc., in early 2018. His organization is committed to bringing together patients, caregivers, researchers,


Nathan Peck and family

pharmaceutical companies, other nonprofits, and industry to identify treatments and ultimately a cure for this rare, genetic disease. In November 2021, Cure VCP Disease was one of 40 organizations selected to join the Chan Zuckerberg Initiative's Rare As One Project, which awarded $13 million dollars in grants aimed at supporting the work that patient communities are doing to drive progress in the fight against rare diseases.

Nathan explains that the most important aspect of his nonprofit is patient involvement. "Patients have to tell their story. Otherwise, no one will understand the burden of your disease." His nonprofit is currently funding two natural history studies, one with Nationwide Children's Hospital and another with Casimir, and he explains that it is vital for patients to participate as much as possible. "Patients are the most important catalyst in rare disease research, and it is up to each of us to get involved … Our rare diseases have a much better chance of finding a cure when patients enroll in registries, participate in natural history studies, and become active members on social media groups. This is the best way to take control of your disorder and be your own health advocate."

To learn more about VCP, please visit **CureVCP.org**. ▪

Written by Nathan Peck
Founder, CureVCP Disease, Inc.

Contributed by Rebecca Lucas Gregg

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Your Voice Will Make a Difference!

The LGMD community will be leading an Externally-Led Patient-Focused Drug Development (EL-PFDD) meeting with the Food and Drug Administration (FDA) and other stakeholders on September 23, 2022.

What will happen at this EL-PFDD meeting? This important, monumental effort will give individuals diagnosed with limb-girdle muscular dystrophy types 2A, 2C, 2D, 2E, 2F, and 2I an opportunity to share with the FDA and other stakeholders about the experiences and challenges of living with LGMD.

What do we hope to gain? The EL-PFDD meeting is designed to engage patients and elicit their unique perspectives. With this information, our goal is to enable the FDA and other stakeholders to knowledgeably review and approve LGMD therapies that meet the needs and expectations of our patient community.

Coalition to Cure Calpain 3 — Overcoming Weakness With Strength
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For more information and to learn how to get involved in this endeavor, please visit www.TheSpeakFoundation.com/PFDD.