COALITION TO CURE CALPAIN 3
OVERCOMING WEAKNESS WITH STRENGTH

FAQs for Patients and Families

Updated March 2022

What is LGMD2A/R1 and what are its key symptoms and features?

Limb-girdle muscular dystrophy type 2A/R1 (LGMD2A/R1) is a progressive muscle-wasting disease caused by defects in the calpain 3 gene. LGMD2A/R1 is sometimes referred to as calpainopathy or limb-girdle muscular dystrophy type R1-calpain 3 related. The calpain 3 gene encodes the calpain 3 enzyme, which is involved in the maintenance of muscle integrity and function. There are several theories about the function of calpain 3 and why mutations in calpain 3 cause muscular dystrophy, but the exact role of calpain 3 in proper muscle functioning is not fully understood.

Because LGMD2A/R1 is genetically inherited, patients are born with the disease, but the age of symptom onset can vary, from early childhood to well into adulthood. In most cases, patients experience symptoms by age 20. Typically, the earlier the onset of the disease, the more severe the symptoms will be over time. The speed of progression varies between people and is often not linear.

Individuals with LGMD2A/R1 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. About half of LGMD2A/R1 patients experience muscle contractures, which may cause toe-walking and scoliosis and may be painful. LGMD2A/R1 affects large muscles most, and results in both weakness and reduced exercise endurance. Eventually, patients have difficulty with daily living activities such as climbing stairs, rising from a chair or getting up off of the floor. Patients typically lose their ability to walk within 10-30 years from the first onset of symptoms.

Unlike some other forms of muscular dystrophy, heart and lung involvement is fortunately rare, and life expectancy may be near normal. LGMD2A/R1 does not affect muscles in the face or cause intellectual impairment or behavioral disorders.

What is the difference between LGMD2A/R1 and other muscular dystrophies?

Each form of muscular dystrophy is caused by a different genetic defect, which is why each of these diseases must be studied separately to develop therapeutics that will be effective. The large differences in the biology of muscular dystrophies make it important to obtain an accurate diagnosis.

LGMD2A/R1 is the most common single form of limb-girdle muscular dystrophy (LGMD), representing an estimated 20% of all LGMD cases. However, LGMD2A/R1 is a rare disease; while scientists do not know precisely how common it is, it is estimated that it affects about 1-10 in every 100,000 people.

LGMD2A/R1 is less severe than more common forms of muscular dystrophy, such as myotonic dystrophy and Duchenne, and unlike Duchenne it affects both genders. One unique feature of LGMD2A/R1 is that the mutation affects the calpain 3 enzyme, as opposed to a structural protein as is the case in most muscular dystrophies. This may make the treatment of LGMD2A/R1 more straightforward.

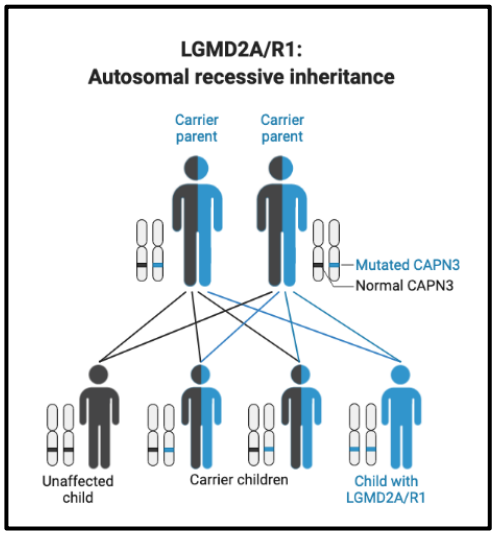
How is LGMD2A/R1 diagnosed?

The most reliable way to diagnose LGMD2A/R1 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, LGMD2A/R1 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 for LGMD2A/R1. Knowing a patient's exact mutation(s) is necessary for future clinical trials to evaluate potential therapies for LGMD2A/R1. Additionally, clinical trials will likely require a genetic diagnosis for eligibility, since researchers must be sure that study participants are affected by LGMD2A/R1 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 LGMD2A/R1 and you are having difficulty obtaining a genetic test, please contact us at info@curecalpain3.org

How is LGMD2A/R1 inherited?

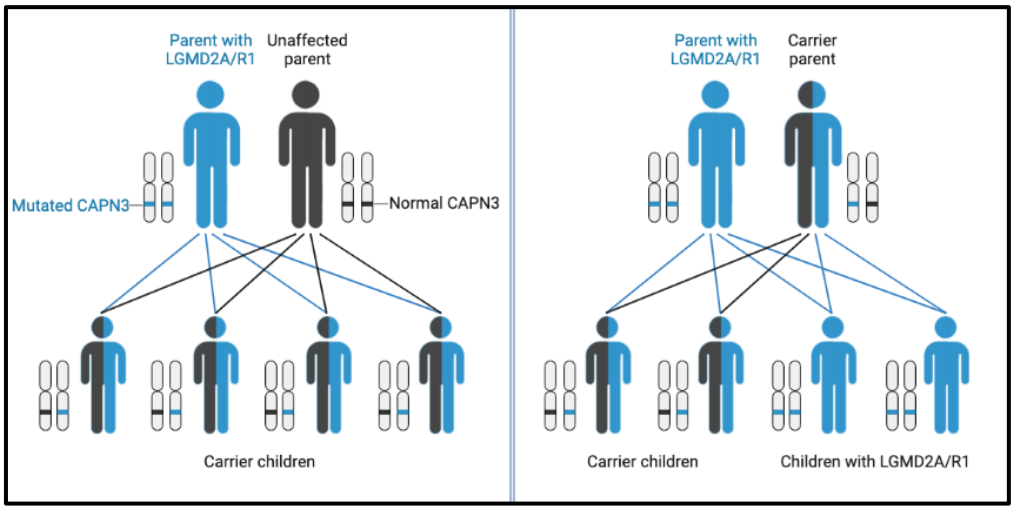
LGMD2A/R1 is inherited in an autosomal recessive manner, which means that it can be passed on through families, and that siblings can have the disease. In this recessive form, two copies of the abnormal gene must be present to develop LGMD2A/R1. Individuals who have one copy of the abnormal gene are 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).



Another form of calpainopathy, LGMD1I (also called limb-girdle muscular dystrophy type D4-calpain 3 related or LGMDD4) is inherited in an autosomal dominant manner. More information about inheritance of LGMD2A/R1 and LGMD1I/D4 is available here. 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. If an individual with LGMD2A/R1 has children with an individual with 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 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.

What treatments are currently available?

There is currently no treatment that stops the progression of LGMD2A/R1. However, some interventions may be helpful for certain symptoms of the disease. For example, stretching and physical therapy help prevent or lessen muscle contractures. Some people take certain dietary supplements such as coenzyme Q10; however, there is no data to support the benefit of supplements for LGMD2A/R1.

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 LGMD2A/R1 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 and cardiac complications may develop in some patients, which may require monitoring by an appropriate specialist.

How might the disease be treated or cured?

A cure for LGMD2A/R1 would involve gene editing where the calpain 3 gene mutations are 'fixed,' or gene therapy where the healthy calpain 3 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 muscular dystrophies are currently being tested in clinical trials.

Some scientists believe that stem cell therapy might also be able to cure LGMD2A/R1. 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 calpain 3 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 LGMD2A/R1 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 LGMD2A/R1; these are usually called natural history studies. There are also trials studying certain types of therapies, such as gene therapies, which may help in treating several diseases including LGMD2A/R1 but are not currently being studied for LGMD2A/R1.

The best way to stay up-to-date on clinical trials is to join the C3 mailing list and our patient registry, 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 on our website; this page will be updated regularly. You can also search http://www.clinicaltrials.gov for information about LGMD-related trials in the United States.

What is Coalition to Cure Calpain 3 (C3)?

Coalition to Cure Calpain3 (C3) is a non-profit organization founded in 2010 by two individuals affected by LGMD2A/R1. C3's mission is to drive high-potential research and clinical trials as we educate the global community about calpainopathy.

C3 is specifically dedicated to understanding and curing LGMD2A/R1. LGMD2A/R1 is one of over 50 different diseases addressed by the Muscular Dystrophy Association (MDA), and MDA has not historically funded research focused on LGMD2A/R1. Because LGMD2A/R1 is less frequent and usually less severe than some common forms of muscular dystrophy, such as Duchenne Muscular Dystrophy, it attracts significantly fewer research dollars and thus fewer researchers are working to understand the disease and discover a cure.

The 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 initiatives related to patient outreach and accurate diagnosis for the LGMD2A/R1 registry.

To advance this mission, C3 is currently focused on developing a "toolbox" of building blocks essential for scientists to conduct research on LGMD2A/R1 and for pharmaceutical companies to be

able to conduct clinical trials in the disease. This toolbox will include 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:

- Forming a Scientific Advisory Board that includes scientific leaders in LGMD2A/R1 research
- Launching the first and only global LGMD2A/R1 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 LGMD2A/R1, held in the US and Europe, which represented the first-ever gathering of scientists from around the world for the sole purpose of exchanging knowledge and ideas about LGMD2A/R1
- Establishing a research grant program to stimulate research into both the biology of LGMD2A/R1 and the development of therapies. As of March 2022, 14 LGMD2A/R1-related research grants have been awarded to investigators around the world, including University of California Los Angeles, Harvard Medical School, Généthon, and the Jackson Laboratories, with a total funding commitment of nearly $2,000,000.
- Attracting renowned researchers to the field of LGMD2A/R1 research, which helps us build a critical mass of scientists and ideas to drive potential treatments and future approved drugs

What is the purpose of the LGMD2A/R1 patient registry?

Without an organized patient community, LGMD2A/R1 is likely to remain a neglected disease: researchers and pharmaceutical companies will be discouraged from conducting research and clinical trials, and fundraising will be extremely difficult. In order to conduct clinical trials to evaluate therapies and learn about the disease, researchers need to have an accurate estimate of the number of patients with LGMD2A/R1.

If a drug is discovered which might be effective for LGMD2A/R1, pharmaceutical companies will only fund its development if there is evidence that a sufficient number of patients can be enrolled in clinical trials and that there will be a market for the drug after it is approved. Therefore, our registry is essential to demonstrate to pharmaceutical drug developers and funding organizations that there is a population of patients who are affected by LGMD2A/R1 and interested in a cure.

Please register at http://www.LGMD2A.org Our registry has a robust privacy policy, and personally identifiable patient data is never shared with a third party without obtaining permission from the registrant.

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 http://www.LGMD2A.org.

You should also join the C3 email list to stay informed about our organization and the latest news on LGMD2A/R1 research.

Beyond joining the patient registry, the best thing you can do to help C3 find a cure is to donate to us and help us fundraise. C3 has assembled a reputable 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. However, C3 is focused on making a big impact with small investments by focusing on C3 foundational research that will attract interest in the disease.

To make a donation, please visit https://donatenow.networkforgood.org/C3. If you are interested in magnifying your impact by hosting a fundraiser, we would be happy to assist you; please contact us at info@curecalpain3.org.

Who can I contact with additional questions?

For general questions, please e-mail C3 at info@curecalpain3.org. For questions related to the patient registry, please e-mail contact@LGMD2A.org.