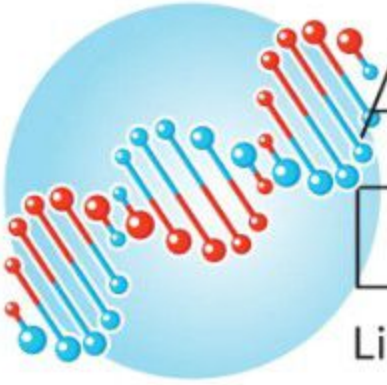
Written By Andrew Findlay, MD
Washington University St. Louis



Autosomal Dominant

Limb-Girdle Muscular Dystrophies

Clinical Features & Inheritance Patterns of Dominant LGMDs

Dominantly inherited limb-girdle muscular dystrophies (LGMD) have a broad range of clinical features. Dominance refers to the inheritance pattern for this set of disorders. For non-sex chromosomes (X, Y), everyone has two sets of genes, one inherited from each parent. For diseases with recessive inheritance, it takes two pathogenic variants, one on each copy of a gene, to cause disease. For dominantly inherited disorders, it only takes one mutated copy of a gene to cause disease. This means an individual affected by a dominantly inherited disease has a 50% chance of passing the disease on to their child. For recessive subtypes, by contrast, a person generally must inherit a mutation from both parents to have the disease.

Several Broad Generalizations Can Be Made About Dominant LGMDs:

1. They account for about 10% of all LGMD cases.
2. They more commonly have adult onset compared to recessive forms.
3. The diseases typically progress more slowly over time compared to recessive LGMDs.
4. Affected individuals are often in good health at reproductive age. This commonly results in extensive family trees with many affected individuals due to the disease being passed from generation to generation.

Dominant LGMD Nomenclature

In the prior LGMD nomenclature system established in the 1990s, dominantly inherited subtypes were indicated by a 1, followed by a letter based on the order of discovery (e.g., LGMD 1D). With the new nomenclature, dominant inheritance is indicated by a D, followed by a number (e.g., LGMD D1). Several disorders originally labeled as LGMD are no longer classified as LGMDs in the new nomenclature system, as shown in the table. These re-categorized disorders can absolutely cause weakness in a limb-girdle pattern, but their primary clinical manifestations are commonly something different (e.g., distal predominant weakness affecting feet and hands). As new causes for dominantly-inherited muscle disorders continue to be discovered (e.g., mutations in DTNA gene), the list of dominant LGMDs will likely continue to grow.

Old Nomenclature	New Nomenclature	Gene	Protein
LGMD1A	Myofibrillar myopathy	*MYOT*	Myotilin
LGMD1B	Emery Dreifuss Muscular Dystrophy	*LMNA*	Lamin A/C
LGMD1C	Rippling muscle disease	*CAV3*	Caveolin 3
LGMD1D	**LGMDD1 DNAJB6-related**	***DNAJB6***	**DNAJB6**
LGMD1E	Myofibrillar myopathy	*DES*	Desmin
LGMD1F	**LGMDD2 TNPO3-related**	***TNPO3***	**Transportin 3**
LGMD1G	**LGMDD3 HNRPDL-related**	***HNPRDL***	**Heterogeneous nuclear ribonucleoprotein D-like**
LGMD1H		False linkage	
LGMD1I	**LGMDD4 Calpain3-related**	***CAPN3***	**Calpain 3**
Bethlem Myopathy (dominant)	**LGMDD5 Collagen VI-related**	***COL6A1-3***	**Collagen VI**

Table 1: Dominant LGMD Nomenclature

Dominant Disease Mechanisms

Recessively inherited LGMDs are usually caused by mutations resulting in either the absence of the protein or rendering the protein non-functional. These mutations are therefore broadly referred to as causing a "loss of function." In contrast, dominantly inherited disorders can be caused by at least three different mechanisms. In a simplified form, these are as follows:

1. Haploinsufficiency refers to disorders where a mutation on one copy of the gene causes only half the normal amount of functional protein to be produced, and this is insufficient for normal cellular function.
2. A toxic or gain-of-function mechanism results from mutations that either increase the protein's activity, prolong its stability (and thereby increase its effect in the cell), or cause it to gain some additional toxic function unrelated to its normal role.
3. A dominant-negative mechanism results from mutations that negate the activity of the normal copy of the protein. This mechanism is often seen with proteins that group together. The protein complex containing mutant proteins is non-functional, even though it also contains normal proteins.

Therapeutic Strategies for Dominant LGMDs

Currently, there are no approved therapies or clinical trials involving treatments for any of the dominant LGMDs. However, several pre-clinical studies have been completed, investigating treatments for these LGMDs in cells and animal models. The disease mechanisms described above are the basis for the rationale behind the various treatment strategies for dominant LGMDs.

For recessively inherited disorders, gene transfer therapy (where a new, functioning copy of the gene is provided to an individual's cells) will, in theory, be helpful. This approach can also be helpful in the case of dominant disorders caused by haploinsufficiency, where only half the normal amount of functional protein is produced. However, gene transfer therapy wouldn't be expected to help in diseases caused by gain-of-function or dominant-negative mechanisms.

Another approach, called "knockdown," uses chemicals that bind to RNA from the mutated gene to prevent the mutant protein from being produced. This approach is well-suited to dominantly inherited diseases caused by toxic, gain-of-function, or dominant-negative mechanisms.

A variety of knockdown approaches exist. Which approach is best-suited for a disease depends on how much of the affected protein is required for a cell to function normally.

- → If complete absence of the mutant protein is tolerated, a knockdown approach that targets both copies of a gene (both healthy and mutated) can be beneficial for a dominantly inherited disease.
  - LGMD1A is caused by mutations in a protein called myotilin, causing it to misfold and aggregate within muscle. Interestingly, absence of myotilin does not cause abnormalities in mouse skeletal muscle. Mice expressing a mutant *MYOT* gene found in LGMD1A patients were treated with an artificial microRNA (miRNA) targeting human *MYOT* mRNA. This significantly reduced the mutant myotilin levels, improved muscle pathology, reduced protein aggregates, and improved strength in the mice.
- → If at least 50% of the normal protein levels are needed for cellular health, a knockdown treatment that targets only the mutant copy of the gene (allele specific) can be used.
  - LGMDD5 (Bethlem myopathy) is most commonly caused by dominant-negative mutations in the Collagen VI genes. Collagen VI is a key component of the extracellular matrix surrounding muscle fibers. These dominant-negative mutations disrupt assembly of the Collagen VI microfibrils from its three subunits. Collagen

VI is needed for muscles to function correctly, so a total knockdown of the gene isn't a good treatment approach. Selective knockdown of just the mutant allele, however, is a promising treatment strategy for dominant Collagen VI-related dystrophies (and other disorders with dominant-negative mechanisms). Several different approaches are being pursued to apply this strategy to Collagen VI dystrophies.

- Preclinical studies in LGMDD1 have used a slightly different therapeutic approach. LGMDD1 is caused by dominantly inherited point mutations in DNAJB6, a chaperone protein that plays an important role in cellular health by maintaining other proteins in their proper shape and preventing them from aggregating. There are two different versions (isoforms) of the DNAJB6 protein. DNAJB6a is a larger version of the protein that is found mainly within cell nuclei, while DNAJB6b is a smaller version of the protein that localizes to a portion of muscle fibers called the Z-disc. It is thought that DNAJB6b may be primarily responsible for disease pathogenesis in LGMDD1. This is supported by the fact that DNAJB6b is the isoform that localizes to the main site of pathology seen in human biopsies. It's known that an absence of DNAJB6 in mouse embryos prevents them from developing, arguing against using complete knockdown as a treatment strategy. A therapeutic approach involving selective knockdown of the DNAJB6b isoform in LGMDD1 mouse myotubes (muscle precursor cells grown in a dish), resulted in improvement in some of their disease-related abnormalities. The next step will be to test the isoform-specific knockdown in living mice.

→ If more than 50% of the normal protein level is required for cellular health, then a treatment involving complete knockdown of the gene while simultaneously providing a replacement copy of the gene resistant to knockdown can be beneficial. Although it has not been tested in dominant LGMDs, this approach has been found to be beneficial in mouse models of several other dominantly inherited neuromuscular disorders.

Barriers to Developing Treatments for Dominant LGMDs

While the promise of gene-based therapies is becoming a reality, research into these therapies for LGMDs has thus far focused primarily on recessive forms. The gene replacement strategies that are commonly employed for recessive, loss-of-function disorders are not readily translatable to most dominant forms of LGMD, hindering the development of novel treatments for dominant LGMDs. Additionally, dominantly inherited disorders have complex, heterogeneous disease mechanisms as discussed above and, thus, require unique therapeutic approaches. These approaches are not as developed as replacement therapies used for recessive LGMDs.

Also, even if a promising therapy were suddenly available, the natural histories of most dominantly inherited LGMDs are not well characterized yet. Nevertheless, some progress has been made in characterizing the natural history of LGMDD1: recent studies have found that different disease-causing mutations are associated with variable ages of onset, as well as different weakness patterns, where some individuals have weakness in their feet and hands instead of their hips and shoulders. It was also found that particular mutations are associated with different rates of disease progression.

Comparable studies for other dominant LGMDs are lacking and current clinical information are limited to descriptions of individual cases. Characterizing the natural history of disease progression is critically important to identify ideal outcome measures for future clinical trials. Overall, the variability in disease severity and the rarity of all dominantly inherited LGMDs highlight the need for participation in future natural history studies and eventual clinical trials. ▪