FAQ for Patients and Families

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

Limb-girdle muscular dystrophy type 2A (LGMD2A), which is also called calpainopathy, is a progressive muscle wasting disease caused by defects in the calpain-3 gene. 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 yet understood.

As a genetic disease, patients are born with LGMD2A, but the age of onset of symptoms varies widely, 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 over time. The speed of progression varies between people, and is often not linear.

Individuals with LGMD2A typically have normal early motor milestones (i.e. walking age), but signs of muscle deterioration can be detected by elevated creatine kinase (CK) levels. About half of LGMD2A patients experience muscle contractures, which may cause toe-walking and scoliosis. LGMD2A 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 does not affect muscles in the face, or cause intellectual impairment or behavioral disorders.

What is the difference between LGMD2A and other muscular dystrophies?

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

LGMD2A is the most common single form of limb-girdle muscular dystrophy (LGMD), representing an estimated 40% of all LGMD cases. However, LGMD2A is a rare disease; while scientists do not know precisely how common it is, it is estimated that it affects about 1 in every 43,000 people.

LGMD2A is much less severe than more common forms of muscular dystrophy, such as myotonic dystrophy andDuchenne, and unlike Duchenne it commonly affects both genders. One unique feature of LGMD2A 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 more straightforward.

How is LGMD2A diagnosed?

The best way to diagnose LGMD2A is via a genetic test, which can confirm the presence of a specific mutation or mutations in the calpain-3 gene. LGMD2A can also be diagnosed by a muscle biopsy in certain cases, via a calpain-3 immunoblot analysis, or an assay of calpain-3 autolytic function in muscle.

The genetic test for LGMD2A is less expensive and more accurate than a muscle biopsy. A biopsy must be performed in a hospital and requires sedation, while a genetic test is non-invasive and can be analyzed in a lab using a DNA sample such as blood or saliva.

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

Although the cost of genetic testing is falling each year, some insurers remain resistant to reimbursing. If your neurologist suspects you have LGMD2A and you are having difficulty obtaining a genetic test, please contact us at info@curecalpain3.org.

Can LGMD2A be passed on to children?

LGMD2A is autosomal recessive, which means that it can be passed on through families, and that siblings can have the disease. Because it is recessive, for LGMD2A to develop, two copies of the abnormal gene must be present. 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 and neither are affected, there is a 25% chance their child will have LGMD2A, 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).

A graphical illustration of the inheritance pattern is available for download.

What treatments are currently available?

There is currently no treatment or cure available for LGMD2A. However, some interventions may be helpful for certain symptoms of the disease. For example, stretching and physical therapy may help prevent or lessen muscle contractures, and there is suggestive evidence that certain dietary supplements — such as coenzyme Q10 — may slow the rate of deterioration in muscle strength.

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 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. Because pulmonary and cardiac complications can develop in some patients, it is important to have a regular pulmonary function test and echocardiogram (annually, or as recommended by a neurologist) to ensure that the lungs and heart are working normally.

How might the disease be treated or cured?

The most complete cure for LGMD2A would involve direct gene editing or replacement, wherein the correct calpain-3 gene is substituted to replace the defective one. In such a case, cells would begin producing a working calpain-3 enzyme, which would enable the patient's muscles to function and grow normally. Scientists are currently studying gene therapy for LGMD2A as well as other muscular dystrophies. This approach involves

"infecting" the patient with a virus containing cells with a working version of the gene, which could then partially restore calpain-3 expression.

Some scientists believe that stem cell therapy might also be able to cure LGMD2A. In this case, stem cells with a working calpain-3 gene would be introduced into the patient, where they could differentiate into muscle cells.

It is also likely that a drug could be developed to either treat or cure LGMD2A. Scientists are currently attempting to understand the basic workings of the calpain-3 enzyme, including the pathways in which it interacts in muscle cells. Once these pathways are understood, researchers will be able to search for drug compounds which interact with the same pathways, to substitute for a working calpain-3 enzyme. Or, if another similar enzyme is discovered, researchers could develop a drug which might substitute for the absent calpain 3 enzyme.

Other therapies downstream of the calpain-3 enzyme, which do not directly cure the disease, might improve patient strength and function, and/or slow the progression of the disease. For example, there is some evidence that myostatin inhibitors — which are currently being developed by several pharmaceutical companies — might be effective in treating LGMD2A.

Are there any clinical trials underway?

There are some clinical trials underway to study the progression of different forms of muscular dystrophy, including LGMD2A; these are usually called natural history studies. There are also trials underway studying certain therapies, such as myostatin inhibition, which may be effective in treating several diseases including LGMD2A. However, there are currently no clinical trials evaluating a specific therapy for LGMD2A.

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 studies and clinical trials. You can also search http://www.clinicaltrials.gov for information about LGMD-related trials in the United States, and follow C3's Facebook group.

What is Coalition to Cure Calpain 3 (C3)?

Coalition to Cure Calpain 3 (C3) is a non-profit organization founded in 2010 by two individuals affected by LGMD2A. C3's mission is to fund high-potential research and clinical trials as we educate the global community about calpainopathy.

Before C3, there was no organization dedicated specifically to understanding and curing calpainopathy. For example, LGMD2A is just one of 42 different diseases encompassed by the Muscular Dystrophy Association (MDA), and MDA has not historically funded research focused on LGMD2A in a material way. Because LGMD2A is less prevalent and usually less severe than the some common forms of muscular dystrophy, it attracts significantly fewer research dollars and thus fewer researchers working to understand the disease and discover a cure.

The sole focus of C3 is to support research for a cure; C3 does not provide services to those who have the disease. All funds that are raised go directly into activities such as research grants, conferences to bring researchers together to exchange ideas and collaborate, and supporting initiatives related to to patient outreach and diagnosis.

To advance this mission, C3 is currently focused on building a "tool box" of building blocks necessary for scientists to conduct research on LGMD2A and for pharmaceutical companies to become interested in the disease. This toolbox will include a patient repository, 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.

What has C3 accomplished since its founding?

C3's accomplishments since its founding in 2010 include:

- Assembling a dedicated Board of Directors, and a Scientific Advisory Board composed of respected scientists and professors, to advance our mission
- Launching the first and only global LGMD2A patient registry, and conducting extensive patient outreach via social media
- Hosting two scientific conferences, held in Los Angeles and Amsterdam, which represented the first-ever gathering of scientists from around the world for the sole purpose of exchanging knowledge and ideas about LGMD2A

- Awarding 3 LGMD2A-related research grants, valued at over $500,000, to investigators at UCLA, Harvard Medical School, and Généthon

What is the purpose of the LGMD2A patient registry?

Without an organized patient community, LGMD2A is likely to remain a neglected disease: researchers will be discouraged from doing work which requires patient studies, and fundraising will be extremely difficult.

In order to conduct clinical trials to evaluate therapies and learn about the disease, researchers need a way to contact patients with LGMD2A so that they can recruit participants. Additionally, if a drug is discovered which might be effective for LGMD2A, pharmaceutical companies will only be willing to fund its development if they believe there will be a market for the drug after it is approved. In this way, our registry is essential to demonstrate to researchers and funding organizations that there is a critical mass of patients affected by LGMD2A and interested in a cure.

In addition to clinical trials, we also plan to begin distributing regular questionnaires to registrants regarding their symptoms and general health. These responses will help scientists learn about the progression of the disease in different individuals.

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 newsletter to stay informed about our organization and the latest news on LGMD2A research.

Beyond joining the patient registry, the best thing you can do to help C3 find a cure is to donate to us, or — even better — 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 discovery and regulatory approval of a treatment or cure will cost millions of dollars. However, C3 is focused on making a big impact with small investments by focusing on

foundational research that will attract new 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.