## What is Calpainopathy (LGMD2A, LGMDR1, and LGMDD4)?

The limb-girdle muscular dystrophies (LGMD) are a group of genetically inherited, progressive, muscle-wasting diseases. Limb-girdle muscular dystrophyies types 2A/R1 (LGMD2A/R1) and D4 (LGMDD4) are subtypes specifically caused by defects in the calpain 3 gene (*CAPN3*).

LGMD2A is the way the disease has been classified since its discovery, but LGMDR1 is an updated way to describe the same disease, with the R referring to the recessive mode of inheritance. More recently, researchers have observed that some families pass on the condition in a dominant mode of inheritance. This is called LGMDD4, with the D referring to dominant. Collecively, these are called Calpainopathy.

The calpain 3 gene provides instructions for making the calpain 3 enzyme in our bodies. The calpain 3 enzyme is a protein involved in the maintenance of muscle integrity and function. When there is a mutation, or change, in the *CAPN3* gene, it causes the enzyme to not work as it should, leading to the symptoms related to Calpainopathy. There are several theories about the function of calpain 3 and why mutations in calpain 3 cause muscular dystrophy, including its involvement in the process of muscle rebuilding. However, the exact role of calpain 3 in proper muscle functioning is not fully understood.

Because Calpainopathy is a genetically inherited condition, patients are born with the disease, but the age when symptoms begin can vary from early childhood to well into adulthood. In most cases of LGMD2A/R1, patients experience symptoms by age 20. Individuals with LGMDD4 tend to have a later onset. Typically, earlier onset of the disease is related to more severe symptoms over time. The speed of progression varies between patients, even within the same family, and is often not linear.

## What is the prevalence of Calpainopathy?

Calpainopathy is the most common form of limb-girdle muscular dystrophy, representing an estimated 20% of all LGMD cases. However, LGMD2A/R1 and LGMDD4 are still categorized as rare diseases; scientists estimate that they affect about 1-5 in every 100,000 people.

## What are the key symptoms and features of Calpainopathy?

Patients with Calpainopathy typically have normal early motor milestones (i.e. walking age), but signs of muscle deterioration can be detected by elevated creatine kinase (CK) levels in the blood. Early signs include a “waddling” gait, walking on tiptoes, scapular winging (shoulder blades protrude from the back), and/or difficulty climbing stairs. Some patients also report fatigue or muscle pain as early symptoms.

Calpainopathy affects large muscles the most, and results in both weakness and reduced exercise endurance. About half of patients experience muscle contractures, which may cause toe-walking and reduced range of motion.

Eventually, patients have difficulty with daily living activities such as climbing stairs, rising from a chair, or getting up off the floor. Patients typically lose their ability to walk within 10-30 years from the first onset of symptoms, although this varies greatly from person to person.

Unlike some other forms of muscular dystrophy, heart and lung involvement is fortunately rare, and life expectancy may be near normal. Calpainopathy does not affect muscles in the face or cause intellectual impairment or behavioral disorders.

## What is the difference between Calpainopathy and other muscular dystrophies?

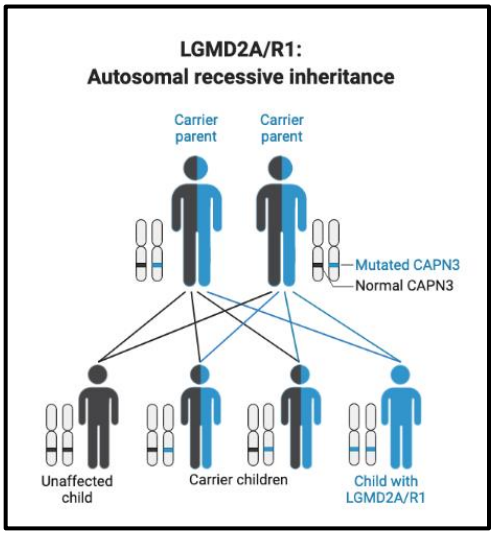
Each form of muscular dystrophy is caused by a different genetic defect, which is why there are such large differences between the ages of onset, the types of symptoms, and the progression of symptoms. Calpainopathy is less severe than more common forms of muscular dystrophy, such as myotonic dystrophy and Duchenne, and unlike Duchenne, it affects both genders. The large differences in the biology of muscular dystrophies make it important to obtain an accurate diagnosis.

Each of these diseases must be studied separately to develop therapeutics that will be effective. One unique feature of Calpainopathy is that the mutation affects the calpain 3 enzyme, as opposed to a structural protein, as in many muscular dystrophies. This difference means that therapies that work for one type of muscular dystrophy – or even one type of LGMD - will not necessarily be effective for Calpainopathies.

## How is LGMD2A/R1 inherited?

We all receive two copies of each gene, one from each of our parents. Genes contain copies of instructions for how our body should look, grow, and develop. Within each of those genes, there are variations present that make us unique as individuals. These changes can be passed down from parent to child. Sometimes, those changes don't allow the gene product - in this case, Calpain 3 - to work as it should.

LGMD2A/R1 is inherited in an autosomal recessive manner, which means that a person needs two abnormal copies of the gene to develop LGMD2A/R1. This type of inheritance often – though not always – leads to siblings who have the same condition.

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## What are LGMD2A/R1 carriers?

Individuals who have one copy of the abnormal gene containing an LGMD2A/R1-associated gene variant are not affected but are carriers and can pass the abnormal gene to their children. If both parents are carriers for LGMD2A/R1 and neither is affected, there is a 25% chance their child will have LGMD2A/R1, a 50% chance the child will be a carrier for the disease, and a 25% chance the child will have two normal genes (unaffected and not a carrier).

More information about inheritance of LGMD2A/R1 and LGMDD4 is available here: [www.curecalpain3.org/did-you-know-there-are-two-ways-that-Calpainopathy-can-be-inherited/](www.curecalpain3.org/did-you-know-there-are-two-ways-that-Calpainopathy-can-be-inherited/)

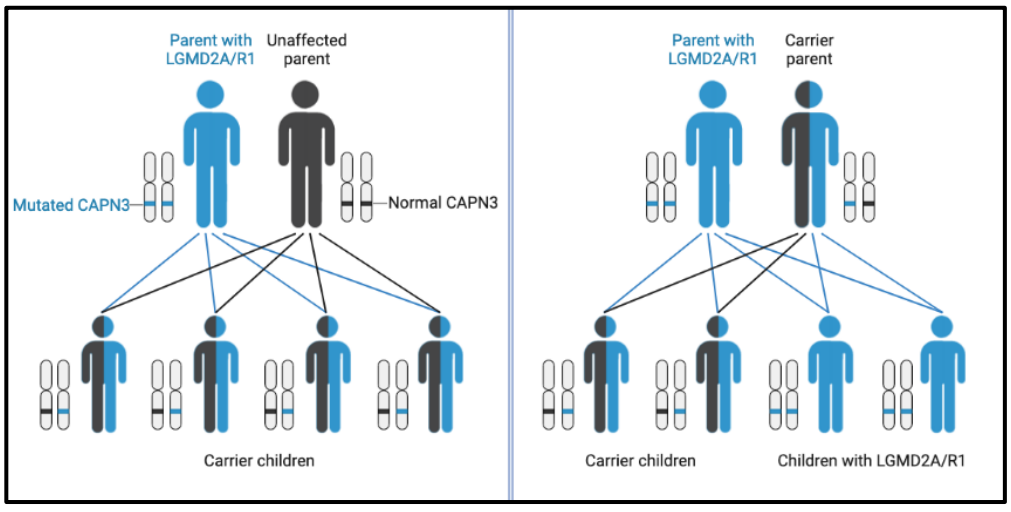
A genetic counselor can help you understand your genetic test results.

## Can an individual with LGMD2A/R1 pass the disease on to their children?

Transmission of LGMD2A/R1 to children depends on the mutational status of each parent's *CAPN3* gene. The presence of *CAPN3* mutations can be detected by genetic testing blood or saliva samples. Your healthcare provider can help you determine which test is best for you.

An individual affected with LGMD2A/R1 has two non-working copies of *CAPN3*, so their children will, by default, inherit a non-working copy. If their partner has two normal copies of the *CAPN3* gene, then their children will each have one normal and one mutated gene. This means that all children will be carriers and will not be affected by LGMD2A/R1. Because *CAPN3* mutations (also referred to as variants) are very rare, this is the most common scenario.

In the unlikely situation where one parent is affected and one parent is a carrier, each child has a 50% chance of being a carrier and a 50% chance of having LGMD2A/R1.

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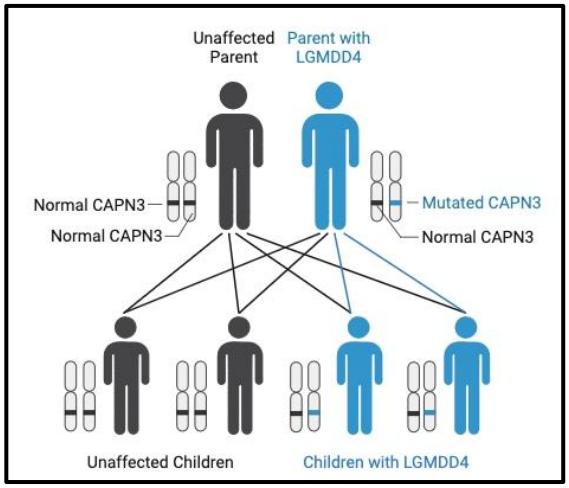
A genetic counselor can help you assess your risk of passing on LGMD2A/R1 to future children.

## How is LGMDD4 inherited?

LGMDD4 is inherited in an autosomal dominant manner, which means just one abnormal copy of the gene causes an individual to develop the condition. This type of inheritance can lead to parents passing on the condition to their children.

If one parent is affected by LGMDD4, then there is a 50% chance their child will have muscular dystrophy and a 50% chance that the child will have two normal genes (unaffected and not a carrier).

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Click here for a list of CAPN3 variants that have been associated with autosomal dominant inheritance. A genetic counselor can help you understand your genetic test results.

## How is Calpainopathy diagnosed?

The most reliable way to diagnose Calpainopathy is by performing a genetic test on a blood or saliva sample, which can confirm the presence of one or more mutations in the calpain 3 gene. Alternatively, Calpainopathy can be diagnosed by performing calpain 3 immunoblot analysis on tissue collected via a muscle biopsy. These studies can tell us whether the protein is present and whether it has the normal, expected, biological activity. A biopsy must be performed in a hospital and requires sedation, while a genetic test is non-invasive and usually less expensive.

C3 strongly encourages all patients to obtain a genetic diagnosis. Knowing a patient's exact variant(s) is necessary for future clinical trials to evaluate potential therapies. Additionally, clinical trials will likely require a genetic diagnosis for eligibility, since researchers must be sure that study participants are affected by LGMD2A/R1 or LGMDD4 and not some other condition.

Several companies provide genetic testing for patients with undiagnosed muscle weakness. Although the cost of genetic testing is falling each year, some insurers remain resistant to reimbursing. If your neurologist suspects you have Calpainopathy and you are having difficulty obtaining a genetic test, please contact us at info@curecalpain3.org

## What treatments are currently available?

There is currently no treatment that stops the progression of Calpainopathy. However, some interventions may be helpful for certain symptoms of the disease. For example, stretching and physical therapy help prevent or lessen muscle contractures. Gentle exercise can help to maintain muscle strength and reduce the effects of disease progression. All exercise regimens should be undertaken cautiously and with the guidance of a neurologist, since too much high intensity activity could actually increase the rate of muscle deterioration.

Individuals with Calpainopathy should see a neurologist regularly (usually every 6-12 months) to monitor the progression of the disease. The neurologist can make referrals to other specialists and physical therapists as needed and address secondary symptoms which may arise. For example, pulmonary complications may develop in some patients, which may require monitoring by an appropriate specialist.

## How might the disease be treated or cured?

Coalition to Cure Calpain 3 is actively funding scientific research projects to find a treatment or cure for Calpainopathy.

One potential cure cure for Calpainopathy would involve gene editing where the *CAPN3* gene mutations are “fixed,” or gene therapy where the healthy gene is introduced to replace the defective one. In both cases, cells would begin producing a working calpain 3 enzyme, which would enable the patient’s muscles to function and grow normally. There is early research currently studying gene editing and gene therapy for LGMD2A/R1. Gene therapies for several other types of LGMDs are currently being tested in clinical trials.

Some scientists believe that stem cell therapy might also be able to cure Calpainopathy. Stem cells are cells that have the unique ability to self-renew and to transform into many specialized cell types. In this case, stem cells with a working gene would be introduced into the patient, where they could develop into muscle cells. It is important to understand that this type of treatment is still in development and has not been proven to treat muscular dystrophy. “Stem cell clinics” advertising a cure for Calpainopathy are exploiting the hopes of patients and their families. Not only are these treatments unproven and unlikely to be beneficial to patients, but they can even harm patients. Additionally, patients who undergo these procedures may be ineligible to participate in future clinical trials.

Scientists are currently attempting to understand the basic workings of the calpain 3 enzyme, including the molecular function(s) it has in muscle cells. Once these roles are

understood, researchers will be able to search for drugs which regulate the same functions. This approach will not directly cure the disease, but might improve patient strength and muscle health, and/or slow the progression of the disease.

### Are there any clinical trials underway?

There are some clinical trials underway to study the usual progression of different forms of muscular dystrophy, including Calpainopathy; these are usually called natural history studies.

The best way to stay up-to-date on clinical trials is to join the C3 mailing list and our patient registry (https://LGMD2A.iamrare.org), as we will use these mailing lists to keep members informed about the latest research and clinical trials. C3 has compiled information about clinical research and a list of studies that are currently recruiting at www.curecalpain3.org/clinical-research-study-opportunities/ ; this page is updated regularly.

### What is Coalition to Cure Calpain 3 (C3)?

Coalition to Cure Calpain 3 (C3) was founded in October 2010 as a non-profit organization to fulfill a mission to fund high potential research and clinical trials while educating the global community about Calpainopathy, a rare muscle-wasting disease. Our founders Jordan Boslego, Kristine Kurnit, Lee Wrubel, and Michele Wrubel were frustrated that LGMD2A/R1 attracted significantly fewer research dollars than some of the more common forms of muscular dystrophy (MD), such as Duchenne MD, and thus fewer researchers focused on understanding the disease and discovering a cure. The pinpoint focus of C3 is to drive research for a cure. Funds that are raised support scientific research grants, conferences to bring researchers together to exchange ideas and collaborate, and the LGMD2A/Calpainopathy Registry.

Dr. Jennifer Levy, C3 Scientific Director, is advancing this mission. C3 is currently focused on developing a “toolbox” of building blocks essential for scientists to conduct research on Calpainopathy and for pharmaceutical companies to be able to conduct clinical trials in the disease. This toolbox includes a patient registry, natural history studies and outcome measures, animal models, and fundamental research on the biology of the disease. C3 is also funding research into potential therapeutic methods, such as gene therapy, gene editing, and non-genetic drug therapies.

### What has C3 accomplished since its founding?

C3’s accomplishments since its founding in 2010 include:

- Establishing a research grant program to stimulate research into both the biology of Calpainopathy and the development of therapies: As of May 2026, 24 Calpainopathy-related research grants have been awarded to investigators around the world, including University of California Los Angeles, Harvard Medical School, Généthon, and Stanford University, with a total funding commitment of $3,000,000+.

- Attracting renowned researchers to the field of Calpainopathy research, which helps us build a critical mass of scientists and ideas to drive potential treatments and future approved drugs
- Building a Scientific Advisory Board that includes scientific leaders in Calpainopathy research
- Launching the first and only global Calpainopathy patient registry and conducting extensive patient outreach:It is critical for future clinical trials that we have a registry that is comprehensive and accurate. This is essential for the planning and conducting of clinical trials, so we encourage all patients to obtain a genetic diagnosis.
- Organizing scientific conferences dedicated specifically to Calpainopathy, held in the US and Europe: The 2011 meetingwas the first-ever gathering of scientists from around the world, convened forthe sole purpose of exchanging knowledge and ideas about LGMD2A/R1 and LGMDD4. The most recent conference in 2024 included researchers, industry representatives, clinicians, physical therapists, and patients.
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## What is the purpose of the LGMD2A/Calpainopathy Registry?

A patient registry is a collection of standardized information about a group of patients who share a condition. The information may be used for a variety of purposes such as conducting natural history studies and supporting disease-specific clinical trial recruitment. The LGMD2A/Calpainopathy Registry serves to:

- Support the design of clinical trials that explore new Calpainopathy treatments;
- Describe the people who have Calpainopathy and how Calpainopathy may be different for different people;
- Understand how Calpainopathy changes over a person's lifetime;
- Learn how Calpainopathy is treated and how people respond to those treatments;
- Help to develop best practices, management guidelines, and recommendations so that clinicians can know how to give the best care to improve the quality of life and outcomes of people with Calpainopathy; and
- Identify people with Calpainopathy who might be willing to take part in other research studies or clinical trials. You will be able to choose whether you want to hear about these other studies. If you choose to, you will be contacted by registry staff on behalf of outside researchers to inform you about these studies.

The LGMD2A/Calpainopathy Registry is sponsored by Coalition to Cure Calpain 3 and hosted by the National Organization for Rare Disorders (NORD®) on their IAMRARE® platform. Learn more here.

## How can I help find a cure?

If you are a patient, it is important to join our patient registry and keep your contact information up-to-date so that you can be contacted if there are clinical trial opportunities. The registry can be found at https://LGMD2A.iamrare.org.

If you are a patient, family member, friend, or anyone interested in our work, we encourage you to join the C3 email list to stay informed about our organization and the latest news on our research and scientific advances in the field: https://conta.cc/4bqW04D

Beyond joining the patient registry, the best thing you and your supporters can do to help C3 find a cure is to donate to us and help us fundraise. C3 has assembled an esteemed Scientific Advisory Board to help us identify the most promising research avenues, which we then fund from our donations. Scientific research is very expensive, and the development and regulatory approval of a therapy will cost hundreds of millions of dollars. For this reason, C3 is focused on making a big impact with small investments by focusing on foundational Calpainopathy research that will attract interest in the disease from larger funding organizations and industry.

To make a donation, please visit our site and click on the DONATE button.

### Who can I contact with additional questions?

We are always happy to connect with patients and their families! For general questions, please e-mail C3 at info@curecalpain3.org. For questions related to the patient registry, please e-mail registry@curecalpain3.org.