Limb girdle muscular dystrophy

What Is Limb Girdle Muscular Dystrophy?

The muscular dystrophies are a group of muscle diseases which have three features in common: they are hereditary; they are progressive; and each causes a characteristic, selective pattern of muscle weakness.

Limb girdle muscular dystrophy (LGMD) is the common name for a diverse group of muscular dystrophies affecting mainly the pelvic (hip) and shoulder regions. There are more than 20 different subtypes - each caused by alterations to different genes. The different types of LGMD vary in severity, age of onset (when symptoms are first noticed) and how they are inherited. Some types 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. For this reason some of the information in this factsheet will not be relevant to everybody with a diagnosis of LGMD.

In this factsheet:

- What are the different types of LGMD?
- What are the symptoms of LGMD?
- What causes LGMD and how is it inherited?
- How is LGMD diagnosed?
- Why is genetic counseling important?
- What can be done to manage the symptoms?
- What research is being done?
- Further information

What are the different types of LGMD?

The LGMDs are classified into type 1 or 2 depending on how they are inherited (see 'how is LGMD inherited below'). Type 1 LGMDs are inherited in what is called an 'autosomal dominant' pattern (with rare exceptions) and are much less common than the type 2 LGMDs which are inherited in an 'autosomal recessive' pattern. They are further classified using letters depending on the gene alteration that causes it. Below is a table describing ten of the more common types of LGMD.

LGMD type	Gene affected	Age of onset	Breathing usually affected?	Heart usually affected?	Comments
1A	myotilin	Adult	no	yes	- very rare - mutations in this gene also cause myofibrillar myopathy - speech and swallowing difficulties common
1B	lamin A/C	5 to 20 years	yes	yes	- mutations in this gene also cause Emery-Dreifuss muscular dystrophy and congenital muscular dystrophy - usually slow progression - contractures common
1C	caveolin 3	Any age	no	no	- may have weakness in distal muscles (feet, ankles, calves, hands and wrists) and 'rippling muscle disease' - cramps and muscle pain after exercise are common - usually slow progression
2A	calpain 3	Early teens usually, can range from 2 to 50 years of age	no	no	- a common form of LGMD worldwide - not usually very rapidly progressive - joint contractures may be present
2B	dysferlin	15-25 usually (variable)	no	no	- usually slow progression - muscle pain and swelling in calves can be present
2C, 2D, 2E, 2F (sarco-glycanopathies)	gamma, alpha, beta or delta sarcoglycan	Usually in childhood	yes	yes	- rate of progression of the condition is extremely variable - joint contractures and scoliosis may be present
2I	FKRP	10 to 20 years (may be earlier or later, with a range from two to 40 years).	yes	yes	- common in the UK and Northern Europe - rate of progression of the condition is extremely variable - joint contractures may be present

What are the symptoms of LGMD?

People with LGMD experience weakness in the muscles in the top part of the arms, shoulders, hips and thighs. The weakness usually affects the legs first followed by the arms. Symptoms that might be noticed first include frequent falls and difficulty climbing stairs, running and rising from the floor.

Weak shoulder muscles can make it difficult to raise arms above the head, hold the arms outstretched, or carry heavy objects. Some types of LGMD may also cause weakness in the feet, ankles, calves, hands and wrists. A few specific types of LGMD may cause heart problems or weakness of the breathing muscles. Usually the muscles of the face are unaffected and the brain, intellect, and the senses are not impaired.

As the condition progresses, people with LGMD may start to have problems with walking and may need to use a wheelchair over time. LGMD is generally thought of as a condition that affects adults but some types do appear in young children. Severity can range from severely disabling with a wheelchair required in the teens to people who are still able to walk in their 50s and beyond.

It is difficult to give generalised information on how the condition will progress because LGMDs all progress at different rates, even within the same family. In addition, each different type has some specific features and characteristics, such as age of onset of symptoms and particular muscles involved.

What causes LGMD and how is it inherited?

The LGMDs are genetic conditions caused by the presence of a mistake in the DNA (which is often referred to as a 'mutation'). These DNA errors are within genes that contain the instructions for the production of proteins that are important for muscle maintenance and repair. The protein is then either not produced or doesn't work properly.

Changes to the DNA code of at least 20 genes have been found to cause the different types of LGMD (see table above for some of the more commonly affected genes).

There are a number of ways that genes can be passed on through the generations. About 90% of the LGMDs are inherited in a pattern known as "autosomal recessive" – these are the type 2 LGMDs. We all generally have two copies of each gene one inherited from each parent. For an individual to have autosomal recessive LGMD, they need to inherit two altered genes - one from their mother and one from their father. The parents of an individual with Type 2 LGMD each carry one copy of the altered gene, and are known as 'carriers', but they typically do not show signs and symptoms of the condition. Their other 'good' copy of the gene is enough to prevent the condition developing. In order for carrier parents to have a child affected by LGMD type 2, both parents must pass the altered gene on to their child. If both parents are carriers the likelihood of a child inheriting the condition is 25 percent, or 1 in 4.

The inheritance of one altered copy of the gene from either parent is sufficient for a person to be affected by type 1 LGMDs which are called "autosomal dominant" disorders. The single altered gene is sufficient to over-ride the normal functioning copy inherited from the other parent. Each affected person usually has one affected parent. The chance of a child inheriting the condition from a parent with the condition is 50 percent, or 1 in 2.

How is LGMD diagnosed?

Diagnosing LGMDs starts with the medical history and clinical signs observed by the doctor. Family history is also used to identify the pattern of inheritance. Further testing is then done which may include:

- a muscle enzyme blood test (creatine kinase)
- electrical tests (EMG) on the muscle
- MRI (Magnetic Resonance Imaging) scans may be used to identify muscles for biopsy and show the clinician the pattern of muscle involvement
- a muscle biopsy (taking a small sample of an affected muscle)
- genetic tests on DNA obtained from a blood sample

Usually the first three tests listed above are used to give the doctor clues, along with the clinical signs and medical history, as to what gene might have an error in it and narrow down which genes and proteins need to be examined in the muscle biopsy and by genetic testing. The sample of muscle taken in the biopsy is examined under a microscope and specific stains used to indicate which proteins are missing or reduced. If this is inconclusive, genetic tests are also done. Some people (about 1 in 4) are found not to have changes in any of the genes known to cause LGMD and so the cause is unknown. Research is ongoing to find more genes causing LGMD so that these people can gain a genetic diagnosis.

Why is genetic counselling important?

Soon after the diagnosis of LGMD genetic counselling should be arranged, together with appropriate tests for those members of the family who are at risk of being carriers. Genetic counselling provides information on the inheritance pattern, risks to other family members, and the 'prognosis' (likely outcome of the disorder). Family members who are found to be carriers of the condition can discuss with a genetic counsellor family planning options to reduce the risk of passing the condition on to future children.

What can be done to manage the symptoms?

While there is no specific treatment to correct the mutations that cause the LGMDs, there is a lot that can be done to manage the condition.

Weakness of the breathing and heart muscles can affect people with some types of LGMD so regular monitoring by a respiratory physician and/or cardiologist is needed. Early detection and prompt treatment can be lifesaving. People without a genetic diagnosis should also be carefully monitored as their risk of heart and breathing problems is unknown.

It is important that patients are aware of the early signs of breathing difficulty which might only occur at night. These signs include frequent chest infections, daytime sleepiness and morning headaches. If a breathing problem is detected a non-invasive ventilator device can be used, which is usually only needed at night. It is recommended that the flu vaccine is given to people with respiratory weakness and that any respiratory infections are promptly treated.

For people with LGMD types 1B, 2C-F and 2I the monitoring of heart function is especially vital. If a heart problem is detected, medication or the implantation of a pacemaker or defibrillator might be necessary. If the heart problem is particularly severe patients may be considered for a heart transplant.

Maintaining good levels of mobility is important and receiving the right physiotherapy to achieve this is vital. A physiotherapist can recommend stretches to keep joints supple and if necessary special splints (orthoses) to prevent muscle shortening (contractures) which are common in some types of LGMD. If contractures are severe surgery might be needed to release the contracture. Curvature of the spine (scoliosis) sometimes occurs especially after becoming a full time wheelchair user so special attention should be paid to correct seating.

Gentle exercise is recommended to help maintain the muscle strength that remains as well as having positive effects on general health and wellbeing. There are no precise guidelines about the type or intensity of activities; however, it is recommended that any exercise undertaken is within comfortable limits. Extreme tiredness, muscle pain and cramps during or after activities can mean that you have pushed yourself too hard and therefore you should take it easier. Swimming is beneficial because all of the muscles of the body are used and the support of the water prevents undue strain. Long periods of immobility, for example after surgery or during illness, should be avoided.

What research is being done?

Much of the research into LGMD is aimed at understanding how the genetic mutations cause the symptoms of the conditions and also at identifying new causative genes. This is essential for the development of therapies and for some types of LGMD clinical trials are being planned or have already started.

One of the promising treatments being researched for LGMD is gene therapy. The aim of gene therapy is to introduce a healthy synthetic copy of a gene into the body to compensate for the one that is faulty. A harmless virus is used to deliver the gene into the cells of the body where these instructions are used to make the missing protein. The size of gene that the virus can carry is limited, which can make it difficult for it to be used for some genetic diseases. However, the sarcoglycan genes which cause LGMD2C-2F are very small, making these conditions ideal candidates for gene therapy.

In August 2012 French researchers released results from a Phase 1 clinical trial of gene therapy for LGMD2C. An adeno-associated virus (AAV) was used to introduce a healthy copy of the gamma-sarcoglycan gene - the gene that is affected in LGMD2C - into one wrist muscle of nine people with LGMD2C. They found that none of the participants suffered from a serious side effect and the three participants who received the highest dose produced gamma-sarcoglycan protein in the treated muscle. This trial proved that in theory gene therapy could be used to treat LGMD2C and further trials are being planned to test if it is possible to deliver the gene throughout the muscles of the body, for example via the blood stream, and to determine if the treatment improves muscle strength.

Researchers in the USA have also conducted a gene therapy clinical trial for LGMD2D. Results were reported in 2010. In this clinical trial six children with LGMD2D had an AAV containing a healthy copy of the alpha-sarcoglycan gene injected into a muscle in their foot. The gene therapy was deemed to be safe and a significant amount of alpha-sarcoglycan protein was produced in five out of the six participants which persisted for at least three months. Following on from this clinical trial, another was started in 2013 to deliver the gene therapy by circulating it through the blood vessels of the legs. Click here for more information about this gene therapy clinical trial for LGMD2D.

Gene therapy is also being considered for LGMD2B but the gene that causes it – dysferlin – is too large to fit inside the standard viruses used. One way around this is to engineer a smaller version of dysferlin which has any unnecessary parts removed. This is being explored in the laboratory but a fully functional mini-gene has not yet been discovered. Another option is to cut the gene into two pieces and deliver them in separate viruses. Once inside the cell the two pieces are joined together. This has been shown to be possible in mice but the efficiency is low so more research is required.

Another possibility for LGMD2B is to use a technique called 'exon skipping' which is currently in clinical trial for Duchenne muscular dystrophy. This involves encouraging the cell to ignore the portion (called an exon) of a gene where the mutation occurs when the DNA instructions are read. The cell can then use the remaining instructions to produce a protein, albeit missing a small part in the middle. By contrast, when the mutation is included, this interferes with the reading of the rest of the gene's DNA code so that no functional protein is made. Some preliminary experiments using this approach have been done in the laboratory to show that this is theoretically possible but no testing in animal models or humans has been published yet. This exon skipping would not be applicable for all people with LGMD2B as some parts of the dysferlin gene are essential and can't be 'skipped'. Also this would be a very personalized medicine approach and would require different drugs to be designed to treat different mutations, which could be costly and time consuming.

Scientists have proposed that a technique called 'gene silencing' could be used for the dominantly inherited type 1 LGMDs. This uses similar technology to exon skipping, but the DNA code is manipulated in such a way that gene is switched off. This could theoretically be useful for these conditions because the mutation results in the production of a dysfunctional protein that is detrimental to the cell. No research has been published testing this idea for LGMD yet.

In some types of LGMD (such as LGMD2B and LGMD 2C-2F) it has been noted that the muscles show signs of inflammation so it is thought that suppressing this inflammation with medication may help to alleviate some of the symptoms of the condition. Research into this is underway.

To help facilitate the planning and running of clinical trials patient registries have been established for the LGMDs. These databases collect information about patients with the aim of better understanding the conditions and allowing rapid recruitment to clinical trials when they begin. The patient registries currently available for LGMD are:

- LGMD2A (calpain-3 gene) http://www.lgmd2a.org/
- LGMD2B (dysferlin gene). http://www.dysferlinregistry.org/
- LGMD2I (FKRP gene) http://www.fkrp-registry.org/
- The Congenital Muscle Disease International Registry (CMDIR) collects data on some types of limb girdle muscular dystrophy (LGMD2K, LGMD2I, LGMD2L and LGMD2N)

People with the condition or their family members can register through the registry websites.

NOTE: Research is moving forward at a fast pace, so this research summary may not be up-to-date at the time of reading. Feel free to contact MDA's Scientific Communications Officer for an update on the latest developments - kristina.elvidge@mda.org.au.

Further information

- Clinical trials – your questions answered
- More information about patient registries
- Information about LGMD on the TREAT-NMD website
- Muscular Dystrophy Campaign factsheets on LGMD
- You can get regular updates by becoming a friend of the MDA Facebook page or follow our Scientific Communications Officer on Twitter (@kelvidge).

For further information on any of the areas discussed above,
please contact MDA on (03) 9320 9555, email info@mda.org.au

Glossary

Gene: Genes are made of DNA and each carries instructions for the production of a specific protein. Genes usually come in pairs, one inherited from each parent. They are passed on from one generation to the next, and are the basic units of inheritance. Any alterations in genes (mutations) can cause inherited disorders.

Mutation: A permanent change in the DNA code that makes up a gene. Depending on where the mutation occurs, and the type of mutation, they can either have no effect or result in genetic diseases such as muscular dystrophy. Mutations can be passed on from generation to generation.

Protein: Proteins are large molecules composed of one or more chains of building blocks called 'amino acids' in a specific order. The order is determined by the gene that contains the instructions for the construction of the protein. Proteins are required for the structure, function, and regulation of the body's cells, tissues, and organs. They are the building blocks of our bodies. We have millions of different proteins in our body and each has unique functions. Two examples are the enzymes in our stomach that digests our food and the collagen which holds our skin together.

References

Norwood F. et al. EFNS guideline on diagnosis and management of limb girdle muscular dystrophies. Eur J Neurol. 2007 Dec;14(12):1305-12.

Barthélémy F. et al. Translational research and therapeutic perspectives in dysferlinopathies. Mol Med. 2011 Sep-Oct;17(9-10):875-82.

Revised and uploaded February 2014