REVIEW ARTICLE

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The Limb-Girdle Muscular Dystrophies

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ABSTRACT

PURPOSE OF REVIEW: The limb-girdle muscular dystrophies (LGMDs) are a group of inherited muscle disorders with a common feature of limb-girdle pattern of weakness, caused by over 29 individual genes. This article describes the classification scheme, common subtypes, and the management of individuals with LGMD.

RECENT FINDINGS: Advances in genetic testing and next-generation sequencing panels containing all of the LGMD genes have led to earlier genetic confirmation, but also to more individuals with variants of uncertain significance. The LGMDs include disorders with autosomal recessive inheritance, which are often due to loss-of-function mutations in muscle structural or repair proteins and typically have younger ages of onset and more rapidly progressive presentations, and those with autosomal dominant inheritance, which can have older ages of presentation and chronic progressive disease courses. All cause progressive disability and potential loss of ability to walk or maintain a job due to progressive muscle wasting. Certain mutations are associated with cardiac or respiratory involvement. No disease-altering therapies have been approved by the US Food and Drug Administration (FDA) for LGMDs and standard treatment uses a multidisciplinary clinic model, but recessive LGMDs are potentially amenable to systemic gene replacement therapies, which are already being tested in clinical trials for sarcoglycan and *FKRP* mutations. The dominant LGMDs may be amenable to RNA-based therapeutic approaches.

SUMMARY: International efforts are underway to better characterize LGMDs, help resolve variants of uncertain significance, provide consistent and improved standards of care, and prepare for future clinical trials.

INTRODUCTION

The limb-girdle muscular dystrophies (LGMDs) were originally described by John Walton and F. J. Nattrass in 1954 to distinguish limb-girdle pattern muscle disorders, which can affect men or women, from X-linked Duchenne muscular dystrophy.[1] The name defined the pattern of weakness and helped distinguish it from other common dystrophies, such as facioscapulohumeral muscular dystrophy and myotonic dystrophy. More than 29 different LGMD subtypes have been identified, but they all share several features: (1) they are all autosomally

inherited; (2) they typically can present in childhood to adulthood; and (3) they result in progressive proximal weakness. Outside of these features, several characteristics differentiate the LGMDs. Most important for clinicians is the variation in dominant or recessive inheritance and the impact of the subtype on cardiac or pulmonary function.

This article reviews LGMDs beginning with their classification scheme, discusses diagnostic approaches, and highlights subtypes that are commonly seen or require specific management. The article concludes with an evaluation of current standards of care and a discussion of potential new therapeutic directions.

CLASSIFICATION

The classification scheme for the LGMDs has been recently revised. Historically, they were subdivided by autosomal dominant or recessive inheritance. The original classification scheme denoted dominant inheritance as LGMD1 and recessive inheritance as LGMD2, followed by a letter to indicate the subtype as designated by the genetic mutation, in order of discovery (eg, LGMD2A). However, new LGMD subtypes were regularly discovered and classified, and by 2016 the recessive forms were numbered LGMD2A to LGMD2Z. The preponderance of subtypes and lack of new letters for LGMD2 genes spurred a movement to revisit the definition of disease-causing mutations and the classification scheme. In the new nomenclature, dominant forms are LGMDD and recessive forms are LGMDR. In a controversial attempt to restrict LGMDs to their original definition, five subtypes were removed by limiting the predominant phenotype to limb-girdle pattern weakness. In all instances, the muscle pathology of the removed subtypes did not demonstrate a truly dystrophic process, or the genes fit within alternative categories, like metabolic or myofibrillar myopathy.[2] As shown in TABLE 7-1, the new nomenclature also includes an additional descriptive element related to the genetic mutation. In practice, clinicians often use these classification schemes interchangeably, so we present both here. Finally, it is important to recognize that although Duchenne and Becker muscular dystrophies are clinically similar to the LGMDs, they are considered separately. The LGMDs demonstrate both genetic heterogeneity, where multiple mutations in different genes lead to similar phenotypes, and genetic pleiotropy, where mutations in the same gene lead to different phenotypic presentations. Certain distal myopathies or congenital muscular dystrophies share the same genetic cause as LGMDs, with the difference being the pattern of muscular presentation or age of onset, and indeed may ultimately just represent a genetic spectrum of the same disorder. Similarly, the wide availability of genetic testing has collapsed some disorders that were originally clinically defined separately into a spectrum of genetic presentations for the same disorder, such as in Myoshi distal myopathy and LGMDR2 dysferlin-related, where large MRI studies have revealed an overlapping spectrum of muscle involvement.[3] By definition, if the predominant clinical presentation is limb-girdle pattern weakness, they would be classified as LGMD.

The autosomal dominant LGMDs tend to have an older age of onset, relatively slower progression, and often minimal to no elevation in creatine kinase (CK). They represent approximately 10% of LGMDs (TABLE 7-2). The autosomal recessive LGMDs have a younger age of onset and relatively faster progression, may have significant elevation in CK, and are by far the most prevalent forms of LGMDs.

KEY POINTS

- Limb-girdle muscular dystrophies can be inherited in autosomal dominant or recessive patterns.
- Limb-girdle muscular dystrophies affect children and adults, and both men and women.
- Autosomal recessive limb-girdle muscular dystrophies affect muscle structural, maintenance, or repair proteins.
- Autosomal dominant limb-girdle muscular dystrophies are less prevalent than autosomal recessive LGMDs, tend to affect individuals at older ages, and are chronically progressive.
- Autosomal recessive limb-girdle muscular dystrophies often have younger age of onset, more rapid loss of strength, and higher creatine kinase than autosomal dominant LGMDs.

EPIDEMIOLOGY

The LGMDs represent a collection of over 29 different disorders. In a study of over 4600 individuals in the United States who participated in a sponsored genetic testing program, LGMDR1 was the most frequently observed subtype, followed by LGMDR2.[4] Taken together, the LGMDs have a worldwide estimated prevalence of 0.8 to 6.9 cases per 100,000 people. This yields a conservative estimate of 2800 to 24,150 affected individuals in the United States. Prevalence estimates taken from a variety of public databases and using bayesian modeling suggest the possibility that certain LGMDs may be more prevalent than clinically appreciated, with the most prevalent estimated subtype being LGMDR12 (2L).[5] Limits to prevalence estimates include a paucity of free genetic testing programs prior to 2014, and a lack of any central registry for tracking LGMDs.

SYMPTOMS AND SIGNS

As a set of related disorders, the LGMDs present with proximal weakness that is slowly progressive. The weakness initially affects the shoulder girdle and hip girdle and spreads to other muscles. Regarding the shoulder girdle, patients may report arm fatigue when reaching up, or inability to lift objects over the head.

TABLE 7-1 **Nomenclature Associated With Limb-Girdle Muscular Dystrophy**

Gene	Old Nomenclature	Proposed Nomenclature
CAPN3	LGMD2A/LGMD1I	LGMDR1/D4 calpain3-related
DSYF	LGMD2B	LGMDR2 dysferlin-related
SGCA	LGMD2D	LGMDR3 α-sarcoglycan-related
SGCB	LGMD2E	LGMDR4 β-sarcoglycan-related
SGCG	LGMD2C	LGMDR5 γ-sarcoglycan-related
SGCD	LGMD2F	LGMDR6 δ-sarcoglycan-related
TCAP	LGMD2G	LGMDR7 telethonin-related
TRIM32	LGMD2H	LGMDR8 TRIM32-related
FKRP	LGMD2I	LGMDR9 FKRP-related
TTN	LGMD2J	LGMDR10 titin-related
POMT1	LGMD2K	LGMDR11 POMT1-related
ANO5	LGMD2L	LGMDR12 anoctamin5-related
FKTN	LGMD2M	LGMDR13 fukutin-related
POMT2	LGMD2N	LGMDR14 POMT2-related
POMGnT1	LMGD2O	LGMDR15 POMGnT1-related
DAG1	LGMD2P	LGMDR16 α-dystroglycan-related
PLEC	LGMD2Q	LGMDR17 plectin-related

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They may need to rest their arm on a table to bring their hand to their mouth or may report inability to lift objects off the floor, like a backpack or grocery bag. Hand grip strength is typically preserved until later in the disease course. People with LGMDs may notice wasting of muscle bulk. Regarding the hips, patients may report difficulty getting up off the floor (ie, having to turn over and use their arms in a modified Gowers maneuver) or needing to use a chair to climb off the floor. They may have trouble going up or down stairs, needing the railing for stability, or losing the ability to climb stairs in a reciprocal gait pattern. People with LGMDs may have difficulty playing sports or note their legs giving out on uneven surfaces. Strength in the muscles around the ankle is typically preserved until later in the disease course, but in certain subtypes the inability to stand on the toes may be an early presentation of LGMD, followed later by hip girdle weakness (eg, LGMDR2 dysferlin-related). In some subtypes, the pattern of muscles affected outside of the limb girdle is specific, as detailed below. In recessive forms of LGMD, the progression of the weakness often leads to the need for mobility devices. In dominant forms of LGMD, the need for mobility devices is less frequent due to the later age of onset. Depending on the subtype, patients may develop respiratory failure later in the disease course. This respiratory weakness

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Gene	Old Nomenclature	Proposed Nomenclature
TRAPPC11	LGMD2S	LGMDR18 TRAPPC11-related
GMPPB	LGMD2T	LGMDR19 GMPPB-related
ISPD	LGMD2U	LGMDR20 ISPD-related
COL6A1,2,3	Bethlem myopathy	LGMDR22/D5 collagen 6-related
LAMA2		LGMDR23 laminin α 2-related
POMGNT2		LGMDR24 POMGNT2-related
DNAJB6	LGMD1D	LGMDD1 DNAJB6-related
TNP03	LGMD1F	LGMDD2 TNP03-related
HNRNPDL	LGMD1G	LGMDD3 HNRNPDL-related
Myot	LGMD1A	Myofibrillar myopathy[a]
DES	LGMD1E/2R	Myofibrillar myopathy[a]
LMNA	LGMD1B	Emery-Dreifuss muscular dystrophy[a]
CAV3	LGMD1C	Rippling muscle disease[a]
GAA	LGMD2V	Pompe disease[a]
PINCH2	LGMD2W	PINCH-2 related myopathy[a]
BVES	LGMD2X	BVES related myopathy[a]
TOR1AIP1	LGMD2Y	TOR1AIP1 related myopathy[a]

[a] Reclassified using Revised European Neuromuscular Center (ENMC) criteria.

often follows pelvic girdle weakness, becoming more common once a patient has lost the ability to walk. Patients may report a weakened cough, difficulty taking deep breaths, or discomfort when lying flat in bed. Diaphragmatic involvement is more prominent in the sarcoglycan-related LGMDs (R3 to R6). Cardiomyopathy may develop as the disease progresses, but the heart is typically spared in most LGMDs. The exceptions include the sarcoglycan-related LGMDs (R3 to R6), *FKRP*-related LGMD (R9), and telethonin-related LGMD (R7).

Pain, when present, is most frequently musculoskeletal in nature and can be related to compensatory posture changes in the shoulders or back or related to unstable joints (eg, the knees). Additionally, pain may develop with immobility or contractures. Cognition is not typically impacted, differentiating the LGMDs from congenital muscular dystrophies in allelic disorders. Exceptions to this are commonly seen in α-dystroglycan-related disorders, some of which may be experienced as a continuum of severity from congenital muscular dystrophies to the LGMDs.

DIAGNOSTIC APPROACH

The advent of next-generation sequencing panels sponsored by pharmaceutical companies or patient advocacy groups nearly a decade ago revolutionized the diagnostic approach for LGMDs. Historically, diagnosis of LGMDs relied on diagnostic flow diagrams which included branches for suspected patterns of inheritance or assumed prevalence of mutation types. Typically, this started with a motor examination for the pattern of weakness, patient history for age of onset and inheritance pattern, evaluation of serum CK, muscle imaging, and a muscle biopsy (FIGURE 7-1). For autosomal recessive LGMDs, muscle biopsies demonstrating absence of sarcolemmal protein by immunohistochemistry were diagnostic, confirmed by single gene testing. But these tests and approaches had limited sensitivity or specificity. The serum CK is most useful when it is greater than 1000, which is highly suggestive for a muscle disorder or an autosomal recessive LGMD.[6] EMG is most useful when ruling out alternative diagnoses or when findings are inconclusive, for example, to distinguish between myopathic and neurogenic causes of weakness. Muscle biopsy has a sensitivity of about 70% to 80% for muscle disease but low specificity and is more important when genetic tests are inconclusive.[7] Muscle ultrasound or MRI can help build the argument

TABLE 7-2 **Dominant and Recessive Forms of Limb-Girdle Muscular Dystrophy**

Feature	Dominant Limb-Girdle Muscular Dystrophy	Recessive Limb-Girdle Muscular Dystrophy
Inheritance	Autosomal dominant	Autosomal recessive
Population %	10% of total patients	90% of total patients
Subtypes	5	24
Typical age of onset	Adolescence to late adulthood	Childhood to young adulthood
Limb weakness	Mild	Moderate to severe
Creatine kinase levels	Normal to mildly elevated	Mildly to highly elevated

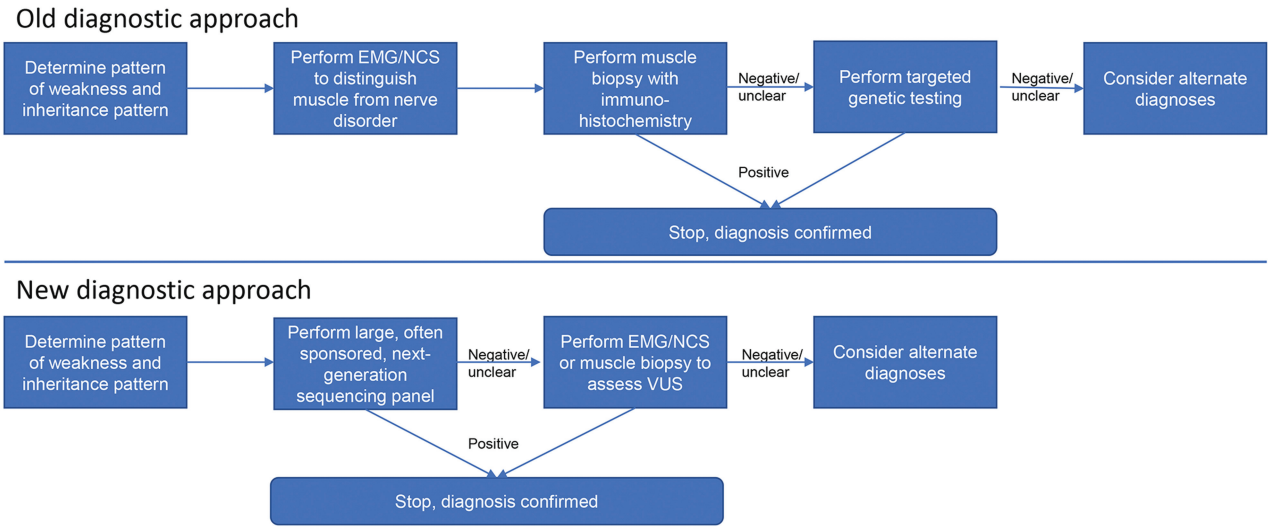

FIGURE 7-1

Diagnostic algorithm for limb-girdle muscular dystrophy. *A*, The previous diagnostic approach relied on muscle biopsy and targeted sequencing. *B*, The newer approach focuses on large-panel genetic testing. This testing is often sponsored and free for patients.

NCS = nerve conduction study; VUS = variant of uncertain significance.

for LGMD by showing clear muscle involvement or by the pattern of muscle involvement, or by helping to select a muscle for biopsy. Taken together, a serum CK greater than 1000, myogenic EMG, and MRI suggestive of muscle involvement have a sensitivity and specificity for muscle disease of roughly 89% and 88%, respectively, but would still require genetic testing for confirmation.[8] Importantly, a similar presentation may be seen in both inherited and acquired muscle diseases, including myotonic dystrophy type 2, facioscapulohumeral muscular dystrophy, neuromuscular junction disorders, inflammatory myopathies, metabolic myopathies, and some congenital myopathies.

Patient advocacy groups such as the Muscular Dystrophy Association and the Jain Foundation sponsored next-generation sequencing panels that made genetic testing accessible and affordable in routine clinical care. Free next-generation sequencing programs vary over time but may be found at perkinelmergenomics.com/testing-services/sponsored-testing-programs/the-lantern-project/ or invitae.com/en/physician/tests/03304/. This has led to a dramatic change in the order of diagnostic testing, with many clinicians starting with an LGMD next-generation sequencing panel in patients with slowly progressive proximal weakness. An LGMD next-generation sequencing panel along with a characteristic clinical examination is diagnostic in about one-fourth of individuals; however, while next-generation sequencing has increased the number of individuals diagnosed with LGMD overall, it has also created a new problem: about half of individuals will have a variant of uncertain significance in a gene of interest. In a large sequencing program of over 4600 individuals, 27% had a confirmed pathogenic mutation, with the relative outcome of LGMD genetic testing in the US shown in TABLE 7-3.[4] Variants of uncertain significance were identified in over 73% of the cohort. Variants of uncertain significance represent an indeterminant test result. In the setting of a variant of uncertain

significance, familial testing, testing for serum CK, muscle imaging, or muscle biopsy become important. Sometimes large-panel testing will identify multiple variants of uncertain significance. In these instances, the clinician should plan to prioritize those variants most consistent with the phenotype and potential diagnosis. Standardization of genetic testing reports has allowed for initial interpretation of variants of uncertain significance in the clinical setting. On the genetic testing report, data are provided about the population allele frequency (see the Genome Aggregation Database, gnomad.broadinstitute.org) and predicted outcome of the variant. In instances where the variant is uncommon in the general population and computational analysis suggests a deleterious or indeterminant effect, it may be necessary to perform additional steps to resolve the significance of the variant. FIGURE 7-2 outlines one approach to resolving variants of uncertain significance. It is important to identify if the number of variants in a gene represents the appropriate inheritance pattern (dominant versus recessive); a single heterozygous variant of uncertain significance or single pathogenic mutation in a gene associated with autosomal recessive LGMD would mean either the wrong diagnosis, or another mutation exists in a region not covered by the next-generation sequencing panel (eg, intronic mutation). Targeted sequencing of affected and unaffected family members can help identify if these variants segregate appropriately with the disease. In addition, in autosomal recessive disorders where two mutations in the same gene are identified, it is still important to determine if the mutations are in cis or trans (ie, on the same parental allele or different alleles). If the variants of uncertain significance are seen in the proband and only one parent, they are in cis and unlikely to be pathogenic. Outside of family testing, a muscle biopsy may be warranted to demonstrate immunohistochemical loss of the protein involved. Alternatively, a western blot may be required to demonstrate loss of protein. Patients should be informed of inconclusive results if these approaches fail to confirm the genetic diagnosis. On follow-up visits, it is incumbent on the clinician to check online resources like ClinVar (ncbi.nlm.nih.gov/clinvar) to see if the variant has been reclassified as pathogenic or likely pathogenic.[9]

Repeat expansion disorders or contractions are not detected with current next-generation sequencing panels; thus, two of the three most prevalent muscular dystrophies (myotonic dystrophy and facioscapulohumeral muscular dystrophy) would not be detected on an LGMD next-generation sequencing

TABLE 7-3 **Outcome of a Large Sequencing Program for Limb-Girdle Muscular Dystrophy[a]**

Testing Result	Percentage (%)
Variant of unknown significance	72
Pathogenic variant	23
Likely pathogenic variant	3
Pseudodeficiency allele	0.7

[a] Data from Nallamilli BRR, et al, Ann Clin Transl Neurol.[4]

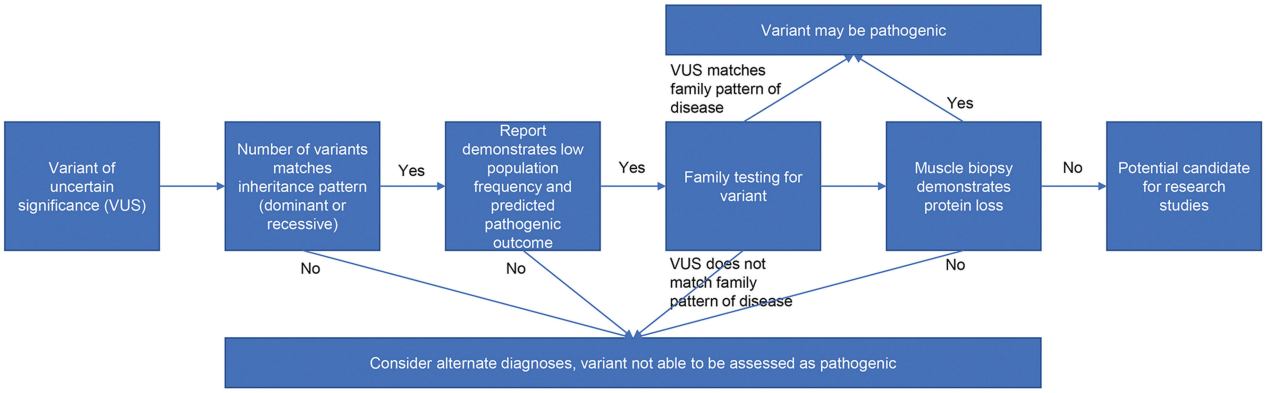

FIGURE 7-2
Approach to resolving a variant of uncertain significance (VUS) as pathogenic or benign.

panel. Additional attention to which genes are tested (and which are not) and the area of coverage is important in the event of a negative test result. In some instances, other sequencing modalities may be considered, including whole exome sequencing, whole genome sequencing, and RNA sequencing. Whether these other sequencing modalities improve the sensitivity of the genetic testing varies but is related to the relative match of the clinical phenotype, the depth of sequencing of the original coverage panel, and the breadth of the genes on the original panel. At the publishing of this article next-generation sequencing panels for LGMDs include over 100 genes, so the increased yield of a genetic diagnosis using whole-exome approaches is likely incremental and may only change the diagnosis following next-generation sequencing panels in less than 5% of patients. Active research programs are investigating the sensitivity of the whole-genome and RNA-sequencing approaches.

MRI and Limb-Girdle Muscular Dystrophies

The increased use of neuroimaging in muscular dystrophies has also impacted the understanding of LGMDs. Many studies have attempted to define patterns of muscle involvement diagnostic for LGMD subtypes, but MRI has been most useful in better understanding the spectrum of muscle involvement associated with LGMDs, which can have both a proximal and a distal presentation of weakness. As shown in FIGURE 7-3, different LGMD subtypes have different patterns of involvement. For example, in LGMDR2 (see Recessive Limb-Girdle Muscular Dystrophy Type 2 section) early gastrocnemius involvement is quite common, and a distal myopathy has also been described (ie, Miyoshi myopathy). However, more recent natural history studies have suggested that these seemingly disparate presentations exist on a spectrum, with the predominant phenotype consistent with LGMDs.[10] MRI has also been proposed as an outcome measure for clinical trials, where features like the fat fraction of a given group of muscles are more likely to show the evolution of disease over time frames of 1 year, a typical time frame for clinical trials. In these instances, the investigators have adopted the same quantitative magnetic resonance biomarkers seen in Duchenne muscular dystrophy, but their use in clinical practice is still limited. Some LGMD subtypes have well-recognized patterns of muscle involvement and identifying these patterns may supplant the need to obtain a confirmatory

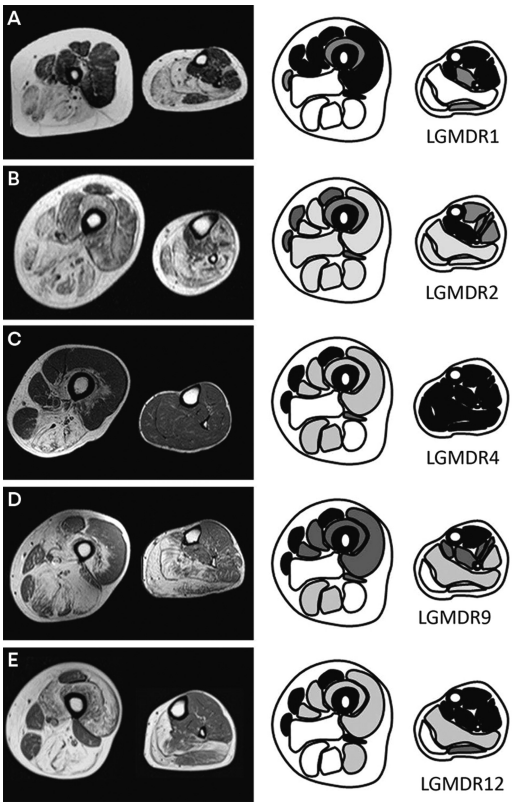

FIGURE 7-3

Muscle MRI patterns in limb-girdle muscular dystrophy (LGMD), showing the relative propensity of different LGMD subtypes to affect different muscle groups. The figure shows sample MRI images demonstrating the fat replacement pattern by LGMD subtype, along with a stylized graphic showing the pattern of fat replacement (*white*) compared to preserved muscle (*black*). *A*, Posterior compartment involvement in LGMDR1. *B*, Broader involvement of both the posterior and anterior compartments in LGMDR2. *C*, In LGMDR4, proximal involvement is greater than distal involvement. *D*, Broad muscle involvement in LGMDR9 with sparing of the tibialis anterior. *E*, Early involvement of the quadriceps in LGMDR12.

Reprinted with permission from Straub et al, Elsevier.[39]

muscle biopsy; however, the initial diagnostic step is still genetic testing. The use of MRI versus muscle biopsy after this step depends significantly on the location of practice (eg, in the United States or Europe).

COMMON SUBTYPES OF THE LIMB-GIRDLE MUSCULAR DYSTROPHIES

In this section we describe the most common subtypes of the limb girdle muscular dystrophies, starting with the dominant form before moving on to common recessive forms. In general, the dominant subtypes tend to have an older age of onset and slower progression than the recessive subtypes. Currently available genetic testing panels will identify the subtypes described below most commonly. It is possible that ultrarare forms of LGMD will be identified; the published natural history of these forms of LGMD is sparse and clinicians should follow the same general management as for the more common forms.

Dominant Limb-Girdle Muscular Dystrophy Type 1

LGMDD1 (formerly 1D) is caused by a mutation in the gene *DNAJB6*, which has a chaperone function. This disorder is inherited in an autosomal dominant manner. As with other dominant forms of LGMD, the typical age of onset is in the thirties or forties, although considerable variation can occur, including childhood onset. The pattern of weakness is typical for LGMDs, with greater posterior than anterior muscle involvement, and can include prominent distal muscle weakness. The need for a wheelchair may occur late in the disease. CK is typically mildly elevated. On muscle biopsy, individuals with LGMDD1 may have rimmed vacuoles and aggregates.[11] Involvement of the cardiac or pulmonary system does not typically occur.

Recessive Limb-Girdle Muscular Dystrophy Type 1

LGMDR1 is caused by biallelic mutations in the *CAPN3* gene.[12,13] Calpain 3 is thought to be related to control of the calcium efflux at the sarcoplasmic reticulum[14]; however, it has also been shown to impact membrane repair. Many hundreds of mutations have been associated with LGMDR1, and founder populations have been identified in the Amish and in the Basque region.[15,16] As with other autosomal recessive conditions, age of onset is earlier, often in the teens. While some individuals may present with characteristic weakness of the shoulder and hip girdles, several other patterns of weakness have been identified, including early scapular winging and peroneal weakness. The quadriceps are often spared. Muscular presentation can be asymmetric and may be mistaken for facioscapulohumeral muscular dystrophy. Contractures, particularly in the ankles, may develop early in the disease course. Loss of ambulation is common in LGMDR1. Respiratory involvement is rare and typically follows pelvic girdle weakness once an individual requires a wheelchair. Cardiac involvement is typically not reported, and CK level may be very elevated. Muscle biopsy findings are variable and may include dystrophic features (eg, necrosis and regeneration) or may show endomysial inflammation that is mistaken for a myositis. The gold standard for diagnosis is genetic confirmation; however, it may be necessary to confirm variants of uncertain significance using western blot (**CASE 7-1**). LGMDD4 is an extremely rare autosomal dominant form of LGMD associated with *CAPN3* in which weakness develops later and progresses more slowly.[17-19]

Recessive Limb-Girdle Muscular Dystrophy Type 2

LGMDR2 is caused by loss of function of the dysferlin gene. Dysferlin is thought to be involved in membrane fusion and repair.[20] A number of common *DYSF* mutations cause LGMDR2, although several founder mutations associated with a milder or more severe phenotype exist in Japanese populations.[21] LGMDR2 has a distinctive pattern of weakness. Aside from progressive shoulder and hip girdle weakness, the gastrocnemius is affected. On examination, individuals with LGMDR2 are often unable to walk on their toes. In fact, Miyoshi myopathy is also caused by mutations in *DSYF*. Prior classification schemes focused on whether the weakness developed proximally (and could therefore be classified as LGMDR2) or remained distal (Miyoshi myopathy). More recent natural history studies suggest that this classification scheme is actually a continuum, with most patients having a combination of distal and proximal weakness (**CASE 7-2**).[22] The same mutation may present as LGMDR2 or Miyoshi myopathy. It has been reported that early aerobic exercise may trigger disease presentation.[23] Cardiac muscles are not typically affected, but it is possible to develop respiratory failure as the disease progresses. Many individuals lose ambulation over a prolonged disease course. Similar to LGMDR1, CK can be very high in LGMDR2. Muscle biopsy demonstrates dystrophic features. Immunohistochemical staining of dysferlin should demonstrate reduced or absent staining. Alternatively, protein quantification may demonstrate reduced protein in monocytes.[24]

Recessive Limb-Girdle Muscular Dystrophy Types 3 to 6

The sarcoglycanopathies form a complex at the sarcolemmal membrane. A loss-of-function mutation of any subunit results in a severe form of LGMD. Loss of α-sarcoglycan results in LGMDR3 (2D), loss of β-sarcoglycan results in

KEY POINTS

- Cardiac involvement, while rare, is suggestive of particular limb-girdle muscular dystrophies.
- New next-generation sequencing panels can include all limb-girdle muscular dystrophy genes, and have upended traditional flowcharts of diagnostics, with gene testing coming earlier.

LGMDR4 (2E), loss of δ-sarcoglycan causes LGMDR6 (2F), and loss of γ-sarcoglycan causes LGMDR5 (2C). LGMDR3 is the most common and LGMDR6 is the least common.[25] LGMDR4 has a founder population in the Amish population and LGMDR5 has a founder mutation in Tunisia and North Africa.[26,27] Combined, the sarcoglycanopathies are the fourth most common subtype of LGMDs. In many instances, these individuals have a more severe disease course and may present early in childhood. Given the age of onset and high CK, boys with sarcoglycanopathies may be mistakenly misdiagnosed with the more common Duchenne muscular dystrophy. Weakness is in a characteristic LGMD pattern. Loss of ambulation may occur during the teenage years. Respiratory failure is a common feature of late disease. Cardiac function is not typically clinically affected, although it may be rarely impacted very late in the disease course, especially in LGMDR4.[28] CK is often very high in

CASE 7-1

A 35-year-old woman presented for a neurologic evaluation for weakness. She first noticed difficulty getting up from the floor in her mid-twenties, having to roll over and push up with her arms. She noticed difficulty going up stairs, with wasting in the backs of her thighs, and later knee hyperextension when walking. Later she noted difficulty reaching above her head, and loss of bulk in her biceps bilaterally. She had no family history of muscular dystrophy.

On examination, she had a limb-girdle pattern of weakness with scapular winging and loss of bulk in her thighs. A muscle biopsy, performed prior to her visit, showed nonspecific chronic progressive dystrophic changes, variability in fiber size, increased connective tissue, and some fatty replacement. A limb-girdle muscular dystrophy (LGMD) next-generation sequencing panel revealed one pathogenic mutation in *CAPN3*, and one variant of uncertain significance. In addition, she had one variant of uncertain significance in *DYSF*. Additional testing was performed to help resolve the variant of uncertain significance. Her serum creatine kinase was 800 U/L and EMG showed a chronic myopathy. Further genetic testing of her parents revealed that the mutations in *CAPN3* were in the trans position. Immunohistochemical staining performed on her muscle biopsy showed normal dysferlin staining. A Western blot was performed and revealed absence of *CAPN3*.

She was diagnosed with compound heterozygous LGMDR1 calpain-related: she showed a common limb-girdle presentation of weakness, with no known family history, and genetic testing yielded one pathogenic variant and one variant of uncertain significance, requiring additional testing to confirm the diagnosis.

COMMENT

This case of LGMDR1 demonstrates a typical presentation of the autosomal recessive condition, including scapular winging as a distinguishing feature, and describes a possible path for resolving variants of uncertain significance using parental testing and protein quantification.

these individuals. Muscle biopsy findings include a dystrophic pattern. Immunohistochemical staining demonstrating loss of the relevant sarcoglycan subunit is diagnostic. As these proteins occur in a complex, the loss of a subunit may result in reduced or absent staining of multiple subunits. Genetic testing is the gold standard.

Recessive Limb-Girdle Muscular Dystrophy Type 9

LGMDR9 (2I) is caused by a loss of function of the *FKRP* gene. FKRP is part of the enzymatic pathway responsible for glycosylating α-dystroglycan. As a result, LGMDR9 is often referred to as one of the α-dystroglycanopathies. It is very common in Scandinavia and parts of England, often with a common homozygous mutation (L276I).[29] A founder mutation in Mexico (c.1387A>G) is associated with a more severe disease phenotype.[30] In general, homozygous mutations result in a less severe disease course than compound heterozygous mutations (CASE 7-3).[31] Weakness often develops in adolescence, although this is variable and somewhat related to the mutation. Proximal shoulder and hip girdle weakness is common. Calf hypertrophy is present in most patients. Exercise has been reported to induce symptoms, and in multiple instances the initial presentation was rhabdomyolysis or myoglobinuria.[32,33] Compared to other forms of LGMD, patients will often report exercise-induced pain. Loss of ambulation typically occurs in the twenties and thirties, particularly with heterozygous mutations. Respiratory function is affected earlier in the disease course compared to many other subtypes. Patients may also develop mild cardiomyopathy. CK is high, but less so than in LGMDR1 to LGMDR6. Muscle biopsy may show reduced staining of α-dystroglycan. Genetic testing is the gold standard.

CASE 7-2

A 21-year-old man presented for a neurologic consultation for progressive weakness. He first noticed difficulty standing on his toes when in grade school. This was followed by loss of bulk in his calf muscles. Early in high school he had trouble going up stairs or running, and in college he developed difficulty reaching over his head. He reported pain in both legs with activity and between the shoulder blades.

On examination he had limb-girdle pattern weakness and was unable to close his legs when seated. Serum creatine kinase was 10,000 U/L. A limb-girdle muscular dystrophy (LGMD) next-generation sequencing panel revealed only one pathogenic mutation in *DYSF*. A muscle biopsy revealed absence of dysferlin staining, and a dysferlin enzyme test revealed decreased activity. This patient was diagnosed with LGMDR2 dysferlin-related.

COMMENT

This case shows that some LGMDs present with distal weakness before proximal, and for LGMDR2 about one-sixth to one-fifth of individuals will only have one pathogenic mutation on genetic testing, requiring further testing to confirm absence of dysferlin staining or enzyme activity.

Recessive Limb-Girdle Muscular Dystrophy Type 12

LGMDR12 (2L) is due to a loss of function in *ANO5*. Loss of anoctamin 5 may lead to defective membrane repair.[34] LGMDR12 is common in Northern Europe. As opposed to other recessive forms of LGMD, LGMDR12 has a later age of onset and possibly a slower rate of progression.[35] On presentation, patients may have significant quadriceps atrophy and weakness. The legs are often more affected than proximal arm muscles. LGMDR12 may also cause a distal Miyoshi-like myopathy (Myoshi muscular dystrophy 3), which is common in Finland. Similar to LGMDR9, patients may have pain with exercise and may present with rhabdomyolysis. With a later age of onset and slower progression, it is uncommon for patients to lose ambulation. Respiratory and cardiac function are usually not affected. CK is highly variable and may be normal or highly elevated. Muscle biopsy may be normal or demonstrate dystrophic features. Genetic testing is the gold standard.

CASE 7-3A

Patient A's parents noticed delayed motor milestones when he was developing: he only started walking at age 2, and by age 6 he had difficulty getting off the floor, having to use a Gowers maneuver, and had trouble reaching above his head. The weakness was progressive and by age 15 he needed help with ambulation, using a wheelchair for distance, and in his late teens he used a wheelchair all the time. He noticed decreased ability to take a deep breath in his teenage years and began to use noninvasive ventilation in his late teens. His cardiologist noted a drop in his ejection fraction by his mid-teens and prescribed an angiotensin-converting enzyme inhibitor and a beta-blocker to reduce his afterload. He had no known family history of similar disorders.

CASE 7-3B

Patient B was never athletic but by age 15 she noticed trouble when trying to run short distances or when climbing stairs. In her early twenties she noticed difficulty getting off the ground without some assistance and would have to prop her arms on the wall of the shower when washing her hair. She started to use a walker by her mid-twenties, and by age 40 would use a wheelchair for distances. She had a maternal cousin who was affected, and her family had Dutch heritage.

The patient in case CASE 7-3A was compound heterozygous for pathogenic missense mutations in *FKRP* (~15% of total *FKRP* mutations), and the patient in CASE 7-3B was homozygous for the common *FKRP* mutation (826C>A; >70% of total *FKRP* mutations).

COMMENT

Compound heterozygous mutations in *FKRP* are associated with a more severe, Duchenne-like presentation, while the more common homozygous mutation is associated with a chronic progressive course, with loss of ambulation often occurring after age 40. Cardiac involvement can be common in LGMDR9.

TREATMENT OF THE LIMB-GIRDLE MUSCULAR DYSTROPHIES

No disease-modifying therapies are known for LGMDs, although research has led to new possibilities, as described below. Similar to Duchenne muscular dystrophy, steroids have been proposed as a treatment for certain subtypes with either a Duchenne-like early progressive presentation (LGMDR9) or high CK and inflammation on biopsy (LGMDR2); however, no study has confirmed the efficacy of using steroids to alter disease progression.

Treatment is supportive and best performed in a multidisciplinary clinic with access to allied disciplines. At each visit, a thorough evaluation for current motor abilities and review of functional adaptations are recommended, including evaluations by both physical and occupational therapy. Use of assistive devices (eg, ankle-foot orthoses, walkers, wheelchairs) may be required to improve mobility and independence.

Monitoring of cardiac function via echocardiogram or cardiac MRI is highly dependent on the subtype. Cardiac involvement may be seen in LGMDR3 to LGMDR6, LGMDR10, and more commonly in LGMDR9 and LGMDR11. Monitoring is similar to other forms of muscular dystrophy and generally involves annual echocardiograms or at the frequency determined by the cardiologist. Care for patients with cardiomyopathy is similar to care for other adults with heart failure and should include the core principles of afterload reduction and reducing the cardiac workload using medications such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and aldosterone inhibitors. In patients without a genetic diagnosis, it is reasonable to monitor for cardiomyopathy every 5 years. Similarly, pulmonary function should be screened at baseline and the serial frequency of screening is determined by the subtype diagnosis. In the absence of a subtype, annual screening of pulmonary function is recommended, and screening should typically occur once someone begins to lose the ability to walk independently.

While some of the subtypes of autosomal recessive LGMD have noted associations between exercise and earlier age of onset or exercise and myoglobinuria, the role of exercise in the progression of LGMD is still unknown. In general, aerobic exercise is felt to be beneficial for cardiopulmonary health, and individual recommendations should be clinically based on the patient and their situation.

Individuals with poor mobility are at risk of osteopenia or osteoporosis. Supplementation with vitamin D and calcium is recommended. Serial dual-energy x-ray absorptiometry (DEXA) scans to assess for osteoporosis may be indicated in nonambulant individuals.

LGMD is a genetic disorder, and it is important for clinicians to provide appropriate counseling to family members about the risk of having the condition. For autosomal dominant LGMDs the risk is 50% for each child of an affected parent; for autosomal recessive LGMDs the risk of passing on the disease is dependent on pathogenic allele frequency in the general population, as the affected individual passes on one pathogenic allele, and children are typically carriers. Similar to all autosomal recessive disorders, if both parents are carriers, the risk of a second child being affected is 25%. Patients or family members who plan to have children may be counseled about preimplantation genetic testing with in vitro fertilization to prevent passing the mutation to the embryo.

KEY POINT

- **Standard care addresses weakness and any other limb-girdle muscular dystrophy–related area of disability and is most commonly performed in multidisciplinary clinics.**

KEY POINTS

- Systemic gene replacement therapies are being developed for many autosomal recessive limb-girdle muscular dystrophies, including clinical trials underway for sarcoglycan and *FKRP* mutations.
- Autosomal dominant limb-girdle muscular dystrophies may be amenable to RNA-based modulating therapies.

RESEARCH

The development of systemic retrovirus-delivered gene replacement therapies is promising. In this approach, adeno-associated virus (AAV) vectors are modified to contain a nonintegrating plasmid that expresses the gene of interest. This approach is most promising for recessive forms of LGMD, where a loss-of-function mutation may be replaced. The challenge with AAV-based therapies is developing muscle tropism to avoid hepatotoxicity in adults. However, early-phase clinical trials for LGMDR4, LGMDR5, and LGMDR9 are currently ongoing.[36,37] The approach for autosomal dominant conditions is less clear, but the use of RNA-based therapies like antisense knockdown approaches may provide some opportunities for applying these disease-modifying strategies in these disorders. Outside of the gene modification approaches, a clinical trial for a precursor to ribose, ribitol, as a supplement for LGMDR9 is ongoing.[38] One challenge with therapeutic development in the LGMDs is the overall number of subtypes and sparsity of natural history data to inform the trial design. Efforts by the GRASP-LGMD Consortium (Genetic Resolution and Assessments Solving Phenotypes in LGMD, grasp-lgmd.org) are ongoing to develop natural history data to support clinical trial development. In this consortium, the investigators have taken a platform approach, studying multiple subtypes at a time. Central to this effort is the hypothesis that the same rate of progression on clinical outcomes will be seen across multiple subtypes, allowing gene therapy trials to rapidly move into those most rare subtypes.

CONCLUSION

The LGMDs comprise a group of disorders with the common presentation of limb-girdle pattern weakness. The most common autosomal recessive forms of LGMD are due to loss-of-function mutations affecting proteins involved in muscular structure or repair. Autosomal recessive LGMDs are potentially amenable to systemic gene replacement therapy, and clinical trials are already underway for the sarcoglycanopathies. Autosomal dominant LGMDs tend to have a milder disease course, with later age of onset. RNA-based therapies may provide novel approaches to future treatments, and the most common autosomal dominant LGMD, LGMDD1, may be amenable to approaches targeting protein chaperones. While taken together the LGMDs represent the fourth most common type of muscular dystrophy, individually they are rare, and better natural history studies and a better understanding of the disorders as measured by standard clinical outcome assessments can lead to improved clinical care and prepare the field for impending clinical trials.

REFERENCES

1 Murphy AP, Straub V. The classification, natural history and treatment of the limb girdle muscular dystrophies. J Neuromuscul Dis 2015;2(s2):S7-S19. doi:10.3233/JND-150105

2 Straub V, Murphy A, Udd B, LGMD workshop study group. 229th ENMC international workshop: limb girdle muscular dystrophies–nomenclature and reformed classification Naarden, the Netherlands, 17-19 March 2017. Neuromuscul Disord 2018;28(8):702-710. doi:10.1016/j.nmd.2018.05.007

3 Harris E, Bladen CL, Mayhew A, et al. The Clinical Outcome Study for dysferlinopathy. Neurol Genet 2016;2(4):e89. doi:10.1212/NXG.0000000000000089

4 Nallamilli BRR, Chakravorty S, Kesari A, et al. Genetic landscape and novel disease mechanisms from a large LGMD cohort of 4656 patients. Ann Clin Transl Neurol 2018;5(12):1574-1587. doi:10.1002/acn3.649

5 Liu W, Pajusalu S, Lake NJ, et al. Estimating prevalence for limb-girdle muscular dystrophy based on public sequencing databases. Genet Med 2019;21(11):2512-2520. doi:10.1038/s41436-019-0544-8

6 Constantinides VC, Papahatzaki MM, Papadimas GK, et al. Diagnostic accuracy of muscle biopsy and electromyography in 123 patients with neuromuscular disorders. In Vivo 2018;32(6):1647-1652. doi:10.21873/invivo.11427

7 Paganoni S, Amato A. Electrodiagnostic evaluation of myopathies. Phys Med Rehabil Clin N Am 2013;24(1):193-207. doi:10.1016/j.pmr.2012.08.017

8 Cardy CM, Potter T. The predictive value of creatine kinase, EMG and MRI in diagnosing muscle disease. Rheumatology (Oxford) 2007;46(10):1617-1618. doi:10.1093/rheumatology/kem211

9 ClinVar [Internet]. Cited December 14, 2021. https://www.ncbi.nlm.nih.gov/clinvar/

10 Diaz-Manera J, Fernandez-Torron R, LLauger J, et al. Muscle MRI in patients with dysferlinopathy: pattern recognition and implications for clinical trials. J Neurol Neurosurg Psychiatry 2018;89(10):1071-1081. doi:10.1136/jnnp-2017-317488

11 Harms MB, Sommerville RB, Allred P, et al. Exome sequencing reveals DNAJB6 mutations in dominantly-inherited myopathy. Ann Neurol 2012;71(3):407-416. doi:10.1002/ana.22683

12 Sáenz A, Leturcq F, Cobo AM, et al. LGMD2A: genotype-phenotype correlations based on a large mutational survey on the calpain 3 gene. Brain 2005;128(Pt 4):732-742. doi:10.1093/brain/awh408

13 Barp A, Laforet P, Bello L, et al. European muscle MRI study in limb girdle muscular dystrophy type R1/2A (LGMDR1/LGMD2A). J Neurol 2020;267(1):45-56. doi:10.1007/s00415-019-09539-y

14 Kramerova I, Kudryashova E, Wu B, et al. Novel role of calpain-3 in the triad-associated protein complex regulating calcium release in skeletal muscle. Hum Mol Genet 2008;17(21):3271-3280. doi:10.1093/hmg/ddn223

15 Allamand V, Broux O, Bourg N, et al. Genetic heterogeneity of autosomal recessive limb-girdle muscular dystrophy in a genetic isolate (Amish) and evidence for a new locus. Hum Mol Genet 1995;4(3):459-463. doi:10.1093/hmg/4.3.459

16 Urtasun M, Sáenz A, Roudaut C, et al. Limb-girdle muscular dystrophy in Guipúzcoa (Basque Country, Spain). Brain 1998;121(Pt 9):1735-1747. doi:10.1093/brain/121.9.1735

17 Martinez-Thompson JM, Niu Z, Tracy JA, et al. Autosomal dominant calpainopathy due to heterozygous CAPN3 C.643_663del21. Muscle Nerve 2018;57(4):679-683. doi:10.1002/mus.25970

18 Cerino M, Campana-Salort E, Salvi A, et al. Novel CAPN3 variant associated with an autosomal dominant calpainopathy. Neuropathol Appl Neurobiol 2020;46(6):564-578. doi:10.1111/nan.12624

19 González-Mera L, Ravenscroft G, Cabrera-Serrano M, et al. Heterozygous CAPN3 missense variants causing autosomal-dominant calpainopathy in seven unrelated families. Neuropathol Appl Neurobiol 2021;47(2):283-296. doi:10.1111/nan.12663

20 Lennon NJ, Kho A, Bacskai BJ, et al. Dysferlin interacts with annexins A1 and A2 and mediates sarcolemmal wound-healing. J Biol Chem 2003;278(50):50466-50473. doi:10.1074/jbc.M307247200

21 Takahashi T, Aoki M, Tateyama M, et al. Dysferlin mutations in Japanese Miyoshi myopathy: relationship to phenotype. Neurology 2003;60(11):1799-1804. doi:10.1212/01.wnl.0000068333.43005.12

22 Harris E, Bladen CL, Mayhew A, et al. The Clinical Outcome Study for dysferlinopathy: an international multicenter study. Neurol Genet 2016;2(4):e89. doi:10.1212/NXG.0000000000000089

23 Moore UR, Jacobs M, Fernandez-Torron R, et al. Teenage exercise is associated with earlier symptom onset in dysferlinopathy: a retrospective cohort study. J Neurol Neurosurg Psychiatry 2018;89(11):1224-1226. doi:10.1136/jnnp-2017-317329

24 Ho M, Gallardo E, McKenna-Yasek D, et al. A novel, blood-based diagnostic assay for limb girdle muscular dystrophy 2B and Miyoshi myopathy. Ann Neurol 2002;51(1):129-133. doi:10.1002/ana.10080

25 Alonso-Pérez J, González-Quereda L, Bello L, et al. New genotype-phenotype correlations in a large European cohort of patients with sarcoglycanopathy. Brain 2020;143(9):2696-2708. doi:10.1093/brain/awaa228

26 Driss A, Amouri R, Ben Hamida C, et al. A new locus for autosomal recessive limb-girdle muscular dystrophy in a large consanguineous Tunisian family maps to chromosome 19q13.3. Neuromuscul Disord 2000;10(4-5):240-246. doi:10.1016/s0960-8966(00)00099-7

27 Duclos F, Broux O, Bourg N, et al. Beta-sarcoglycan: genomic analysis and identification of a novel missense mutation in the LGMD2E Amish isolate. Neuromuscul Disord 1998;8(1):30-38. doi:10.1016/s0960-8966(97)00135-1

28 Politano L, Nigro V, Passamano L, et al. Evaluation of cardiac and respiratory involvement in sarcoglycanopathies. Neuromuscul Disord 2001; 11(2):178-185. doi:10.1016/s0960-8966(00)00174-7

29 Sveen ML, Schwartz M, Vissing J. High prevalence and phenotype-genotype correlations of limb girdle muscular dystrophy type 2I in Denmark. Ann Neurol 2006;59(5): 808-815. doi:10.1002/ana.20824

30 Lee AJ, Jones KA, Butterfield RJ, et al. Clinical, genetic, and pathologic characterization of FKRP Mexican founder mutation c.1387A>G. Neurol Genet 2019;5(2):e315. doi:10.1212/NXG.0000000000000315

31 Gedlinske AM, Stephan CM, Mockler SRH, et al. Motor outcome measures in patients with FKRP mutations: a longitudinal follow-up. Neurology 2020;95(15):e2131-e2139. doi:10.1212/WNL.0000000000010604

32 Lindberg C, Sixt C, Oldfors A. Episodes of exercise-induced dark urine and myalgia in LGMD 2I. Acta Neurol Scand 2012;125(4):285-287. doi:10.1111/j.1600-0404.2011.01608.x

33 Brun BN, Mockler SRH, Laubscher KM, et al. Childhood activity on progression in limb girdle muscular dystrophy 2I. J Child Neurol 2017;32(2): 204-209. doi:10.1177/0883073816677680

34 Chandra G, Defour A, Mamchoui K, et al. Dysregulated calcium homeostasis prevents plasma membrane repair in Anoctamin 5/TMEM16E-deficient patient muscle cells. Cell death Discov 2019;5:118. doi:10.1038/s41420-019-0197-z

35 Magri F, Del Bo R, D'Angelo MG, et al. Frequency and characterisation of anoctamin 5 mutations in a cohort of Italian limb-girdle muscular dystrophy patients. Neuromuscul Disord 2012;22(11): 934-943. doi:10.1016/j.nmd.2012.05.001

36 Mendell JR, Rodino-Klapac LR, Rosales-Quintero X, et al. Limb-girdle muscular dystrophy type 2D gene therapy restores alpha-sarcoglycan and associated proteins. Ann Neurol 2009;66(3): 290-297. doi:10.1002/ana.21732

37 Pozsgai ER, Griffin DA, Heller KN, et al. Systemic AAV-mediated β-sarcoglycan delivery targeting cardiac and skeletal muscle ameliorates histological and functional deficits in LGMD2E mice. Mol Ther 2017;25(4):855-869. doi:10.1016/j.ymthe.2017.02.013

38 Cataldi MP, Lu P, Blaeser A, Lu QL. Ribitol restores functionally glycosylated α-dystroglycan and improves muscle function in dystrophic FKRP-mutant mice. Nat Commun 2018;9(1):3448. doi:10.1038/s41467-018-05990-z

39 Straub V, Carlier PG, Mercuri E, editors. TREAT-NMD workshop: Pattern recognition in genetic muscle diseases using muscle MRI, 25-26 February, 2011, Rome, Italy. Elsevier, 2012: S42-S53.

DISCLOSURE

Continued from page 1698

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