The Limb-Girdle Muscular Dystrophies and the Dystrophinopathies

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ABSTRACT

Purpose of Review: The classic approach to identifying and accurately diagnosing limb-girdle muscular dystrophies (LGMDs) relied heavily on phenotypic characterization and ancillary studies including muscle biopsy. Because of rapid advances in genetic sequencing methodologies, several additional LGMDs have been molecularly characterized, and the diagnostic approach to these disorders has been simplified. This article summarizes the epidemiology, clinical features, and genetic defects underlying the LGMDs.

Recent Findings: In recent years, the advent of next-generation sequencing has heralded an era of molecular diagnosis in conjunction with physical characterization. Inadvertently, this process has also led to the ''next-generation aftermath,'' whereby variants of unknown significance are identified in most patients. Similar to the published diagnostic and treatment guidelines for Duchenne muscular dystrophy, diagnostic and treatment guidelines have recently been published for LGMDs. In addition, the first medication (based on the exon-skipping strategy) for treatment of patients with a subset of Duchenne muscular dystrophy has been recently approved by the US Food and Drug Administration (FDA).

Summary: The LGMDs are a heterogeneous group of hereditary, progressive, and degenerative neuromuscular disorders that present with primary symptoms of shoulder girdle and pelvic girdle weakness. Although a combination of clinical and molecular genetic evaluations may be sufficient for accurate diagnosis of LGMDs in many cases, the contribution of imaging and histopathologic correlations still remains a critical, if not a necessary, component of evaluation in some cases.

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INTRODUCTION

The limb-girdle muscular dystrophies (LGMDs) are a heterogeneous group of genetic disorders generally characterized by weakness of the shoulder and the pelvic girdle muscles. Based on the inheritance patterns, autosomal dominant (LGMD type 1), autosomal recessive (LGMD type 2), and X-linked forms of LGMD have been described. Successive letters of the alphabet have been used to name the LGMDs according to the chronology of identification of the genetic locus. While straightforward and convenient, this system has sometimes generated confusion in regard to more traditionally named entities (eg, Emery-Dreifuss muscular dystrophy) and with entities not necessarily presenting in a limb-girdle pattern of weakness (eg, dysferlinopathies).

The dawn of molecular genetics in the 1990s and, more recently, the increasing application of next-generation massive parallel-sequencing technologies have resulted in a fundamental change in how these disorders are defined, identified, diagnosed, and managed. For example, in the traditional approach, muscle biopsies were performed routinely on essentially all patients with LGMD as part of the characterization and diagnostic process. However, the lack of specificity

and significant overlap in biopsy findings among the various LGMDs (eg, the presence of inflammatory cells) have rendered this invasive technique less useful and necessary in this day of readily available genetic testing. However, some muscle biopsy findings are fairly characteristic of certain LGMDs (eg, the presence of eosinophils in calpainopathy) and are useful diagnostic tools in some cases when next-generation sequencing analysis of a patient with LGMD fails to establish a genetic diagnosis. Similarly, ultrasound or MRI of the muscle may be helpful in providing data about the pattern of involved muscles and serve as a useful guide for the appropriate muscle for biopsy or to help guide focused genetic testing.

EPIDEMIOLOGY

The LGMDs have a general estimated incidence of 1 to 6 out of 100,000. However, this is likely an underestimate given that significant genetic, phenotypic, and regional variability confound these figures, as do variable and incomplete penetrance, and care access. While population-based whole-genome sequencing strategies may be helpful in estimating the prevalence more accurately, this approach is currently not practical because of the cost and labor intensiveness of the current whole-genome sequencing technologies. In the United States, calpainopathy, dysferlinopathy, and dystrophinopathies are the most common forms of LGMD.

CLINICAL FEATURES AND DIAGNOSIS

Although the LGMDs are, by definition, congenital disorders, clinical manifestations can begin at almost any time from early childhood to late adulthood. Most of the disorders, in fact, manifest in adulthood with a range of presentation as late as the seventies and eighties. LGMDs often manifest with the simultaneous onset of weakness in both the pelvic and shoulder girdle muscles, although specific disorders may initially manifest more prominently in one region (eg, hips) compared to the shoulders. With progression, weakness may spread outside of the pelvic and the shoulder girdle to more distal groups, the neck and axial muscles, or both. Depending on the type of LGMD, the pulmonary musculature and heart may also be involved. Creatine kinase (CK) levels may be normal, mildly elevated (usually in LGMD1s), or highly elevated (usually in LGMD2s or X-linked LGMD) depending on the disorder. Extraocular muscles are usually spared, as are cranial muscles, except in certain disorders where the facial muscles may be involved.

The current diagnostic approach still relies on careful phenotypic delineation of the pattern of weakness, a search for other associated features (eg, contractures, heart involvement), distinctive EMG findings (including abnormal spontaneous activity, complex repetitive discharges, myotonic discharges), and focused genetic testing for suspected causative gene defects. Currently, multigene next-generation panels are commercially available and permit testing of a large number of genes in one step. For example, specific LGMD panels may evaluate 25 to 35 genes, or a general myopathy panel may evaluate 180 genes in a single pass. Although powerful, the process of screening multiple genes at the same time (multigene panel testing) for LGMDs typically results in identification of multiple so-called variants of unknown significance. These may include novel variants not reported in disease or population databases, which in many cases are not causative. When variants of unknown significance (either single or multiple) are identified, family testing to establish segregation as well as additional muscle biopsy studies (such as immunostaining) may help establish the diagnosis, at least in some cases. While intuitively and intellectually appealing, such large panel testing increases cost

KEY POINTS

- Limb-girdle muscular dystrophies have an estimated incidence of 1 to 6 out of 100,000.
- Limb-girdle muscular dystrophies are of dominant, recessive, or X-linked forms.
- The typical pattern of weakness in limb-girdle muscular dystrophies involves the shoulder girdle and the pelvic girdle muscles, with variable involvement of the cardiac and pulmonary musculature.
- The combination of phenotypic evaluation, electrodiagnostic and muscle biopsy features, and gene panel testing are helpful in diagnosis of the limb-girdle muscular dystrophies.
- Contractures and scoliosis are common in limb-girdle muscular dystrophies.

and invariably leads to testing of genes irrelevant to the presenting phenotype and, worse yet, identification of unexpected/irrelevant variants of unknown significance in other unwanted genes in the panel. Therefore, the selection of the most appropriate gene panel from the many available must be based on precise phenotypic and laboratory characterization and the best guess as to the most likely diagnosis.

Even with multigene panel testing, a significant proportion of LGMD cases (up to 25% in some instances) may remain undiagnosed.[1] In such cases, whole-exome sequencing may be performed, a process that typically involves sequencing of all known exons in a given individual, with variants called based on comparisons made to standard sequences. Although evidence suggests that whole-exome sequencing of the trio (the patient and the biological mother and father) increases the diagnostic hit rate,[2] it is important to bear in mind that exome sequencing does not provide complete coverage of all coding exons and typically does not detect deletions and duplications. In addition, genetic diagnosis via multigene panel testing and whole-exome sequencing may be limited by insurance coverage, requires technical expertise, and is usually restricted to specialized neuromuscular centers around the country. The genetic evaluation of patients with negative results in whole-exome sequencing is therefore best pursued only at specialized research centers.

Genetic and molecular characterizations have revealed that the LGMD gene products are localized to various parts of the muscle fiber (nucleus, cytosol, Golgi apparatus, sarcolemma, sarcoplasmic reticulum, extracellular matrix, cytoskeleton [cytoplasmic structural framework], and contractile cytoskeleton [motor and motor-associated proteins]) and perform a variety of related functions, resulting in a plethora of clinical phenotypes. In certain disorders, different allelic alterations result in different phenotypic expressions from defects in the same gene. For example, LGMD2B (dysferlinopathy) can present as a classic LGMD phenotype or a distal-predominant myopathy (ie, Miyoshi myopathy). The following discussion highlights the characteristics of the various LGMDs based on the standard alphanumeric nomenclature followed in parentheses by the involved protein.

Limb-Girdle Muscular Dystrophy Type 1 (Dominant Forms of Limb-Girdle Muscular Dystrophy)

To date, eight LGMD1 loci with dominant inheritance have been described based on clinical and genetic criteria; other dominant LGMDs will certainly be identified in the future. Sporadic forms of LGMD1 are often encountered since de novo dominant mutations can present with the disease phenotype (with an obvious lack of family history). At times, the lack of penetrance and expressivity and broad range of clinical variability precludes the identification of the phenotype in the carrier parent. The LGMD1 disorders are usually adult onset and in general have a milder phenotype than the LGMD2 disorders so that affected patients are usually in good health at reproductive age. To date, mutations in seven genes have been identified as causative for LGMD1 disorders, with commercial testing available for most of the disorders. The LGMD1 subtypes, characteristic features, clinical features, and limited gene information are summarized in **Table 10-1**[3] and described briefly in the following sections.

Limb-girdle muscular dystrophy type 1A (myotilinopathy). The onset of this late-onset disease is variable from the midtwenties to midseventies. Weakness is symmetric and starts in the legs and then progresses to the arms. Distal weakness is observed with further

TABLE 10-1 Limb-Girdle Muscular Dystrophy Type 1 Characteristics[a]

	Clinical Information				Gene Information	
Type	Typical Onset	Progression[b]	Creatine Kinase Level	Heart Involvement	Gene/ Locus	Protein
LGMD1A	Adulthood	Slow	1–15X	Yes	*MYOT*	Myotilin
LGMD1B	Variable; childhood to adulthood	Slow	1–6X	Yes	*LMNA*	Lamin A/C
LGMD1C	Childhood	Slow to moderate	10–15X	Yes	*CAV3*	Caveolin 3
LGMD1D	Adulthood	Slow	1–6X	Not usual	*DNAJB6*	HSP40
LGMD1E	Adulthood	Slow	2–4X	Yes	*DES*	Desmin
LGMD1F	Variable; infancy to adulthood	Rapid	Variable; normal to 15X	No	*TNPO3*	Transportin 3
LGMD1G	Adulthood	Slow	Variable; normal to 10X	No	*HNRPDL*	Heterogeneous nuclear ribonucleoprotein D–like protein
LGMD1H	Variable; childhood to adulthood	Slow	Variable; normal to 10X	No	3p23	To be identified

LGMD = limb-girdle muscular dystrophy.
[a] Modified with permission from Iyadurai SJ, Kassar D, Springer.[3] © 2013 Springer Science+Business Media.
[b] Progression of the disease as noted by time frame (arbitrarily assigned) of loss of ambulation: rapid is 2 years from diagnosis; moderate is 5 years from diagnosis; slow is more than 5 years from diagnosis.

progression, although some patients may present with footdrop. In the upper extremities, weakness is noticed in the wrist extensors, fingers extensors, and deltoid muscles. Facial and neck extensor muscle weakness may occur. Some patients develop dysarthria (due to palatal weakness),[4] myalgia, and joint contractures mainly of the ankles. Tendon reflexes are absent at the knees and the ankles but loss of tendon reflexes may be diffuse. Cardiomyopathy is present in one-half of patients, with onset between ages 60 and 70. Progression of weakness is slow, with loss of ambulation usually within 10 years of onset. Serum CK can be normal to 15-fold elevated. Needle EMG reveals myopathic changes and fibrillation potentials, and myotonic discharges are seen in some patients. Muscle biopsy reveals a myopathic pattern with significant size variability, rounded fibers, rimmed or autophagic vacuoles, hyaline inclusions, and spheroid bodies on ATPase staining. Mutations in myotilin gene cause LGMD1A.

Limb-girdle muscular dystrophy type 1B (laminopathy). LGMD1B usually manifests before the age of 20 with symmetrical weakness affecting the proximal lower extremities (**Case 10-1**). However, a variant of this syndrome (Arg377His mutation of the lamin A/C gene, *infra vida*) may result in early and predominant quadriceps involvement. Progression is generally slow, with the upper extremities usually involved in the third or fourth decade. Cardiac abnormalities are noted in

about 60% of patients and are typified by cardiomyopathy, atrioventricular conduction block, bradycardia, and sudden cardiac death.[5] Specific mutations such as the Arg377His have been associated with dilated cardiomyopathy. Serum CK may be either normal or mildly elevated. Muscle biopsy shows rounded fibers, variability in fiber size, increased endomysial thickness, and mislocalized and aggregated lamin. Mutations in the lamin A/C gene underlie the LGMD1B phenotype and also many other phenotypes. For example, patients with certain mutations in the lamin A/C gene manifest as Emery-Dreifuss muscular dystrophy phenotype characterized by contractures of the posterior cervical

Case 10-1

This 28-year-old woman with diffuse weakness and atrophy was seen initially as a 16-month-old girl when her mother noted that she had difficulty running and arising from the floor. Muscle biopsy revealed a dystrophic process. On follow-up examination at age 4, the patient used a wheelchair for all mobility. Laboratory evaluation showed a mildly elevated creatine kinase level at that time. On follow-up examination at age 21, generalized atrophy of the appendicular muscles was noted. The cranial, facial, and truncal muscles were spared. Contractures were noted in the hips, ankles, and elbows. Pulmonary function tests showed a vital capacity of 75% predicted. Gene sequencing identified a mutation in the lamin A/C gene compatible with limb-girdle muscular dystrophy type 1B (**Figure 10-1**).

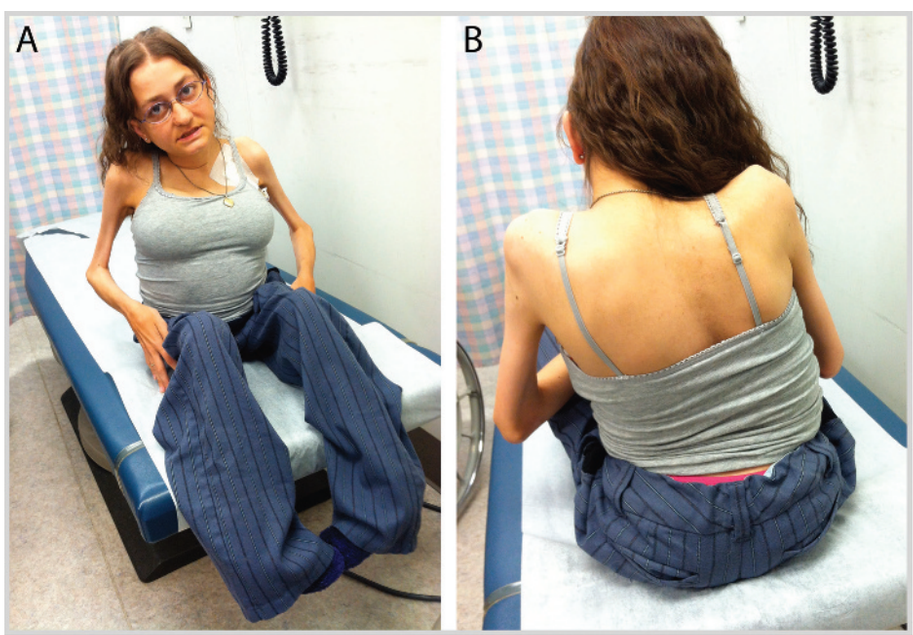

FIGURE 10-1 Patient in **Case 10-1** with limb-girdle muscular dystrophy type 1B. Notice the sparing of cranial musculature and severe atrophy of arm muscles (*A*). Elbow and knee contractures, scoliosis, and scapular winging are common (*B*).

Comment. This case demonstrates a classic onset and progression as would be expected in patients with lamin A/C mutations, an autosomal dominant limb-girdle muscular dystrophy. These patients have delayed motor milestones, contractures, scoliosis, elevated creatine kinase levels, and develop pulmonary dysfunction and cardiac abnormalities. Cranial nerves are not usually affected.

muscles, elbows, and ankles; cardiac involvement; slowly progressive weakness involving the humeral and peroneal muscles with some pelvic girdle involvement; tendon areflexia; and slight elevation in CK levels. Recently, recessive mutations in lamin A/C resulting in the LGMD1B phenotype have been described.

Limb-girdle muscular dystrophy type 1C (caveolinopathy and rippling muscle disease). LGMD1C is an early-onset disorder with manifestation between 5 years of age and adulthood. Proximal weakness in the lower extremities, difficulty walking, and a positive Gowers sign are usually noted. Patients with LGMD1C may also experience cramps after exercise. Variable clinical manifestations may occur in a single family, and the disorder often has a benign clinical course. No evidence of respiratory impairment occurs, and life expectancy is not reduced. Hypertrophic cardiomyopathy has been noted in patients, although rarely. EMG may be normal or reveal myopathic changes. Usually, muscle biopsy demonstrates variability in muscle fiber size, fibers with internal nuclei, degenerating and regenerating fibers, and increased connective tissue. Caveolin 3 mutations underlie LGMD1C. In muscle biopsies obtained from patients with LGMD1C, caveolin 3 is invariably reduced both by immunohistochemistry and immunoblot analysis.

Another manifestation of patients with caveolin 3 mutations results in rippling muscle disease phenotype. Rippling muscle disease is characterized by several specific behaviors of the muscle: wormlike movements on the surface of the muscle, percussion-related contraction, and muscle mounding. Muscle hypertrophy is common in caveolinopathy. At times, a parent may be a benign carrier with muscle hypertrophy but have no other signs or symptoms. The presenting manifestations are usually fatigue, tiptoe walking difficulty, and myalgia. The patients usually experience muscle cramps, pain, and stiffness (particularly with exercise), and serum CK is elevated up to 10 times the normal value.

Limb-girdle muscular dystrophy type 1D (HSP40 proteinopathy). LGMD1D usually presents with onset of weakness at 20 to 60 years of age, although most patients have weakness, slowness, and clumsiness of movements as children. Hip girdle weakness and waddling gait are noted first, followed variably by progression to the shoulder girdle. Progression is gradual, with need for a wheelchair usually occurring 20 to 30 years after diagnosis. Dysphagia occurs in about 20% of the patients, and dysarthria may occur. Cardiac or respiratory involvement has not been observed with LGMD1D. Most patients have elevated serum CK (up to five times normal). Mild calf hypertrophy may be present. Myopathic changes are noted on EMG. Muscle biopsy usually shows varied fiber size, rounded fibers, endomysial thickening, rimmed vacuoles, eosinophilic cytoplasmic bodies, and dystrophic fibers. Mutations in *DNAJB6* underlie LGMD1D phenotype.[6]

Limb-girdle muscular dystrophy type 1E (desminopathy). LGMD1E is characterized by dilated cardiomyopathy, cardiac conduction system disease, and adult-onset myopathy.[7] Cardiac manifestations include arrhythmia, which manifests at 20 to 25 years of age, and congestive heart failure with four-chamber enlargement during the third to fifth decade. Cardiac sudden death has been noted as a major familial symptomatology.[8] Muscle biopsy shows significant variability is fiber size, increased endomysial thickening, cytoplasmic bodies, and eosinophilic inclusions. Mutations in desmin gene were found to be causative of LGMD1E phenotype.

Limb-girdle muscular dystrophy type 1F (transportinopathy). Onset of LGMD1F is typically in the third or fourth decade but can manifest in infancy. All

KEY POINT

- Patients with certain mutations in the lamin A/C gene manifest as Emery-Dreifuss muscular dystrophy phenotype characterized by contractures of the posterior cervical muscles, elbows, and ankles; cardiac involvement; slowly progressive weakness involving the humeral and peroneal muscles with some pelvic girdle involvement; tendon areflexia; and slight elevation in creatine kinase levels.

KEY POINT

■ In most of the limb-girdle muscular dystrophy type 2 disorders, the creatine kinase is quite elevated. Although limb-girdle muscular dystrophy type 2 disorders are usually of early childhood onset and quite debilitating, adult-onset forms have also been described.

affected patients show characteristic pelvic and shoulder girdle proximal weakness. Pelvic girdle impairment precedes the shoulder girdle weakness, and distal weakness often occurs later. Respiratory muscles are clinically affected in some patients with juvenile-onset LGMD1F. Serum CK is normal in 40% of patients and varies between normal to as high as 15 times the normal levels. EMG of proximal muscles shows myopathic changes including short-duration, low-amplitude potentials and polyphasia. No abnormalities in sensory and motor nerve conduction velocities are noted. Muscle biopsy shows fiber size variability, increased connective tissue (both endomysial and perimysial), rimmed vacuoles, central nuclei, and scattered dystrophic fibers. Gene defects in transportin 3 are associated with LGMD1F.

Limb-girdle muscular dystrophy type 1G (HNRPDL proteinopathy). The age of onset in LGMD1G is in the third or fourth decade. The initial symptoms are seen in the proximal lower limbs associated with muscle cramps followed by weakness of the upper limbs. Progressive finger and toe flexion limitation with decreased range of motion in interphalangeal joints also occurs. However, intrinsic hand muscles are not usually affected. CK may be normal or elevated up to 10 times the upper level of normal. Muscle biopsy shows fiber size variability, perimysial thickening, rimmed vacuoles, and necrotic fibers. Interestingly, scattered areas of angulated fibers may also be noted. Mutations in the heterogeneous nuclear ribonucleoprotein D–Like protein underlie the LGMD1G phenotype.

Limb-girdle muscular dystrophy type 1H. LGMD1H is extremely rare and has been described in only 11 members of a single large family. The disease onset is usually in the fifth decade and manifests with proximal weakness in upper and lower extremities and follows a relatively slow course. However, atrophy of shoulder and pelvic girdle muscles is noted. Generalized hyporeflexia and calf hypertrophy are also characteristically noted. Serum CK levels are usually elevated but can be normal (normal to 10 times the normal level). EMG reveals nonirritable myopathic changes. Muscle histology shows abnormal fiber size and shape variation and increased presence of endomysial and perimysial connective tissue. Central nuclei are occasionally present. Although the LGMD1H mutation has been linked to 3p23–p25.1,[9] the gene defect is unknown.

Limb-Girdle Muscular Dystrophy Type 2 (Recessive Forms of Limb-Girdle Muscular Dystrophy)

Twenty-three distinct LGMD2 loci with recessive inheritance have been described. In most of these disorders, the CK is quite elevated. Although LGMD2s are usually of early childhood onset and quite debilitating, adult-onset forms have also been described. A variable, progressive course is typical. Although LGMD2I (FKRP deficiency) is the most common form of all LGMDs in northern Europe, LGMD2A (calpainopathy) is the most prevalent in many other European countries, as well as in Turkey, Brazil, Japan, Russia, and Australia. LGMD2I, LGMD2B, and LGMD2A remain the most common autosomal recessive LGMDs in North America. The LGMD2 subtypes, characteristic features, clinical features, and genetic information are listed in **Table 10-2**. Individual LGMD2 subtypes are described in the following sections.

Limb-girdle muscular dystrophy type 2A (calpainopathy). LGMD2A is characterized by a wide variability in clinical features and rates of progression. Although the mean age at onset is approximately 14 years, a considerable variation in presentation from ages 2 to 40 years has

TABLE 10-2 The Subtypes of Limb-Girdle Muscular Dystrophy Type 2[a]

	Clinical Information				Gene Information	
Type	Typical Onset	Progression	Creatine Kinase Level	Heart Involvement	Gene	Protein
LGMD2A	12–30 years	Slow	Markedly elevated	No	*CAPN3*	Calpain 3
LGMD2B	Adolescence	Slow	10X	Possible; not common	*DYSF*	Dysferlin
LGMD2C	Early childhood	Moderate to rapid	20–30X	Yes	*SGCG*	γ-Sarcoglycan
LGMD2D	Variable	Rapid	20X	Yes	*SGCA*	α-Sarcoglycan
LGMD2E	Early childhood	Moderate to rapid	20X	Yes	*SGCB*	β-Sarcoglycan
LGMD2F	Early childhood	Rapid	10–50X	Yes	*SGCD*	σ-Sarcoglycan
LGMD2G	Childhood, adolescence	Moderate	3–30X	Yes, approximately 50%	*TCAP*	Telethonin
LGMD2H	Adolescence, adulthood	Slow	1–20X	No	*TRIM32*	E3 ubiquitin ligase
LGMD2I	Early childhood and late adulthood	Rapid to slow	5–40X	Yes	*FKRP*	Fukutin-related protein
LGMD2J	Childhood, adulthood	Slow	10–15X	No	*TTN*	Titin
LGMD2K	Childhood	Slow	10–40X	No	*POMT1*	Protein O-mannosyltransferase 1
LGMD2L	Adulthood	Slow	1–100X	No	*ANO5*	Anoctamin 5
LGMD2M	Early infancy	Slow	50–100X	Possible	*FKTN*	Fukutin
LGMD2N	Prenatal to infancy	Rapid	6–12X	No	*POMT2*	Protein O-mannosyltransferase 2
LGMD2O	Late childhood	Moderate	2–10X	No	*POMGNT1*	Protein O-linked mannose β1,2-N-acetylglucosaminyltransferase
LGMD2P	Early childhood	Moderate	20X	No	*DAG1*	Dystroglycan
LGMD2Q	Early childhood	Slow	10–50X	No	*PLEC1*	Plectin 1
LGMD2R	Childhood to young adulthood	Slow	Normal	Yes	*DES*	Desmin
LGMD2S	Early childhood	Slow	10–15X	No	*TRAPPC11*	Trafficking protein particle complex 11

Continued on page 1962

TABLE 10-2 The Subtypes of Limb-Girdle Muscular Dystrophy Type 2[a] *Continued from page 1961*

	Clinical Information				Gene Information	
Type	Typical Onset	Progression	Creatine Kinase Level	Heart Involvement	Gene	Protein
LGMD2T	Variable	Slow	Variable	Possible	*GMPPB*	GDP-mannose pyrophosphorylase B
LGMD2U	Early childhood	Rapid to moderate	6–50X	Possible	*ISPD*	Isoprenoid synthase domain containing
LGMD2V	Variable	Usually slow	1–20X	Yes, predominantly in infantile-onset cases	*GAA*	Acid α-1,4-glucosidase
LGMD2W	Childhood	Variable, but usually slow	Up to 25X	Possible	*LIMS2*	LIM zinc finger domain containing 2

LGMD = limb-girdle muscular dystrophy.
[a] Modified with permission from Iyadurai SJ, Kassar D, Springer.[3] © 2013 Springer Science+Business Media.

been described. Ambulation is affected during adolescence but is affected earlier in infantile-onset disease. The disorder is characterized by a symmetric, selective atrophic involvement of limb-girdle and trunk muscles.[10] Muscle weakness usually begins in the pelvic girdle, with difficulty running, climbing stairs, or rising from a chair. The pelvic girdle muscles are the most severely affected, even when the disease starts in the shoulder girdle. Hip adductors and gluteus maximus are the earliest clinically affected muscles and, to a lesser degree, the hip flexors and posterior thigh muscles are also affected. The distal leg muscles and proximal hip abductors are relatively spared. The weakness in the upper extremity muscles and the shoulder girdle occurs later in the disease course. Scapular winging is evident. Abdominal muscles may also be involved. Early in the disease course, contractures are seen in the calves, wrists, elbows, and fingers. As a result, toe walking may be noted in early stages. In later disease, contractures in the proximal parts of the body (including the spine) are noted.

Although no significant cardiac involvement occurs, worsening of respiratory function may lead to cardiac complications. Strangely, CK levels may be normal or elevated, even up to 500 times the normal values. With progression of the disease, the CK values may begin to drop, consistent with worsening atrophy of the affected muscles. EMG shows an irritable myopathy characterized by increased insertional activity, fibrillation potentials, and positive sharp waves. Muscle biopsy shows variability of muscle fiber size, endomysial thickening, necrotic fibers and rare regenerating fibers, type 1 predominance, lobulation of type 1 fibers, and inflammation in perivascular or endomysial areas.[11] Eosinophilic infiltrates are characteristic. Imaging of the thigh muscles may show marked atrophy of the hamstrings and hip adductors and moderate atrophy in quadriceps with sparing of the sartorius. With progression of the disease, other thigh muscles are also affected depending on clinical severity; the adductors and semimembranosus muscles are involved in young patients with minimal functional motor impairment. In patients

with restricted ambulation, a diffuse involvement of the posterolateral muscles of the thigh and of the vastus intermedius is found with relative sparing of the vastus lateralis, sartorius, and gracilis. Imaging of the calf muscles reveals involvement of the soleus muscle and the medial head of the gastrocnemius with relative sparing of the lateral head. LGMD2A is caused by mutations in the *CAPN3* gene, which encodes for a muscle-specific proteolytic enzyme called calpain 3 (**Case 10-2**).

Limb-girdle muscular dystrophy type 2B (dysferlinopathy). LGMD2B has a wide range of clinical presentations, from a classic limb-girdle presentation to specific distal myopathies such as Miyoshi myopathy (also known as Miyoshi muscular dystrophy type 1) and distal myopathy with anterior tibial onset. Symptom onset of LGMD2B ranges from adolescence to late adulthood (10 to 40 years of age), with significant variability in presentation between family members and different families. Usually, the muscle weakness starts in the pelvic girdle, manifesting as difficulty running and walking up the stairs. Early difficulty with walking is usually associated with involvement of the gastrocnemius (specifically the medial head). In later stages of the disease, upper extremity muscles are involved.

Case 10-2

A 50-year-old woman presented with arm and leg weakness and a history of motor difficulties that she had experienced since childhood. (She stated, ''I was a klutzy kid.'') However, she had experienced noticeable weakness only at age 30 when she had difficulty going up stairs. Laboratory evaluations showed an elevated creatine kinase level of 1300 IU/L (six times the upper limit of normal). Muscle biopsy demonstrated significant size variability, many small rounded fibers, central nuclei, increased endomysial connective tissue, and necrotic fibers, but no inflammation. Physical examination showed normal cognition, normal cranial nerves, scapular winging, proximal and distal weakness, hyperlordotic posture, generalized atrophy, and normal sensation (**Figure 10-2**). Gene testing revealed compound heterozygous mutations in the calpain 3 gene, diagnostic of limb-girdle muscular dystrophy (LGMD) type 2A.

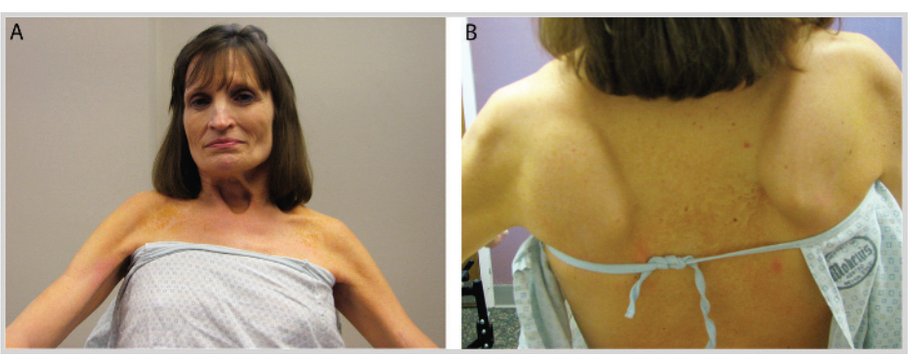

FIGURE 10-2 Patient in Case 10-2 with limb-girdle muscular dystrophy type 2A. The patient has notable shoulder abduction weakness (*A*) and scapular winging (*B*).

Comment. This case demonstrates common features associated with autosomal recessive LGMDs. Creatine kinase is usually elevated to a higher level (compared to autosomal dominant LGMDs in general). Early-onset motor delay and normal cognition are usually noted. While scapular winging can be variably seen, cranial musculature is usually preserved.

KEY POINT

- Miyoshi and limb-girdle muscular dystrophy phenotypes can be present in the same family. The exact reason behind the differences in presentation within a given family is unclear.

Specifically, biceps are affected approximately 10 years after the onset of lower extremity weakness. The disease follows a fairly slow course of progression, and loss of ambulation is noted at 30 years of age. However, some patients do not lose ambulation until age 60. Hypertrophy of several muscles (deltoid, biceps, and the calves) is noted early in the course of the disease. Classic diamond on quadriceps sign is seen in most patients. This sign represents the characteristic shape acquired by the anterior compartment muscles of the thigh when the patient attempts to sit down (lower his or her torso or back as if sitting in a chair) with feet firmly and flatly planted on the ground. In some patients, cramps and muscle discomfort may be the only early presenting symptoms. The allelic form of Miyoshi distal myopathy may present in early adulthood with the inability to walk on or get up on toes. However, the anterior tibial–onset variant may present with footdrop and steppage gait. In these distal-predominant allelic forms, the proximal muscles and the upper limbs become affected later in the disease course.

Serum CK levels are considerably increased. Muscle imaging confirms a selective involvement of the soleus and gastrocnemius (medial head) and early muscle edema. Miyoshi and LGMD phenotypes can be present in the same family. The exact reason behind the differences in presentation within a given family is unclear. EMG shows typical myopathic changes. Muscle pathology shows inflammation, necrosis, and degeneration of muscle fibers, fiber size variability, and rarely, fiber splitting. Endomysial thickening is also commonly noted. Amyloid deposition at the muscle membrane, endomysium, or perivascular spaces are noted in some patients. Given the predominant inflammation seen in the muscle biopsies in these patients, a misdiagnosis of polymyositis is not uncommon. However, in these patients, dysferlin immunostaining reveals either a reduction or lack of staining. Mutations in the skeletal muscle protein dysferlin underlie LGMD2B.

Limb-girdle muscular dystrophy types 2C TO 2F (α, β, γ, and σ sarcoglycanopathies). The age of onset and clinical presentation has a wide inter- and intrafamilial variability. The clinical presentation can vary from a Duchenne muscular dystrophy (DMD)–like course to intermediate to a mild Becker muscular dystrophy (BMD)–like phenotype in a given family. The onset of the disease is approximately 5 or 6 years of age with involvement mainly of proximal muscles, although distal involvement may occur. The inability to walk may occur anywhere between the second and the fourth decade. The glutei, adductors, paraspinal, abdominal, subscapular, and soleus muscles are affected whereas quadriceps is spared in some patients.[12] Patients may develop calf and tongue hypertrophy and deafness. Respiratory failure occurs in the third decade of life. Cardiac functions are fairly spared. Serum CK is noted to be extremely high. EMG shows small-amplitude, short-duration, polyphasic motor unit action potentials. Muscle biopsy shows fiber size variability, rounded fibers, increased endomysial thickness, and necrotic fibers. Rarely, inflammatory infiltrates are also found. The immunoreactivity of the affected sarcoglycan may be reduced or absent. Secondary reductions in other sarcoglycans may also be noted. Occasionally, reductions in dystrophin staining may also be noted. However, how the secondary reduction in other sarcoglycan or decreased dystrophin staining relate to the phenotype is unclear. The individual sarcoglycans and their deficiencies relate to the specific LGMD type (2C, 2D, 2E, and 2F). Sarcoglycans appear to play a role in maintaining muscle membrane integrity.

Limb-girdle muscular dystrophy type 2G (telethoninopathy). Patients with LGMD2G usually present at a mean age

of onset of 12 years with difficulty walking, running, and climbing stairs. Although this condition spares the gastrocnemius (which is affected in LGMD2B/dysferlinopathy), these patients have difficulty walking on their heels. The tibialis anterior is severely affected, and difficulties with foot dorsiflexion and footdrop ensue. Atrophy of the shoulder girdle muscles is prominent. In the lower extremities, the pelvic girdle muscles and distal muscles are affected. About 40% of patients with LGMD2G become nonambulatory by the third or fourth decade. Interestingly, calf atrophy or hypertrophy may be noted as the first sign of disease in one-half of patients. Serum CK may be mildly elevated (three times the normal level) or quite highly elevated (30 times the normal level). Muscle biopsy shows significant variability in fiber size, increased number of fibers with central nuclei, necrotic and regenerating fibers, and rimmed vacuoles. In Western blot analysis, telethonin is absent. LGMD2G is most commonly seen in patients with Brazilian ancestry and is caused by mutations in the gene encoding telethonin.[13,14] Other variant telethonin syndromes include dilated cardiomyopathy 1N and congenital muscular dystrophy.

Limb-girdle muscular dystrophy type 2H (TRIM32 proteinopathy/sarcotubular myopathy). To date, LGMD2H has been described only in the Hutterite population of North America[15] and is a mild form of recessive LGMD with a variable clinical presentation. Disease onset is usually within the second or third decade of life and progression is slow; most patients continue walking into their sixth decade. Quadriceps and pelvic girdle muscles are primarily involved, and patients show a waddling gait and difficulty rising from the squatting position. Cardiac and facial involvement does not occur. The serum CK is high (up to 20 times the normal level), and EMG shows myopathic changes. Muscle histology reveals mild dystrophic changes including fiber size variability, endomysial fibrosis, and muscle fiber degeneration and regeneration. Fiber splitting and internal nuclei are observed.

Another allelic variant of LGMD2H is sarcotubular myopathy. As the name implies, distinctive features in muscle biopsy led to the name. Patients with the sarcotubular myopathy allelic variant present with exercise-induced fatigue and muscle pain. In addition to the weakness of pelvic and shoulder girdle muscles, neck flexion weakness is also noted. Other accompanying features include mild facial weakness, scapular winging, calf hypertrophy, and Gowers sign. In general, the muscle atrophy noted in successive examinations is a fair indication of progressive weakness. Contractures in the Achilles tendons are noted frequently, and deep tendon reflexes are either normal or depressed. Serum CK levels may be elevated up to 20 times the normal values. Muscle biopsy shows fiber size variability, rounded fibers, and in addition, small rounded vacuoles in type 2 fibers. Small abnormal spaces are noted in segments of many muscle fibers. The gene mutations underlying LGMD2H involve the gene encoding tripartite motif-containing protein32 (TRIM32).

Limb-girdle muscular dystrophy type 2I (fukutin-related proteinopathy). LGMD2I is one of the most common LGMDs with a carrier frequency of 1 in 400 in the white population. The combination of limb-girdle weakness, respiratory insufficiency, and dilated cardiomyopathy is noted in patients with LGMD2I.[16] The disease onset may be as early as infancy (5 months) or as late as midadulthood (40 years). Patients with early-onset disease symptoms may present with hypotonia and display delayed motor milestones. Tongue hypertrophy is often noted, although other muscles may also display hypertrophy. These patients usually lose ambulation by their early teens (much like

KEY POINT

- Limb-girdle muscular dystrophy type 2I is one of the most common limb-girdle muscular dystrophies with a carrier frequency of 1 in 400 in the white population.

patients with DMD). The loss of ambulation is usually followed by cardiomyopathy.[17] The patients with adult-onset symptoms usually have a milder form of the disease and a slow course of progression. However, hypertrophy of muscles may be noted; the calf, anterior thigh muscles, brachioradialis, and tongue may be prominently involved. These patients may also report nonspecific symptoms such as cramps and myalgia, especially after exercise. In selected cases, myoglobinuria may occur. Brain MRI and cognition are normal.[18] Serum CK is elevated between 10 to 30 times the normal level. Muscle biopsy shows fiber size variation, necrosis, and regeneration of muscle fibers, increased endomysial connective tissue, and type 1 predominance. LGMD2I is caused by mutation in Fukutin-related protein gene (*FKRP*), which also affects glycosylation of dystroglycans, which is discussed in the following section on LGMD types 2K, 2M, 2N, 2O, and 2P.

Limb-girdle muscular dystrophy type 2J (titinopathy/Finnish distal myopathy). LGMD2J is most prevalent in patients from Finland or of Finnish origin. The onset of symptoms may be variable and can occur anywhere from childhood to adulthood (third decade). LGMD2J classically presents as a myopathy involving distal muscles, specifically of the leg. The initial manifestation is noted in the tibialis anterior muscle, and hence is also known as tibial muscular dystrophy. MRI of the muscles show prominent involvement of the tibialis anterior and the extensor digitorum longus. In general, LGMD2J follows a slow course of progression. Usually patients become nonambulatory about 20 years after symptom onset. In these patients, cardiomyopathy is not usually noted. Serum CK can be elevated up to 20 times the normal level. Muscle biopsy shows myopathic features. Immunohistochemistry reveals secondary reduction in calpain 3.[19] Mutations in the titin gene are responsible for LGMD2J. However, it should be emphasized that titin is a large protein, and mutations/truncations affecting several distinct domains within the protein may lead to specific phenotypes including selective involvement of the cardiac, skeletal, or respiratory muscles. The details of the genotype-phenotype correlation are still being worked out.

Limb-girdle muscular dystrophy type 2L (anoctaminopathy). LGMD2L usually presents as an asymmetric disorder and that involves the muscles of the scapula. The onset is usually in adulthood, anywhere from 20 years to 55 years. Asymmetric atrophy of muscles is commonly noted in quadriceps femoris, biceps brachii, and gastrocnemius. In some patients, calf hypertrophy is noted; however, calf atrophy ensues with progression of the disease, usually in an asymmetric fashion. While proximal weakness is prominent in both the shoulder and the pelvic girdle, distal weakness is not usually noted. Selected patients may develop subtle facial weakness. Myalgia, either due to exertional or nonexertional causes, is a common presenting symptom in these patients. Serum CK can have a very wide range, from normal levels to 80 times the normal level. EMG shows an irritable myopathy. Muscle biopsy shows rounded fibers, fiber size variability, increased endomysial connective tissue, degenerating fibers, and occasionally inflammatory infiltrates and fiber splitting. Mutations in the anoctamin 5 (*ANO5*) gene underlie LGMD2L. Recently, dominant mutations in *ANO5* have been noted to be associated with the LGMD2L phenotype.

Limb-girdle muscular dystrophy types 2K, 2M, 2N, 2O, 2P. This group of LGMD disorders shares a common feature in that they all result from hypoglycosylation of α-dystroglycan. The proteins involved are as follows: type 2K: POMT1 proteinopathy; type 2M:

fukutinopathy; type 2N: POMT2 proteinopathy; type 2O: POMGNT1 proteinopathy; and type 2P: dystroglycan 1 proteinopathy. These disorders all usually present in early childhood as congenital muscular dystrophies with multiple organs involved (muscle, eye, brain). Variable rates of progression, proximal muscle weakness, mild pseudohypertrophy, microcephaly, and mild mental retardation with an IQ ranging from 50 to 76 is usually noted. Joint contractures occur in about one-half of patients.[20] The serum CK is 40 times the normal level. Muscle histology shows fiber size variability and reduced α-dystroglycan. In LGMD2M, muscle hypertrophy is seen in the posterior leg and, in some patients, the tongue. Spinal rigidity, joint contractures, and cardiomyopathy may occur.[21,22] Although brain MRI may be normal, vermis hypoplasia and polymicrogyria may be seen.

Limb-girdle muscular dystrophy type 2Q (plectinopathy). Plectinopathy has been reported in Turkish, Indian, English, and Egyptian families/backgrounds. The disease onset occurs in early childhood and is usually accompanied by microcephaly and mental/intellectual disabilities. The CK is elevated up to 20 times the normal level. EMG shows myopathic changes, and muscle biopsy reveals a dystrophic picture, varied fiber size, internal nuclei, necrosis/regeneration, and reduced plectin staining. Mutations in the plectin gene underlie LGMD2Q.

Limb-girdle muscular dystrophy type 2R (desminopathy). Patients with this desmin variant syndrome (as opposed to LGMD1E) have a recessive mode of inheritance. The disease onset is usually early (childhood to the second decade of life) and involves facial weakness and respiratory muscle weakness in addition to the proximal weakness. High-arched palate and scoliosis are also noted. All patients have severe atrioventricular conduction defects and require cardiac pacemaker placement. Muscle pathology is significant for hyaline accumulations and amorphous subsarcolemmal inclusions. Recessive mutations in desmin underlie LGMD2R. As noted in the previous section, dominant mutations in desmin underlie LGMD1E.

Limb-girdle muscular dystrophy type 2S (TRAPPC11 proteinopathy). Patients with LGMD2S have an early childhood onset of proximal weakness, scapular winging, and mild myopathic facies. CK is elevated up to 10 times the normal values. In addition, global developmental delay, infantile-onset hyperkinetic movements (dystonia/chorea), and truncal ataxia are noted. EMG reveals a myopathic picture, and MRI of the brain may reveal cerebral volume loss. The gene defect underlying this LGMD is in the trafficking protein particle complex 11 gene.

Limb-girdle muscular dystrophy type 2T (GDP-mannose pyrophosphorylase B proteinopathy). The disease onset is quite variable with onset from birth to age 40 and has a fairly slow progression of proximal weakness. Infants with early-onset LGMD2T have hypotonia at birth and intellectual disabilities, sometimes with concurrent onset of seizures. In older patients, enlarged calves, rhabdomyolysis, and cramps are noted. Some patients may have cardiac involvement. EMG is myopathic and muscle biopsy reveals a dystrophic picture, internal nuclei, muscle fiber necrosis, and endomysial thickening. The gene defect underlying this LGMD has been localized to the GDP-mannose pyrophosphorylase B gene.

Limb-girdle muscular dystrophy type 2U (ISPD proteinopathy). The disease onset is in early childhood with a progressive course of proximal-predominant weakness. Hypotonia, gait disorder, and Gowers sign may be noted. Loss of ambulation occurs early, around 10 to 12 years

KEY POINT

- Limb-girdle muscular dystrophy types 2K, 2M, 2N, 2O, and 2P usually present in early childhood as congenital muscular dystrophies with multiple organs involved (muscle, eye, brain).

KEY POINTS

- Identification of limb-girdle muscular dystrophy type 2V (Pompe disease, also known as acid maltase deficiency) is crucial since IV enzyme replacement therapy is life-saving for infants with the disorder and improves ambulation and respiratory status in adults with the disease.
- Pompe disease can have infantile-onset, adolescent-onset, and adult-onset forms. Respiratory insufficiency and thigh adductor weakness is commonly seen in conjunction with proximal weakness.
- For most patients with a limb-girdle muscular dystrophy, physical therapy and occupational therapy should be encouraged to prevent the formation of contractures and to maximize limb use.
- In the subset of patients with a limb-girdle muscular dystrophy with heart involvement, serial ECG and echocardiograms are mandatory for monitoring cardiac status, and cardiac MRI is increasingly being used to identify early myocardial fibrotic changes.

of age. Hypertrophy of muscles may be noted. Cardiac involvement with left ventricular dysfunction may be noted as well. MRI of the brain is usually normal. CK is usually elevated three to 50 times the normal level. Muscle biopsy shows a dystrophic picture. The gene defect associated with this disease is in the isoprenoid synthase domain-containing gene.

Limb-girdle muscular dystrophy type 2V (Pompe disease). Preisler and colleagues[23] have suggested that Pompe disease (acid maltase deficiency or α-1,4-glucosidase deficiency) should be included as an LGMD because it was identified in 8% of patients in a group of unclassified LGMDs. Pompe disease can have infantile-onset, adolescent-onset, and adult-onset forms. Respiratory insufficiency and thigh adductor weakness is commonly seen in conjunction with proximal weakness. EMG reveals complex repetitive discharges and myotonic discharges, specifically in thoracic paraspinal muscles. Muscle biopsy shows characteristic subsarcolemmal periodic acid-Schiff–positive inclusions. The gene defect lies in the deficiency of the acid α-glucosidase enzyme (GAA). Identification of this disorder is crucial since IV enzyme replacement therapy is life-saving for infants with the disorder and improves ambulation and respiratory status in adults with the disease.

Limb-girdle muscular dystrophy type 2W (LIMS2 proteinopathy). LGMD2W has onset in childhood with severe weakness noted proximally and with fairly slow progression. Cardiac involvement may happen in the third decade. Macroglossia, calf hypertrophy, and triangular tongue are unique features of this condition. CK is elevated up to 25 times the normal level. Muscle biopsy shows variability in fiber size, internal nuclei, and increased endomysial thickness. Defects in the *LIMS2* gene underlie LGMD2W.

General Treatment Approach for the Dominant and Recessive Forms of Limb-Girdle Muscular Dystrophies

All of the LGMD syndromes cause progressive weakness, although the rates of progression vary considerably. Certain LGMD syndromes have cardiac involvement, and affected patients are prone to cardiac conduction system defects, which may lead to sudden death. Rarely, respiratory insufficiency may occur, but usually in late stages of the disease and in patients severely affected. In general, later-onset disease predicts a better prognosis. Except for LGMD2V (acid maltase deficiency), where enzyme replacement therapy is an available treatment option, no specific disease-altering treatments currently exist for any of the LGMD1 or LGMD2 disorders, although corticosteroids have been reported helpful in maintaining muscle function in LGMD2I. However, novel therapies and treatment approaches are being explored in disorders where inflammatory pathways may play a role (eg, dysferlinopathies). Exon-skipping strategies are also being explored in several disorders.

For most patients, physical therapy and occupational therapy should be encouraged to prevent the formation of contractures and to maximize limb use. Some patients with LGMD report cramps in the muscles, and symptomatic treatment may be provided with either baclofen, tizanidine, or gabapentin. Genetic counseling may be helpful for the affected families and the patients.

In the subset of patients with heart involvement (ie, LGMD types 1A, 1B, 1C, 2C, 2D, 2E), serial ECG and echocardiograms are mandatory for monitoring cardiac status. In these patients, cardiac MRI is increasingly being used to identify early myocardial fibrotic changes. In these patients, cardiologic follow-up is crucial for management of cardiomyopathy and

placement of intracardiac pacemaker or defibrillators when indicated. Respiratory involvement is common in most LGMD types, especially in those with severe peripheral weakness (including Pompe disease), and pulmonary function tests are useful in identification of respiratory weakness. Noninvasive or invasive methods of ventilation are helpful in this clinical setting, although which is preferable is somewhat controversial.

X-Linked Limb-Girdle Muscular Dystrophy

The X-linked LGMDs are summarized in **Table 10-3**. Only the dystrophinopathies will be discussed in this article.

Dystrophinopathies. Dystrophinopathies, as the name implies, result from gene alterations in the X-linked dystrophin gene (and resultant abnormal dystrophin protein), leading to a phenotypic spectrum that includes a milder BMD to severe DMD. However, dystrophinopathies can also manifest as isolated quadriceps myopathy, asymptomatic or symptomatic hyperCKemia, "aches, cramps, and pains" syndrome, rhabdomyolysis, manifesting female carriers, X-linked dilated cardiomyopathy, and disorders of cognition such as developmental delay, attention deficit hyperactivity disorder, and impaired intelligence.

Dystrophin gene structure, clinical and molecular genetic diagnosis. Mutations in the dystrophin gene, located on the X chromosome, cause DMD/BMD. The dystrophin gene is one of the largest

KEY POINTS

- Duchenne muscular dystrophy is caused by alterations in the dystrophin gene, and the incidence has been reported to be 1 per 3500 male live births.
- Boys with Duchenne muscular dystrophy usually present between ages 2 and 5 years.

TABLE 10-3 Selected List of X-linked Limb-Girdle Muscular Dystrophies[a]

	Clinical Phenotype			Gene Information		
Condition	Typical Onset	Progression	Creatine Kinase Level	Allelism	Gene	Protein
Duchenne muscular dystrophy	Early childhood	Slow to moderate	100–200X	Becker muscular dystrophy	*DMD*	Dystrophin
Becker muscular dystrophy	Late childhood	Slow	10–15X	Duchenne muscular dystrophy	*DMD*	Dystrophin
Barth syndrome	Infancy	Moderate	Normal	X-linked dilated cardiomyopathy	*TAZ*	Tafazzin
Emery-Dreifuss muscular dystrophy type 1	Variable; teenage years	Slow	2–10X	X-linked sinus node dysfunction	*EMD*	Emerin
Emery-Dreifuss muscular dystrophy type 6	Adulthood	Slow	2–10X	Hyaline body myopathy; X-linked myopathy with postural muscles atrophy	*FHL1*	Four-and-one-half-LIM domains 1
Danon disease	Early childhood	Moderate	4–35X	X-linked vacuolar cardiomyopathy and myopathy	*LAMP2*	Lysosomal-associated membrane protein 2

[a] Modified with permission from Iyadurai SJ, Kassar D, Springer.[3] © 2013 Springer Science+Business Media.

KEY POINT

- Boys with delayed motor milestones, enlarged calves, proximal weakness (including Gowers sign), and elevated creatine kinase levels (100 to 200 times the normal level) should be suspected of having Duchenne muscular dystrophy.

genes in the human genome (by genomic size, including large introns), spanning about 2.3 megabases. The extent of intronic sequences is such that out of the whole transcript (pre–messenger RNA), the 79 exons only make 0.6% of the gene. The dystrophin gene encodes a major 3685 amino acid, 427 kD skeletal muscle protein. Eight other promoters direct transcription of seven other transcripts, with expression in skeletal, cardiac, and smooth muscle cells and in multiple other tissue cell types including the brain. The dystrophin protein connects the contractile apparatus to the extracellular matrix via the muscle membrane.

The dystrophinopathies are inherited in an X-linked recessive fashion; ie, a male child receives (inherits) the mutation from the mother. However, in a sizeable minority of cases (20% to 30%), the mutation identified in the affected son is not identified in the mother by gene testing. In such cases, the mutation is thought to arise de novo or reflect germline mosaicism. In a mother who tests negative for the mutation because of germline mosaicism, the possibility of delivering another affected boy in a subsequent pregnancy is not excluded, and caution should be used in genetic counseling in such cases. Prenatal diagnosis or preimplantation genetic testing is available for mothers who test negative for their son's mutation or in whom germline mosaicism is suspected. Female carriers may exhibit a DMD/BMD-like phenotype (including dilated cardiomyopathy) due to random lyonization of the X chromosome (heterochromatinization or inactivation of the X chromosome). If lyonization occurs to the chromosome containing the wild-type dystrophin, and the chromosome containing the mutant dystrophin is expressed, a DMD/BMD-like phenotype may be observed in the female patient.

A positive family history, in conjunction with an elevated CK level, cardiomyopathy, or limb-girdle–type weakness should raise suspicion of the condition. Boys with delayed motor milestones, enlarged calves, proximal weakness (including Gowers sign), and elevated CK levels (100 to 200 times the normal level) should be suspected having of DMD. Diagnosis relies on DNA analysis of the dystrophin gene. Deleterious DNA alterations include deletions (50% to 60%; in frame or out of frame), sequence alterations (20% to 35%), duplications (5% to 10%), or leading missense and nonsense mutations, splice site–altering mutations, and cryptic intronic mutations. Deletions and duplications may be detected by multiplex polymerase chain reaction (PCR), multiplex ligation-dependent probe amplification, and chromosome microarray techniques; sequence alterations may be detected by Sanger or next-generation sequencing.

Epidemiology. The incidence of DMD in live male births is estimated between 1 in 3500 and 1 in 5000. BMD is much less common with a prevalence of 1 in 17,500 to 1 in 50,000. As expected, the prevalence of BMD is higher in comparison to that of DMD mainly because of the shortened survival in the latter group.

Clinical features. Boys with DMD present at a young age, usually between 2 and 5 years of age with delayed motor milestones, falls, and difficulties running and jumping. Prominent head lag, calf enlargement (often termed pseudohypertrophy, a partial misnomer as the enlargement results from a combination of fibrotic replacement and true fiber hypertrophy), and Gowers sign are almost always seen. Progression is steady, and untreated patients typically are in wheelchairs by age 12. Clinically, respiratory and cardiac issues ensue. By classic convention, boys still walking after their 16th birthday are considered to have BMD, and boys who stop walking by age 12 are considered to have DMD. This distinction is in some ways artificial since corticosteroid therapy may prolong ambulation by

1 to 3 years, thus blurring the clinical distinction between BMD and DMD.

Patients with dystrophinopathy have highly elevated CKs, usually 100 to 200 times the normal level. EMG usually shows an irritable, proximal-predominant myopathy. Currently, muscle biopsy is very seldom indicated but will show rounded fibers, significant size variability, increased endomysial thickness, hypercontracted fibers, inflammatory cells, and occasional ring fibers. Immunohistochemical stains with antibodies generated against the various epitopes (DYS3, DYS1, and DYS2) may show absent staining in certain fibers.

Dystrophinopathies are multisystem disorders with multidisciplinary teams necessary for optimal management. Patients with dystrophinopathies eventually have involvement of the cardiac, pulmonary, musculoskeletal, and cognitive systems. Cardiac involvement progresses with progression of the muscle disease. Sinus tachycardia, arrhythmia, dilated or hypertrophic cardiomyopathy, and congestive heart failure are common. Regular surveillance with ECG, long-term heart monitoring, and echocardiogram in conjunction with a cardiologist is recommended. Angiotensin-converting enzyme inhibitors and beta-blockers have been proven to be beneficial. Lung functions decline with disease progression as well. Pulmonary functions can be followed with time, and necessary noninvasive/invasive strategies may be employed (in conjunction with a pulmonologist) to improve the quality of life. In consultation with orthopedic surgeons, scoliosis may be surgically fixed if indicated and necessary. Patients with DMD demonstrate calf hypertrophy (**Figure 10-3**) in earlier stages and contractures in later stages (**Figure 10-4**) and may experience severe nighttime cramps. Cramps may be readily treated with nighttime stretches and gabapentin. Several types of cognitive issues, including attention deficit disorder, autism spectrum disorders, obsessive-compulsive disorder,

KEY POINTS

- Steroids help patients with Duchenne muscular dystrophy prolong ambulation and increase longevity.
- Cardiomyopathy is common in patients with Duchenne muscular dystrophy.

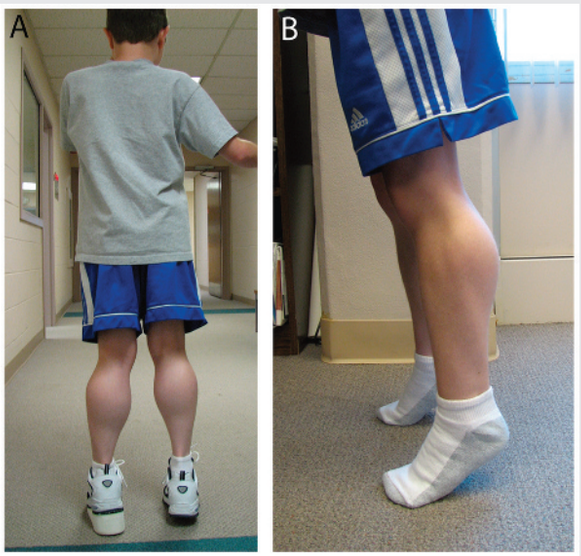

FIGURE 10-3 Images of a 6-year-old boy with Duchenne muscular dystrophy showing calf hypertrophy evaluated from posterior view (*A*) and from lateral view, further accentuated by standing on toes (*B*).

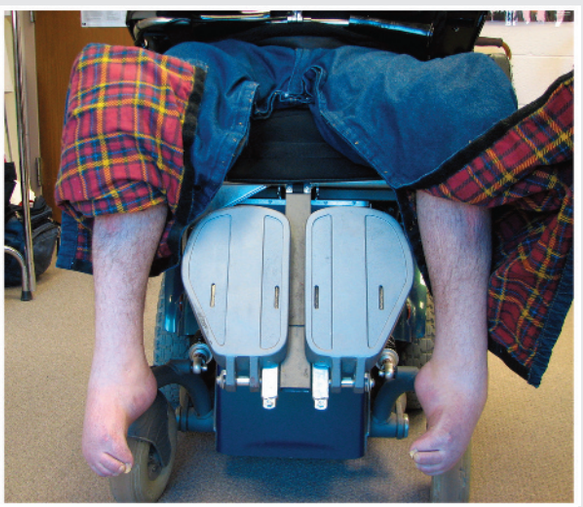

FIGURE 10-4 Contractures in a patient with Duchenne muscular dystrophy. Ankle and foot contractures are common in the later course of Duchenne muscular dystrophy.

KEY POINT

- Female carriers of dystrophin mutations may present with a Duchenne muscular dystrophy–like phenotype and may have cardiomyopathy as well.

and depression are commonly seen. Referral to a psychiatrist and treatment of these disorders are helpful in improving the quality of life of the patient and the family members (**Case 10-3**).

Becker muscular dystrophy. In general, patients with BMD display a milder phenotype in comparison to patients with DMD, and the weakness onset is also later. Late onset of weakness is associated with a milder phenotype. Despite the milder weakness noted in the skeletal muscles, the cardiac muscles are affected just the same as in patients with DMD. Therefore, treatments for cardiac management should not be delayed. Breathing functions are affected as in patients with DMD, but at a later time course. Some patients with BMD may require noninvasive ventilation. Although the benefit of corticosteroids in patients with BMD is unclear, some clinicians employ prednisone at 0.75 mg/kg/d in patients with BMD as well.

Female carriers of dystrophin mutations. Female carriers of the X-linked dystrophin mutations may present with a DMD-like phenotype. However, it is

Case 10-3

A 5-year-old boy was brought by his mother to his pediatrician because of ''running difficulties.'' The mother noted that the boy was the product of a normal pregnancy, but was not able to walk until 16 months of age. She also had noticed prominent calves in the boy. She volunteered the history of her brother who had had similar calves and had died at the age of 12 with heart complications. The patient's vital signs were significant for mild hypertension. Examination revealed normal cranial nerves, proximal weakness of the upper and lower extremities, calf hypertrophy, diminished reflexes (except at the ankles), normal sensation, and normal plantar responses bilaterally. Laboratory evaluation revealed an elevated creatine kinase level at 200 times the upper limit of normal. Based on the clinical presentation and family history, Duchenne muscular dystrophy (DMD) was suspected, and the patient was referred to a local neuromuscular expert for further evaluation. Gowers sign (**Supplemental Digital Content 10-1**, *links.lww.com/CONT/A210*) was noted on that examination. DNA analysis of the dystrophin gene revealed a deletion of exons 21 to 24, leading to premature termination of the dystrophin protein, and a diagnosis of DMD was confirmed. The patient was started on prednisone 1 mg/kg/d, and a cardiology referral was made.

Comment. This case demonstrates a classic presentation of DMD in a young boy with early-onset motor delay and calf hypertrophy. Whenever high creatine kinase, motor delay, and calf hypertrophy are encountered, dystrophinopathy should be considered.

more common in affected women at ages 30 or older. In subtle cases, the manifestation may be related to asymptomatic or symptomatic hyperCKemia or nocturnal cramps. Although these symptoms may be benign, dilated cardiomyopathy and left ventricular dilatation are noted in 20% of the carriers.[24] These patients should be referred to cardiologists as well for optimal management and treatment. For this reason, from a genetic standpoint, female first-degree relatives of male patients with DMD/BMD and sisters of mothers of male patients with DMD/BMD should be offered testing for the dystrophin mutation identified in the affected male relative.

Treatment of dystrophinopathies. As with the other LGMDs, no definitive treatment for dystrophinopathies currently exists. In addition to the general outline for treatments described previously for all of the LGMDs, patients with DMD (and probably BMD) respond to treatment with various regimens of corticosteroids (prednisone, deflazacort, or prednisolone) with unequivocal benefit in prolonging ambulation, delaying the decline of muscle function, reducing falls, and delaying pulmonary and (probably) cardiac complications.[25] Corticosteroids (mainly prednisone in the United States) are usually started in patients of ages 5 and up, but some clinicians choose to start corticosteroid treatment at diagnosis, even at younger ages. Prednisone treatment of 0.75 mg/kg/d has been used quite widely. Other regimens involve combining this weekly dose to be distributed on Saturdays and Sundays. Prophylaxis with calcium, vitamin D, proton pump inhibitors, and antidepressants may be necessary, concomitant with steroid treatment. A large international FOR-DMD (Finding the Optimal Steroid Regimen for Duchenne Muscular Dystrophy) study is currently comparing deflazacort and prednisone regimens for managing DMD.

In addition, novel treatment methodologies have relied on correcting the DMD mutation either by supplying additional wild-type dystrophin or minidystrophin under high-expression promoters (gene therapy strategies), or "reading" through premature stop codons introduced by missense mutations (premature termination elimination), or skipping the exons containing out-of-frame mutations (exon skipping technology). Clinical trials are underway to assess the efficacy of these specific therapeutic agents in patients with DMD/BMD, with several companies seeking approval by the US Food and Drug Administration (FDA) for specific exon skipping agents. At the time of this writing, the FDA has approved the first exon-skipping medication, eteplirsen, for use in a select subset of patients with DMD. This medication enables pre–messenger RNA to skip exon 51 in the dystrophin reading frame, producing truncated dystrophin. Approximately 20% of boys with DMD have mutations in exon 51 of the dystrophin gene and may benefit from this treatment. However, although the medication has been approved by the FDA, there remains some controversy within the academic community over whether the studies to date demonstrate enough clinical benefit to justify the approval. The study that was done contained only 12 patients and used historical controls to assess changes in a 6-minute walk test, which was the functional end point. Follow-up biopsies did show a significant increase in dystrophin, but this was not clearly shown to correlate with functional improvement.[26,27]

KEY POINT

- Gene therapy, exon-skipping strategies, and suppression of premature termination approaches are being developed for treatment of Duchenne muscular dystrophy.

CONCLUSION

The LGMDs are a heterogeneous group of disorders that, as the name suggests, manifest as weakness in the shoulder girdle and the pelvic girdle muscles. Dominant, recessive, and X-linked forms of LGMDs have been described. The current classification system of LGMDs uses the notation type 1 for dominant forms and type 2 for recessive

forms. Physical characterization and diagnostic imaging may be helpful in identifying the specific form. Specific distinguishing characteristics (**Table 10-4**), involvement of muscle pattern on MRI (**Table 10-5**) and muscle biopsy features (**Table 10-6**) may be helpful in delineating between the subtypes. However, definite diagnosis is achieved by genetic testing. Several commercial next generation–based multigene LGMD panel gene-testing options are available to help with diagnosis. Multigene panel testing combined with traditional phenotype-based approaches have been instrumental in identifying newer LGMDs. With the advancement of sequencing technologies, the list of LGMDs has grown and is expected to grow. Understanding of gene functions

TABLE 10-4 Distinguishing Features of Limb-Girdle Muscular Dystrophies

Type	Feature
LGMD1A (myotilinopathy)	Upper extremities distal weakness and contractures, dysarthria, palatal hypophonia, footdrop, and areflexia
LGMD1B (laminopathy)	Contractures and cardiac conduction defects
LGMD1C (caveolinopathy)	Rippling muscles and muscle hypertrophy
LGMD1E (desminopathy)	Facial weakness and cardiac conduction defect
LGMD1F (transportinopathy)	Early respiratory muscle involvement
LGMD1G (HNRPDL proteinopathy)	Finger and toe flexion limitation
LGMD2A (calpainopathy)	Contractures and atrophy of shoulder and pelvic girdle muscles
LGMD2B (dysferlinopathy)	Medial gastrocnemius atrophy
LGMD2C, LGMD2D, LGMD2F (sarcoglycanopathies)	Tongue hypertrophy
LGMD2H (sarcotubular myopathy, TRIM32 proteinopathy)	Scapular winging and calf hypertrophy
LGMD2I (fukutinopathy)	Tongue and calf hypertrophy, cardiac and respiratory muscle involvement
LGMD2L (anoctaminopathy)	Asymmetric atrophy of muscles, mandibular dysplasia
LGMD2R (desminopathy)	Facial weakness, respiratory muscle involvement, high-arched palate
LGMD2S (TRAPPC11 proteinopathy)	Scapular winging, hyperkinetic movements
LGMD2V (acid maltase deficiency)	Proximal weakness and respiratory insufficiency
LGMD2W (LIMS2 proteinopathy)	Calf and tongue hypertrophy and triangular tongue
Dystrophinopathy	Calf hypertrophy, distal contractures, preserved ankle reflex despite the weakness

LGMD = limb-girdle muscular dystrophy.

TABLE 10-5 **Pattern of Affected Thigh Muscles in Magnetic Resonance Imaging Evaluation of Patients With Limb-Girdle Muscular Dystrophy**

Type	Affected Thigh Muscle(s)
LGMD1A (myotilinopathy)	Adductor magnus, biceps femoris, semimembranosus, vastus medialis, vastus intermedius
LGMD1B (laminopathy)	Adductor magnus, biceps femoris, vastus medialis and vastus lateralis
LGMD1C (caveolinopathy)	Normal at the level of the thigh
LGMD1D (HSP40 proteinopathy)	Adductor magnus, biceps femoris, semimembranosus, adductor longus
LGMD1E (desminopathy)	Semitendinosus, sartorius, gracilis
LGMD1F (transportinopathy)	Vastus lateralis
LGMD2A (calpainopathy)	Adductor magnus, semimembranosus
LGMD2B (dysferlinopathy)	Adductor magnus, vastus lateralis, semimembranosus
LGMD2I (fukutinopathy)	Adductor magnus, biceps femoris, semimembranosus
LGMD2L (anoctaminopathy)	Adductor magnus, biceps femoris, semimembranosus, semitendinosus, rectus femoris, vastus medialis and vastus lateralis
LGMD2V (acid maltase deficiency)	Adductor magnus, vastus medialis, vastus intermedius, biceps femoris
Dystrophinopathy (Duchenne muscular dystrophy)	Adductor magnus, vastus medialis and vastus lateralis, rectus femoris
Dystrophinopathy (Becker muscular dystrophy)	All anterior and posterior compartment muscles, sparing sartorius, gracilis

LGMD = limb-girdle muscular dystrophy.

TABLE 10-6 **Muscle Biopsy Features of Limb-Girdle Muscular Dystrophies**

Type	Feature(s)
LGMD1A, LGMD1E, LGMD1F, LGMD1G	Rimmed or autophagic vacuoles
LGMD1A, LGMD2R	Hyaline inclusions, spheroid bodies
LGMD1B	Mislocalization of lamin
LGMD1C, LGMD2A, LGMD2B, sarcoglycanopathies, LGMD2L, dystrophinopathies	Inflammation
LGMD1E	Eosinophilic inclusions, cytoplasmic bodies
LGMD1F, LGMD1H	Central nuclei

Continued on page 1976

TABLE 10-6 **Muscle Biopsy Features of Limb-Girdle Muscular Dystrophies** *Continued from page 1975*

Type	Feature(s)
LGMD1G	Atrophic angular fibers
LGMD2A	Lobulated fibers
LGMD2A	Eosinophilic infiltrates
LGMD2A	Amyloid deposition (Congo red positivity)
LGMD2H	Small rounded vacuoles in type 2 fibers
LGMD2I	Type 1 predominance
LGMD2Q, LGMD2T, LGMD2W	Increased internal nuclei
LGMD2R, LGMD2V	Periodic acid-Schiff–positive or –negative, amorphous subsarcolemmal inclusions
Dystrophinopathies	Hypercontracted fibers
Dystrophinopathies	Ring fibers

LGMD = limb-girdle muscular dystrophy.

and mutation pathology will give insight into the disease process and possible therapy in the future. Given the lack of definitive treatment, as of now, only strategies for management and supportive treatment have been suggested as guidelines.[25,28] However, several clinical trials utilizing various therapeutic approaches are currently underway. The day of definitive treatments for these inherited disorders is not far away.

VIDEO LEGEND
Supplemental Digital Content 10-1

Gowers sign. A 5-year-old boy with Duchenne muscular dystrophy demonstrating the Gowers sign. Notice how he "climbs on himself" to stand up.

links.lww.com/CONT/A210

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