Limb-girdle muscular dystrophy

Understanding this group of inherited disorders.

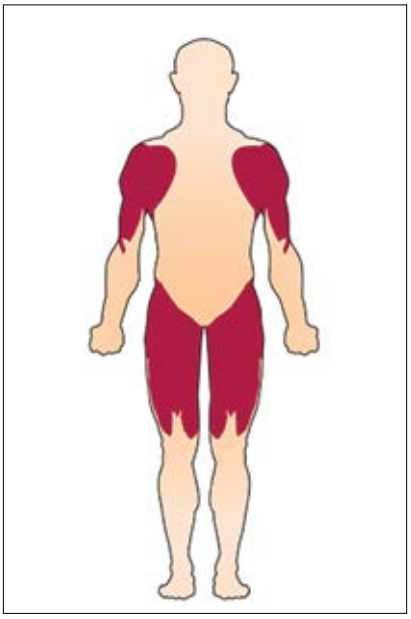
What is Limb-girdle muscular dystrophy?

Limb-girdle muscular dystrophy (LGMD) is a group of inherited disorders that cause weakness and wasting of the proximal skeletal muscles. These are the muscles closest to the body such as the hip and shoulder areas. The shoulder girdle is the bony structure that surrounds the shoulder area, and the pelvic girdle is the bony structure surrounding the hips. Collectively, these are called the limb girdles, and it is the observed weakness and atrophy (wasting) of the muscles connected to the limb girdles that has given this group of disorders its name. These conditions are progressive, and worsen over time.

In LGMD involuntary muscles of the digestive system, bowel and bladder are not affected, and sexual function is also normal. Intellectual and cognitive abilities also remain unaltered, as do sensations such as touch, temperature and pain.

The onset of LGMD varies and can occur in childhood or symptoms may not be apparent until adolescence or adulthood. Males and females are equally affected. Prevalence of LGMD is estimated to range from 1 in 14,500 to 1 in 123,000 individuals.

In the early stages of limb-girdle muscular dystrophy, affected



The muscles that experience weakness are highlighted.

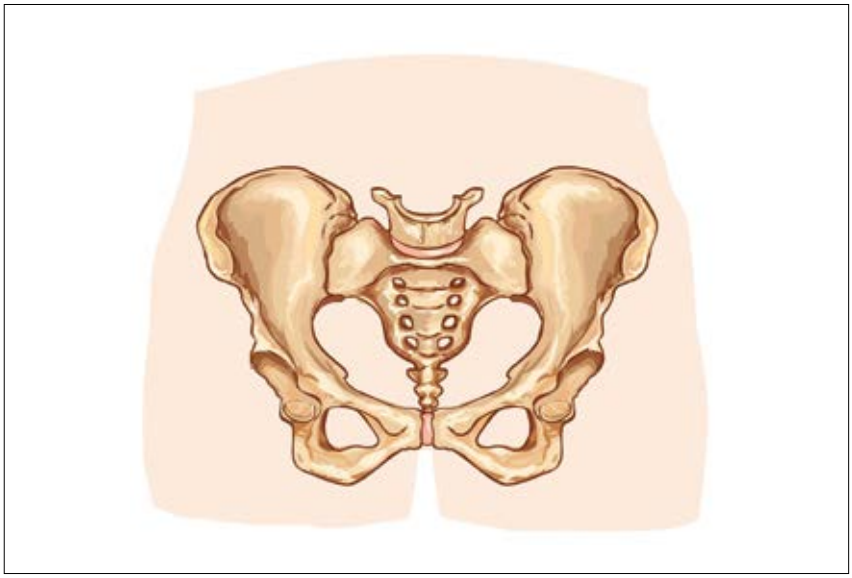
individuals may have weakness in hip and thigh muscles resulting in an unusual walking gait, such as waddling or walking on the balls of the feet, and may also have difficulty climbing stairs, running and getting up from a squatting or sitting position. The muscle weakness and atrophy may also result in lower back pain.

LGMD will progress to the shoulders, which can 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 hair. Some individuals find it increasingly harder to type, and may even have trouble feeding themselves.

Muscle wasting may also cause changes in posture. For example, weak shoulder muscles tend to make the shoulder blades protrude, known as scapular winging. Affected individuals may also have an abnormally curved lower back or a spine that curves to the side known as scoliosis. Spinal bracing may be required, and in more severe cases, spinal fusion surgery. An orthopaedic specialist is beneficial in monitoring scoliosis if present. Some individuals develop joint stiffness or contractures that can restrict movement in the hips, knees, ankles, or elbows. Surgery may be an option to release them. For some people, contractures may be an early sign.

Progressively, muscles of the face and distal muscles, such as the lower legs, feet, forearms and hands, may become affected and lead to considerable weakness. Calf muscles may appear unusually large (pseudo hypertrophy) as fatty deposits accumulate and replace lost muscle tissue.

Mobility may become increasingly restricted and 20-30 years from onset, individuals with LGMD may lose independent mobility and a wheelchair may be needed for mobility. Wheelchair options can be discussed with an occupational and/or seating therapist at the appropriate time.



The pelvic girdle is the bony structure surrounding the hips.

Genetics and classification of LGMD

Several different genes that normally lead to the production of muscle proteins have been identified as mutated in LGMD.

Most types of LGMD are inherited in an autosomal recessive manner, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Several rare forms of limb-girdle muscular dystrophy are inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

As there are many forms of LGMD, they are classified based on inheritance pattern and genetic cause, with '1' being designated for types that are inherited in an autosomal manner and '2' being the designation for those types which are inherited in an autosomal recessive fashion.

Mutations in the lamina gene (LMNA) cause LGMD1B.

LGMD1C is one of a group of muscle disorders called caveolinopathies caused by mutations in the caveolin gene (CAV3).

Calpainopathy, or LGMD 2A, is caused by mutations in the calpain (CAPN3) gene, this is the most common form, accounting for about 30 percent of cases. Dysferlinopathy, also called LGMD2B, is caused by mutations in the dysferlin (DYSF) gene.

Sarcoglycanopathies are forms of LGMD caused by mutations in the sarcoglycan genes (SGCA, SGCB, SGCG, and SGCD) These are known as types 2D, 2E, 2C, and 2F respectively.

A titan (TTN) gene mutation causes LGMD2J, which was first identified only in the Finnish population. Mutations in the ANO5 gene cause LGMD2L. Mutations in several other genes cause forms of LGMD called dystroglycanopathies, including LGMD 2I, 2K, 2M, and 2N.

Other rare forms of limb-girdle muscular dystrophy are caused by mutations in several other genes, some of which have not been identified.

According to the NZ NMD Registry 24 per cent of people have genetic confirmation of their LGMD.

As more and more genes are identified in the cause of LGMD, there will be a greater understanding of which and how proteins are implicated in the symptoms of LGMD.

Diagnosis usually commences after the identification of key early symptoms of LGMD.

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Muscle biopsies show typical signs of damage, the presence of certain cell types, such as inflammatory cells, and can establish whether certain proteins are reduced or absent.

Electromyographies (EMG) can be used to observe the electrical activity of muscles and its consistency with activity typical of LGMD individuals. Blood testing can also be requested to look for elevated levels of creatine

A good diet with plenty of fresh fruit and vegetables is very important in ensuring excessive weight does not impede mobility.

phosphokinase (CPK) which are indicative of muscle problems. It is strongly recommended that genetic counselling is arranged. following a diagnosis of LGMD.

Implications and management

Cardiac problems can arise, such as weakness of the heart muscle (cardiomyopathy) or abnormal heartbeat (conduction abnormalities or arrhythmias). Arrhythmias can result in increased risk for heart palpitations (fast or irregular heartbeat) and syncope (loss of consciousness due to lack of oxygen to the brain). The heart must be monitored regularly and some problems may be controlled or treated with medication or devices (such as pacemakers), though severe forms can be fatal.

Respiratory muscles may also be affected resulting in breathing difficulties. When necessary, several options may be available to help maintain respiratory ability, ranging from exercises to the use of ventilators. Like cardiac problems, respiratory problems can be fatal and therefore need to be monitored closely. Many researchers have noted that progression of LGMD is often faster and more severe when the onset is earlier, in comparison to individuals who develop LGMD later in adolescence or adulthood.

From an early stage, it is important to undergo regular exercise and stretching programmes, with the help of a physiotherapist, to maintain muscle strength and flexibility. Swimming is an excellent option to exercise and mobilise all muscles and joints.

Combined with physical activity, a good diet with plenty of fresh fruit and vegetables is important to manage body weight, which helps with overall well-being and mobility.

Swimming is an excellent exercise option for people living with the condition.