

Primer of Limb-Girdle Dystrophies

General: The term Limb-Girdle Muscular Dystrophy (LGMD) was initially proposed as a broad category to include muscular disorders that did not fit into phenotypically defined myopathies such as Duchenne and Becker dystrophies (DMD/BMD), fascioscapulohumeral dystrophy (FSH), and myotonic dystrophies. With the advent of specific immunohistochemical staining of muscle biopsy tissue for structural proteins that are separate from contractile proteins and genetic analysis, LGMD is divided into a growing number of distinct disorders that is expanding rapidly.

Another broad category of muscle disorders that must be separated from LGMD is congenital muscular dystrophies (CMD). They are defined as weakness evident at birth or during the first few months of life and lack of specific histochemical features on muscle biopsy. Of note, mutations in the same gene can give rise to phenotypes of LGMD (adult onset with mild weakness) or CMD (infantile onset with severe weakness).

CMD, in turn is separated from congenital myopathies that have

distinct histochemical findings that descriptive names, such as nemaline rods (nemaline myopathy), cores within muscle fibers (central core and multicore myopathies), aggregates within muscle fibers (tubular aggregate myopathy), and others.

Genetics: LGMD is divided into two groups based on genetic patterns; type 1 is autosomal dominant and type 2 is autosomal recessive. Within each group are letters to denote different genetic loci; LGMD1A, 1B, 1C and LGMD2A, 2B, 2C, etc. Recessive forms are 10x more common than dominant forms, and X-linked forms are rare.

There is a spectrum of mutations, including large and small deletions and point mutations.

Pathogenesis: LGMDs are attributed to defects in proteins, some of which link the contractile protein actin to the basal lamina and extracellular matrix and others that are involved in muscle development and trafficking of other proteins. The main protein structures are in the dystrophin-glycoprotein complex which consists of several component protein groups: 1) Dystroglycan complex is made up of two

recessive or dominant, and occasionally X-linked

Calpainopathy (LGMD2A):

Calpain-3 is a calcium-activated protease in the cytosol. Its function is surmised, and has a role in the control of expression of muscle-specific transcription factors. This is a relatively common disorder, with onset of weakness in late childhood-adolescence to early adulthood. Weakness is associated with prominent muscle atrophy, and is progressive leading to loss of ambulation.

Dysferlinopathy (LGMD2B):

Dysferlin is a transmembrane protein, and the same mutation can cause markedly different patterns of weakness. The Miyoshi phenotype preferentially affects the gastrocnemius muscle, while other phenotypes affect proximal muscles. This suggests the presence of a modifier gene to account for the clinical differences. Serum CK levels are very high (>10,000). Progression is slow.

Sarcoglycanopathies (LGMD2C, D, E, and F): The associated LGMD forms with the subunits are LGMD2D (α -sarcoglycan), LGMD2E (β -sarcoglycan), LGMD2C (γ -sarcoglycan), and LGMD2F (δ -sarcoglycan). The

clinical course is progressive, with loss of ambulation. Subclinical cardiomyopathies may occur.

Telethoninopathy (LGMD2G):

Telethonin is a cytosolic protein that is a substrate for titin kinase, and telethonin may be a binding site for sarcomeric proteins and sarcomere assembly. There is predominant weakness of distal muscles.

TRIM32-related dystrophy

(LGMD2H): Rare and described among Hutterites communities in Canada.

Fukutin-related proteinopathy

(LGMD2I): Mutations affect glycosylation of α -dystroglycan, and abnormalities of laminin can give rise to early onset severe forms of CMD and to later onset with milder weakness that may mimic clinically DMD/BMD.

Laminin is a complex structure that forms the backbone of the basement membrane. Laminin-2 interacts α -dystroglycan

Titinopathy (LGMD2J): Rare and has variable phenotype with distal or proximal weakness.

Myotilin myopathy (LGMD1A):

Myotilin is a protein that is attached to Z-dic and cross-links with actin and has a role in maintaining contractile

organization. Identical mutations can cause different phenotypes, suggesting the existence of modifying genes.

Laminopathy (LGMD1B): This is allelic with autosomal dominant Emery-Dreifuss Muscular Dystrophy and is caused by mutations in the lamin A/C gene. Laminin A/C and the protein Emerin are nuclear proteins that may stabilize the nuclear membrane. The clinical features are similar to X-linked Emery-Dreifuss, and include early-onset joint contractures, progressive weakness and cardiomyopathy with cardiac conduction block requiring a pacemaker.

Concavulinopathy (LGMD1C): Caveolin is a component of the caveolae membrane that are implicated in signal transduction. The spectrum of clinical features broad, including distal distribution of weakness, myalgias, rippling muscle disease, and asymptomatic elevations in CK.

LGMD1D: Rare, slowly progressive and may have cardiac conduction abnormalities.

There are several other proximal dystrophies that are sometimes included in the category of limb-girdle.

Emery-Dreifuss (X-EMD): This is X-linked and the gene encodes the protein, emerin, which is in the nuclear membrane. There are early-onset joint contractures, proximal weakness, and cardiac conduction block. The autosomal dominant form (AD-EMD) involves the lamin A/C, and there may be a emrin-lamin A/C complex.

Ocular-pharyngeal muscular dystrophy (OPMD): This involves weakness of extra ocular, pharyngeal and proximal limb muscles leading to ophthalmoplegia and the inability to swallow.

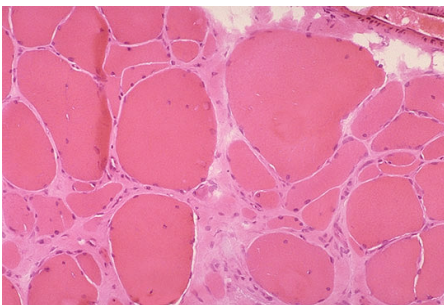
Bethlem and Ullrich myopathy: Mutations affect type VI collagen. Bethlem is autosomal dominant with proximal weakness with distal contractures. Ullrich is both autosomal dominant and recessive, has early onset with proximal joint contractures and distal hyperextensible joints.

Diagnosis: Onset of weakness among the LGMDs can be at any age. The muscles that become weak at onset are variable, including pelvic or shoulder girdle muscles, or distal muscles. Calf muscle pseudohypertrophy is frequent, but not invariant. There can be marked intrafamilial variability in the pattern of weakness. Weakness is

progressive, but highly variable in rate. CK is usually elevated, but to varying degrees.

Muscle biopsy is essential to: 1) Establish histologic presence of a dystrophy. 2) Exclude a dystrophinopathy (DMD/BMD), 3) Determine the specific pattern of antibody staining of the various proteins that lead to the diagnosis.

Dystrophic changes in muscle include: 1) Variations in muscle fiber diameter with rounded cross sectional features. 2) Chronicity in the form of excess connective tissue between muscle fibers (endomysial fibrosis) and replacement of fibers with adipose cells. 3) Presence of degenerating and regenerating fibers. Inflammatory cells may be present.



H and E stain showing variation in muscle fiber diameters and extra endomysial tissue,

Staining for dystrophin is essential because LGMD excludes dystrophinopathies.

The diagnosis of LGMD is made by showing an absence of staining of a particular proteins

Treatment: There is no specific therapy for the weakness.

Management: There is a wide spectrum in the degree and distribution of weakness, and the goal of management is to maintain function and independence. For some, periodic EKGs and cardiac evaluations are necessary. Joint contractures should be addressed early on and treated with physical therapy.