Facts about Limb-Girdle Muscular Dystrophy

What is Limb-Girdle Muscular Dystrophy?

Limb-girdle muscular dystrophy (LGMD) isn’t really one disease. It’s a group of disorders affecting voluntary muscles, mainly those around the hips and shoulders — the pelvic and shoulder girdles, also known as the limb girdles.

You may also hear the term proximal used to describe the muscles that are most affected in LGMD. The proximal muscles are those closest to the centre of the body. Distal muscles are farther away from the centre (for example, in the hands and feet). The distal muscles are affected late in LGMD, if at all.

Over time (usually many years), the person with LGMD loses muscle bulk and strength. Eventually, he or she may need a power wheelchair or scooter, especially for long distances.

LGMD can begin in childhood, adolescence, young adulthood or even later. Both genders are affected equally. When limb-girdle muscular dystrophy begins in childhood, some physicians say, the progression is usually faster and the disease more disabling. When the disorder begins in adolescence or adulthood, they say, it’s generally not as severe and progresses more slowly.

What are the forms of Limb-Girdle Muscular Dystrophy?

There are at least 15 forms of LGMD, and they’re classified by the genetic flaws that appear to cause them (see “Known Forms of Limb-Girdle Muscular Dystrophy” below). By 2005, 11 genes that lead to production of muscle proteins had been implicated as definite causes of LGMD when they’re flawed.

Genes, located on chromosomes in each cell in the body, are the codes, or recipes, for production of the body’s various proteins. The genes associated with LGMD normally make proteins necessary for muscle function.

When protein problems arise because one of these genes is faulty, the result is that the cells in the muscles don’t work properly. Gradually, the muscles become weak enough that people experience the symptoms of limb-girdle muscular dystrophy. Because LGMD is progressive, the muscles continue to get weaker throughout the person’s lifetime.

Six of the genes that, when flawed, cause LGMD lead to production of proteins that are normally located in the muscle cell membrane, a thin sheath that surrounds each muscle cell, helping to protect it from injury during muscle contraction. If any of these proteins is missing because the gene for it is flawed, the membrane probably loses some of its “shock absorber” qualities and has a harder time protecting the muscle cell from injury during normal contraction and relaxation cycles.

In LGMD, the muscle membrane may also be “leaky”, letting substances in or out that are supposed to stay on one side of the membrane or the other. Membrane proteins,
when they’re made correctly and are in their normal positions, may also perform other essential functions in the cell; these functions may be missing when one or more of the proteins is absent.

Not all of the muscle proteins associated with LGMD are in the membrane, however. Calpain-3 is probably located in the main part of the muscle cell, and myotilin and telethonin are located in the part of the muscle cell that allows it to contract and relax.

The types of LGMD are generally classified by letters and numbers that indicate which gene is known or suspected to be involved and whether the disorder is inherited as a dominant or recessive condition, meaning whether one or two flawed genes are needed to cause it. (See “Does It Run in the Family?” below.) Some physicians classify LGMD according to which protein is missing or deficient, if this is known. For example, one form may be called alpha-sarcoglycan deficiency and another is known as beta-sarcoglycan deficiency. In the future, the term limb-girdle muscular dystrophy may become obsolete and be replaced by more specific terms.

Muscles and muscle cells in Limb-Girdle Muscular Dystrophy

The muscles most affected in limb-girdle muscular dystrophy (LGMD) are those surrounding the shoulders and hips, with nearby muscles in the upper legs and arms sometimes also weakening with time. These muscles are shown in red.

Inside each muscle cell, many proteins, some of which are shown here in blue and yellow-orange, help the cell contract and protect it from the stress of contractions.

When any of the proteins shown here in yellow-orange are missing or non-functional, LGMD is the result. At least six of these proteins are normally found in the muscle cell membrane, a sheath surrounding each cell. They form part of the structure of the membrane.

Determining which proteins are missing in LGMD and what their normal functions are in the muscle cell are crucial steps in developing treatments.

What happens to someone with LGMD, and how is it treated?

It’s not yet possible to predict the course of LGMD in an individual. Some forms of the disorder progress to loss of walking ability within a few years and cause serious disability, while others progress very slowly over many years and cause minimal disability. At this time, progression in each type of LGMD can’t be predicted with certainty. By understanding what’s known about the way the disease progresses, you can help your doctors monitor your health and you can adjust to the changes the disease brings.

Your health care team will treat your LGMD with physical and occupational therapy, assistive devices to help with mobility, monitoring for heart and breathing complications, and attending to such complications when necessary. These techniques can’t reverse the symptoms of LGMD or strengthen already weakened muscles, but
they can help preserve strength for as long as possible and help maintain general health.

LGMD isn’t in itself a fatal disease. Most of the danger comes from weakening heart or respiratory muscles. Awareness of these problems and treatment for them leads to a longer and higher-quality life.

Often, people with LGMD first notice a problem when they begin to walk with a “waddling” gait because of weakness of the hip and leg muscles. They may have trouble getting out of chairs, rising from a toilet seat or climbing stairs.

Weakness in the shoulder area may make reaching over the head, holding the arms outstretched or carrying heavy objects difficult. It may become increasingly hard to keep the arms above the head for such activities as combing your hair or arranging things on a high shelf. Some people find it harder to type on a computer or other keyboard and may even have trouble feeding themselves.

Assistive devices can make these tasks much easier. A wheelchair or scooter becomes convenient when weakness in the pelvic girdle and upper legs causes frequent falls. People whose LGMD has reached this stage often find that a great deal of their independence returns, and they’re much less fatigued, when they begin using a power wheelchair or scooter.

The heart can be affected in LGMD, but this doesn’t occur as often as it does in some other forms of muscular dystrophy. Heart problems can take two forms — weakness of the heart muscle (cardiomyopathy) and abnormal transmission of signals that regulate the heartbeat (conduction abnormalities or arrhythmias). The heart should be monitored for these complications. When necessary, medications or devices (such as pacemakers) can be used to treat them.

Respiratory (breathing) function can decline over time, and this, too, should be monitored regularly. There are several treatments to help maintain respiratory ability, ranging from exercises to the use of non-invasive ventilation at night.

Recent research has shown some correlation between the gene involved and the course and severity of the disease, but these correlations aren’t absolutely reliable, and more work must be done before statements can be made with certainty.
Does it run in the family?

On being told they have a genetic disorder such as LGMD, bewildered patients often ask, “But it doesn’t run in the family, so how could it be genetic?” LGMD can run in a family, even if only one person in the biological family has it. This is because of the ways in which genetic diseases are inherited.

LGMD can be inherited in one of two basic ways, known as the *autosomal dominant pattern* and the *autosomal recessive pattern*. “Known Forms of LGMD” (below) shows which types follow each pattern.

The word *autosomal* means that the genes involved aren’t on the X or Y chromosome and, therefore, don’t have a preference for either men or women.

In diseases with *dominant* inheritance patterns, a person who inherits a flawed gene from one parent will have disease symptoms. That parent would also have the disease.

In diseases with *recessive* inheritance, a person must inherit two flawed genes — one from each parent — to have disease symptoms. The parents may or may not have the disease.

A recessive form of LGMD can show up in one person when there’s no family history. Other family members may have been *carriers*, having no disease symptoms. Carriers have the genetic flaw (*mutation*) on a chromosome and can have a child with the disease, but only if the child’s other parent is also a carrier. So it isn’t unusual for carriers of a rare recessive disease not to know they’re carriers until someone in the family develops the disease.

Just to make things a little more complicated, a person with LGMD may have a brand new genetic mutation (after all, they have to start somewhere), so there may really be no family history or even carriers of the disorder in the family. However, once someone develops a genetic disease, even if the mutation is spontaneous (new) with that person, he or she can then pass on the mutation to any offspring, thereby introducing the gene for the disease into the family.

The details of inheritance risks for any particular form of LGMD depend on many circumstances, including exactly which type of LGMD has been diagnosed. A good way to find out more is to talk to your doctor or ask to see the genetic counsellor. You can also read our fact sheet “Genetics and Neuromuscular Diseases.”

In what ways is a person affected by LGMD?

LGMD, like other muscular dystrophies, is primarily a disorder of skeletal muscle. Other names for skeletal muscle are *voluntary* and *striated* muscle (because of its microscopic appearance). These are the muscles you use to move the limbs, neck, trunk and other parts of the body that are under voluntary control.

Heart muscle, which is slightly different from skeletal muscle, and respiratory muscles, which are actually skeletal muscles, are sometimes also involved in LGMD.

The *involuntary* or *smooth* muscles, such as those that control the body’s digestive and elimination processes, usually aren’t affected in LGMD. Recent research in animals
suggests that some forms of LGMD may affect the involuntary muscles responsible for normal blood vessel contraction and relaxation, and that this involvement could be a factor in some of the heart problems occasionally seen in LGMD.

Pain isn’t a major part of LGMD, but limited mobility sometimes leads to muscle soreness and joint pain. Exercises to keep joints limber, moving around as much as possible, warm baths and, if needed, medication can keep this kind of discomfort to a minimum.

The brain, the intellect and the senses are unaffected in LGMD. People with LGMD can think, see, hear and feel sensations as well as those without muscular dystrophy. They maintain control over their bowel and bladder functions, and sexual function is normal.

What tests are used to diagnose LGMD?

In diagnosing any form of muscular dystrophy, a doctor usually begins by taking a patient and family history and performing a physical examination. Much can be learned from these, including the pattern of weakness. The history and physical examination go a long way toward making the diagnosis, even before any laboratory tests are done.

The doctor also wants to determine whether the patient’s weakness results from a problem in the muscles themselves or in the nerves that control them. Muscle-controlling nerves, or motor nerves, originating in the spinal cord and reaching out to all the muscles, can cause weakness that looks like a muscle problem but really isn’t.

Usually, the origin of the weakness can be pinpointed by a physical exam. Occasionally, special testing called electromyography is done. In this kind of test, the electrical activity of the muscles is measured and nerves stimulated to see where the problem lies. Electromyography is uncomfortable but not usually very painful.

Early in the diagnostic process doctors often order a special blood test called a CK level. CK stands for creatine kinase, an enzyme that leaks out of damaged muscle. When elevated CK levels are found in a blood sample, it usually means muscle is being destroyed by some abnormal process, such as a muscular dystrophy or an inflammation. Therefore, a high CK level suggests that the muscles themselves are the likely cause of the weakness, but it doesn’t tell exactly what the muscle disorder might be.

To determine which disorder is causing a problem, a doctor may order a muscle biopsy, the surgical removal of a small sample of muscle from the patient. By examining this sample, doctors can tell a great deal about what’s actually happening inside the muscles. Modern techniques can use the biopsy to distinguish muscular dystrophies from inflammatory and other disorders as well as between different forms of dystrophy.

Tests on the biopsy sample can also provide information about which muscle proteins are present in the muscle cells, and whether they’re present in the normal amounts and in the right locations. This can tell the doctor and patient what’s wrong with the cells’ proteins and provide likely candidates as to which genes are responsible for the problem. The correlation between missing proteins on the muscle biopsy and genetic flaws isn’t yet perfect, however.
Can you find out what genetic type of LGMD a person has?

At this time, genetic testing to determine an individual’s exact type of LGMD is available for only a few LGMD forms. However, the availability of DNA tests, using either blood cells or muscle cells to get precise genetic information, is expanding rapidly. You can ask your doctor what tests are available.

Four types of LGMD are caused by defects in genes for muscle membrane proteins known as sarcoglycans. Tests for these particular genetic mutations may soon be available because a great deal of research is being done with these proteins.

In the meantime, your family history can help determine the inheritance pattern of your disorder. Muscle biopsy results can help you and your doctor narrow down the possible causes of your LGMD.

Treatment for LGMD, mainly involving physical and occupational therapy, assistive devices, and monitoring for heart and breathing complications, is essentially the same in all forms of the disease. An individual’s precise genetic defect makes little difference in these interventions.

Understanding your inheritance pattern may, however, be important for family planning.

Can special diets help in LGMD?

At this time, no special dietary restrictions or additions are known to help in LGMD.

Many people, when they hear the words “lack of a protein,” logically ask, “should I eat more protein?” Unfortunately, eating more protein has no effect on any of the proteins missing in LGMD. It’s true that when you eat a steak, you’re ingesting many muscle proteins (from the cow). Your body then breaks down these proteins into their component parts and uses them to build its own proteins. But a person who lacks the genetic instructions to make these new proteins won’t be able to make them no matter how much protein he eats.

A doctor may advise a weight reduction or weight stabilization diet for some people with LGMD. Being markedly overweight puts greater stress on already weakened muscles.

Are there special exercises that can help?

A physiotherapy program is usually part of the treatment for LGMD. Your doctor will refer you to a physiotherapist for a thorough evaluation and an individualized program.

The primary goals of physical therapy are to allow greater motion in the joints and to prevent both contractures (freezing of the joints) and scoliosis (curvature of the spine). These problems can arise when movement is limited, and it’s important for the patient’s comfort to avoid them.

Doctors and therapists have different opinions on the relative value or danger of various exercise regimens in people with muscular dystrophy. In LGMD, certain kinds of stress-causing exercises may actually hasten muscle damage.
Some experts recommend swimming and water exercises as a good way to keep muscles as toned as possible without causing undue stress on them. The buoyancy of the water helps protect against certain kinds of muscle strain and injury. Before undertaking an exercise program, make sure you’ve had a cardiac evaluation. And don’t swim alone.

Occupational therapy focuses more on specific activities and functions, particularly use of the hands, while physiotherapy emphasizes mobility and (where possible) strengthening of large muscle groups. Your doctor can also refer you to the occupational therapy department, where you can receive help with tasks related to your job, recreation or daily living. For example, arm supports can make tasks such as using a computer or fixing your hair less tiring.

### Known forms of Limb-Girdle Muscular Dystrophy

<table>
<thead>
<tr>
<th>Type</th>
<th>Pattern of Inheritance</th>
<th>Gene or Chromosome</th>
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<tbody>
<tr>
<td>LGMD1A</td>
<td>Autosomal dominant</td>
<td>Myotilin gene</td>
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<tr>
<td>LGMD1B</td>
<td>Autosomal dominant</td>
<td>Lamin A/C gene</td>
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<tr>
<td>LGMD1C</td>
<td>Autosomal dominant</td>
<td>Caveolin gene</td>
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<td>LGMD1D</td>
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<td>LGMD1E</td>
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<td>Calpain-3 gene</td>
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<td>Titin gene</td>
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These forms of LGMD have been identified since the early 1990’s. More forms will undoubtedly be discovered as research continues.
Search for treatments and cures

LGMD was the first muscle disorder targeted in human gene therapy trials, replacing a flawed gene with a new one in the muscle cells. In 1999, a clinical trial to test the safety of inserting genes for the sarcoglycan proteins began, involving a handful of people with LGMD. Unfortunately, the trial was halted in response to dangers that became evident in an unrelated study. Later analysis showed that one of the two participants who received the gene injections had begun producing sarcoglycan protein molecules from the gene.

Other researchers are investigating a strategy using a substance called insulin-like growth factor 1. IGF-1 may be able to help muscles overcome a degenerative disease such as muscular dystrophy even in the face of a flawed gene.

Another avenue of investigation is blocking a natural protein called myostatin, which puts a brake on muscle growth.

Still another idea is to use stem cells, primitive cells found in the bone marrow and muscles, to help ailing muscles regain strength. These cells could, in the future, be used to carry new genes to the muscle cells, or just to replenish their capacity to repair themselves even without a complete set of working genes.

Experiments in other types of muscular dystrophy have suggested that it may be possible to use medications to change the way cells “read” genetic instructions, so that certain types of genetic defects could be “re-read” and corrected.

Researchers worldwide continue to pursue every avenue leading to potential treatments.