

The Limb-Girdle Muscular Dystrophies



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KEYWORDS

- Limb-girdle muscular dystrophy • Calpain 3 • Dysferlin • Sarcoglycan
- Fukutin-related protein • Anoctamin 5 • Lamin A/C

KEY POINTS

- Limb-girdle muscular dystrophies (LGMDs) are genetic muscle diseases with onset after birth of progressive weakness and muscle atrophy predominantly affecting the hips, shoulders, and proximal extremity muscles.
- As a group, the LGMDs are the fourth most common genetic muscle condition, with a minimum prevalence of approximately 1 in 20,000.
- LGMDs stem from protein defects throughout the muscle fiber, including the nucleus, sarcoplasm, sarcomere, sarcolemma, and extracellular matrix.
- The most prevalent LGMD subtypes derive from defects in the following proteins in muscle: calpain, dysferlin, the sarcoglycans, fukutin-related protein, anoctamin 5, and lamins A and C.

INTRODUCTION

The most common presentation of muscle disease involves weakness in the hip girdle, thighs, shoulder girdle, and proximal arms. Many acquired and genetic muscle disorders present with this limb-girdle pattern (see the article by Barohn elsewhere in this issue). Of the 3 most common muscular dystrophies, the dystrophinopathies (see the article by Flanigan elsewhere in this issue) also have this proximal predominant limb-girdle pattern, whereas facioscapulohumeral muscular dystrophy (FSHD) (see the article by Statland and Tawil elsewhere in this issue) and myotonic dystrophy (see the article by Thornton elsewhere in this issue) have relatively unique phenotypes.

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Definition

The LGMDs are genetic muscle diseases with onset after birth of progressive weakness and muscle atrophy predominantly affecting the hips, shoulders, and proximal extremity muscles.

LGMDs are named based on a consensus nomenclature,^{1,2} which divides LGMD by inheritance pattern into autosomal dominant (LGMD1) and autosomal recessive (LGMD2) subtypes. Overlaid on this division is an alphabetical lettering system that delineates the order of discovery of the chromosomal locus for each LGMD (LGMD1A was mapped prior to LGMD1B and so forth). Twenty-seven genetic muscle diseases are currently classified as LGMDs (**Table 1**) and the differential diagnosis for the LGMDs is broad. LGMDs derive from protein defects from all locations throughout the muscle fiber, including the nucleus, sarcoplasm, sarcomere, sarcolemma, and extracellular matrix (**Fig. 1**).

LGMD differential diagnosis

- Dystrophinopathies
- Bethlem myopathy
- X-linked Emery-Dreifuss muscular dystrophy (EDMD)
- Myofibrillar myopathies
- Metabolic myopathies
- Inclusion body myopathies
- Pompe disease
- FSHD (facial sparing)

This article discusses the diagnostic features of the 6 most prevalent LGMD subtypes: LGMD2A (calpain), LGMD2B (dysferlin), LGMD2C–F (α -, β -, γ -, and δ -sarcoglycans), LGMD2I (fukutin-related protein), LGMD2L (anoctamin 5), and LGMD1B (lamin A/C) (**Fig. 2**).³

LGMD2A—CALPAIN

LGMD2A, due to mutations in the calpain 3 gene, *CAPN3*, is the most common LGMD subtype in nearly all population studies to date, ranging from 15% to 40% of cases.⁴ Mutations in *CAPN3* have also been reported in hyperCKemia and in children and adults with eosinophilic myositis.^{5,6} Calpain is a muscle-specific calcium-activated neutral protease that binds to titin and is likely important for muscle regeneration during sarcomere remodeling.^{7–9}

Clinical

Onset of weakness varies widely in reported cases (ie, 2–53 years) but most often begins in later childhood or young adulthood, with 75% of cases having onset prior to 20 years of age.¹⁰ Hyperlordosis and a waddling gait are common. Proximal lower extremity muscles are weaker than shoulder girdle muscles from the outset. Hip extensor, knee flexor, and hip adductor muscles often display disproportionately severe weakness.¹¹ Facial muscles may be weak in early-onset and severe disease but oculomotor and velopharyngeal muscles are uniformly spared. Respiratory and cardiac dysfunction is essentially nonexistent, although asymptomatic reductions in forced vital capacity may occur 20 years into the course.¹² Abdominal laxity and scapular winging are common. Hip, knee, and elbow contractures develop after loss of ambulation. The disease

LGMD	Gene	Protein	Usual Age at Onset (y)	Creatine Kinase Level
1A	<i>MYOT</i>	Myotilin	20–40	NL–15×
1B	<i>LMNA</i>	Lamin A/C	5–25	NL–20×
1C	<i>CAV3</i>	Caveolin 3	5–25	2×–30×
1D	<i>DNAJB6</i>	DNAJB6 protein	30–50	NL–5×
1E	<i>DES</i>	Desmin	15–50	NL–4×
1F	<i>TNPO3</i>	Transportin 3	10–40	NL–15×
1G	Unknown	Unknown	30–47	NL
1H	Unknown	Unknown	16–50	NL–10×
2A	<i>CAPN3</i>	Calpain 3	5–25	NL–60×
2B	<i>DYSF</i>	Dysferlin	10–30	2×–160×
2C–F	<i>SGCG, A, B, D</i>	γ -, α -, β -, δ -sarcoglycan	3–20	5×–120×
2G	<i>TCAP</i>	Telethonin	2–15	2×–25×
2H	<i>TRIM32</i>	TRIM32	5–30	NL–20×
2I	<i>FKRP</i>	Fukutin-related protein	1–40	5×–50×
2J	<i>TTN</i>	Titin	5–20	NL–5×
2K	<i>POMT1</i>	POMT1	<5	5×–40×
2L	<i>ANO5</i>	Anoctamin 5	20–50	NL–160×
2M	<i>FKTN</i>	Fukutin	<5	5×–30×
2N	<i>POMT2</i>	POMT2	<2	15×–30×
2O	<i>POMGnT1</i>	POMGnT1	12	10×–50×
2P	<i>DAG1</i>	α -Dystroglycan	3	10×–20×
2Q	<i>PLEC1</i>	Plectin	<5	20×–30×
2R	<i>DES</i>	Desmin	1–25	NL–2×
2S	<i>TRAPPC11</i>	TRAPPC11	5–10	2×–30×

Abbreviation: NL, normal.

progresses steadily with most patients no longer ambulatory 2 decades into their disease. Later onset of disease follows a milder course. Cases of LGMD2A have been confused with FSHD due to the prominent scapular winging, abdominal laxity, and occasional facial involvement.¹³

LGMD2A: Key diagnostic features
<ul style="list-style-type: none"> • Most common LGMD • 75% onset 5–20 years of age • Hip extensor, hip adductor, and knee flexor weakness • Scapular winging • Calf hypertrophy • Abdominal laxity • Achilles contractures • Rare facial involvement • Creatine kinase (CK) level = 500–20,000 U/L • Lobulated fibers on biopsy • Diagnosis via genetic testing

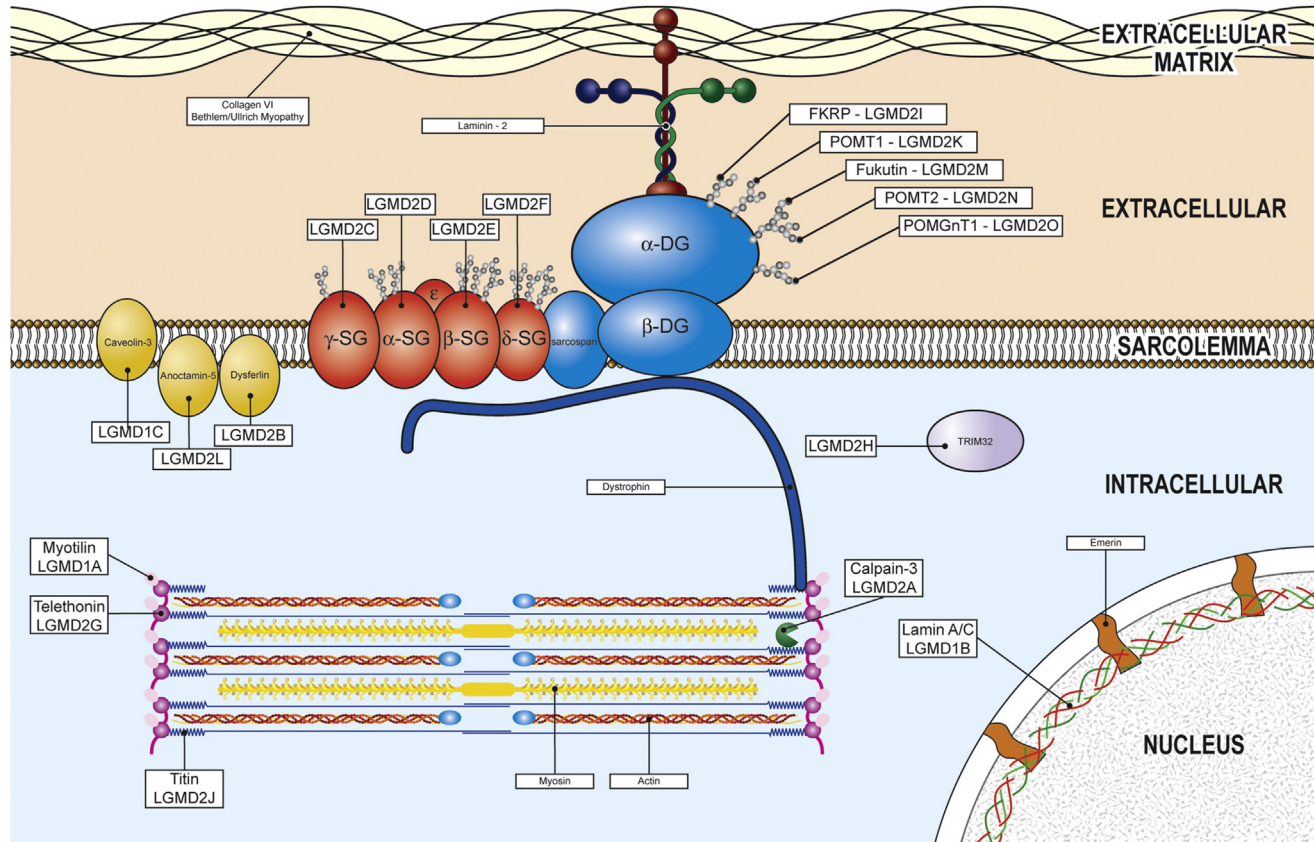


Fig. 1. Schematic diagram illustrating a muscle fiber and the associated LGMD proteins. DG, dystroglycan; SG, sarcoglycan.

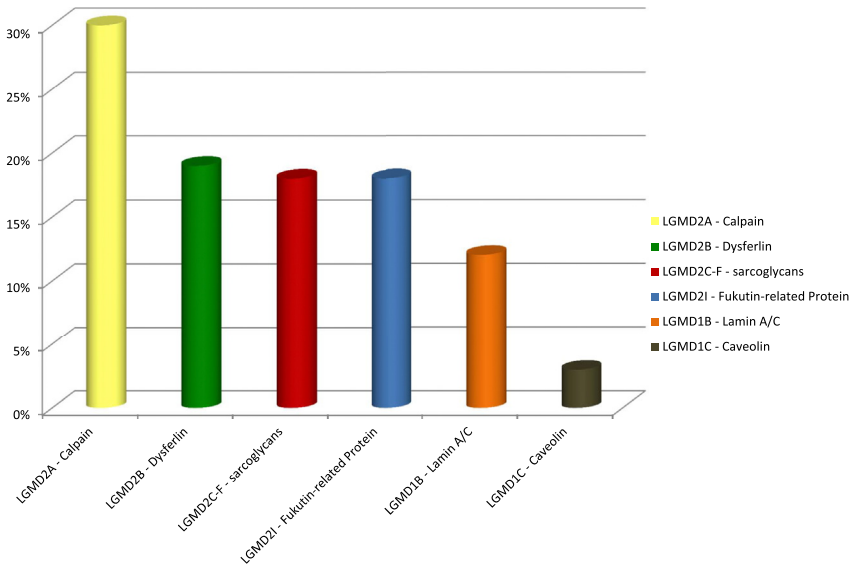


Fig. 2. Relative prevalence of the LGMD subtypes in the United States. This graph portrays the relative prevalence of LGMD subtypes. The data were derived from a US cohort with 488 genetically confirmed cases.³ (Only the genes for these LGMDs were evaluated in this study, which was conducted prior to the discovery of *ANO5*, the gene for LGMD2L—anoctamin 5).

Laboratory

Evaluation reveals serum CK levels elevated 20-fold in typical patients with a range of 2 to 110 times the upper limit of normal.¹⁴ Needle EMG yields abnormalities compatible with a myopathy. Although useful in documenting involvement of muscle in LGMD, muscle imaging (CT and MRI) is not reliable or accurate in discriminating one LGMD subtype from another.¹⁵ Although rarely needed for diagnosis, muscle biopsy reveals variation in fiber size, internal nuclei, increased endomysial connective tissue, and necrotic and regenerating fibers, without inflammatory cells. Lobulated fibers can be seen in more than half of muscle biopsies (Fig. 3).¹⁶

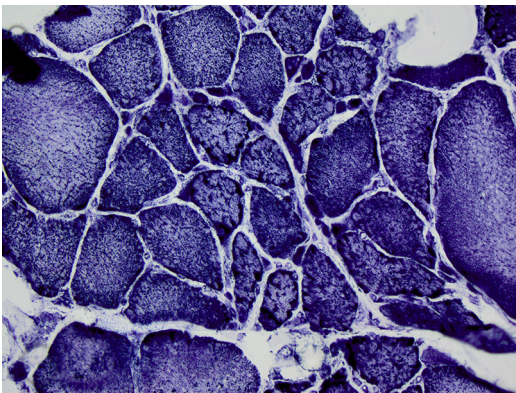


Fig. 3. Muscle biopsy with lobulated fibers from a patient with LGMD2A—calpainopathy. (NADH, original magnification 400×).

Diagnosis

Genetic testing is the diagnostic procedure of choice. Hundreds of mutations in *CAPN3* have been delineated with no apparent hot spots.^{17,18} Complicating matters is that in approximately one-fifth of cases with a typical phenotype and absent calpain-3 on Western blot, only a single mutation of *CAPN3* is found. For this reason, many laboratories also test for deletions and duplications in this situation.

Treatment

No disease-specific treatment is available for calpainopathies. One 11-year-old girl with LGMD2A, however, presented with concurrent eosinophilic myositis and improved on immunosuppressive medications.¹⁹

Case 1

A 22-year-old young man presented with weakness. His motor development was equivalent to peers as a youth. At 13 years of age, he noted an awkward running style. Although his lower extremity weakness progressed, he continued to play basketball through high school. He was not as quick in his junior and senior years but was still used at the end of games for his incredible 3-point accuracy. At approximately his 19th birthday, proximal upper extremity weakness developed. Currently, he has trouble getting his arms over his head and must pull on a banister ascending stairs. He has always had large calves. There are no oculobulbar, respiratory, or cardiac symptoms. He has never had episodes of dark urine.

On examination, he had no facial weakness. There was marked bilateral scapular winging, very large calves, mild bilateral ankle contractures, and strength as follows—Medical Research Council (MRC) scale: upper extremities normal except shoulder abductors 5 3₊ and elbow flexors 5 4; and in the lower extremities strength was hip flexors 5 4₁, hip extensors 5 2, hip abductors 5 5, hip adductors 5 0, knee extensors 5 5, and knee flexors 5 4₋.

His CK level was 16,483 U/L. His nerve conduction study/electromyography (EMG) revealed a mostly nonirritable myopathy. His muscle biopsy when 15 years old revealed dystrophic features and 30% lobulated fibers. Genetic testing revealed 2 disease-associated mutations in *CAPN3*: n.245C>T; p.Pro82Leu and n.1465C>T; p.Arg489Trp.

This real-life case reveals all the key diagnostic features in LGMD2A.

LGMD2B—DYSFERLIN

LGMD2B is one phenotype associated with mutations in *DYSF*, the gene for dysferlin.²⁰ Dysferlin plays an important role in membrane trafficking, fusion, and, most notably, membrane repair.²¹ Adeno-associated virus-mediated transfer of a mini-dysferlin or up-regulation of fetal myoferlin, however, correct this resealing function in a membrane laser wounding assay but do not rescue the histology in vivo. Thus, the pathogenesis of dysferlinopathies does not seem to be due exclusively to impaired membrane repair.²² Dysferlin deficiency also reduces release of chemotactic cytokines resulting in an attenuated regeneration response.²³ Dysferlin additionally plays roles in myoblast differentiation and T-tubule system development.^{24,25}

Clinical

LGMD2B is likely the second most prevalent subtype and responsible for 5% to 35% of cases.²⁶ Dysferlinopathies can present with numerous, often overlapping phenotypes: LGMD2B with proximal weakness, Miyoshi myopathy with distal weakness of calf muscles, early involvement of the anterior compartment muscles of the lower legs, a proximodistal pattern, biceps atrophy with deltoid hypertrophy, combination calf and deltoid hypertrophy, rigid spine syndrome, a pseudometabolic presentation,

and asymptomatic hyperCKemia.^{27–31} Heterozygous gene carriers may develop mild weakness later in life. In LGMD2B, onset generally occurs between 15 and 30 years of age, although congenital cases and symptomatic onset in the 70s have been reported.^{32,33} Patients develop normally in cognitive and motor spheres, and some patients are actually gifted athletically when young.^{30,31} Weakness begins in the legs in nearly all cases, the initial site of involvement determining the nomenclature. LGMD2B patients often show mild distal leg weakness and may have difficulty standing on their toes early in disease. Weakness progresses slowly over 10 to 20 years to wheelchair use in many. Occasional patients, however, report precipitous onset and progression with rapid loss of ambulation over 1 to 2 years, especially linked to pregnancy.³¹ Upper limb weakness develops after onset of gait difficulties, but scapular winging is not a feature of this disorder. Cardiac or respiratory compromise in LGMD2B is uncommon, occurs late in life, and usually remains clinically silent.^{34,35}

LGMD2B: Key diagnostic features

- Onset 15–35 years of age
- Legs affected first
- Some distal leg weakness in many
- Athletic prowess when young
- No facial weakness or dysphagia
- No clinical respiratory involvement
- No clinical cardiac involvement
- CK = 1000–40,000 U/L
- Inflammation on biopsy in approximately 40%
- Diagnosis via genetic testing

Laboratory

Serum CK levels may be substantially elevated, as great as 200-times normal. EMG frequently shows small, brief motor units with early recruitment, although long-duration polyphasic motor units with decreased recruitment often pop up in weak calf muscles. Muscle biopsies may reveal dystrophic features, vacuoles (a minor feature),³⁶ amyloid deposition (only with certain mutations and not in most cases),³⁷ and, importantly, endomysial and perivascular inflammatory infiltrates in more than 50% of biopsies in some series (mostly CD4⁺ cells and macrophages).^{38,39} This inflammation has been thought a secondary reaction to degeneration but has led to misdiagnosis of dysferlinopathies as treatment refractory polymyositis.⁴⁰

Diagnosis

Immunostaining of muscle biopsies and protein-based monocyte assays are available for diagnosis. These modalities do not, however, detect all cases with *DYSF* mutations, and dysferlin deficiency can occur in other muscle disorders. Thus, genetic testing is the most appropriate and accurate methodology for diagnosis of LGMD2B.⁴¹

Treatment

Although there may often be inflammation on the muscle biopsy in dysferlinopathies, treatment with deflazacort (1) was associated with significant steroid side effects, (2)

did not improve strength, and (3) perhaps worsened disease progression.⁴² Genetic-based therapies are in phase 2 clinical trials.

Case 2

A 21-year-old young woman presented with weakness. Her motor development was normal as a child. In elementary school, she was actually faster and stronger than the other children. At 15 years of age, she noted that when she ran, she “just could not go.” In high school softball, she could hit the ball very far but was slow running the bases. Over the ensuing 6 years, her leg weakness slowly progressed. Since at least age 16 years, she recalls she could not stand on her tiptoes. Her arms remain strong, and there are no oculobulbar, respiratory, or cardiac symptoms. She has never had cramps or episodes of dark urine.

On examination, she had diminished calf bulk but no facial weakness and no scapular winging. Her neck and upper extremity strength was normal. In her lower extremities, she had the following (MRC scale): hip flexors = 4+, hip extensors = 4+, hip abductors = 4+, hip adductors = 4+, knee extensors = 4–, knee flexors = 4+, ankle dorsiflexors = 5, ankle eversion = 4+, ankle inversion = 4+, and ankle plantar flexors = 4–. She had normal sensation and a mild Trendelenburg gait.

Her CK levels were 12,962 U/L, 8663 U/L, and 5575 U/L when checked on 3 successive years. Electrodiagnostic testing was not performed. A muscle biopsy showed mildly dystrophic features with diminished (but not absent) dysferlin immunostaining. Genetic testing revealed homozygous, known pathogenic, missense mutations in *DYSF* (c.5429G>A; p.Arg1810Lys).

This real-life case reveals many key diagnostic features in LGMD2B.

LGMD2C— α -, β -, γ -, AND δ -SARCOGLYCANS

Four sarcoglycans (γ , α , β , and δ) form a heterotetrameric complex spanning the sarcolemma in association with sarcospan, dystrophin, and the dystroglycans (see Fig. 1). This dystrophin-glycoprotein complex (DGC) provides a mechanical bridge between the extracellular basement membrane, the cytoskeleton, and the intracellular contractile mechanism of muscle fibers.⁴³ Additionally, the DGC facilitates cell signaling and trafficking in concert with neuronal nitric oxide synthase, dystrobrevin, and caveolin-3.⁴⁴ Muscular dystrophies due to mutations in the different sarcoglycan subunits yield similar clinical and laboratory characteristics. γ -Sarcoglycan is the first sarcoglycan gene locus discovered and is thus labeled LGMD2C. LGMD2D, -2E, and -2F correspond to α -, β -, and δ -sarcoglycan deficiencies, respectively.

Clinical

LGMD, due to mutations in one of the four sarcoglycans, comprise 10–20% of LGMD cases.^{4,45} Onset is predominantly in childhood, most often between 5 and 10 years of age (range 1–30 years). Weakness starts in the pelvic girdle with decremental shoulder girdle strength a few years later. Proximal limb extensors (quadriceps and triceps brachii) are comparatively spared versus flexors (biceps brachii and hamstrings). Common examination features include calf hypertrophy, scapular winging, macroglossia, and lumbar hyperlordosis. Many patients are wheelchair dependent within 10 years.^{46–48} Most patients' disease course mirrors a severe, Duchenne-like progression. Milder cases with slower progression and some with only exercise intolerance, myoglobinuria, or minimal muscle weakness dot the literature.^{49–51} Additionally, a case of eosinophilic myositis was recently revealed to be due to mutations of γ -sarcoglycan.⁵² As in Duchenne dystrophy, cardiac and respiratory dysfunction frequently afflicts patients. Symptomatic respiratory dysfunction along with arrhythmogenic, dilated, or hypertrophic cardiomyopathies are detected in one-third of patients 10 years into disease.^{53,54}

LGMD2C–F: Key diagnostic features

- Usual onset 5–15 years of age
- Proximal leg weakness
- Scapular winging
- Calf hypertrophy
- Lumbar lordosis
- Cardiorespiratory dysfunction common 10–20 years into illness
- CK = 500–20,000 U/L
- Muscle biopsy usually has decreased immunostaining for all 4 sarcoglycans.
- Diagnosis via genetic testing

Laboratory

Serum CK values range from 5 to 120 times normal. Muscle biopsies show variability in fiber size, central nuclei, degenerating and regenerating fibers, and increased connective tissue, most often with normal immunostaining for dystrophin. Abnormal staining for all 4 skeletal muscle sarcoglycans occurs with mutations in any one particular sarcoglycan, and the staining pattern cannot be used to predict the genotype.⁵⁵ Cases exist of isolated immunostaining abnormalities for a single sarcoglycan (with preservation of staining for the other 3 sarcoglycans) in both γ -sarcoglycan⁵⁶ and α -sarcoglycan,⁵⁷ and in those cases the mutation analysis reflects the immunostaining pattern. Immunostaining and Western blot analysis for dystrophin may occasionally be simultaneously reduced in sarcoglycanopathies and tend to portend a more severe phenotype.⁵⁸

Diagnosis

Muscle biopsy with immunostaining is often performed first, followed by genetic testing. Genetic testing is commercially available for the 4 sarcoglycan genes.

Case 3

A 12-year-old girl from Brazil presented in a wheelchair. She sat at 7 months and walked at 13 months. At 4 years of age, she preferred to be carried in the grocery store. At 6 years of age, she began to fall, had to pull on a banister to climb stairs, and could no longer run. By 10 years of age, she used a wheelchair fulltime.

On examination, there was mild, symmetric, bilateral scapular winging. Her calves were disproportionately large compared with her thighs. There was mild neck flexor weakness. Upper extremity strength was MRC grade 4 proximally. Lower extremity strength was 2 to 3 at the hips, 4– in the knee flexors and extensors, 4 in the ankle dorsiflexors, and 5 in the ankle plantar flexors. She had normal sensation.

Her CK levels were 17,006 U/L at age 6 years, 7993 U/L at age 10 years, and 4122 U/L at age 12 years. Her ECG demonstrated mild prolongation of the P–R interval. EMG revealed mild muscle membrane instability in most muscles along with small, myopathic motor units with early recruitment. A muscle biopsy showed a moderate to severe dystrophic pattern with diminished (but not absent) immunostaining for all γ -, α -, β -, and δ -sarcoglycans and for the N-terminal, rod, and C-terminal domains of dystrophin. Genetic testing revealed 2 heterozygous, disease-associated, missense mutations in the gene for α -sarcoglycan, SGCA and c.229C>T; p.Arg77Cys and c.850C>T; p.Arg284Cys.

This real-life case reveals many key diagnostic features in LGMD2D.

Treatment

Treatment requires attention to cardiac, respiratory, and orthopedic complications. A phase 1 human trial of gene therapy involved injection of α -sarcoglycan DNA via an adeno-associated virus vector into the extensor digitorum brevis muscle of 3 patients. This rescued treated muscles, demonstrating robust α -sarcoglycan gene expression at the sarcolemma of 57% to 69% of muscle fibers.⁵⁹ Further trials of this approach are in progress.

LGMD2I—FUKUTIN-RELATED PROTEIN

Expressed throughout human tissues, with highest levels in skeletal and cardiac muscle, fukutin-related protein (FKRP) demonstrates sequence similarities to a family of proteins involved in modifying cell surface glycoproteins and glycolipids. Mutations in *FKRP* are responsible for several phenotypes, including a congenital muscular dystrophy (MDC1C), milder patients with later-onset (LGMD2I), recurrent myoglobinuria, asymptomatic hyperCKemia, and isolated dilated cardiomyopathy.^{60–64}

Clinical

Onset occurs over a broad range, from 1 to 50 years, but on average in the second decade of life. In Northern European neuromuscular centers, LGMD2I represents one of the most common LGMDs, constituting 20% to 40% of patients.^{65,66} The prevalence in Southern Europe, however, is only approximately 5% and only 10% to 15% in North America.^{3,67,68} Prominent respiratory and cardiac dysfunction may arise early in the clinical course and may not correlate with skeletal muscle involvement.^{69,70} Strength may stabilize for years in patients, then progress once again. Often, patients walk well past the fourth decade. Initial pelvifemoral weakness subsequently spreads to the distal lower extremities and proximal upper extremities. Calf hypertrophy and lumbar lordosis are nearly universally present, sometimes leading to a misdiagnosis of Becker muscular dystrophy. Scapular winging, macroglossia, cognitive dysfunction, and MRI abnormalities are found in some cases.^{71,72}

LGMD2I: Key diagnostic features

- Usual onset 10–20 years of age
- Proximal leg weakness
- Calf hypertrophy
- Lumbar lordosis
- Scapular winging
- Macroglossia
- Cardiorespiratory dysfunction
- 20%–30% May require bilevel positive airway pressure (BiPAP).
- CK = 500–20,000 U/L
- Muscle biopsy with decreased staining for α -dystroglycan
- Diagnosis via genetic testing

Laboratory

Serum CK ranges from 3 to 50 times normal but is nearly always more than 10 times the upper limit of normal. Myoglobinuria is common in patients with very high CK

levels.⁶² Echocardiography often reveals a dilated cardiomyopathy.⁷⁰ Forced vital capacity is reduced on pulmonary function testing in 30% to 50% of patients, and 20% to 30% of patients require BiPAP or ventilator support.^{65,66} MRI of the pelvis and thigh often reveal disproportionate signal change (reflecting fibrosis and fatty infiltration) in the iliopsoas and thigh adductor muscles.⁷³ Muscle biopsies reveal dystrophic features (variability in fiber size, internal nuclei, degeneration, and regeneration with fatty and fibrous replacement) without distinctive features, such as rimmed vacuoles, inclusions, or inflammation.

Diagnosis

Biopsies reveal reduced or absent immunostaining for glycosylated α -dystroglycan. Confirmatory genetic testing is commercially available. There is a common mutation in the fukutin-related protein—*FKRP* 826C>A. Approximately two-thirds of patients are homozygous for this mutation, and these patients tend to have a milder clinical course.

Treatment

Of utmost importance in LGMD2I, monitoring of respiratory and cardiac function should take place in alternate years in asymptomatic patients and more frequently for those with previous testing abnormalities. Respiratory support with noninvasive ventilation and early treatment of cardiac dysfunction with medications, pacemakers, defibrillators, and transplantation improve quality of life.

Case 4

A 16-year-old young man from the north of England ran more slowly than other children since primary school. Lately, he has noted greater difficulties navigating stairs and arising from chairs and the floor. In his work at a pizza shop, he has trouble lifting pizzas out of the top ovens. At school, he has an individualized educational plan for mild learning difficulties.

On examination, there was no scapular winging, but he had large calves (Fig. 4). He had grade 4 strength proximally in his arms and legs, could not ascend steps 2 at a time, and was unable to run. On arising from a squat, he had a modified Gower sign.

His CK levels were 5683 U/L and 6084 U/L; his ECG, pulmonary function tests, and echocardiogram were normal; and his muscle biopsy showed a moderate to severe dystrophic pattern with absent immunostaining for glycosylated α -dystroglycan. Genetic testing revealed homozygous *FKRP* 826C>A mutations.

A 13-year-old, "asymptomatic" brother was not athletic. This brother's CK level was 9386 U/L, and he also harbored homozygous *FKRP* 826C>A mutations.

This real-life case reveals key diagnostic features in LGMD2I.

LGMD2L—ANOCTAMIN 5

LGMD2L due to mutations in *ANO5*, the gene for anoctamin 5, is a common LGMD subtype in Northern European populations, ranging from 15% to 40% of cases.⁷⁴ Its prevalence in the United States has not been determined. Anoctamin 5 is a putative calcium-activated chloride channel, but its exact function is not yet known. Dominant mutations in *ANO5* can cause gnathodiaphyseal dysplasia.⁷⁵ Recessive mutations may lead to either LGMD2L or to a distal myopathy with predominant calf involvement, similar to Miyoshi myopathy.⁷⁶

Clinical

Weakness in LGMD2L usually begins in adulthood between 20 and 50 years of age.⁷⁶ The pattern of weakness in LGMD2L was initially described as involving quadriceps



Fig. 4. A 16-year-old boy with LGMD2I and large calves.

and biceps atrophy.⁷⁷ Asymmetries were common. More recently, the phenotypic spectrum of ANO5-related genetic muscle disease has significantly expanded to include not only proximal upper and lower extremity weakness (limb-girdle pattern) but also a distal myopathy (Miyoshi-like with calf atrophy), proximal lower extremity weakness alone, proximal upper extremity weakness alone, proximodistal lower extremity weakness, isolated calf hypertrophy, and asymptomatic hyperCKemia.⁷⁸ Exercise intolerance and myalgias are common.⁷⁹ One-quarter of patients may require wheelchair use 10 to 20 years into disease. Cardiac and pulmonary involvement, however, has not been reported.

LGMD2L: Key diagnostic features

- Usual onset 20–50 years of age
- Proximal leg weakness
- Asymmetric weakness
- Early inability to stand on toes
- No cardiac or respiratory involvement
- CK = 2000–7000 U/L
- Muscle biopsy may have amyloid staining
- Diagnosis via genetic testing

Laboratory

CK levels tend to be elevated 10 to 40 times the upper limit of normal. On MRI of the lower limbs, the gracilis, sartorius, short head of the biceps femoris and tibialis anterior

muscles tend to be spared.⁸⁰ Progression of muscle degeneration may be seen over a 3- to 7-year span on serial MRIs. Muscle biopsies reveal dystrophic features. Occasionally, Congo red staining may reveal amyloid deposits in the intramuscular blood vessel walls and within the interstitium.⁷⁹

Diagnosis

Commercial genetic testing is available and is the only means to diagnose the condition.

Treatment

Supportive interventions, such as physical therapy, braces, and ambulatory aids, are the modalities available for this newly discovered entity. Gene-based interventions may be forthcoming in the future.

Case 5

A 45-year-old gentleman of Northern European heritage presented due to subjective weakness and hyperCKemia. He has noted a reduction in the size of his thighs over the past 1 to 2 years and only very occasionally has had difficulty arising from a kneeling position over the past year. A former heavy drinker, his aspartate aminotransferase and alanine aminotransferase were in the 400 range 5 years ago but remained elevated even after cessation of alcohol.

On examination, there was no scapular winging and no calf hypertrophy or atrophy. There was prominent quadriceps atrophy bilaterally, however. Facial, neck, and extremity strength was graded MRC grade 5 throughout.

His CK levels were 3753 U/L and 4684 U/L on repeat. ECG, stress test, echocardiogram, Holter monitor, and spirometry were normal. EMG revealed an irritable myopathy. He has 3 quadriceps muscle biopsies, each spaced a year apart. The first was normal, and the second showed minimal nonspecific changes. The third was dystrophic with marked variability in fiber size, copious fibers with internal nuclei, and endomysial fibrosis. There was no inflammation and a battery of immunostains for muscular dystrophies was negative. Genetic testing revealed homozygous mutations in *ANO5* (c.172C>T; p.Arg58Trp).

One year after diagnosis, his right leg was definitely weaker than his left, he was having more difficulty ascending and descending stairs, he was unable to arise from a squat, and he had a sensation his calves were constantly tight or stiff.

This real-life case reveals many key diagnostic features in LGMD2L.

LGMD1B—LAMIN A/C

Mutations in *LMNA*, the gene for lamins A and C, cause an array of human disease with numerous phenotypes. Five have skeletal muscle involvement. Nonskeletal muscle disorders include familial partial lipodystrophy, the Dunnigan-type (FPLD)⁸¹; autosomal recessive, axonal, peripheral polyneuropathy (Charcot-Marie-Tooth disease type 2A [AR-CMT2])⁸²; autosomal dominant, axonal, peripheral polyneuropathy (Charcot-Marie-Tooth disease type 2 [AD-CMT2]) with or without leukonychia⁸³; mandibuloacral dysplasia⁸⁴; premature aging (Hutchinson-Gilford progeria syndrome)⁸⁵; an isolated dilated cardiomyopathy⁸⁶; heart-hand syndrome of the Slovenian type⁸⁷; a fatal, infantile, restrictive dermopathy⁸⁸; and the metabolic syndrome.⁸⁹ The syndromes with predominant skeletal muscle involvement include LGMD1B,⁹⁰ autosomal dominant⁹¹ and recessive⁹² EDMD (AD-EDMD), congenital muscular dystrophy,⁹³ and autosomal dominant dilated cardiomyopathy with atrioventricular block (CMD1A),⁸⁶ which on occasion also has clinically evident skeletal muscle weakness. The skeletal muscle phenotypes are overlapping syndromes exhibiting greater or lesser degrees of

muscle weakness, joint contractures, and cardiac dysfunction. Nonpenetrance from generation to generation is not uncommon for the various laminopathy phenotypes.⁹⁴ LGMD1B makes up 5% to 10% of cases LGMD.

LGMD1B: Key diagnostic features

- Usual onset 2–25 years of age
- Variable penetrance generation to generation
- Limb-girdle or humeroperoneal pattern of weakness
- Joint contractures common
- Cardiac involvement by the second or third decade
- CK = 200–2000 U/L
- Diagnosis via genetic testing

Clinical

Onset may occur in the first decade and even as a congenital syndrome but can begin in the 20s, 30s, or 40s.⁹⁵ The pattern of weakness and atrophy tends to be humeroperoneal (biceps and below the knees) or limb girdle (proximal legs and arms). Calf hypertrophy and scapular winging occur infrequently. Joint contractures, although often subtle, are almost always present and can be helpful in suggesting the diagnosis, with elbow and neck flexors more so affected than ankle, knee, hip, and wrist joints. Although skeletal muscle weakness manifests from birth through the fourth decade, cardiac disease relatively uniformly begins in the second and third decades, independent of skeletal muscle involvement.⁹⁶ Cardiac manifestations include early dysrhythmias and conduction block. Dilated cardiomyopathy comes later in the course. Arrhythmias requiring pacemaker placement affect nearly all patients by the 20s, whereas progressive heart failure responds to cardiac transplantation.

Laboratory

CK values range up to 10-times normal. Needle EMG reveals myopathic motor units whereas nerve conduction studies remain normal. Muscle biopsies disclose variability in fiber size, increased internal nuclei, fiber splitting, and mild to moderate connective tissue replacement and fatty infiltration. Electron microscopy reveals abnormal distribution of heterochromatin in the nuclei of muscle fibers and satellite cells.^{97,98}

Diagnosis

Muscle is not readily stained for lamin A/C; thus, DNA analysis is preferred for definitive diagnosis. Gene sequencing is commercially available from several sources.

Treatment

Currently, treatment remains supportive. Physical therapy enhances functional independence by augmenting range of motion and minimizing contractures. Monitoring cardiac involvement with cardiology consultations, ECGs, echocardiography, and Holter monitors can be lifesaving. For symptomatic patients, cardiac pacemakers, defibrillators, and transplantation should be considered early in the clinical course.

Case 6

A 28-year-old woman presented due to worsening weakness. She was never able to run or jump. She never could fully straighten her elbows. As a cheerleader, she was always reprimanded to straighten her elbows, and she could not. She currently works as a school bus driver and is having greater difficulties getting onto the bus. She states she walks just like her father, paternal aunt, and paternal grandmother. Her 6-year-old daughter cannot keep up with other children when running. The patient has had occasional palpitations.

On examination, there were 20° elbow flexor contractures. There was no scapular winging. Her strength was full except as follows (MRC scale): neck flexors 4, shoulder abductors 4+, elbow flexors 4–, elbow extensors 4+, hip flexors 4, hip extensors 3, hip abductors 4, hip abductors 4–, knee extensors 4+, and knee flexors 4. She had a mild Trendelenburg gait.

With testing, her CK level was 349 U/L. ECG was normal, but a Holter monitor revealed 5- to 40-second runs of a supraventricular tachycardia. EMG revealed a nonirritable myopathy. Genetic testing revealed the following mutation in *LMNA*: c.652A>C; p.Thr219Pro. This same mutation was found in her affected paternal aunt and her 6-year-old daughter.

This real-life case reveals many key diagnostic features in LGMD1B.

SUMMARY

When evaluating both men and women with limb-girdle weakness and a presumed genetic cause, clinicians should initially exclude dystrophinopathies and Pompe disease. For the LGMDs, there are 3 general diagnostic strategies. (1) Phenotype driven—if the clinical features, family history, examination, and creatine kinase level all point to a distinct diagnosis, many clinicians go directly to targeted genetic testing of a particular gene. Computer-based, smart algorithms are available to help guide to the most likely LGMD diagnosis (Jain Foundation Automated LGMD Diagnostic Assistant).⁹⁹ This tool is fairly adept at delineating the correct diagnosis in LGMDs with a common presentation. (2) Biopsy driven—if the phenotype approach does not yield an answer, or if the precise clinical diagnosis is unclear, muscle biopsy with immunostaining for a panel of muscular dystrophies is a reasonable next step. The results of the muscle biopsy can then direct further genetic testing. (3) Genetic testing driven—finally, if the first 2 strategies do not prove fruitful, genetic testing via gene panels or exome/genome sequencing is now available. Panels with 12, 50, or 163 muscle genes are available. The advantage of gene panels is they cast a broad net. The disadvantage is that often the results return with variants of unknown significance. Additionally, many of these panels only sequence genes and thus miss deletions, duplications, repeat sequences, and intronic mutations. The optimal strategy often depends on the comfort of the clinician, resources available, and insurance authorizations and may benefit from input from a geneticist or genetic counselor. As the technology improves and costs are reduced, direct genetic testing will probably assume a more prominent role in diagnosing LGMDs.

Using these strategies, a genetic diagnosis can be made in more than 60% of LGMD patients. The clinical features point to a correct diagnosis in approximately half the cases. Obtaining a precise genetic diagnosis in LGMD is important in defining the long-term prognosis, delineating other organ system involvement, clarifying the pattern of inheritance, avoiding unnecessary treatments (eg, immunosuppressants for dystrophies with inflammation on the biopsy), and providing proactive management of disease (eg, physical and occupational therapy, pacemaker-defibrillators for arrhythmias, and noninvasive positive airway pressure for ventilatory failure).

As a group, the LGMDs are the fourth most common genetic muscle condition, with a minimum prevalence of 3 to 5 per 100,000 (or approximately 1 in 20,000). This article

highlights key features of what are widely thought the most common LGMDs. As knowledge of the genetic basis and pathophysiology of the LGMDs expands, the hopes of patients and families for effective treatments for these conditions may become a reality.

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