The limb-girdle muscular dystrophies (LGMDs)

This factsheet is for people for whom a diagnosis of limb-girdle muscular dystrophy (LGMD) has been suggested. This is a complicated subject since there are many different types of limb-girdle muscular dystrophy. Not all of the things that we talk about in this fact sheet will be relevant to everybody with the diagnosis.

What is limb-girdle muscular dystrophy?
Muscular Dystrophy is the name given to a group of inherited conditions where there is a progressive wasting and weakening of muscle. There are many different types of muscular dystrophy. One of the ways in which the different types of muscular dystrophy are distinguished is by noting the groups of muscle that are involved first. The limb-girdle group of muscular dystrophies is so called because generally they cause weakness in the shoulder and pelvic girdle for example the big muscles around the top (proximal) part of arms and legs (hip, thigh and shoulder muscles). Usually weakness of the legs is noticed before that of the arms and usually the muscle of the face are unaffected.

Specialised tests for LGMD are now available through a national scheme for specialised diagnosis, the National Commissioning Group (NCG). Further information can be found at the end of this factsheet.

What are the common features?
LGMD are rare conditions and they present differently in many people, even within the same family, with regard to age of onset, areas of muscle weakness, heart and respiratory involvement, rate of progression and severity.

The different types of LGMD may have different features associated with them and some of these are described in the table below. However, the common features to all people in this group will be weakness of the big muscles of the legs and/or arms. This may result in frequent falls, difficulty in running, climbing stairs and rising from the floor. As the condition progresses, people can have problems with walking and may need to use a wheelchair over time.

The involvement of shoulder and arm muscles can lead to difficulty in raising arms over head and in lifting objects. In some types of LGMD, the heart and breathing muscles may be involved. Consequently regular checks of heart and breathing function may be needed in order to identify any changes and treat them as necessary.

What causes it?
There are many different genetic faults associated with LGMD and these are listed in the table below. These genes contain the necessary information to make muscles function. When a person has faults in a LGMD gene, the muscles can not work properly and weakness occurs.

Quite often complex tests may be needed to work out the causes of LGMD in an individual person, which may include examination of a muscle biopsy and a blood sample for DNA testing.

What are the different types of limb-girdle muscular dystrophy?
The different types of LGMD have all gone through various name changes and reclassifications over the last few years. They are listed in the table below. All forms of LGMD have a genetic basis.

The LGMDs are divided into two main groups depending on the way they are passed on in families. On this basis, they are grouped into autosomal recessive or type 2 LGMD and the much rarer group of
autosomal dominant or type 1 LGMD. They can now be further subdivided on the basis of the faulty gene or the muscle protein deficiency which may tell us exactly where the problem lies.

<table>
<thead>
<tr>
<th>Names</th>
<th>Inheritance</th>
<th>Protein involved</th>
<th>Clinical features</th>
<th>CK level</th>
<th>Genetic test available</th>
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| LGMD2A Calpainopathy Calpain3 deficiency   | AR          | Calpain3         | - A common form of LGMD worldwide  
- Onset of muscle symptoms: 8-15 yrs though may be earlier or later  
- Weakness and wasting in the hip, thigh and shoulder muscles  
- Not usually very rapidly progressive  
- Joint contractures may be present  
- Heart and breathing involvement is not a common feature of the condition.                                                                 | Elevated  | Yes                    |
| LGMD2B Dysferlinopathy Dysferlin deficiency | AR          | Dysferlin        | - Onset of muscle symptoms: 20 yrs though may be earlier or later  
- Same people with a typical hip and shoulder muscle weakness (LGMD2B); other people with difficulty standing on toes and hand weakness (Miyoshi myopathy or distal myopathy)  
- Usually slow progression  
- Muscle pain and swelling in calves can be present  
- Heart and breathing involvement is not a common feature of the condition.                                                                 | Markedly elevated | Yes                    |
| LGMD2C, 2D, 2E, 2F Sarco-glycanopathies     | AR          | One of the sarcoglycan proteins (□□□□□) | - Onset of muscle symptoms: usually in childhood  
- Weakness and wasting in the hip, thigh and shoulder muscles  
- Rate of progression of the condition is extremely variable  
- Joint contractures may be present  
- Heart and breathing muscles may be involved                                                                                                                                                                           | Elevated  | Yes                    |
<p>| LGMD2G                                     | AR          | Telethonin       | So far only reported in Brazil                                                                                                                                                                                        | Elevated  | No                     |
| LGMD2H                                     | AR          | TRIM32           | So far only reported in Canada                                                                                                                                                                                       | Elevated  | No                     |</p>
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| LGMD2I     | AR          | FKRP (Fukutin related protein) | - A common form of LGMD in the UK and in the North of Europe  
- Onset of muscle symptoms: 10-20 yrs though may be earlier or later (with a range from 2 to 40 yrs)  
- Rate of progression of the condition is extremely variable  
- Joint contractures may be present  
- Heart and breathing muscles may be involved | Elevated | Yes                    |
| LGMD2J     | AR          | Titin                 | So far only reported in Finland  
- People with one copy of the faulty gene have a distal muscle myopathy | Elevated | No                     |
| LGMD2K     | AR          | POMT1                 | - Onset of muscle symptoms: childhood  
- Weakness and wasting in the hip, thigh and shoulder muscles  
- Severe learning difficulties  
- The gene is also involved in a severe congenital muscular dystrophy  
- Few cases described | Elevated | Yes                    |
| LGMD2L     | AR          | Fukutin               | - Onset of muscle symptoms: childhood  
- Weakness and wasting in the hip, thigh and shoulder muscles  
- The gene is also involved in a severe congenital muscular dystrophy  
- Few cases described  
- Deterioration of weakness with viral infections  
- Heart and breathing muscles may be involved | Elevated | Yes                    |
| LGMD2M     | AR          | Not known             | - Onset of muscle symptoms: 10-50 years  
- Weakness in the hip, thigh and shoulder muscles  
- Asymmetric wasting of leg muscle (quadriceps femoralis) | Elevated | Yes                    |
| LGMD2N     | AR          | POMT2                 | - Recently described  
- Faults in this gene are responsible for a wide spectrum of symptoms, ranging from severe muscle weakness and wasting, learning difficulties and eye problems at birth to a milder form of LGMD | Elevated | Yes                    |
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<td>LGMD1A</td>
<td>AD</td>
<td>Myotilin</td>
<td>So far described only in two families  - Faults in this gene also cause another autosomal dominant muscular disease, called Myofibrillar myopathy, - Onset of muscle symptoms: adulthood - Some affected individuals can have a particular nasal pattern of speech (dysarthria) - Heart and breathing muscles may be involved</td>
<td>Normal or mildly elevated</td>
<td>Yes</td>
</tr>
<tr>
<td>LGMD1B</td>
<td>AD</td>
<td>Lamin A/C</td>
<td>- Faults in this gene also cause AD Emery-Dreifuss muscular dystrophy, peripheral neuropathy and an unusual condition called lipodystrophy. - Onset of muscle symptoms: 5-20 years - Usually slow progression - Heart involvement is frequent and can be the only manifestation of the muscular condition - Breathing problems are not common</td>
<td>Normal or mildly elevated</td>
<td>Yes</td>
</tr>
<tr>
<td>LGMD1C</td>
<td>AD</td>
<td>Caveolin3</td>
<td>- Onset of muscle symptoms: from childhood to adult life - People can present weakness and wasting in the hip, thigh and shoulder muscles (LGMD), a distal muscle weakness and “rippling muscle disease” - Cramps and muscle pain after exercise are common - Usually slow progression - Heart and breathing involvement is not a common feature of the disease</td>
<td>Mildly elevated</td>
<td>Yes</td>
</tr>
<tr>
<td>LGMD1D, 1E, 1F</td>
<td>AD</td>
<td>Not known</td>
<td>- Very rarely reported so far</td>
<td>Normal or mildly elevated</td>
<td>No</td>
</tr>
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**How is limb-girdle muscular dystrophy diagnosed?**

The first clue towards the diagnosis of LGMD is usually obtained when your doctor takes your medical history and examines you. The patient’s family history can help to identify the pattern of inheritance and to distinguish between autosomal dominant and autosomal recessive forms.

A physical examination, particularly a neurological evaluation including a muscle strength assessment, can help the doctor determine the pattern of the muscle involvement. Occasionally this may suggest a particular form of muscular dystrophy but usually a number of different tests will be needed to make
the diagnosis. These may include a selection of blood tests, electrical tests, radiological investigations and very importantly a muscle biopsy.

Blood tests can show raised creatine kinase (CK) levels which suggest there may be a problem in the muscles. CK is a muscle enzyme, which is released into the bloodstream at high levels when there is muscle fibre damage. In addition to elevated CK serum levels, some people often have elevated transaminates levels. These enzymes are also referred to as liver enzymes and people with muscular dystrophy can therefore, sometimes, be wrongly diagnosed as having liver disease.

Electromyography (or EMG) is a test that measures the muscle’s response to stimulation of its nerve supply and the electrical activity in the muscle. Electromyography and radiological investigations (MRI scan) can help to identify the pattern of the muscle involvement which may suggest a particular form of muscular dystrophy.

Each of the tests on their own can indicate that LGMD may be a likely diagnosis. It is, however, usually by studying a muscle biopsy that we can be most clear about what type of LGMD someone might have. This is because we are now able to look directly at the proteins which may be reduced or absent in different types of LGMD. In most situations the muscle biopsy gives the best chance of reaching a precise diagnosis. However, even today the muscle biopsy alone is sometimes not enough to distinguish between the exact types of LGMD and therefore genetic tests may be needed to confirm or identify a precise diagnosis.

In approximately 25% of all LGMD patients, a precise diagnosis can not be found in spite of all testing which is available.

**What does the muscle biopsy show?**

A muscle biopsy is a surgical procedure in which a small sample of muscle is removed from your leg or your arm and examined under a microscope. Healthy muscle has a characteristic appearance, and is made up of closely packed fibres which are more or less evenly sized. The muscle biopsy of a person affected by LGMD shows a loss and change of size to some of these muscle fibres and some are even substituted with fat.

In other tests (immunochemistry (A), immunoblotting (B)), we are able to look directly at the muscle proteins which may be reduced or absent in different types of LGMD. This can lead to confirmation of a precise diagnosis.
How has our understanding of the limb-girdle muscular dystrophies improved?

Our understanding of the LGMDs has improved dramatically over the last few years. When the term “limb-girdle” muscular dystrophy was first coined by Dr Walton and Dr Nattrass in 1954 there was no clear understanding of what the condition really involved. It was something of a “catch all” term used fairly widely to distinguish people with predominant limb-girdle weakness from other types of muscular dystrophy, such as Becker, Duchenne, facioscapulohumeral and congenital. Because this was not a very specific use of the term, a lot of people who were thought initially to have had LGMD in fact turned out to have other conditions. On the other hand, the diagnosis of LGMD has been delayed in other people. This was partly because there are many other conditions that can cause weakness of the big muscle of the arms and legs.

Research over the last few years has changed things very dramatically. We can now understand the real cause for a number of different types of limb-girdle muscular dystrophy and can even distinguish different types. By studying the muscle biopsy, we can identify many of the proteins which are absent in muscle and are the causes of the different types of LGMD. We also know the genes responsible for these conditions which are now available by genetic tests. This leads us to have greater understanding about the progression of the condition, the prominent muscle involvement and the complications more frequently associated with the different types.

What other tests are available?

Once the exact subtype of LGMD has been defined, it may be possible to offer other testing such as prenatal diagnosis or carrier testing for other family members. This is so variable from condition to condition and family to family that you will need to explore this with your consultant or ask for referral to a geneticist to discuss in more details.

What are the genetic implications?

Approximately 90% of LGMD is inherited as an autosomal recessive disorder. For someone to have one of these conditions they have to have two faulty copies of the gene responsible. All of our genes come in pairs, one from our mother and one from our father. If someone has an autosomal recessive type of LGMD both of their parents must be carriers (see diagram). These parents will, together, have a 1 in 4 chance of having another baby with LGMD.

People with autosomal recessive types of LGMD rarely have affected children (for the risk of meeting and having a child by a carrier of the same faulty gene will be rare); all of their children will have inherited one copy of the faulty gene but are unaffected.

The remaining subtypes of LGMD show what is known as autosomal dominant in inheritance. This means that the condition can be passed on from parent to child (of either sex). However, it is important to note that we are increasingly recognising that autosomal dominant conditions can arise as a result...
of a so-called new fault in the gene (a “new mutation”) meaning that someone can have an autosomal dominant condition without either parent being affected. For the affected person, there is a 50-50 chance that their children could also be affected.

**How will it progress?**
All types of LGMD tend to get worse with time, but this is highly variable from condition to condition and from person to person. It is best to discuss this with your consultant to be sure the information is relevant to your specific case.

**Is there a treatment?**
There are at this stage no specific treatments or cure for the muscle weakness that arises in LGMD, though clinical trials of experimental treatments are being planned. At present these are not available for patients. Your consultant and the Muscular Dystrophy Campaign can give you up to date and scientific information about clinical trials and potential suitable treatments for patients. However, that is not to say that this means that there is nothing that can be done for people with LGMD.

One very important reason for knowing exactly which type of LGMD someone has is to make sure that people are getting the right follow up and management.

Maintaining good mobility is important for all patients affected by muscular dystrophy. There are not any guidelines about the type or intensity of activities however it is recommended that any exercise undertaken is done within a person’s limitation and remains comfortable. Extreme tiredness, muscle pain and cramps during or after activities can mean that a person has pushed himself too hard and therefore should be avoided. Swimming is a good activity because it promotes movement of all muscles without increased strain.

Access to physiotherapy may be very important to keep people mobile and to keep joints supple.

Watching out for breathing problems may lead to treatments that can be life saving and the same is true for proper follow up of the heart. Prematurely identification of any breathing and heart problems is important in order to promptly start proper treatments. It is very important that all patients have access to this kind of regular follow up.

**What financial help is available to people with neuromuscular conditions?**
Depending on the degree of disability, some people may be entitled to social services benefits, which may include Disability Living Allowance (DLA), Independent Living Fund (ILF), Direct Payments and Home Adaptation Grants. These benefits can be accessed by contacting your local social services department (asking for an assessment of need), Citizens Advice Bureau (CAB), GP, primary health care team and/or Job Centre.

**What is the National Commissioning Group (NCG)?**
NCG is commissioned by the NHS and offers a diagnostic and advisory service to all patients in the UK with Limb Girdle Muscular Dystrophy (LGMD). This service is based at the Institute of Human Genetics in Newcastle upon Tyne. If patients wish to have this specialist assessment, they need to be referred via their GP or consultant. The service is available at no cost to the referring doctor.

**Other relevant factsheets from the Muscular Dystrophy Campaign**
LGMB1B
LGMB1C
LGMB2A
LGMB2B
Sarcoglycanopathies: LGMB2C, LGMD2D, LGMD2E and LGMD2F
LGMB2I.
MC15
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