Limb-girdle muscular dystrophy

Limb-girdle muscular dystrophy is a term for a group of diseases that cause weakness and wasting of the muscles in the arms and legs. The muscles most affected are those closest to the body (proximal muscles), specifically the muscles of the shoulders, upper arms, pelvic area, and thighs.

The severity, age of onset, and features of limb-girdle muscle dystrophy vary among the many subtypes of this condition and may be inconsistent even within the same family. Signs and symptoms may first appear at any age and generally worsen with time, although in some cases they remain mild.

In the early stages of limb-girdle muscular dystrophy, affected individuals may have an unusual walking gait, such as waddling or walking on the balls of their feet, and may also have difficulty running. They may need to use their arms to press themselves up from a squatting position because of their weak thigh muscles. As the condition progresses, people with limb-girdle muscular dystrophy may eventually require wheelchair assistance.

Muscle wasting may cause changes in posture or in the appearance of the shoulder, back, and arm. In particular, weak shoulder muscles tend to make the shoulder blades (scapulae) "stick out" from the back, a sign known as scapular winging. Affected individuals may also have an abnormally curved lower back (lordosis) or a spine that curves to the side (scoliosis). Some develop joint stiffness (contractures) that can restrict movement in their hips, knees, ankles, or elbows. Overgrowth (hypertrophy) of the calf muscles occurs in some people with limb-girdle muscular dystrophy.

Weakening of the heart muscle (cardiomyopathy) occurs in some forms of limb-girdle muscular dystrophy. Some affected individuals experience mild to severe breathing problems related to the weakness of muscles needed for breathing. In some cases, the breathing problems are severe enough that affected individuals need to use a machine to help them breathe (mechanical ventilation).

Intelligence is generally unaffected in limb-girdle muscular dystrophy; however, developmental delay and intellectual disability have been reported in rare forms of the disorder.

Frequency

It is difficult to determine the prevalence of limb-girdle muscular dystrophy because its features vary and overlap with those of other muscle disorders. Prevalence estimates range from 1 in 14,500 to 1 in 123,000 individuals.
Causes

The various forms of limb-girdle muscular dystrophy are caused by mutations in many different genes. These genes provide instructions for making proteins that are involved in muscle maintenance and repair.

Some of the proteins produced from these genes assemble with other proteins into larger protein complexes. These complexes maintain the physical integrity of muscle tissue and allow the muscles to contract. Other proteins participate in cell signaling, cell membrane repair, or the removal of potentially toxic wastes from muscle cells.

Limb-girdle muscular dystrophy is classified on the basis of its inheritance pattern and genetic cause. Limb-girdle muscular dystrophy type 1 includes forms of the disorder that have an inheritance pattern called autosomal dominant. Limb-girdle muscular dystrophy type 2 includes forms of the disorder that have an inheritance pattern called autosomal recessive.

Calpainopathy, or limb-girdle muscular dystrophy type 2A, is caused by mutations in the \textit{CAPN3} gene. Type 2A is the most common form of limb-girdle muscular dystrophy, accounting for about 30 percent of cases. Dysferlinopathy, also called limb-girdle muscular dystrophy type 2B, is caused by mutations in the \textit{DYSF} gene.

Sarcoglycanopathies are forms of limb-girdle muscular dystrophy caused by mutations in the \textit{SGCA}, \textit{SGCB}, \textit{SGCG}, and \textit{SGCD} genes. These sarcoglycanopathies are known as limb-girdle muscular dystrophy types 2D, 2E, 2C, and 2F respectively.

A \textit{TTN} gene mutation causes limb-girdle muscular dystrophy type 2J, which has been identified only in the Finnish population. Mutations in the \textit{ANO5} gene cause limb-girdle muscular dystrophy type 2L. Mutations in several other genes cause forms of limb-girdle muscular dystrophy called dystroglycanopathies, including limb-girdle muscular dystrophy types 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. In addition, for certain forms that are classified by some researchers as limb-girdle muscular dystrophy, other researchers propose grouping them with different, related disorders, such as myofibrillar myopathy, Emery-Dreifuss muscular dystrophy, rippling muscle disease, or Pompe disease.

Inheritance Pattern

Limb-girdle muscular dystrophy can have different inheritance patterns.

Most forms of this condition are inherited in an autosomal recessive pattern, 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.

Other Names for This Condition
- LGMD
- limb-girdle syndrome
- myopathic limb-girdle syndrome

Diagnosis & Management

Genetic Testing Information
- What is genetic testing? /primer/testing/genetictesting
- Genetic Testing Registry: Limb-girdle muscular dystrophy https://www.ncbi.nlm.nih.gov/gtr/conditions/C0686353/
- Jain Foundation: Diagnostic Resources http://www.jain-foundation.org/patient-physician-resources/diagnostic-resources

Research Studies from ClinicalTrials.gov
- ClinicalTrials.gov https://clinicaltrials.gov/ct2/results?cond=%22limb-girdle+muscular+dystrophy%22

Other Diagnosis and Management Resources
- Johns Hopkins Medicine https://www.hopkinsmedicine.org/neurology_neurosurgery/centers_clinics/muscular_dystrophy/conditions/limb_girdle_muscular_dystrophy.html
- Washington University (St. Louis) Neuromuscular Disease Center https://neuromuscular.wustl.edu/musdist/lg.html

Additional Information & Resources

Health Information from MedlinePlus
- Encyclopedia: Limb-Girdle Muscular Dystrophies https://medlineplus.gov/ency/article/000711.htm
- Health Topic: Muscular Dystrophy https://medlineplus.gov/musculardystrophy.html

Genetic and Rare Diseases Information Center
- Limb-girdle muscular dystrophy https://rarediseases.info.nih.gov/diseases/6907/limb-girdle-muscular-dystrophy
Additional NIH Resources

- National Institute of Neurological Disorders and Stroke (NINDS): Muscular Dystrophy
  https://www.ninds.nih.gov/Disorders/All-Disorders/Muscular-Dystrophy-Information-Page

Educational Resources

- MalaCards: limb-girdle muscular dystrophy
  https://www.malacards.org/card/limb_girdle_muscular_dystrophy

- Orphanet: Limb-girdle muscular dystrophy
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=263

- Washington University (St. Louis) Neuromuscular Disease Center
  https://neuromuscular.wustl.edu/musdist/lg.html

Patient Support and Advocacy Resources

- Jain Foundation
  http://www.jain-foundation.org/

- Muscular Dystrophy Association
  https://www.mda.org/sites/default/files/publications/Facts_LGMD_P-209.pdf

- Muscular Dystrophy Association New Zealand
  https://www.mda.org.nz/Neuromuscular-Conditions/Conditions-Overview/Muscular-Dystrophies/Limb-Girdle-Muscular-Dystrophy-LGMD

- Muscular Dystrophy Australia
  http://www.mda.org.au/disorders/overview/lgmd/

- Muscular Dystrophy Canada: Types of Neuromuscular Disorders
  http://muscle.ca/discover-md/types-of-neuromuscular-disorders/

- Muscular Dystrophy UK
  https://www.musculardystrophyuk.org/about-muscle-wasting-conditions/limb-girdle-muscular-dystrophy/

- National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/limb-girdle-muscular-dystrophies/

Clinical Information from GeneReviews

- Calpainopathy
  https://www.ncbi.nlm.nih.gov/books/NBK1313

- Dysferlinopathy
  https://www.ncbi.nlm.nih.gov/books/NBK1303
Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Muscular+Dystrophies,+Limb-Girdle%5BMAJR%5D%29+AND+%28limb-girdle+muscular+dystrophy%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY (LIMB-GIRDLE), TYPE C, 1
  http://omim.org/entry/609308
- MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY (LIMB-GIRDLE), TYPE C, 2
  http://omim.org/entry/613158
- MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY (LIMB-GIRDLE), TYPE C, 3
  http://omim.org/entry/613157
- MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY (LIMB-GIRDLE), TYPE C, 4
  http://omim.org/entry/611588
- MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY (LIMB-GIRDLE), TYPE C, 5
  http://omim.org/entry/607155
- MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY (LIMB-GIRDLE), TYPE C, 7
  http://omim.org/entry/616052
- MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY (LIMB-GIRDLE), TYPE C, 8
  http://omim.org/entry/618135
- MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY (LIMB-GIRDLE), TYPE C, 9
  http://omim.org/entry/613818
- MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY (LIMB-GIRDLE), TYPE C, 12
  http://omim.org/entry/616094
- MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY (LIMB-GIRDLE), TYPE C, 14
  http://omim.org/entry/615352
• MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL DOMINANT 1
  http://omim.org/entry/603511
• MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL DOMINANT 2
  http://omim.org/entry/608423
• MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL DOMINANT 3
  http://omim.org/entry/609115
• MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL DOMINANT 4
  http://omim.org/entry/618129
• MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL RECESSIVE 1
  http://omim.org/entry/253600
• MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL RECESSIVE 2
  http://omim.org/entry/253601
• MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL RECESSIVE 3
  http://omim.org/entry/608099
• MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL RECESSIVE 4
  http://omim.org/entry/604286
• MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL RECESSIVE 5
  http://omim.org/entry/253700
• MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL RECESSIVE 6
  http://omim.org/entry/601287
• MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL RECESSIVE 7
  http://omim.org/entry/601954
• MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL RECESSIVE 8
  http://omim.org/entry/254110
• MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL RECESSIVE 10
  http://omim.org/entry/608807
• MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL RECESSIVE 12
  http://omim.org/entry/611307
• MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL RECESSIVE 17
  http://omim.org/entry/613723
• MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL RECESSIVE 18
  http://omim.org/entry/615356
• MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL RECESSIVE 21
  http://omim.org/entry/617232
• MUSCULAR DYSTROPHY, LIMB-GIRDLE, TYPE 1H
  http://omim.org/entry/613530
Medical Genetics Database from MedGen

- Limb-girdle muscular dystrophy
  https://www.ncbi.nlm.nih.gov/medgen/151940

Sources for This Summary

- Angelini C, Giaretta L, Marozzo R. An update on diagnostic options and considerations in limb-girdle dystrophies. Expert Rev Neurother. 2018 Sep;18(9):693-703. doi: 10.1080/14737175.2018.1508997. Epub 2018 Aug 21. Review. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30084281

- Chu ML, Moran E. The Limb-Girdle Muscular Dystrophies: Is Treatment on the Horizon? Neurotherapeutics. 2018 Oct;15(4):849-862. doi: 10.1007/s13311-018-0648-x. Review. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30019308 
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6277288/

- Khadilkar SV, Patel BA, Lalkaka JA. Making sense of the clinical spectrum of limb girdle muscular dystrophies. Pract Neurol. 2018 Jun;18(3):201-210. doi: 10.1136/practneurol-2017-001799. Epub 2018 Feb 22. Review. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29472383

- Liewluck T, Milone M. Untangling the complexity of limb-girdle muscular dystrophies. Muscle Nerve. 2018 Aug;58(2):167-177. doi: 10.1002/mus.26077. Epub 2018 Feb 7. Review. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29350766

- Liu W, Pajusalu S, Lake NJ, Zhou G, Ioannidis N, Mittal P, Johnson NE, Weihl CC, Williams BA, Albrecht DE, Rufibach LE, Lek M. Estimating prevalence for limb-girdle muscular dystrophy based on public sequencing databases. Genet Med. 2019 May 20. doi: 10.1038/s41436-019-0544-8. [Epub ahead of print] 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/31105274

- Mah JK, Korngut L, Fiest KM, Dykeman J, Day LJ, Pringsheim T, Jette N. A Systematic Review and Meta-analysis on the Epidemiology of the Muscular Dystrophies. Can J Neurol Sci. 2016 Jan;43(1):163-77. doi: 10.1017/cjn.2015.311. Review. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26786644

- Mitsuhashi S, Kang PB. Update on the genetics of limb girdle muscular dystrophy. Semin Pediatr Neurol. 2012 Dec;19(4):211-8. doi: 10.1016/j.spen.2012.09.008. Review. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23245554

- Straub V, Murphy A, Udd B; LGMD workshop study group. 229th ENMC international workshop: Limb girdle muscular dystrophies - Nomenclature and reformed classification Naarden, the Netherlands, 17-19 March 2017. Neuromuscul Disord. 2018 Aug;28(8):702-710. doi: 10.1016/j.nmd.2018.05.007. Epub 2018 May 24. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30055862

- Thompson R, Straub V. Limb-girdle muscular dystrophies - international collaborations for translational research. Nat Rev Neurol. 2016 May;12(5):294-309. doi: 10.1038/nrneurol.2016.35. Epub 2016 Apr 1. Review. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/27033376

- Wicklund MP, Kissel JT. The limb-girdle muscular dystrophies. Neurol Clin. 2014 Aug;32(3):729-49, ix. doi: 10.1016/j.ncl.2014.04.005. Review. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25037088
