Limb-Girdle Muscular Dystrophy Overview

[*LGMD*]

PMID: 20301582

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Initial Posting: June 8, 2000.
Last Revision: July 23, 2009.

Summary

Disease 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. Individuals with LGMD generally show weakness and wasting restricted to the limb musculature, proximal greater than distal. Most individuals with LGMD show relative sparing of the heart and 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) performed on a muscle biopsy can establish the diagnosis of LGMD subtypes sarcoglycanopathy, calpainopathy, and dysferlinopathy. In some cases, demonstration of complete or partial deficiencies for any particular protein can then be followed by mutation studies of the corresponding gene. Molecular genetic testing for *CAPN3*, *FKRP*, *LMNA*, *POMT1*, *SGCA*, *SGCB*, *SGCD*, and *SGCG* is available on a clinical basis. In addition, testing for *DYSF* is available for individuals of Libyan Jewish ancestry.

Management. No definitive treatments for the limb-girdle muscular dystrophies exist. Management is tailored to each individual and each specific subtype. 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 subtypes with cardiac involvement, and social and emotional support and stimulation.

Genetic counseling. The term LGMD previously referred to muscular dystrophies inherited in an autosomal recessive manner; it is now recognized that limb-girdle muscular dystrophy also includes rare subtypes inherited in an autosomal dominant manner. Difficulties in accurate diagnosis and

determination of inheritance in an individual family make genetic counseling particularly complicated. 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. Prenatal diagnosis for dysferlinopathy, alpha-sarcoglycanopathy, beta-sarcoglycanopathy, delta-sarcoglycanopathy, gamma-sarcoglycanopathy, LGMD1B, and LGMD2K is available for families in which the causative mutations have already been identified.

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).

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.

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.

While most individuals with LGMD show relative sparing of the heart and 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, and dysferlinopathy) the diagnosis can be established based on "biochemical testing," i.e., immunostaining 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 disease-causing mutations.
- Inflammatory myopathy should be excluded during the diagnostic process.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

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

- **The dystrophinopathies** are caused by mutations in the *DMD* gene. 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.
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 the *DMD* gene and, when necessary, by dystrophin immunostaining of a muscle biopsy.
- Females should be evaluated by dystrophin immunostaining of a muscle biopsy.
  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 mutations in *EMD*, the gene encoding emerin; the dominant/recessive forms are caused by mutations 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 four months of age. 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 (between the 4th and 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 over 50 years of age 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, many 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 immuno-modulation therapy can be considered for dysferlin testing. (See Dystrophinopathies.)

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 to be 1:211; while Hackman et al [2005] estimate the carrier frequency of sarcogycanopathy to be about 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. Autosomal Recessive Limb-Girdle Muscular Dystrophy (LGMD): Molecular Genetics

% of Individuals with AR LGMD	Disease Name	Populations with Founder Mutations	Locus Name	Gene Symbol	Locus	Protein Product
Up to 68% of individuals with childhood onset and ~10% with adult	Alpha-sarcoglycan-opathy	None	LGMD2D	*SGCA*	17q12-q21.3	Alpha-sarcoglycan
	Beta-sarcoglycan-opathy	Amish	LGMD2E	*SGCB*	4q12	Beta-sarcoglycan
	Gamma-sarcoglycan-	North Africans;	LGMD2C	*SGCG*	13q12	Gamma-sarcoglycan

onset [1]	opathy (formerly SCARMD) [2]	Gypsies [3]				
	Delta-sarcoglycan-opathy	Brazilian [4]	LGMD2F	*SGCD*	5q33	Delta-sarcoglycan
~10%-80% [5]	Calpainopathy	Amish, La Reunion Island, Basque (Spain), Turkish	LGMD2A	*CAPN3*	15q15.1-q21.1	Calpain-3
~10%	Dysferlinopathy, Miyoshi distal myopathy	Libyan Jewish	LGMD2B	*DYSF*	2p13.3-p13.1	Dysferlin
3%	Telethonin-opathy	Italian (?)	LGMD2G	*TCAP*	17q12	Telethonin
Unknown	LGMD2H	Manitoba Hutterites only	LGMD2H	*TRIM32*	9q31-q34.1	Tripartite motif protein 32
6% [6]	LGMD2I	Unknown	LGMD2I	*FKRP*	19q13.3	Fukutin-related protein
Unknown	LGMD2J	Finland	LGMD2J	*TTN*	2q24.3	Titin
Unknown	LGMD2K	Turkish	LGMD2K	*POMT1*	9q34.1	Protein O-mannosyl-transferase 1
Unknown	LGMD2L	Unknown	LGMD2L	*FKTN*	9q31	Fukutin
Unknown	LGMD2M	Unknown	LGMD2M	*POMGNT1*	1p34-p33	Protein O-linked-mannose beta-1,2-N-acetylglucosaminyltransferase 1
Unknown	LGMD2N	Unknown	LGMD2N	*POMT2*	14q24.3	Protein O-mannosyl-transferase 2

1. Vainzof et al [1999]
2. SCARMD = severe childhood autosomal recessive muscular dystrophy
3. Merlini et al [2000]
4. Nigro et al [1996], Vainzof et al [1999]
5. Ranges from 10% in the Caucasian population [Chou et al 1999] to 80% in the Basque country [Urtasun et al 1998]. Actual frequency depends on the population.
6. Boito et al [2005]

Sarcoglycanopathies. (α-sarcoglycanopathy, LGMD2D; β-sarcoglycanopathy, LGMD2E; γ-sarcoglycanopathy, LGMD2C; δ-sarcoglycanopathy, LGMD2F). 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 outbred populations, the relative frequency of mutations in the four genes is alpha >> beta >> gamma >> delta in a 8:4:2:1 ratio [Duggan et al 1997a]. No common mutations have been identified in outbred populations except the R77C mutation, which accounts for up to one-third of the mutated *SGCA* alleles [Hackman et al 2005]. Founder mutations have been observed in certain populations (Table 1).

Calpainopathy (LGMD2A). To date, over 130 mutations in *CAPN3* have been described.

Dysferlinopathy (LGMD2B). Although the function of dysferlin is still unknown, dysferlin includes C2 domains thought to be important for calcium-mediated membrane fusion and membrane repair of skeletal muscle fibers [Bansal et al 2003]. Although intra- and interfamilial clinical variability is significant, no specific genotype-phenotype correlations have been established [Cagliani et al 2003].

Telethoninopathy (LGMD2G). Homozygosity for a *TCAP* mutation has been identified in four Brazilian families [Moreira et al 2000]. One Italian family has been described with compound heterozygous *TCAP* mutations in affected individuals.

***TRIM32* deficiency (LGMD2H).** All reported cases of LGMD2H have been caused by a D487N homozygous mutation in the *TRIM32* gene. This founder mutation has been seen primarily 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 mutation in *TRIM32* [Schoser et al 2005]. *TRIM32* codes for a E3-Ub ligase responsible for post-translational regulation of protein levels [Frosk et al 2002].

Dystroglycanopathies (*FKRP*: LGMD2I, *POMT1*: LGMD2K; *FKTN*: LGMD2L; *POMGNT1*: LGMD2M, *POMT2*: LGMD2N). 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. Mutations of these genes have been associated with muscular dystrophies of variable severity ranging from congenital muscular dystrophies with various eye and brain involvement (see Congenital Muscular Dystrophy Overview) to milder forms with later onset (limb-girdle muscular dystrophies). Relatively few individuals have been reported with mutations in *POMT1*, *FKTN*, *POMGNT1*, *POMT2* and a LGMD phenotype [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 missenses or nonsense mutations. No common mutations have been reported except in LGMD2I.

LGMD2I. Individuals who are homozygous or compound heterozygous for missense mutations in the *FKRP* gene have a LGMD phenotype. In contrast, individuals who are homozygous or compound heterozygous for nonsense mutations (complete loss of function) have a severe congenital muscular dystrophy (MDC1C) (see Congenital Muscular Dystrophy Overview).

To date, two common mutations, C826A and C427A, 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 mutations and other asymptomatic individuals who are compound heterozygous for the common mutations suggests that other genes modify the disease presentation and/or age of onset [Boito et al 2005]. Note that the second mutation in compound heterozygotes may be any one of a number of missense, nonsense, deletion, and insertion mutations. Individuals homozygous for the C826A common mutation have a milder phenotype than those who are compound heterozygous [Brockington et al 2001, Mercuri et al 2003, Poppe et al 2003].

LGMD2J. 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 mutation is common in the Finnish population. In the heterozygous state this mutation causes Udd distal myopathy [Hackman et al 2002].

LGMD2K. A form of LGMD2 with mild mental retardation identified in five individuals from consanguineous families [Balci et al 2005], LGMD2K is caused by a missense mutation (A200P) in

POMT1, the gene associated with Walker-Warburg syndrome (see Congenital Muscular Dystrophy Overview).

Clinical Findings

Table 2. Autosomal Recessive LGMD: Clinical Findings

Disease Name	Presentation		Other Findings		Age	
	Symptoms	Weakness	Calf Muscle	Contractures / Scoliosis	Onset (Average)	Wheelchair Bound
Sarcoglycan-opathies: LGMD2C, LGMD2D, LGMD2E, LGMD2F	Complete deficiency: difficulty run, walk	Proximal	Hypertrophy	Late	3-15 yrs (8.5 yrs)	~15 yrs
	Partial deficiency: cramps, exercise intolerance				Adolescent - young adulthood	
Calpain-opathy (LGMD2A)	Difficulty run, walk, toe walk; stiff back (rare)	Proximal (normal hip extensors and adductors), scapular winging	Atrophy	Early	2-40 yrs (8-15 yrs)	11-28 yrs after onset
Dysferlin-opathy (LGMD2B	Inability to tiptoe; difficulty run, walk	Distal and/or pelvic-femoral (no scapular winging)	Transient hypertrophy (rare)		17-23 yrs	
Telethonin-opathy (LGMD2G)	Difficulty run, walk; foot drop	Proximal and distal lower limb; proximal upper limb			9-15 yrs	~18 yrs after onset
LGMD2H	Facial weakness; waddling gait, difficulty with stairs	Proximal lower limb; neck	Muscle wasting	Not reported	1-9 yrs	Late in life
LGMD2I	Difficulty run, walk	Proximal; upper > lower limb	Hypertrophy	Rare, late	1.5-27 yrs (11.5 yrs)	23-26 yrs after onset
LGMD2J		Proximal			5-25 yrs	Average 20 yrs after

						onset
LGMD2K	Fatigability, difficulty climbing stairs and running; cognitive delay with limited language development	Mild weakness; proximal > distal	Hypertrophy of calves and thighs	Ankle contractures present in 2 of 5 individuals; elbow, spine, and neck contractures in one individual	1-3 yrs	~17 yrs (based on 1 individual; 4 remaining individuals, ages 7-17, still ambulatory)
LGMD2L	Early-onset muscle weakness, difficulties climbing stairs, severe weakness after intercurrent illness - steroid responsive	Proximal; lower > upper limb	Hypertrophy of calves, thighs, and triceps	Not reported	4 mo - 4 yrs	Not reported
LGMD2M	Difficulties raising from sitting and climbing stairs; severe myopia	Proximal > distal	Hypertrophy of calves and quadriceps; wasting of hamstrings and deltoids	Ankle contractures	12 yrs	19 yrs (1 patient)
LGMD2N	Slowness in running and getting up	None	Hypertrophy of calves	Scapular winging and mild lordosis; mental retardation	18 mo; asymptomatic at 5 yrs	20 yrs (1 patient)

Sarcoglycanopathies. (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]. Overall, about 30% of individuals have evidence of cardiomyopathy by ECG and echocardiogram. Significant discordance between siblings has been observed, including two siblings with *SGCA* mutations: 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 mutations of *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 mutation 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 [Dincer et al 1997, Duggan et al 1997a, Duggan et al 1997b, Vainzof et al 1999, Merlini et al 2000].

Calpainopathy (LGMD2A). 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: (1) pelvi-femoral 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; (2) scapulo-humeral 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 (3) 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.

Dysferlinopathy. 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].

Telethoninopathy (LGMD2G). 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].

***TRIM32* deficiency (LGMD2H).** Severity ranges from asymptomatic to severe proximal weakness. Facial weakness and a "flat smile" are common. Affected individuals can remain ambulatory well into adulthood with some reports of ambulation (with difficulty) into the sixth decade [Weiler et al 1998]. Sarcotubular myopathy (STM), caused by the same mutation in the *TRIM32*, represents the severe end of the LGMD2H phenotype [Schoser et al 2005].

LGMD2I. 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, Muller 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 (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.

LGMD2J. 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. Of the five affected individuals reported, all have exhibited mild proximal weakness with significant developmental delay (average IQ is 54). Individuals retain the ability to walk for at least 15 years after disease onset. All individuals had CK levels 20-40 times the normal range [Balci et al 2005].

LGMD2L. All five affected individuals reported from three families presented with 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 were cognitively normal. Interestingly three individuals showed severe weakness after intercurrent illness with a remarkable response to steroid [Godfrey et al 2006, Godfrey et al 2007].

LGMD2M. One affected female has been reported. Her early motor milestones were normal. Progressive muscle weakness was first reported at 12 years of age 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 and wasting of the hamstring and deltoid muscles and ankle contractures. The woman had severe myopia and was cognitively normal [Clement et al 2008].

LGMD2N. Two affected individuals have been reported with discordant phenotype. One affected female was asymptomatic at age 5, but neurological 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 mental retardation and right bundle branch block [Godfrey et al 2007].

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. Autosomal Dominant LGMD: Molecular Genetics

Disease Name	Locus Name	Gene Symbol	Chromosomal Locus	Protein Product
LGMD1A (myotilinopathy)	LGMD1A	*TTID*	5q31	Myotilin
LGMD1B	LGMD1B	*LMNA*	1q21.2	Lamin A/C
Caveolinopathy	LGMD1C	*CAV3*	3p25	Caveolin-3
LGMD1D	CMD1F	Unknown	6q23	Unknown
LGMD1E	LGMD1E	Unknown	7q	Unknown
LGMD1F	LGMD1F	Unknown	7q31.1-q32.2	Unknown
LGMD1G	LGMD1G	Unknown	4q21	Unknown

Myotilinopathy (LGMD1A). Two missense mutations (T57I and S55F) have been described in two families in the *TTID* gene encoding the myotilin protein [Hauser et al 2000, Hauser et al 2002]. Mutations

in the *TTID* gene 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. Mutations 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 mutations 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 mutations that also cause LGMD1B. To date all *LMNA* mutations resulting in LGMD1B have been found in exons 1 to 11 [Mercuri et al 2005].

LGMD1C (caveolinopathy). *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]. Mutations in *CAV3* were first identified in a few Italian families [Minetti et al 1998]. (See Caveolinopathies.)

LGMD1D. Haplotype analysis performed on a single family revealed linkage to 6q23. Although a number of genes in this region, including two genes encoding laminin, are highly expressed in striated muscle, a third as-yet unknown gene enoding another laminin may be causative [Messina et al 1997].

LGMD1E. In two of five families with this form of LGMD, Speer et al [1999] established linkage to the 7q region. These two families may share a common ancestor.

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

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

Clinical Findings

Table 4. Autosomal Dominant LGMD: Clinical Findings

Name	Onset (Average)	Presentation		Late Findings
		Symptoms	Signs	
Myotilinopathy (LGMD1A)	18-35 years (27)	Proximal weakness	Tight Achilles tendons Nasal, dysarthric speech (50%)	Distal weakness
LGMD1B	Birth to adulthood; ~1/2 with childhood onset	Proximal lower limb weakness		Mild contractures of elbows Arrhythmia and other cardiac complications (25-45 years) Sudden death
Caveolinopathy (LGMD1C)	~5 years	Cramping Mild-moderate proximal weakness Rippling muscle disease	Calf hypertrophy	
LGMD1D	<25 years	Dilated cardiomyopathy Cardiac conduction		All individuals remain ambulatory

		defect Proximal muscle weakness		
LGMD1E	9-49 years (30)	Proximal lower and upper limb weakness	Pelger-Huet anomaly	Contractures Dysphagia
LGMD1F	1-58 years	Proximal lower and upper limb weakness	Serum CK (normal to 20x normal)	Distal weakness
LGMD1G	30-47 years	Proximal lower limb weakness	Progressive limitation of finger and toe flexion	Proximal upper limb weakness

Myotilinopathy (LGMD1A). Findings in two large families (North American with German and Argentinean ancestry) have been reported [Hauser et al 2000, Hauser et al 2002]. 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). Mutations 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, mild to moderate proximal weakness. Cardiac involvement is common [Hayashi et al 2004].

LGMD1D. In the only family reported to date, 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, one with dysphagia [Speer et al 1999].

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.

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 causative genes are involved.
- Mutations in no one gene account for the majority of cases.
- Few clinical or laboratory findings help identify the causative gene for a given individual.
- The lack of common mutations prevents efficient screening by genotype.
- About 50% of currently identified LGMD would have no molecular diagnosis, even if all 14 currently known genes were fully sequenced.

Table 5. Testing Used to Establish LGMD Type

Type	Serum CK Concentration	Muscle Biopsy Histology	Muscle Protein (Biochemical) Testing [1, 2]	Test Availability	
				Molecular Genetic Testing	Protein (Biochemical) Testing
Autosomal Recessive					
Alpha-sarcoglycanopathy	Mildly to greatly elevated	Myopathic changes	Reduced or complete absence of sarcoglycan antibodies [3]	Clinical Testing	Clinical (immuno-histochemistry)
Beta-sarcoglycanopathy				Clinical Testing	
Gamma-sarcoglycanopathy				Clinical Testing	
Delta-sarcoglycanopathy				Clinical Testing	
Calpainopathy	Often 5-80 times normal, but can be normal	Fiber degeneration and regeneration, central nuclei, fiber size variation, endomysial fibrosis	Absence of calpain-3 on immunoblotting or western blot [4]	Clinical Testing	Clinical (immuno-histochemistry) [5]
Dysferlinopathy	Often >100 times normal	Significant inflammation sometimes observed [6]	Absence or partial deficiency of dysferlin by immunoblot [6]	Clinical Testing	Clinical (immuno-histochemistry and immunoblot)
Telethoninopathy	3-17 times normal	Myopathic changes with	Absence of telethonin	Clinical Testing	Not available

		rimmed vacuoles			
LGMD2H	4-30 times normal	Fiber size variation with degeneration and regeneration, internal nuclei and endomysial fibrosis	NA	Clinical Testing	Not available
LGMD2I	Normal to greatly elevated	Muscle fiber size variation with type 1 fiber predominance and necrotic and regenerating fibers	Variably decreased *glycosylated* alpha-dystroglycan; slight reduction of laminin alpha 2; normal amounts of beta-dystroglycan; partial loss of α2-laminin [4]	Clinical Testing	Clinical (immuno-histochemistry; alpha- and beta-dystroglycan) [5]
LGMD2J	Greatly elevated	Myopathic changes	Almost complete absence of calpain-3	Clinical Testing	Not available
LGMD2K	20-40 times normal	Mild fibrosis; fiber size variation; regenerating and necrotic fibers; hypertrophic fibers with multiple central nuclei	Decreased *glycosylated* alpha-dystroglycan	Clinical Testing	Clinical (immuno-histochemistry; alpha-dystroglycan) [5]
LGMD2L LGMD2M LGMD2N	4-50 times normal	Muscular dystrophy often with inflammatory infiltrates	Decreased glycosylated alpha dystroglycan	Clinical	Clinical (immunohistochemistry and immunoblotting)
Autosomal Dominant					
LGMD1A	Normal or	Normal	Variable fiber	Clinical	Not available

	mildly elevated	myotilin on immuno-histochemistry; Reduced laminin γ1	size with central nuclei and fiber size variation	Testing	
LGMD1B	Normal or mildly elevated	Myopathic changes	NA	Clinical Testing	Not available
LGMD1D	2-4 times normal	Myopathic changes with endomysial fibrosis	NA	Not available	
LGMD1E	1-3 times normal	Variable fiber size; increased endomysial connective tissue	NA	Not available	
Caveolinopathy	4-25 times normal	Myopathic changes	Caveolin-3 reduced on immuno-fluorescence and Western blotting; dysferlin reduced on immuno-histochemistry and normal on western blot [7]	Clinical Testing	Clinical (immuno-histochemistry)
LGMD1F	Normal to 20 times normal	Variable fiber size with increased connective tissue	NA	Not available	
LGMD1G	Normal to 9 times normal	Fiber size variation with necrotic fibers and rimmed vacuoles	Normal immunostaining for dystrophin, sarcoglycans, calpain-3, telethonin, and dysferlin	Not available	

1. Muscle protein (biochemical) testing:
Immunochemistry = exposing sections of tissue to an antibody to determine if a specific protein is present or absent. Immunohistochemistry 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 available for each of the conditions in Table 5, nor are all protein tests as 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 mutation 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 mutation 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. May lead to misclassification as autoimmune disease

5. Specificity is low.

6. Immunostaining for dysferlin is much less specific than immunoblotting. Immunoblotting of muscle or white blood cells is highly specific for mutations in *DYSF*.

7. Protein quantification is unreliable; diagnosis relies on molecular genetic testing [Woodman et al 2004].

Sarcoglycanopathy. Mutation in any one of the sarcoglycan genes leads to secondary deficiency of all the sarcoglycan proteins detected by immunostaining of muscle. For example, immunostaining of muscle from individuals with mutations 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 mutation 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 mutations 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, LGMD2L, LGMD2M, LGMD2N. Immunostaining of muscle reveals significant reduced 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 mutations in *POMT1*, *POMT2* and *POMGNT1*, but this is not always the case in *FKTN* and *FKRP* gene mutations [Jimenez-Mallebrera et al 2008].

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

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 disease-causing mutation.
- 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 mutations; thus, age of onset and/or disease progression in affected sibs cannot be predicted.

Offspring of a proband

- All offspring are obligate carriers.
- In inbred populations with an autosomal recessive disorder, risks to the offspring of a proband may be considerable and 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

Carrier detection using molecular genetic techniques is available on a clinical basis for some of types of limb-girdle muscular dystrophy once the mutations have been identified in the proband.

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 mutation. The frequency of *de novo* mutations causing any of the subtypes 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 mutant allele, the risk to the sibs of inheriting the mutant allele is 50%.
- Clinical severity and disease phenotype often differ among individuals with the same mutation; 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 mutant allele to each child.
- Clinical severity and disease phenotype often differ among individuals with the same mutation; 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 found to be 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.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which molecular genetic testing is available on a research basis only. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible for some types of limb-girdle muscular dystrophy by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. The disease-causing allele(s) of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation(s) has/have been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Management

Treatment of Manifestations

No definitive treatments for the limb-girdle muscular dystrophies exist. Management should be tailored to each individual and each specific subtype. 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
- Monitoring and surgical intervention as needed for orthopedic complications such as foot deformity and scoliosis
- Monitoring of respiratory function and use of respiratory aids when indicated
- Monitoring for evidence of cardiomyopathy in those subtypes with known occurrence of cardiac involvement
- 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]

Resources

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals. GeneTests provides information about selected organizations and resources for the benefit of the reader; GeneTests is not responsible for information provided by other organizations.—ED.

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page PubMed

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Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Suggested Reading

Bushby KM. The limb-girdle muscular dystrophies-multiple genes, multiple mechanisms. *Hum Mol Genet.* 1999; 8: 1875–82. [PubMed]

Chapter Notes

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Revision History

- 23 July 2009 (cd) Revision: clinical testing available for LGMD1A, telethoninopathy, LGMD2H, and LGMD 2J
- 8 June 2007 (cd) Revision: clinical testing available for caveolinopathies
- 8 February 2006 (cd) Revision: clinical testing available for LGMD2K
- 3 February 2006 (me) Revision: comprehensive update posted to live Web site
- 14 October 2004 (eh) Revision: Differential Diagnosis
- 26 July 2004 (eh) Revision: prenatal testing for LGMD1B; changes to Bethlem myopathy
- 11 February 2004 (eh) Revision: sequence analysis for *LMNA* clinically available
- 14 November 2003 (eh) Revision: molecular genetic testing clinically available
- 14 August 2003 (me) Comprehensive update posted to live Web site
- 31 January 2001 (eh) Author revisions
- 8 November 2000 (eh) Author revisions
- 8 June 2000 (tk, pb) Overview posted to live Web site
- 20 April 2000 (eh) Original submission