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Limb-Girdle Muscular Dystrophy Overview – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonym: LGMD

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Summary

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Clinical characteristics

Limb-girdle muscular dystrophy (LGMD) is a purely descriptive term, generally reserved for childhood- or adult-onset muscular dystrophies that are distinct from the much more common X-linked dystrophinopathies. LGMDs are typically nonsyndromic, with clinical involvement typically limited to skeletal muscle. Individuals with LGMD generally show weakness and wasting restricted to the limb musculature, proximal greater than distal, and muscle degeneration/regeneration on muscle biopsy. Most individuals with LGMD show relative sparing of the bulbar muscles, although exceptions occur, depending on the genetic subtype. Onset, progression, and distribution of the weakness and wasting vary considerably among individuals and genetic subtypes.

Diagnosis/testing

The limb-girdle muscular dystrophies typically show degeneration/regeneration (dystrophic changes) on muscle biopsy, which is usually associated with elevated serum creatine kinase concentration. For any male or female suspected of having limb-girdle muscular dystrophy, it is necessary to first rule out an X-linked dystrophinopathy. Biochemical testing (i.e., protein testing by immunostaining or immunblotting) performed on a muscle biopsy can establish the diagnosis of the following LGMD types: sarcoglycanopathy, calpainopathy, dysferlinopathy, and O-linked glycosylation defects (also known as dystroglycanopathy). In some cases, demonstration of complete or partial deficiencies for any particular protein can then be followed by mutation studies of the corresponding gene. Pathogenic variants in a number of genes have been associated with types of LGMD.

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Genetic counseling

The term LGMD1 (including, e.g., LGMD1A, LGMD1B) refers to genetic types showing dominant inheritance, whereas LGMD2 refers to types with autosomal recessive inheritance. Pathogenic variants at more than 50 loci have been reported, making accurate diagnosis and genetic counseling a challenge. In most instances, the proband represents a simplex case, and the families can be counseled for recurrence risks associated with rare autosomal recessive conditions, which leaves a "significant" risk only for the sibs of the proband. If the causative pathogenic variant(s) have been identified in the family, prenatal testing for pregnancies at increased risk is possible.

Management

No definitive treatments for the limb-girdle muscular dystrophies exist. Management should be tailored as much as possible to each individual and each specific LGMD type. Management to prolong survival and improve quality of life includes weight control to avoid obesity, physical therapy and stretching exercises to promote mobility and prevent contractures, use of mechanical aids to help ambulation and mobility, surgical intervention for orthopedic complications, use of respiratory aids when indicated, monitoring for cardiomyopathy in LGMD types with cardiac involvement, and social and emotional support and stimulation.

Definition

Limb-girdle muscular dystrophy (LGMD) is a purely descriptive term, generally reserved for childhood- or adult-onset muscular dystrophies that are distinct from the much more common X-linked dystrophinopathies, which include Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) (both affected males and symptomatic females).

At one time, the term LGMD was reserved for individuals with onset of weakness in adolescence or adulthood. More severe childhood presentations were previously termed a "severe childhood autosomal recessive muscular dystrophy" (SCARMD); however, SCARMD is now considered a subset of LGMD. The term LGMD1 (including, e.g., LGMD1A, LGMD1B) refers to genetic types showing dominant inheritance, whereas LGMD2 refers to types with autosomal recessive inheritance. Pathogenic variants at more than 50 loci have been shown to cause LGMD.

Clinical Manifestations

Individuals with LGMD generally show weakness and wasting restricted to the limb musculature, proximal greater than distal. Proximal weakness refers to weakness of the muscles closer to the center of the body (including the shoulder, pelvic girdle, upper thighs, and upper arms). Distal weakness refers to weakness in muscles farther from the center of the body (including lower legs and feet, lower arms and hands). Onset, progression, and distribution of the weakness and wasting may vary considerably among individuals and genetic subtypes.

LGMDs are typically nonsyndromic, with clinical involvement typically limited to skeletal muscle. While most individuals with LGMD show relative sparing of the bulbar muscles, exceptions occur, depending on the genetic subtype.

Establishing the Diagnosis

- The clinical course of the limb-girdle muscular dystrophies is typically progressive, though some individuals may show mild symptoms and/or the disease may stabilize.
- Serum creatine kinase (CK) concentration is usually elevated.
- Muscle biopsy typically shows degeneration/regeneration of muscle fibers ("dystrophic changes").

- In some LGMDs (i.e., sarcoglycanopathy, calpainopathy, dysferlinopathy, and glycosylation defects, or dystroglycanopathy) the diagnosis can be established based on "biochemical testing," i.e., immunostaining/immunoblotting of a muscle biopsy to determine if specific proteins are present or absent.
- In some cases, molecular genetic testing can be used to identify the specific pathogenic variants.
- Inflammatory myopathy should be excluded during the diagnostic process.

Differential Diagnosis

The following disorders are included in the differential diagnosis of the limb-girdle muscular dystrophies:

- **The dystrophinopathies** are caused by pathogenic variants in *DMD*. Duchenne muscular dystrophy (DMD) usually presents in early childhood and is rapidly progressive, with affected children being wheelchair-bound by age 12 years. Few survive beyond the third decade. Becker muscular dystrophy) (BMD) is characterized by later-onset skeletal muscle weakness. Affected individuals remain ambulatory into their 20s, but heart failure from dilated cardiomyopathy (DCM) is common. Inheritance is X-linked. DMD/BMD carriers are usually asymptomatic, but about 10% of them may present with muscle weakness or dilated cardiomyopathy.

  Any male or female suspected of having limb-girdle muscular dystrophy must first be evaluated for dystrophinopathy.

  - Males should be evaluated by molecular genetic testing of *DMD* and, when necessary, by dystrophin immunostaining or immunoblotting of a muscle biopsy.
  - Females should be evaluated by dystrophin immunostaining of a muscle biopsy or by molecular genetic testing of *DMD*. Note: In the past, when a female with muscular dystrophy was the only affected family member, a diagnosis of autosomal recessive LGMD was made; however, the affected female is nearly as likely to be a manifesting DMD carrier as to have some form of LGMD [Hoffman et al 1992, Hoffman et al 1996].

- **Facioscapulohumeral muscular dystrophy (FSHD)** typically presents before age 20 years with marked weakness of the facial muscles and the stabilizers of the scapula or the dorsiflexors of the foot. Severity is highly variable. Those individuals without significant facial weakness can closely resemble those with LGMD. Weakness is slowly progressive and approximately 20% of affected individuals require a wheelchair. Life expectancy is not shortened. A deletion of integral copies of a 3.3-kb DNA repeat motif termed D4Z4 is detected in about 95% of affected individuals.

- **Emery-Dreifuss muscular dystrophy (EDMD)** is characterized by the clinical triad of (1) joint contractures that begin in early childhood; (2) slowly progressive muscle weakness and wasting initially in a humero-peroneal distribution and later extending to the scapular and pelvic girdle muscles; and (3) cardiac involvement that may include palpitations, presyncope and syncope, poor exercise tolerance, and congestive heart failure. The X-linked form is caused by pathogenic variants in *EMD*, the gene encoding emerin; the dominant/recessive forms are caused by pathogenic variants in *LMNA*, the gene encoding lamin A/C.

- **Congenital muscular dystrophy (CMD)** is a group of disorders in which weakness is present at birth. Affected infants typically appear "floppy" with low muscle tone and contractures. Diagnosis is based on (1) muscle biopsy, which typically shows a dystrophic or myopathic pattern, with or without fatty infiltration; (2) serum creatine kinase (CK) concentration, which is usually elevated; (3) immunostaining of muscle, which is abnormal in specific subtypes; and (4) brain MRI, which may show structural abnormalities indicative of syndromic congenital muscular dystrophy or abnormal white matter signal. Approximately 50% of CMD is caused by complete merosin deficiency; diagnosis is made by detection of complete

merosin deficiency on immunostaining of muscle biopsy and abnormal white matter signal on MRI after age four months. The congenital muscular dystrophies are inherited in an autosomal recessive manner.

- **Collagen type VI-related disorders** are a continuum from Ullrich congenital muscular dystrophy to Bethlem myopathy. Bethlem myopathy is characterized by the combination of proximal muscle weakness and variable contractures, affecting most frequently the long finger flexors, elbows, and ankles. The onset of Bethlem myopathy ranges from prenatal to mid-adulthood. Prenatal onset is characterized by decreased fetal movements; neonatal onset by hypotonia or torticollis; early childhood onset by delayed motor milestones, muscle weakness, and contractures; and adult onset (4th to 6th decades) by proximal weakness and Achilles tendon or long finger flexor contractures. Because of slow but ongoing progression of the condition, more than two thirds of affected individuals older than age 50 years rely on supportive means for outdoor mobility. Respiratory muscle and diaphragmatic involvement is rare and seems to be related to severe weakness that occurs in later life. Bethlem myopathy is inherited in an autosomal dominant manner and Ullrich congenital muscular dystrophy usually in an autosomal recessive manner.
- **Myositis (inflammatory myopathies)** can share histopathologic features with the LGMDs. Inflammatory diseases typically show more acute onset and respond to immunosuppressive therapy; however, few types of LGMD also respond well to immunosuppressive therapy (i.e., prednisone). Clinical and histologic overlap between dysferlinopathy (LGMD2B) and inflammatory disease is considerable; individuals with myositis on muscle biopsy who do not respond to immunomodulation therapy can be considered for dysferlin testing.

Prevalence

Because of the heterogeneity of limb-girdle muscular dystrophy and the lack of diagnostic specificity, there are few reports on the prevalence of LGMD.

Estimates of prevalence for all forms of LGMD range from one in 14,500 to one in 123,000 [van der Kooi et al 1996, Urtasun et al 1998].

The estimated prevalence of primary sarcoglycanopathies is approximately one in 178,000 [Fanin et al 1997]. According to this estimate, the carrier frequency can be estimated at 1:211; while Hackman et al [2005] estimate the carrier frequency of sarcogycanopathy at 1:150.

Causes

In this section, the type of limb-girdle muscular dystrophy is categorized by mode of inheritance and molecular genetics.

Autosomal Recessive Limb-Girdle Muscular Dystrophy

Molecular Genetics

Table 1. Molecular Genetics of Autosomal Recessive Limb-Girdle Muscular Dystrophy (LGMD)

% of Individuals with AR LGMD	Disease Name (Synonym)	Populations with Founder Variants	Gene	Locus [1]
Up to 68% of individuals with childhood onset and ~10% with adult onset [2]	Alpha-sarcoglycanopathy (LGMD2D)	None	*SGCA*	17q21.33
	Beta-sarcoglycanopathy (LGMD2E)	Amish	*SGCB*	4q12
	Gamma-sarcoglycanopathy (formerly SCARMD) (LGMD2C) [3]	North Africans; Gypsies [4]	*SGCG*	13q12.12
	Delta-sarcoglycanopathy (LGMD2F)	Brazilian [5]	*SGCD*	5q33.3
~10% [6]	Calpainopathy (LGMD2A)	Amish, La Reunion Island, Basque (Spain), Turkish	*CAPN3*	15q15.1
~5%	Dysferlinopathy (LGMD2B)	Libyan Jewish	*DYSF*	2p13.2
3%	LGMD2G	Italian (?)	*TCAP*	17q12
Unknown	LGMD2H	Manitoba Hutterites only	*TRIM32*	9q33.1
6% [7]	LGMD2I (MDDGC5) [8]	Unknown	*FKRP*	19q13.32
Unknown	LGMD2J	Finland	*TTN*	2q31.2
Unknown	LGMD2K (MDDGC1) [8]	Turkish	*POMT1*	9q34.13
~25% in the UK population	LGMD2L	Northern European [9, 10]	*ANO5*	11p14.3
Unknown	LGMD2M (MDDGC4) [8]	Unknown	*FKTN*	9q31.2
Unknown	LGMD2N (MDDGC2) [8]	Unknown	*POMT2*	14q24.3
Unknown	LGMD2O (MDDGC3) [8]	Unknown	*POMGNT1*	1p34.1
Unknown	LGMD2Q	Turkish	*PLEC*	8q24.3

See Autosomal Recessive Limb-Girdle Muscular Dystrophy: Phenotypic Series to view genes associated with this phenotype in OMIM.
1. From omim.org
2. Vainzof et al [1999]
3. SCARMD = severe childhood autosomal recessive muscular dystrophy
4. Merlini et al [2000]
5. Nigro et al [1996], Vainzof et al [1999]
6. Ranges from 10% in the population of European descent [Chou et al 1999] to 80% in the Basque country [Urtasun et al 1998]. Actual frequency depends on the population.
7. Boito et al [2005]
8. MDDG (muscular dystrophy-dystroglycanopathy) [Amberger et al 2011]
9. Hicks et al [2011]
10. Penttilä et al [2012]

Sarcoglycanopathies, including α-sarcoglycanopathy (LGMD2D) caused by mutation of *SGCA*; β-sarcoglycanopathy (LGMD2E) caused by mutation of *SGCB*; γ-sarcoglycanopathy (LGMD2C) caused by mutation of *SGCG*; δ-sarcoglycanopathy (LGMD2F) caused by mutation of *SGCD*. The four different sarcoglycan genes encode proteins that form a tetrameric complex at the muscle cell plasma membrane. This complex stabilizes the association of dystrophin with the dystroglycans and contributes to the stability of the plasma membrane cytoskeleton. The four sarcoglycan genes are related to each other structurally and functionally, but each has a distinct chromosome location (see Table 1).

In nonconsanguineous populations, the relative frequency of pathogenic variants in the four genes is alpha >> beta >> gamma >> delta in an 8:4:2:1 ratio [Duggan et al 1997a]. No common pathogenic variants have been identified in nonconsanguineous populations except the p.Arg77Cys variant, which accounts for up to one third of the mutated *SGCA* alleles [Hackman et al 2005]. Founder variants have been observed in certain populations (Table 1).

Calpainopathy (LGMD2A; caused by mutation of *CAPN3*). Calpain 3 is a calcium-sensitive protease involved in muscle remodeling. To date, more than 450 pathogenic variants in *CAPN3* have been described.

Dysferlinopathy (LGMD2B; *DYSF*). Dysferlin is a sarcolemmal protein that includes C2 domains thought to be important for calcium-mediated vesicle fusion with sarcolemma and membrane repair of skeletal muscle fibers [Bansal et al 2003, Han & Campbell 2007]. Although intra- and interfamilial clinical variability is significant, no specific genotype-phenotype correlations have been established [Cagliani et al 2003].

LGMD2G (*TCAP*). Homozygosity for a *TCAP* pathogenic variant has been identified in four Brazilian families [Moreira et al 2000]. Affected individuals in one Italian family have been found to have compound heterozygous *TCAP* pathogenic variants.

LGMD2H (*TRIM32*). Pathogenic variants reported in *TRIM32* include two missense variants, one codon deletion, and two frameshift variants [Frosk et al 2002, Saccone et al 2008, Cossée et al 2009]. The first-described *TRIM32* pathogenic variant, p.Asp487Asn, is a founder variant in the Hutterite population (of North America); one sib pair has been identified in a non-Hutterite family in Germany (the country of origin of the Hutterites). Sarcotubular myopathy (STM), also observed in the Hutterite population, is now known to be caused by the same pathogenic variant in *TRIM32* [Schoser et al 2005, Borg et al 2009].

TRIM32 codes for an E3-Ub ligase responsible for post-translational regulation of protein levels [Frosk et al 2002].

O-linked glycosylation enzymes (dystroglycanopathies) including LGMD2I (caused by mutation of *FKRP*), **LGMD2K** (*POMT1*), **LGMD2M** (*FKTN*), **LGMD2O** (*POMGNT1*), **LGMD2N** (*POMT2*). These five different genes encode glycosyltransferases involved in the addition of carbohydrate residues to α-dystroglycan and abnormal glycosylation of this molecule is a common finding in these forms of LGMD. Pathogenic variants of these genes have been associated with muscular dystrophies of variable severity ranging from congenital muscular dystrophies with various eye and brain involvement to milder forms with later onset (limb-girdle muscular dystrophies). Relatively few individuals with an LGMD phenotype and pathogenic variants in *POMT1*, *FKTN*, *POMGNT1*, or *POMT2* have been reported [Balci et al 2005, Godfrey et al 2006, Biancheri et al 2007, Godfrey et al 2007, Clement et al 2008]. Reported affected individuals are compound heterozygous for pathogenic missense or nonsense variants. No common pathogenic variants have been reported except in LGMD2I.

LGMD2I (*FKRP*). Individuals who are homozygous or compound heterozygous for pathogenic missense variants in *FKRP* have an LGMD phenotype. In contrast, individuals who are homozygous or compound heterozygous for pathogenic nonsense variants (complete loss of function) have a severe congenital muscular dystrophy (MDC1C).

To date, two common pathogenic variants, 826C>A and 427C>A, have been observed in individuals with LGMD2I but not in those with MDC1C [Brockington et al 2001]. The identification of asymptomatic individuals who are homozygous for either of the common pathogenic variants and other asymptomatic individuals who are compound heterozygous for the common pathogenic variants suggests that other genes modify the disease presentation and/or age of onset [Boito et al 2005]. Note that the second pathogenic variant in compound heterozygotes may be any one of a number of missense, nonsense, deletion, and insertion variants. Individuals

homozygous for the 826C>A common pathogenic variant have a milder phenotype than those who are compound heterozygous [Brockington et al 2001, Mercuri et al 2003, Poppe et al 2003].

LGMD2L (*ANO5*). Anoctamin, encoded by *ANO5*, is a putative calcium-activated chloride channel possibly involved in membrane repair mechanism in muscular dystrophies. To date, a common pathogenic variant, one base-pair duplication c.191dupA (p.Asn64LysfsTer15), has been reported both in the homozygous and heterozygous state; it is considered a founder variant in northern Europe. *ANO5* pathogenic variants identified to date include splice site, missense, and frameshift changes [Bolduc et al 2010, Hicks et al 2011, Penttilä et al 2012]. See *ANO5*-Related Muscle Diseases.

LGMD2J (*TTN*). In this disorder, all affected individuals characterized to date have a homozygous 11-bp deletion/insertion in the last exon (termed Mex6) of *TTN*. The deletion alters four amino acids and is close to the calpain-3 binding site. This pathogenic variant is common in the Finnish population. In the heterozygous state this variant causes Udd distal myopathy [Hackman et al 2002].

LGMD2K (*POMT1*). LGMD2K is a form of LGMD2 with mild intellectual disability identified in five individuals from consanguineous families [Balci et al 2005] and in three additional patients [Godfrey et al 2007]. Pathogenic variants identified include three missense, one nonsense, and one frameshift variant in *POMT1*, the gene associated with Walker-Warburg syndrome. The p.Ala200Pro pathogenic variant is an ancestral founder variant in the Turkish population [Balci et al 2005].

LGMD2Q (*PLEC*). LGMD2Q is an early childhood-onset muscular dystrophy with progressive course and no skin involvement. The *PLEC* pathogenic variant identified in three families is a homozygous 9-bp deletion (c.1_9del) in exon 1f of the gene including the initiation codon. The c.1_9del is an ancestral founder variant in a Turkish population from the Black Sea region [Gundesli et al 2010]. Plectin 1f is one of the particular scaffolds for costameric protein important for precise formation of myofiber structure [Gundesli et al 2010]. Other *PLEC*-associated phenotypes include epidermolysis bullosa simplex with late-onset progressive muscular dystrophy [Pulkkinen et al 1996] and myasthenic syndrome with late-onset myopathy [Banwell et al 1999].

Clinical Findings

Table 2. Autosomal Recessive LGMD: Clinical Findings

Disease Name (Synonym) / Gene	Presentation		Other Findings		Age	
	Symptoms	Weakness	Calf Muscle	Contractures/ Scoliosis	Onset (Average)	Wheelchair Bound
Sarcoglycanopathies: LGMD2C / *SGCG* LGMD2D / *SGCA* LGMD2E / *SGCB* LGMD2F / *SGCD*	Complete deficiency: difficulty run, walk	Proximal	Hypertrophy	Late	3-15 yrs (8.5 yrs)	~15 yrs
	Partial deficiency: cramps, exercise intolerance				Adolescent - young adulthood	
Calpainopathy (LGMD2A) / *CAPN3*	Difficulty run, walk, toe walk; stiff back (rare)	Proximal (normal hip extensors & adductors), scapular winging	Atrophy	Early	2-40 yrs (8-15 yrs)	11-28 yrs after onset
Dysferlinopathy (LGMD2B) / *DYSF*	Inability to tiptoe; difficulty run, walk	Distal and/or pelvic-femoral (no scapular winging)	Transient hypertrophy (rare)		17-23 yrs	

Table 2. continued from previous page.

Disease Name (Synonym) / Gene	Presentation		Other Findings		Age	
	Symptoms	Weakness	Calf Muscle	Contractures/ Scoliosis	Onset (Average)	Wheelchair Bound
LGMD2G /*TCAP*	Difficulty run, walk; foot drop	Proximal and distal lower limb; proximal upper limb			9-15 yrs	~18 yrs after onset
LGMD2H / *TRIM3*	Facial weakness; waddling gait, difficulty w/stairs	Proximal lower limb; neck	Muscle wasting	Not reported	1-9 yrs	Late in life
LGMD2I / *FKRP*	Difficulty run, walk	Proximal; upper > lower limb	Hypertrophy	Rare, late	1.5-27 yrs (11.5 yrs)	23-26 yrs after onset
LGMD2J / *TTN*		Proximal			5-25 yrs	Average 20 yrs after onset
LGMD2K / *POMT1*	Fatigability, difficulty climbing stairs & running; cognitive delay w/ limited language development	Mild weakness; proximal > distal	Hypertrophy of calves & thighs	Ankle contractures present in 2 of 5 individuals; elbow, spine, & neck contractures in 1 patient	1-3 yrs	~17 yrs (based on 1 individual; 4 remaining individuals, ages 7-17, still ambulatory)
LGMD2L / *ANO5*	Adult onset (>20 yrs) of proximal lower & upper limbs weakness &/or difficulties standing on toes	Proximal pelvic-femoral or distal in the lower limbs	Quadriceps, hamstring and biceps brachi atrophy	Contractures (wrist, finger, TA)	Late teens-50s	Not reported
LGMD2M / *FKTN*	Early-onset muscle weakness, difficulties climbing stairs, severe weakness after intercurrent illness -steroid responsive	Proximal; lower > upper limb	Hypertrophy of calves, thighs, & triceps	Not reported	4 mo - 4 yrs	Not reported
LGMD2N / *POMT2*	Slowness in running & getting up	None	Hypertrophy of calves	Scapular winging & mild lordosis; intellectual disability	18 mo; asymptomatic at 5 yrs	20 yrs (1 patient)
LGMD2O / *POMGNT1*	Difficulties raising from sitting & climbing stairs; severe myopia	Proximal > distal	Hypertrophy of calves & quadriceps; wasting of hamstrings & deltoids	Ankle contractures	12 yrs	19 yrs (1 patient)

Table 2. continued from previous page.

Disease Name (Synonym) / Gene	Presentation		Other Findings		Age	
	Symptoms	Weakness	Calf Muscle	Contractures/ Scoliosis	Onset (Average)	Wheelchair Bound
LGMD2Q / *PLEC*	Delayed motor milestone, difficulties climbing stairs, keeping up w/peers	Proximal	Muscle atrophy in 1 patient	Multiple contractures in 1 patient	2-3 yrs	24 yrs (1 patient)

Sarcoglycanopathies, including α-sarcoglycanopathy, (LGMD2D); β-sarcoglycanopathy, (LGMD2E); γ-sarcoglycanopathy, (LGMD2C); δ-sarcoglycanopathy (LGMD2F). Findings range from early childhood onset with severe progression (similar to Duchenne muscular dystrophy) to later onset with milder progression (similar to Becker muscular dystrophy) (see Table 2). Calf hypertrophy is common.

Heart involvement is variable, but typically less severe than in the dystrophinopathies. Cardiomyopathy is common in beta-, delta-, and gamma-sarcoglycanopathy, but rare in alpha-sarcoglycanopathy [Melacini et al 1999, Fanin et al 2003, Kirschner & Lochmüller 2011]. Overall, about 30% of individuals have evidence of cardiomyopathy on ECG and echocardiogram. Significant discordance between sibs has been observed, including two sibs with *SGCA* pathogenic variants: one had onset at age 20 years and the other was asymptomatic at age 35 years [Angelini et al 1998].

Most individuals with severe, childhood-onset limb-girdle muscular dystrophy have pathogenic variants in *SGCA*, *SGCB*, *SGCC*, or *SGCD* [Duggan et al 1997a]. Thus, an individual with a clinical presentation and progression similar to Duchenne muscular dystrophy but with normal dystrophin immunostaining in muscle is likely to have a primary sarcoglycanopathy. In contrast, only about 10% of individuals with limb-girdle muscular dystrophy with milder disease (onset in adolescence or adulthood) have a sarcoglycanopathy.

Some individuals heterozygous for a pathogenic variant in *SGCA* have mild clinical symptoms including scapular winging and calf hypertrophy [Fischer et al 2003].

Genotype/phenotype correlations in large series have been published in multiple populations [Dinçer et al 1997, Duggan et al 1997a, Duggan et al 1997b, Vainzof et al 1999, Merlini et al 2000].

Calpainopathy (LGMD2A; caused by mutation of *CAPN3*). Intra- and interfamilial clinical variability ranges from severe to mild. Three calpainopathy phenotypes have been identified based on the distribution of muscle weakness and age at onset:

- Pelvifemoral LGMD (Leyden-Möbius) phenotype, the most frequently observed calpainopathy phenotype, in which muscle weakness is first evident in the pelvic girdle and later in the shoulder girdle with onset before age 12 years or after age 30 years;
- Scapulohumeral LGMD (Erb) phenotype, usually a milder phenotype with infrequent early onset, in which muscle weakness is first evident in the shoulder girdle and later in the pelvic girdle; and
- HyperCKemia, usually observed in children or young individuals, in which symptomatic individuals have only high serum CK concentrations.

Clinical findings include the tendency to walk on tiptoes, difficulty in running, scapular winging, waddling gait, and slight hyperlordosis. Early Achilles tendon shortening and scoliosis may be present.

Dysferlinopathy (LGMD2B; caused by mutation of *DYSF*). The spectrum of muscle disease is characterized mainly by two phenotypes:

- Limb-girdle muscular dystrophy syndrome (LGMD2B) with early weakness and atrophy of the pelvic and shoulder girdle muscles in adolescence or young adulthood, with slow progression. Respiratory and cardiac muscles are not involved.
- Miyoshi myopathy with muscle weakness and atrophy in young adults, most marked in the distal parts of the legs, especially the gastrocnemius and soleus muscles. Over a period of years, the weakness and atrophy spread to the thighs and gluteal muscles. The forearms may become mildly atrophic with decrease in grip strength, but the small muscles of the hands are spared.

Two other phenotypes are seen:

- Distal anterior compartment myopathy (DMAT), which presents in the third decade with weakness of the anterior tibialis muscles. The disease is rapidly progressive resulting in severe proximal weakness of the lower limbs first, followed by the upper limbs [Illa et al 2001].
- Dysferlinopathy with rigid spine, which presents with lower limb weakness and atrophy in addition to contractures of the neck, chest, hip, and knee [Nagashima et al 2004]

LGMD2G (caused by mutation of *TCAP*). Significant variability has been seen among the 14 individuals reported from four families. Some persons showed distal atrophy while others exhibited calf hypertrophy. All had significant proximal weakness. Cardiac involvement occurred in about half. Females appear to be less severely affected than males [Zatz et al 2003].

LGMD2H (*TRIM32*). Severity ranges from asymptomatic to severe proximal weakness. Facial weakness and a "flat smile" are common [Weiler et al 1998, Saccone et al 2008]. Affected individuals can remain ambulatory well into adulthood with some reports of ambulation (with difficulty) into the sixth decade [Weiler et al 1998, Saccone et al 2008]. Irreversible loss of motility after prolonged immobilization has been reported [Saccone et al 2008].

Sarcotubular myopathy (STM), caused by the same pathogenic variant in *TRIM32*, represents the severe end of the LGMD2H phenotype [Schoser et al 2005, Borg et al 2009].

LGMD2I (*FKRP*). The phenotype ranges from severe (similar to Duchenne muscular dystrophy) to mild with no clinically apparent skeletal muscle involvement [Brockington et al 2001, de Paula et al 2003, Mercuri et al 2003, Poppe et al 2003, Poppe et al 2004, Boito et al 2005, Müller et al 2005]. Cardiomyopathy without skeletal muscle involvement has been reported. When onset is in the first years of life, the ability to walk is lost about the beginning of the second decade. The milder end of the spectrum more closely resembles Becker muscular dystrophy, with later onset (age 6-23 years) and ambulation continuing into the third decade albeit with increasing difficulty. Cardiac involvement occurs in 10%-55% of affected individuals. Cardiomyopathy appears to present earlier in heterozygotes than homozygotes. Poppe et al [2004] identified respiratory involvement (i.e., a forced vital capacity lower than 75%) in about 50% of affected individuals. Memory impairment [Bourteel et al 2009] and mild impairment in executive function and visuo-spatial planning without substantial impairment in global and logic IQ have been reported [Bourteel et al 2009, Palmieri et al 2011]. Brain MRI studies showed a small number of patients with focal abnormal cortical signals consistent with dysplasia, subcortical atrophy, and frontal cortical atrophy with periventricular nonspecific white matter signal [Bourteel et al 2009, Palmieri et al 2011].

LGMD2J (*TTN*). This disorder is the severe (homozygous state) form of the milder tibial muscular dystrophy (TMD). Individuals with LGMD2J have a severe progressive proximal weakness with onset ranging from the first decade to the early 30s. In about half of all reported cases, weakness ultimately involved the distal muscles and individuals required the use of a wheelchair; in other cases ambulation was preserved. Joint contractures have not been associated with LGMD2J [Udd et al 1991].

LGMD2K (*POMT1*). Affected individuals exhibit mild proximal weakness with significant developmental delay. Individuals retain the ability to walk for at least 15 years after disease onset. Microcephaly without structural brain abnormalities, and intellectual disability with low IQ are reported in all patients [Balci et al 2005, Godfrey et al 2007, Lommel et al 2010]. All individuals had CK levels 10-40 times the normal range [Balci et al 2005, Godfrey et al 2007, Lommel et al 2010].

LGMD2L (*ANO5*). Affected individuals present with two distinct phenotypes:

- Late onset proximal pelvic girdle muscle weakness with (often asymmetric) atrophy of the quadriceps femoris and biceps brachii
- Later-onset mild asymmetric calf hypertrophy or early calf weakness without atrophy associated with difficulties walking on tiptoes

As disease progresses the phenotypes overlap and merge into a homogeneous clinical entity [Hicks et al 2011], characterized by severe hip and thigh weakness with distal involvement. Muscle wasting affects quadriceps, hamstrings, and the medial gastrocnemius. Knee hyperextension is a common finding. In later stages of the disease mild weakness and wasting of the upper limbs is observed. Cardiac and respiratory involvement is not observed. See *ANO5*-Related Muscle Diseases.

LGMD2M (*FKTN*). Affected individuals present with mild to moderate proximal muscle weakness in the lower and upper limbs. Weakness was more distal in the upper limb in one individual involving wrist and finger extensor and wrist flexors [Godfrey et al 2006]. Muscle hypertrophy was common. All patients reported are cognitively normal and have normal brain MRI [Godfrey et al 2006, Godfrey et al 2007, Puckett et al 2009]. Of interest, three individuals showed severe weakness after intercurrent illness with a remarkable response to steroid therapy [Godfrey et al 2006]. Minimal proximal weakness, normal intellect, and severe dilated cardiomyopathy have been reported in six Japanese patients [Murakami et al 2006].

LGMD2N (*POMT2*). Two affected individuals with discordant phenotypes have been reported. One affected female was asymptomatic at age five, but neurologic exam showed scapular winging, calf hypertrophy, and slowness in running and getting up. She had normal intellect [Biancheri et al 2007]. The second reported individual had developmental delay but remain ambulant at age 20. Muscle hypertrophy was present. She showed intellectual disability and right bundle branch block [Godfrey et al 2007].

LGMD2O (*POMGNT1*). One affected female has been reported. Her early motor milestones were normal. Progressive muscle weakness was first reported at age 12 years and progressed to the loss of ambulation at age 19 years. Weakness was more proximal than distal, with the neck, hip girdle, and shoulder abductor muscles particularly affected. There was hypertrophy of the calves and quadriceps, wasting of the hamstring and deltoid muscles, and ankle contractures. The woman had severe myopia and was cognitively normal [Clement et al 2008]. Another patient reported by Godfrey [Godfrey et al 2007] had a discordant, milder, phenotype. This individual presented in the second decade with mild proximal weakness and had normal intellectual function.

LGMD2Q (*PLEC*). Six individuals have been reported. Onset was in early childhood and was slowly progressive until the late teenage years, with rapid progression thereafter. Delay in motor milestones was a common presenting symptom. Muscle weakness was proximal and progressive. Loss of ambulation in the late 20s has been observed. Multiple contractures and muscle atrophy were reported in one individual. No cardiac or respiratory involvement was reported and intelligence was normal. No affected individuals had any evidence of a skin disorder [Gundesli et al 2010].

Autosomal Dominant Limb-Girdle Muscular Dystrophy

Most of the autosomal dominant limb-girdle muscular dystrophy loci have been described in single extended pedigrees [Speer et al 1999] (see Table 3 and Table 4). These disorders are considered rare.

Molecular Genetics

Table 3. Molecular Genetics of Autosomal Dominant LGMD

Disease Name	Gene (Locus Name [1])	Chromosome Locus
LGMD1A (myotilinopathy)	*MYOT*	5q31.2
LGMD1B	*LMNA*	1q22
LGMD1C (caveolinopathy)	*CAV3*	3p25.3
LGMD1D	*DES*	2q35
LGMD1E	*DNAJB6*	7q36.3
LGMD1F	Unknown	7q32.1-q32.2
LGMD1G	Unknown	4q21
LGMD1H	Unknown	3p25.1-p23

See Autosomal Dominant Limb-Girdle Muscular Dystrophy: Phenotypic Series to view genes associated with this phenotype in OMIM.

1. Locus name given if gene is unknown

Myotilinopathy (LGMD1A caused by mutation of *MYOT*). Four pathogenic missense variants – p.Thr57Ile and p.Ser55Phe [Hauser et al 2000, Hauser et al 2002], p.Arg450Lys [Shalaby et al 2009], and p.Arg6His [Reilich et al 2011] – have been described in four families in *MYOT* encoding the myotilin protein. Pathogenic variants in *MYOT* have been also reported in myofibrillar myopathy [Selcen & Engel 2004] and in spheroid body myopathy [Foroud et al 2005]. Myotilin is a sarcomeric protein that binds to alpha-actinin and is associated with the Z-line. The normal function of myotilin is to stabilize assembled actin bundles and to facilitate normal myofibril organization. The abnormal protein results in Z-line streaming and myofibril aggregation compromising the structure of the sarcomere [Salmikangas et al 2003].

LGMD1B (*LMNA*). Pathogenic variants in *LMNA* result in at least eleven allelic conditions including LGMD1B, autosomal dominant and autosomal recessive Emery-Dreifuss muscular dystrophy, Dunnigan-type familial partial lipodystrophy (FPLD), mandibuloacral dysplasia, Hutchinson-Gilford progeria syndrome, and Charcot-Marie-Tooth type 2B1. Although missense variants in *LMNA* were believed to be the sole cause of LGMD1B, Todorova et al [2003] found that synonymous changes in *LMNA* can result in splice site variants that also cause LGMD1B. To date all *LMNA* pathogenic variants resulting in LGMD1B have been found in exons 1 to 11 [Mercuri et al 2005].

LGMD1C (caveolinopathy; *CAV3*). *CAV3* encodes caveolin-3, a protein involved in membrane trafficking in the myofiber. Cavelin-3 functions as part of the T-tubule system in skeletal muscle during development but not after maturation; conversely, caveolin-3 is always expressed in smooth muscle [Woodman et al 2004]. Pathogenic variants in *CAV3* were first identified in a few Italian families [Minetti et al 1998].

LGMD1D. A single family showing an autosomal dominant limb-girdle phenotype was genetically mapped, although subsequent refinements of pedigree details altered locus assignment because age-dependent penetrance changed the phenotypic status of critical family members [Greenberg et al 2012]. An intron splice donor site pathogenic variant (IVS+3A>G) in the desmin gene (*DES*) was identified in the family [Greenberg et al 2012]. Most desmin pathogenic variants result in other phenotypes, such as dilated cardiomyopathy, and myofibrillar myopathy.

LGMD1E. *DNAJB6* is a member of the HSP/DNAJ family of molecular co-chaperones involved in protecting proteins from irreversible aggregation during protein synthesis or cellular stress. Pathogenic variants in *DNAJB6* have been identified in two families with AD-LGMD with skeletal muscle vacuoles [Harms et al 2012].

LGMD1F. Mapped in a large Spanish family, the gene has not yet been identified [Palenzuela et al 2003].

LGMD1G. Mapped in one Brazilian-European family, the gene has not yet been identified.

LGMD1H. Mapped in one Italian family, the gene has not yet been identified [Bisceglia et al 2010].

Clinical Findings

Table 4. Autosomal Dominant LGMD: Clinical Findings

Name	Onset (Average)	Presentation		Late Findings
		Symptoms	Signs	
Myotilinopathy (LGMD1A)	18-40 years	Proximal weakness	Tight Achilles tendons; nasal, dysarthric speech (50%); respiratory insufficiency & dysphagia	Distal weakness
LGMD1B	Birth to adulthood; ~1/2 w/childhood onset	Proximal lower-limb weakness		Mild contractures of elbows; arrhythmia & other cardiac complications (age 25-45 yrs); sudden death
Caveolinopathy (LGMD1C)	~5 yrs	Cramping; mild-moderate proximal weakness; rippling muscle disease	Calf hypertrophy	
LGMD1D	<25 yrs	Cardiac conduction defect; proximal muscle weakness		All individuals remain ambulatory.
LGMD1E	18-40 yrs	Proximal or distal weakness in lower limbs progressing to the unaffected regions	Mild heel contractures in 1 patient	Wheelchair bound at age 45-62 yrs
LGMD1F	1-58 yrs	Proximal lower- & upper-limb weakness	Serum CK (normal to 20x normal)	Distal weakness
LGMD1G	30-47 yrs	Proximal lower limb weakness	Progressive limitation of finger & toe flexion	Proximal upper-limb weakness
LGMD1H	16-50 yrs (39)	Proximal lower limb weakness	Muscle hypotrophy of limb girdle muscles w/calf hypertrophy	

Myotilinopathy (LGMD1A). Findings in three families (North American with German and Argentinean ancestry and Turkish) and in one Japanese individual have been reported [Hauser et al 2000, Hauser et al 2002, Shalaby et al 2009, Reilich et al 2011]. In addition to the findings described in Table 4, reduced knee and elbow tendon reflexes are common. Nerve conduction studies are normal [Gilchrist et al 1988].

LGMD1B. Muscle weakness and cardiac involvement are present by the third decade. Left ventricular hypertrophy and atrioventricular conduction defect are common and can progress to second-degree heart block requiring a pacemaker; rarely, dilated cardiomyopathy is present. The onset of skeletal muscle weakness prior to cardiac involvement distinguishes LGMD1B from allelic *LMNA* disorders; the absence of elbow contractures distinguishes LGMD1B from Emery-Dreifuss muscular dystrophy (EDMD) [Mercuri et al 2005].

Caveolinopathy (LGMD1C). Pathogenic variants in *CAV3* are associated with five distinct phenotypes that all demonstrate intrafamilial variability: (1) LGMD1C; (2) rippling muscle disease; (3) hyperCKemia; (4) familial hypertrophic cardiomyopathy; and (4) distal myopathy [Cagliani et al 2003, Fee et al 2004, Hayashi et al 2004, Woodman et al 2004]. Onset ranges from early childhood (first decade) to late adulthood. Those with childhood onset typically show a Gower sign, calf hypertrophy, and mild to moderate proximal weakness. Cardiac involvement is common [Hayashi et al 2004].

LGMD1D. In the only family reported cardiac conduction defects (heart block, ventricular tachycardia, paroxysmal atrial fibrillation, right bundle branch block), dilated cardiomyopathy, and/or muscle weakness were usually present. Conduction defects precede congestive heart failure. Onset is in early adulthood.

LGMD1E. Two families have been reported. In one family, onset was in the fourth decade with a progressive proximal muscle weakness predominant in the lower limbs with a relative sparing of quadriceps compared to hamstrings. In the second reported family, onset was variable between 18 and 35 years with weakness in the distal lower extremities presenting with tripping. Weakness progressed to include the hands and proximal legs, with loss of ambulation after disease duration of 20-30 years [Harms et al 2012].

LGMD1F. One large Spanish family has been reported. Pelvic girdle weakness presented earlier than shoulder girdle weakness. Distal weakness occurred late. A juvenile-onset form and an adult-onset form were observed; the more rapid progression seen in the juvenile-onset form is thought to result from anticipation. A subset of individuals with the juvenile-onset form show scapular winging and facial muscle weakness. No calf hypertrophy, eye involvement, or intellectual impairment has been observed [Gamez et al 2001].

LGMD1G. While symptoms are slowly progressive, all but one individual were still ambulatory ten years after diagnosis. No other joint limitation, aside that noted in Table 4, was observed [Starling et al 2004].

LGMD1H. One large Italian family has been reported. Variable expression in terms of age at onset and disease severity was observed within the family. Patients either presented in the fourth-fifth decade of life with a slowly progressive muscle weakness in both upper and lower limb, or in the second-third decade with calf hypertrophy and/or muscle weakness and occasionally high CK and/or lactate serum level. Subsarcolemmal accumulation of mitochondria and multiple mitochondrial DNA deletion have been observed on muscle biopsy [Bisceglia et al 2010].

Evaluation Strategy

Establishing the type of LGMD can be useful in discussions of the clinical course of the disease and for genetic counseling purposes.

Establishing the specific type of LGMD in a given individual usually involves obtaining the medical history and family history, performing a physical examination, and laboratory testing (see Table 5) including serum CK concentration and muscle biopsy for histologic examination and protein testing [Pogue et al 2001].

Note: (1) Only dysferlin immunoblotting of muscle is currently thought to be specific and sensitive. (2) Results of immunostaining of muscle should be confirmed with molecular genetic testing when it is available.

Use of molecular genetic testing to establish the specific type of LGMD is problematic:

- Many genes are involved.
- Pathogenic variants in no one gene account for the majority of cases.
- Few clinical or laboratory findings help identify the associated gene for a given individual.
- The lack of common pathogenic variants prevents efficient screening by genotype.
- About 50% of currently identified LGMD would have no molecular diagnosis, even if all 20 currently known genes were fully sequenced.

For these reasons, clinicians may consider use of limb-girdle muscular dystrophy multigene panels that include a number of genes associated with LGMD. Note: Panels vary by methods used and genes included; thus, the ability of a panel to detect a causative variant(s) in any given individual with LGMD also varies.

Table 5. Testing Used to Establish LGMD Type

Type		Serum CK Concentration	Muscle Biopsy Histology	Muscle Protein (Biochemical) Testing [1, 2]
AR	Alpha-sarcoglycanopathy; beta-sarcoglycanopathy.;gamma-sarcoglycanopathy; delta-sarcoglycanopathy	Mildly to greatly ↑	Myopathic changes	↓ or complete absence of sarcoglycan antibodies [3]
	Calpainopathy	Often 5-80x normal, but can be normal	Fiber degeneration & regeneration, central nuclei, fiber size variation, endomysial fibrosis	Absence of calpain-3 on immunoblotting, loss of calpain-3 autolytic activity [4]
	Dysferlinopathy	Often >100x normal	Significant inflammation sometimes observed [5]	Absence or partial deficiency of dysferlin by immunoblot [6]
	Telethoninopathy	3-17x normal	Myopathic changes w/rimmed vacuoles	Absence of telethonin
	LGMD2H	4-30x normal	Fiber size variation w/ degeneration & regeneration, internal nuclei & endomysial fibrosis	NA
	LGMD2I	Normal to greatly ↑	Muscle fiber size variation w/type 1 fiber predominance & necrotic & regenerating fibers	Variably ↓ *glycosylated* alpha-dystroglycan; slight ↓ of laminin alpha 2 [5]
	LGMD2J	Greatly ↑	Myopathic changes	Almost complete absence of calpain-3
	LGMD2K	20-40x normal	Mild fibrosis; fiber size variation; regenerating & necrotic fibers; hypertrophic fibers w/multiple central nuclei	↓ *glycosylated* alpha-dystroglycan
	LGMD2L	Greatly ↑	Myopathic or dystrophic changes	NA
	LGMD2M	4-50x normal	Muscular dystrophy often w/ inflammatory infiltrates	↓ glycosylated alpha-dystroglycan
	LGMD2N			
	LGMD2O			
	LGMD2Q	Greatly ↑	Dystrophic or myopathic changes	↓ plectin
AD	LGMD1A	Normal or mildly ↑	Normal myotilin on immunohistochemistry; ↓ laminin γ1	Variable fiber size w/central nuclei & fiber size variation
	LGMD1B	Normal or mildly ↑	Myopathic changes	NA
	LGMD1D	2-4x normal	Myopathic changes w/endomysial fibrosis & rimmed vacuoles; scattered COX-negative fibers	DNAJB6 positive inclusions
	LGMD1E	1-4x normal	Variable fiber size; ↑ endomysial connective tissue	NA
	Caveolinopathy	4-25x normal	Myopathic changes	Caveolin-3 ↓ on immunofluorescence &western blotting; dysferlin ↓ on immunohistochemistry & normal on western blot [7]
	LGMD1F	Normal to 20x normal	Variable fiber size w/↑ connective tissue	NA

Table 5. continued from previous page.

Type		Serum CK Concentration	Muscle Biopsy Histology	Muscle Protein (Biochemical) Testing [1, 2]
	LGMD1G	Normal to 9x normal	Fiber size variation w/necrotic fibers & rimmed vacuoles	Normal immunostaining for dystrophin, sarcoglycans, calpain-3, telethonin, & dysferlin
	LGMD1H	Normal to 10x normal	Myopathic changes & subsarcolemmal mitochondria accumulation; rarely, ragged-red fibers	NA

1. Muscle protein (biochemical) testing:
- Immunochemistry = exposing sections of tissue to an antibody to determine if a specific protein is present or absent; does not quantify the amount of the protein
- Immunostaining = use of a dye to detect the antibody
- Immunofluorescence = use of a fluorescent dye to detect the antibody
- Immunoblot (or western blot) = removing a specific protein from a tissue of interest to quantify the size and amount of the protein
Note: Not all protein tests are equally effective in diagnosing each form of LGMD (e.g., immunoblot for dysferlin is both sensitive and specific for diagnosing LGMD2B, whereas immunostaining for dysferlin is sensitive but not specific).
2. Most protein tests are not specific for proteins altered by a pathogenic variant in a particular gene, but the results can help focus molecular genetic testing.
3. Because of the interdependent nature of the sarcoglycan complex, deficiency of any of the four sarcoglycan proteins on immunostaining can be representative of a pathogenic variant in any of the four sarcoglycan genes. Sensitivity and specificity for the sarcoglycanopathies is high, although specificity for the particular form of sarcoglycanopathy is low.
4. Specificity is low.
5. May lead to misclassification as autoimmune disease
6. Immunostaining for dysferlin is much less specific than immunoblotting. Immunoblotting of muscle or white blood cells is highly specific for pathogenic variants in *DYSF*.
7. Protein quantification is unreliable; diagnosis relies on molecular genetic testing [Woodman et al 2004].

Sarcoglycanopathy. Pathogenic variants in any one of the sarcoglycan genes lead to secondary deficiency of all the sarcoglycan proteins detected by immunostaining of muscle. For example, immunostaining of muscle from individuals with pathogenic variants in the gene encoding alpha-sarcoglycan show marked deficiency or absence of alpha-, beta-, gamma-, and delta-sarcoglycan. Typically a single sarcoglycan antibody (alpha-sarcoglycan) is used to classify an individual as having complete or partial sarcoglycan deficiency. Using antibodies against all four sarcoglycan proteins may identify a sarcoglycan deficiency more precisely; however, no immunostaining pattern is specific enough to identify which of the four genes encoding the sarcoglycan proteins is most likely to be mutated.

Heterozygotes for a pathogenic variant in *SGCA*, the gene encoding alpha-sarcoglycan, have normal levels of alpha-, beta-, gamma-, and delta-sarcoglycan on immunostaining of muscle, despite mild clinical features [Fischer et al 2003].

Because individuals with dystrophinopathy have deficient sarcoglycan proteins detected on immunostaining of muscle, both dystrophin immunostaining and sarcoglycan immunostaining must be performed on the same sample. The finding of normal dystrophin immunostaining and complete deficiency of any of the sarcoglycans suggests that pathogenic variants in one of the genes encoding the sarcoglycan proteins may be causative.

Data suggest that immunostaining of frozen muscle is relatively sensitive for detecting primary sarcoglycanopathy; however, it is not specific.

Calpainopathy. Deficiency of calpain-3 on immunostaining of muscle biopsy is observed in calpainopathy and also as a secondary effect in many types of LGMD. Because sensitivity and specificity for both immunostaining

and western blot analysis are reduced, protein analysis needs to be interpreted with caution and diagnosis needs to be confirmed with molecular genetic testing.

Dysferlinopathy. Immunostaining of muscle usually reveals complete absence of dysferlin, although partial deficiency has also been observed.

LGMD2I, LGMD2K, LGMD2M, LGMD2O, LGMD2N. Immunostaining of muscle reveals significant reduction in the amount of glycosylated alpha dystroglycan with antibodies recognizing glycosylated epitopes of alpha dystroglycan. There is a good correlation between the reduced alpha dystroglycan staining and clinical course in individuals with pathogenic variants in *POMT1*, *POMT2* and *POMGNT1*, but this is not always the case in *FKTN* and *FKRP* pathogenic variants [Jimenez-Mallebrera et al 2009].

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Limb-girdle muscular dystrophy may be transmitted in an autosomal recessive manner or – less commonly – in an autosomal dominant manner. Difficulties in accurate diagnosis and determination of inheritance in an individual family make genetic counseling particularly complicated.

Risk to Family Members – Autosomal Recessive Limb-Girdle Muscular Dystrophy

Parents of a proband

- The parents are obligate heterozygotes and therefore carry a single copy of a pathogenic variant.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.
- Clinical severity and disease phenotype often differ among individuals with the same pathogenic variants; thus, age of onset and/or disease progression in affected sibs cannot be predicted.

Offspring of a proband

- All offspring are obligate carriers.
- In consanguineous populations with an autosomal recessive disorder, risks to the offspring of a proband should be calculated based on the carrier frequency in the population.

Other family members of a proband. Each sib of an obligate carrier is at a 50% risk of being a carrier.

Carrier Detection

If the pathogenic variants in the proband have been identified, carrier testing for at-risk family members is possible through laboratories offering either testing for the gene of interest or custom testing.

Risk to Family Members – Autosomal Dominant Limb-Girdle Muscular Dystrophy

Parents of a proband

- Most individuals diagnosed as having autosomal dominant limb-girdle muscular dystrophy have an affected parent, although symptoms may be variable among family members.
- Occasionally the family history is negative. It should be emphasized that an individual with no family history of LGMD may have a *de novo* dominant pathogenic variant. The frequency of *de novo* variants causing any of the types of limb-girdle muscular dystrophy is unknown.

  Note: Although most individuals diagnosed with autosomal dominant limb-girdle muscular dystrophy have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

Sibs of a proband

- The risk to sibs depends on the genetic status of the proband's parents.
- If one of the proband's parents has a mutated allele, the risk to the sibs of inheriting the mutated allele is 50%.
- Clinical severity and disease phenotype often differ among individuals with the same pathogenic variant; thus, age of onset and/or disease progression cannot be predicted.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low. Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband

- Individuals with autosomal dominant limb-girdle muscular dystrophy have a 50% chance of transmitting the mutated allele to each child.
- Clinical severity and disease phenotype often differ among individuals with the same pathogenic variant; thus, age of onset and/or disease progression cannot be predicted.

Other family members of a proband. The risk to other family members depends on the status of the proband's parents. If a parent is affected, his or her family members are at risk.

Related Genetic Counseling Issues

Uncertainties regarding the specificity of protein-based testing of individual muscle biopsies make accurate genetic counseling difficult when based purely on protein testing of muscle biopsy. Often the mode of inheritance cannot be determined.

In most instances, the families can be counseled for recurrence risks associated with rare autosomal recessive conditions, which leaves a "significant" risk only for the sibs of the proband. Because many of the LGMDs show a later onset, the parents of the proband may have completed their family by the time that the diagnosis is established.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **My46 Trait Profile**
  Limb girdle muscular dystrophy
- **Muscular Dystrophy Association - USA (MDA)**
  222 South Riverside Plaza
  Suite 1500
  Chicago IL 60606
  Phone: 800-572-1717
  Email: mda@mdausa.org
  www.mda.org
- **Muscular Dystrophy UK**
  61A Great Suffolk Street
  London SE1 0BU
  United Kingdom
  Phone: 0800 652 6352 (toll-free); 020 7803 4800
  Email: info@musculardystrophyuk.org
  www.musculardystrophyuk.org

Management

Treatment of Manifestations

No definitive treatments for the limb-girdle muscular dystrophies exist. Management should be tailored as much as possible to each individual and each specific LGMD type. A general approach to appropriate management can prolong survival and improve quality of life. This general approach is based on the typical progression and complications of individuals with LGMD as described by McDonald et al [1995] and Bushby [1999].

- Weight control to avoid obesity
- Physical therapy and stretching exercises to promote mobility and prevent contractures
- Use of mechanical aids such as canes, walkers, orthotics, and wheelchairs as needed to help ambulation and mobility

- Surgical intervention as needed for orthopedic complications such as foot deformity and scoliosis
- Use of respiratory aids when indicated
- Referral to a cardiologist for standard supportive treatment of cardiomyopathy
- Social and emotional support and stimulation to maximize a sense of social involvement and productivity and to reduce the sense of social isolation common in these disorders [Eggers & Zatz 1998]
- Clinical genetics consultation

Surveillance

The following are appropriate:

- Monitoring for orthopedic complications such as foot deformity and scoliosis
- Monitoring of respiratory function
- Monitoring for evidence of cardiomyopathy in those LGMD types known to have cardiac involvement

Agents/Circumstances to Avoid

Weight should be controlled to avoid obesity.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

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Chapter Notes

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