

The Muscular Dystrophies

Kevin M. Flanigan, M.D.¹

¹Departments of Pediatrics and Neurology, The Center for Gene Therapy, The Research Institute, Nationwide Children's Hospital, The Ohio State University, Columbus, Ohio

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Address for correspondence and reprint requests Kevin M. Flanigan, MD, Departments of Pediatrics and Neurology, The Center for Gene Therapy, The Research Institute, Nationwide Children's Hospital, 700 Children's Drive, Columbus, Ohio 43205 (e-mail: kevin.flanigan@nationwidechildrens.org).

Abstract

The muscular dystrophies are disorders of progressive muscular degeneration and weakness. As a group they display clinical heterogeneity that reflects the heterogeneity of molecular mechanisms responsible for them, and range from congenital to adulthood onset. Recent advances in the field include improved methods of diagnosis, continued identification of disease genes, and the development of a unified model of pathogenesis in facioscapulohumeral dystrophy. These advances are reflected in the development of new therapeutic approaches, some of which have already led to clinical trials in the dystrophinopathies and limb-girdle dystrophies.

Keywords

- ▶ muscular dystrophy
- ▶ dystrophinopathy
- ▶ facioscapulohumeral
- ▶ limb-girdle

Muscular dystrophies are a clinically and heterogeneous group of disorders that all share clinical characteristics of progressive muscular weakness. The term “dystrophy,” used in its strictest pathologic sense, refers to chronic and severe myopathic changes within muscle. Most muscular dystrophies share the pathologic features of fibrosis and fatty replacement, particularly late in the disease course. However, some dystrophies show much less muscle pathology (e.g., myotonic dystrophy and some congenital muscular dystrophies), and are classified as dystrophies on a clinical rather than pathologic basis. The disease mechanism varies greatly between specific forms of muscular dystrophy. Disease causing mutations have been described in genes responsible for membrane-associated proteins, protease function, and transcriptional regulation. With such heterogeneity, it is not surprising that the clinical features vary, as do mechanisms of inheritance in age and onset.

Historically, muscular dystrophies hold a special place in the development of modern molecular genetics. In fact, the first gene cloned by positional cloning methodology was the Duchenne muscular dystrophy (DMD) gene, encoding dystrophin.¹ In the past three decades, steady advances in gene mapping and identification have increased our understanding of the genetic spectrum of these disorders, and recent advances in diagnostic and exploratory techniques (such as genome-scale sequencing) promise to identify additional genes that are responsible for rarer syndromes. These same tools are likely to lead to an increased understanding of the

molecular pathogenesis. Although no specific therapy has been approved for any form of muscular dystrophy, as a group these disorders are at the forefront of the development of new classes of molecular therapies, including gene corrective and gene transfer therapies.

The Dystrophinopathies

The dystrophinopathies occur due to mutations in the *DMD* gene, encoding the dystrophin protein. The archetypal disorder is Duchenne muscular dystrophy (DMD), which is usually marked by an onset of symptoms between the ages of 3 and 5 years. The early symptoms are typically related to gait, including delayed onset of walking, toe walking, or a waddling gait. Serum creatine kinase (CK) is typically elevated 50 to 100 times normal.² Because aspartate and alanine aminotransferase (AST and ALT) are expressed in muscle as well as hepatic tissue, boys with DMD are at risk of undergoing an unnecessary liver biopsy.³ Fatty replacement and fibrosis of calf muscles leads to enlargement best termed “pseudohypertrophy” because there is no muscle hypertrophy. Historically, loss of ambulation occurred between the ages of 7 and 12 years, and death by the end of the second decade. In nearly 90% of cases, DMD is due to mutations that truncate the reading frame, leading to an absence of dystrophin expression.^{4,5}

The allelic disorder Becker muscular dystrophy (BMD) also typically presents with a limb-girdle pattern of weakness. In

contrast to DMD, mutations resulting in BMD typically maintain an open reading frame, allowing translation of a protein that may be internally truncated but with partial function, leading to a much broader phenotypic range. More severely affected BMD patients may present in childhood, but loss of ambulation typically occurs after the age of 12. BMD also encompasses syndromes with adult presentation and even preserved ambulation into the seventh or eighth decade.^{6,7} Serum CK can be elevated, sometimes in the absence of clinical symptoms or weakness. CK elevations can also be much higher in BMD than DMD, as patients are able to perform much more motor activity. Rhabdomyolysis has been reported in patients with otherwise mild BMD⁷ yet is seldom seen with DMD.

Mutational analysis of the DMD gene has become a routine clinical test. The gene consists of 79 exons, over a 2.4 megabase region of chromosome Xp21. It encodes a 13 kilobase transcript, translated into a protein of 427 kDa in the predominant muscle isoform. Around 65% of mutations of the DMD gene are deletions of one or more exons, and these predominantly occur at two hotspots within the gene, one near the 5' end and one in the central region of the gene. Exon duplications account for ~6% of mutations, and nonsense mutations account for around 13%. The remainder consist primarily of small frame shift insertion/deletion mutations, and very rare missense mutations that occur in highly conserved regions of the gene.^{5,8} Economical sequence analysis⁹ and further advancements, such as multiplex ligation dependent probe amplification (MLPA) or comparative genomic hybridization permit detection of mutations from genomic blood samples in 93 to 96% of patients^{8,10}. These advances in diagnostics have led to the ability to screen for both elevations of CK and DNA mutations directly from heelstick-derived blood spots from infants. Using these techniques, the incidence among male infants in the United States has been estimated as 1 in 6,291, although analysis of all published reports suggests it is 1 in 4,087.¹¹ A small number of patients have inclusion of an intronic sequence within the mRNA as a "pseudoexon." Such mutations require muscle biopsy to provide mRNA for analysis.^{12,13}

Muscle biopsy is more commonly used to assess protein expression. In practice, assessment is often qualitative, and descriptions of absent dystrophin are meaningful. Protein quantification is in fact more complicated; quantification methods vary between laboratories, and efforts at standardization methods of quantification are underway.¹⁴⁻¹⁶ Immunofluorescent staining is usually the first analysis performed. In DMD, this typically shows complete absence of dystrophin, with scattered fibers that express dystrophin due to secondary somatic mutations or variation in splicing that restore the dystrophin reading frame; these are termed "revertant" fibers and are relatively common in DMD.¹⁷ In contrast, in most cases of BMD, there is decreased or patchy expression of dystrophin, which immunoblot analysis typically reveals to be of altered molecular weight. Asymptomatic and mildly affected Becker patients with central rod domain deletion mutations (and internally truncated dystrophin proteins) demonstrate above 40% of normal dystrophin,¹⁸ whereas

dystrophin levels of 30% of normal are sufficient to prevent skeletal muscle weakness in patients with X-linked dilated cardiomyopathy (an unusual presentation of certain DMD mutations).¹⁹

Therapeutics

To date, the only medications that have been shown to alter the course of Duchenne muscular dystrophy are corticosteroids. Treatment with prednisone at 0.75 mg per day or deflazacort at 0.9 mg/kg per day delays loss of ambulation 1 to 3 years.²⁰ However, corticosteroids are associated with significant side effects, including weight gain, decreased bone mineralization, Cushing syndrome, and behavioral disturbances. Alternate regimens are used in some clinics, including 10 days on and 10 days off, or weekend dosing,^{21,22} although the efficacy of these regimens in comparison to daily dosing is incompletely studied. A growing number of reports suggest that early treatment (before the age of 5 years) is especially beneficial, although the data to support early use is limited.²³ Although in clinical practice corticosteroids are frequently stopped when ambulation is lost, continuation may result in diminished scoliosis along with relative preservation of ventilation.^{24,25}

A variety of other new treatment approaches are being explored in preclinical and clinical trial studies. These can be divided into approaches that are mutation-specific—dependent upon a single mutation class, or a single mutation—and those that could potentially treat DMD patients regardless of mutation. Mutation-specific treatments include gene-corrective strategies, two types of which have reached clinical trials. Nonsense suppression therapies are aimed at inducing ribosomal read-through of premature stop codons, and include both gentamicin²⁶ and ataluren.²⁷ Exon-skipping strategies use antisense oligomers or adeno-associated virus delivered constructs to induce skipping of a particular exon flanking an out-of-frame deletion to restore an open reading frame. Two competing chemistries (morpholinos, and 2'-OMe antisense oligonucleotides) have shown promise in limited clinical trials²⁸⁻³¹, and more definitive trials are underway.

Mutation-nonspecific therapies include those directed at the gene transfer of mini- or microdystrophin constructs, which encode internally truncated proteins that have much of the functionality of full-length dystrophin, but are able to fit within the limitations of adeno-associated virus (AAV) packaging capacity. This virus does not cause illness, and several serotypes have significant muscle tropism.³² An initial trial of AAV-mediated minidystrophin gene transfer was unsuccessful, but did raise issues regarding immunity to the dystrophin protein, which will inform future attempts at therapy.^{33,34} Alternate approaches have shown promise in preclinical models; among these are upregulation of utrophin,³⁵ use of recombinant laminin components for membrane stabilization,³⁶ overexpression of the glycosyltransferase Galgt2 gene,³⁷ and modulation of the activin 2B receptor pathway.³⁸⁻⁴⁰

Issues of Care

Increasing attention has been paid to the cardiac and pulmonary aspects of DMD. Early nocturnal ventilation—often with

spinal surgery—may have significant impact, and in one well-defined cohort added nearly a decade to the mean survival.^{41,42} Cardiomyopathy is a nearly universal feature, with increasing risk with age. As pulmonary care has improved survival, cardiomyopathy has become a more common clinical problem. ACE-inhibitors and β blockade are routinely used.⁴³ Although some debate still exists about presymptomatic use of ACE inhibitors, there is evidence that they are cardioprotective.⁴⁴ In animal models, other medications have shown great promise, including the ACE receptor binding (ARB) drug losartan,⁴⁵ but well-designed clinical trials have yet to be performed.

The Limb-Girdle Muscular Dystrophies

The limb-girdle muscular dystrophies (LGMDs) are a particularly genetically and clinically heterogeneous group of disorders. Several types may present with primarily distal weakness, with clinical heterogeneity within the same family. They are divided into dominant (LGMD1) and recessive (LGMD2) forms.

LGMD1

LGMD1A is due to mutations in the gene-encoding myotilin,⁴⁶ referred to as either the *TTID* or *MYOT* gene. Patients typically present with proximal weakness followed later by distal involvement, and frequently dysarthria. Muscle biopsies typically demonstrate basophilic rimmed vacuoles, fiber splitting, and Z-line abnormalities.⁴⁷ Mutations in the same gene can be associated with more distal predominant weakness, often with myalgias and stiffness, and histopathology consistent with myofibrillar myopathy.^{47,48}

LGMD1B is due to mutations in the *LMNA* gene, encoding the nuclear protein lamin A/C.⁴⁹ Mutations in the same gene are responsible for a variety of phenotypes in addition to LGMD1B, including a congenital muscular dystrophy, autosomal dominant and recessive Emery-Dreifuss muscular dystrophy (EDMD), the axonal Charcot-Marie-Tooth syndrome CMT2B1, and Hutchinson-Gilford progeria syndrome. All neuromuscular phenotypes associated with *LMNA* mutations are associated with age-dependent cardiac involvement, with conduction disturbances more common than cardiomyopathy.⁴⁹⁻⁵¹ Muscle biopsies of LGMD patients typically show relatively mild chronic myopathic changes.⁵⁰

LGMD1C is due to mutations in the *CAV3* gene encoding caveolin-3,⁵² and may be associated with distal or proximal weakness. A clinical clue to diagnosis is the presence of rippling waves of muscle contraction, which may be associated with weakness or complaints of stiffness. This may be the primary manifestation (“rippling muscle disease”).⁵³ Hypertrophic cardiomyopathy is sometimes present. Muscle biopsy may range from mild myopathic to severe dystrophic changes, and caveolin-3 staining is absent or significantly altered.⁵⁴

Recently, mutations have been described in the DNAJB6 gene in LGMD patients.^{55,56} The nomenclature of this syndrome is confusing, with the HUGO Gene Nomenclature Committee using the locus designation LGMD1D, others

using LGMD1E,⁵⁷ and one of the reports⁵⁶ preferring LGMD1D/1E. Both proximal and distal predominant weakness has been described.⁵⁶ Muscle biopsy showing rimmed basophilic vacuoles may suggest the diagnosis.⁵⁵

Additional LGMD1 loci have been mapped, but genes have not been identified.

LGMD2

The most common forms of recessive LGMD in North America are LGMD2A (due to mutations in *CAPN3*, encoding calpain 3⁵⁸) and LGMD2B (due to mutations in *DYSF*, encoding dysferlin⁵⁹). Calpainopathy is frequently associated with profound shoulder-girdle weakness and sometimes scapular winging. Dysferlin deficiency may be associated with distal weakness, and in a purely distal form appears as Miyoshi myopathy (marked by severe calf wasting and elevated serum CK). Phenotypic variability may be observed within the same family, with some individuals presenting with a Miyoshi phenotype and others proximal limb-girdle weakness. LGMD2A and 2B typically present in early adulthood, frequently with normal function into the second or rarely third decade. Serum CK is elevated to 5 to 10 times the normal range in calpain deficiency, and more than 10 times normal in dysferlinopathies and sarcoglycanopathies. Dysferlin deficiency may be detected on immunofluorescent or immunohistochemical analysis, although immunofluorescent studies should be interpreted with caution given the presence of secondary protein-staining changes.⁶⁰⁻⁶² In the case of calpainopathy, no antibody has proven reliable for immunocytochemical analysis; therefore, immunoblot analysis is required. Mutation analysis of both of these genes is available on a commercial clinical basis.

Other recessive forms are due to mutations in the sarcoglycan genes, including LGMD2C (due to mutations in the *SGCG* gene encoding gamma-sarcoglycan),⁶³ LGMD2D (*SGCA*, encoding α -sarcoglycan⁶⁴), LGMD2E (*SGCB*, encoding β -sarcoglycan⁶⁵), and LGMD2F (*SGCD*, encoding delta-sarcoglycan⁶⁶). Although there is some variation in the severity at presentation, mutations in these genes typically present as severe childhood autosomal recessive muscular dystrophy (SCARMD), with phenotypes very similar to Duchenne muscular dystrophy, but with autosomal recessive inheritance. Diagnosis is typically made following muscle biopsy assessed for protein expression of α -, β -, γ -, and δ -sarcoglycan. Expression or localization of any of the four may be altered or absent if any one of the genes has mutated. These proteins play a critical role as anchors to dystrophin as part of the dystrophin-associated glycoprotein complex.

Among the other recessive LGMDs for which mutation analysis is available, two others are also relatively common. LGMD2L is due to mutations in *ANO5*, encoding anoctamin 5,⁶⁷ and may present with typical LGMD or more distal weakness.⁶⁸ In the Northern European population, this is found at a frequency equal to that of LGMD2A and LGMD2B, due to the presence of the founder allele c.191dupA.⁶⁹ Currently, the diagnosis must be made from DNA because no reliably specific antibody for either Western blotting or immunohistochemistry has yet been defined. Nearly as

frequent is LGMD2I, due to mutations in *FKRP*, which encodes fukutin-related protein.⁷⁰ LGMD2I in particular may mimic Duchenne or Becker muscular dystrophy, as both myalgias and dilated cardiomyopathy are frequent.⁷¹ Direct mutation analysis is available, but the diagnosis is frequently made by muscle biopsy following altered staining with an antibody directed toward a glycosylation-dependent epitope of dystroglycan. Mutations in the same gene may also cause a congenital muscular dystrophy,⁷⁰ as discussed in more detail below.

Therapeutics

No specific therapies have been described for these disorders. Supportive care is similar to that provided to patients with Duchenne dystrophy, including early screening for nocturnal ventilatory insufficiency and cardiomyopathy in those subtypes in which it is frequent. However, the prospect of gene transfer is quite promising because several LGMDs are associated with genes that are small enough for the full-length gene to be encapsidated within AAV vector. This has led to a successful human trial of intramuscular injection of the α -sarcoglycan gene in LGMD2D patients.⁷² Interestingly, expression of a full-length dysferlin protein has recently been demonstrated in vivo following AAV5 delivery of virions that apparently package partial *DYSF* cDNAs, but undergo homologous recombination events after delivery,⁷³ a propensity that may be *DYSF* specific and not generally applicable to other LGMDs.

Facioscapulohumeral Muscular Dystrophy

Facioscapulohumeral dystrophy (FSHD) is the third most common form of muscular dystrophy, with an estimated incidence of 1 in 20,000, although in some populations it occurs in up to 1 in 15,000.⁷⁴ It typically presents in adolescence with 80% of patients complaining of shoulder-girdle weakness by the age of 20. Facial weakness is often the earliest feature, resulting in a transverse smile and a weakened pucker. Besides facial and shoulder weakness, humeral compartment weakness is typical; thereafter, the next most common muscle affected is the tibialis anterior. Pelvic-girdle weakness may occur, with loss of independent ambulation in 20 to 25% of patients. Abdominal weakness may result in Beavor's sign,⁷⁵ and musculoskeletal pain is common.⁷⁶

FSHD has several features that assist diagnosis.⁷⁷ The first is asymmetry, which is not unique to FSHD, but is so common in the disease that the absence of asymmetry on history or exam should make one consider other diagnoses. A second is the wide variability of presentation, even within individual families. It is not uncommon to see very mild weakness, even isolated facial weakness, in parents or older relatives of a more symptomatic patient. Along these lines, it has been proposed that anticipation is a feature of the disease,^{78–80} although in large families, in which entire sibships have been examined, this has not been validated.⁷⁷ Hearing loss may occur in up to 60%^{81,82} (although others have found it absent⁸³). A retinal vasculopathy (Coat's syndrome) is frequently detected by fluorescein angiography, but is rarely

symptomatic.⁸⁴ Serum CK is typically only minimally elevated, if at all, and electromyography (EMG) is nonspecific, showing only an irritable myopathy. Muscle biopsy shows nonspecific features in proportion to weakness,⁸⁵ although inflammation may be a prominent feature.^{86,87}

Diagnosis thus depends on recognition of familial features and DNA analysis. Unlike most other dystrophies, diagnosis of FSHD still relies on Southern blot analysis, which requires more DNA and is more time consuming than polymerase chain reaction (PCR-) based tests. The clinical test assesses the integral copy number variation of a macrosatellite repeat element—termed the D4Z4 repeat—at the subtelomeric region of chromosome 4q35.⁸⁸ This is detected by digestion of genomic DNA by the restriction endonuclease *EcoRI*. Complicating molecular diagnosis is the presence of another D4Z4 array on chromosome 10q that displays copy number variation, although a shortened 10q fragment is not associated with disease. Each 10q D4Z4 repeat contains a *BlnI* site, so a double digest using this enzyme is performed to increase the specificity of the result. FSHD is seen only in association with the 4q repeat; it is associated with 1 to 10 repeats on the 4q array, whereas greater than 11 repeats is not associated with symptoms.

Several other issues complicate diagnostic testing. In some patients, exchange between 4q and 10q repeats has occurred, resulting in apparent 10q repeats at the 4q locus, and *BlnI* sensitive fragments associated with disease.⁸⁹ Also, occasional cases have been described in which a deletion encompasses the Southern probe hybridization site, such that no variation is detected. Finally, in some cases, the trait is not associated with a shortening fragment, but is instead associated with hypomethylation of histone markers at the locus resulting in altered chromatin regulation that is important to pathogenesis, as discussed below.⁹⁰ For these reasons, in settings of a high clinical index of suspicion, a negative standard clinical FSHD mutation analysis cannot be considered to rule out the disease, and further specialized testing is warranted.⁹¹

A great advance in FSHD within the past few years is the development of a unified model of pathogenesis⁹² based on the observation that an open reading frame within each D4Z4 repeat, encodes a homeobox domain-like protein DUX4. It had long been noted that FSHD only occurs in the presence of a particular sequence variant telomeric to the repeat element, called the 4qA allele, and not in the presence of an alternate 4qB allele. Critical to the unified model is the identification that only 4qA contains a polyadenylation signal. In this model, either the presence of a shortened D4Z4 repeat structure or altered methylation results in a euchromatic chromatin structure allowing transcription of DUX4 mRNA, which itself remains stable for translation only as transcript from the most distal D4Z4 repeat where it is attached to the 4qA polyadenylation signal. In support of this theory is the observation of DUX4 toxicity in muscle,⁹³ mediated at least in part through the p53 pathway.⁹⁴

Therapeutics

Recognition of the role of DUX4 protein opens the door for novel therapeutic approaches, but no definitive therapies are

available for FSHD. Moderate aerobic exercise is well tolerated and may improve self-reported function, but further controlled trials are required.⁹⁵

The Congenital Muscular Dystrophies

The congenital muscular dystrophies (CMDs) are also a clinically and genetically heterogeneous group of disorders. In contrast to the dystrophinopathies or the LGMDs, the CMDs are marked by weakness that is apparent at birth or in the earliest months. Patients typically demonstrate head lag and poor truncal control, and many never walk. Depending on the specific subtype, other features such as mental retardation or contractures may be common. A full description of the clinical and genetic features is beyond the scope of this article, but the interested reader is referred to one of several recent reviews.^{96,97}

Alpha-Dystroglycanopathies

The clinical distinction between CMD subtypes often relies on the presence or absence of central nervous system (CNS) involvement, and a magnetic resonance image (MRI) of the brain is often the first step in diagnosis. Patients with mutations in the *LAMA2* gene encoding the protein laminin $\alpha 2$ (or merosin)⁹⁸ usually demonstrate white matter abnormalities on MRI. Around 30% have seizures, but only a small subset have other abnormalities, such as cerebellar hypoplasia.⁹⁶ In contrast, defects in the genes encoding proteins essential for O-mannosyl-linked glycosylation of dystroglycan—an essential step for binding of dystroglycan to the extracellular matrix⁹⁹—frequently cause heterotopia, gyral defects, and mental retardation. Other syndromes cause “pure” CMD without CNS involvement. In nearly all cases, muscle biopsy is helpful or even necessary for the diagnosis. In addition to routine histochemical staining, staining for laminin $\alpha 2$ and for the glycosylated epitope of α dystroglycan steers the clinical diagnosis into broad categories.

Mutations have been identified in six genes encoding proven or presumed members of the α -dystroglycan glycosylation pathway: *POMT1* (encoding protein-O-mannosyl transferase 1), *POMT2* (protein-O-mannosyl transferase 2), *POMGnT1* (protein O-mannose β -1,2-nacetylglucosaminyl-transferase), *FKTN* (fukutin), *FKRP* (Fukutin-related protein), and *LARGE*. Muscle biopsies for patients with any of these may show absent or diminished staining with an antibody directed toward the glycosylated α -dystroglycan epitope.^{100,101} The phenotypic spectrum includes muscle-eye-brain (MEB) disease, marked by muscle weakness, ocular symptomatology ranging from poor ocular development and retinal hypoplasia to congenital glaucoma, and brain involvement including mental retardation, cerebellar cysts, and other abnormalities. Walker-Warburg syndrome (WWS) shows more profound mental retardation, lissencephaly and cortical migration defects, and eye malformations. Patients with Fukuyama CMD (FCMD) show profound CNS involvement, with mental retardation, seizures, and severe brain malformations.¹⁰² For the clinician, molecular diagnosis of patients presenting with these phenotypes may present a challenge because significant

genetic heterogeneity exists with overlapping phenotypes. One may argue that diagnosis of CMD patients with brain and ocular involvement represents one of the few times when use of a mutational diagnostic panel (rather than individual gene testing) may be clearly warranted.

Mutations in these same genes are increasingly recognized in milder phenotypes presenting in late childhood or early adulthood. As previously mentioned, mutations in *FKRP* result in the relatively common LGMD2I, and relatively mild limb-girdle phenotypes have been associated with mutations in *POMT1* (LGMD2K),¹⁰³ Fukutin (LGMD2M),¹⁰⁴ *POMT2* (LGMD2N),¹⁰⁵ and *POMGnT1* (LGMD2O).¹⁰⁶

Collagenopathies

Congenital muscular dystrophies are also associated with mutations in pathways unrelated to dystroglycan glycosylation. Among the most important is Ullrich congenital muscular dystrophy (UCMD), associated with mutations affecting genes encoding subunits of the collagen VI protein (*COL6A1*, *COL6A2*, and *COL6A3*).^{107,108} UCMD is marked by congenital contractures of the proximal joints, with simultaneous hyperlaxity of the distal joints, kyphoscoliosis, and early respiratory failure.¹⁰⁹ Originally, this was considered to be a rare syndrome, but improvements in diagnostic methods¹¹⁰ have led to the recognition that this is a quite common identifiable cause of CMD.^{109,111,112} Muscle biopsy may reveal absent or severely reduced collagen 6 staining, although this finding is not uniform. Mutational analysis of the *Col6A* genes is often required. Both autosomal recessive and autosomal dominant inheritance has been described, with the latter usually associated with dominant negative missense mutations affecting conserved glycines within triple helical domains required for subunit assembly.¹¹³ At the same time, both dominant¹¹⁴ and recessive¹¹⁵ mutations in the same genes cause the allelic Bethlem myopathy, which presents in adulthood with slow progression and striking contractures of the deep finger flexors and elbows. Intermediate phenotypes highlight the clinical and genetic overlap between these syndromes.^{116,117}

Selenoprotein N

Another increasingly recognized category of CMD is due to mutations in the *SEPN1* gene, encoding selenoprotein N (SelN). Mutations were first described in patients with the rigid spine muscular dystrophy phenotype,¹¹⁸ which is marked by congenital hypotonia, poor head control, spinal rigidity, joint contractures, and early respiratory insufficiency.¹¹⁹ As with collagenopathies, however, an expanded range of phenotypes have been described. All share early respiratory insufficiency, but a variety of pathologic features have been described, including congenital fiber type disproportion, multi-/minicore myopathy, and Mallory body myopathy.^{120–123} The mechanisms of pathogenesis are unclear, but SelN has been implicated in both oxidative and calcium homeostasis and interaction with the ryanodine receptor.¹²⁴

Therapeutics

The α -dystroglycanopathies represent a tempting target for therapies that increase glycosylation of α -dystroglycan,

independent of which enzyme is mutated. Although no human trials have yet been performed, two approaches show promise. Overexpression of *LARGE* results in functional α -dystroglycan in primary cells derived from patients with FCMD, MEB, and WWS.¹²⁵ Perhaps more strikingly, gene transfer of *GALGT2* (encoding GalNAc transferase) is protective in animal models of *LARGE* deficiency, LGMD2D, and DMD, suggesting not only a general therapy for the α -dystroglycanopathies, but for disorders of the dystrophin-associated glycoprotein complex in general.^{37,99,126,127}

Based upon evidence that primary cells from UCMD patients demonstrate increased apoptosis mediated by mitochondrial signals, six patients were treated with cyclosporine A, which acts at the mitochondrial permeability transition pore. In this open-label trial there was a suggestion of stabilization in limb, but not respiratory strength over 1 to 3.2 years¹²⁸; further trials are required.

Summary

The muscular dystrophies have long stood at the forefront of efforts to map and clone human disease genes. They now stand at the forefront of efforts to treat Mendelian diseases by gene transfer or gene-corrective therapies, and the coming decade will bring clinical trials to test novel therapies in many of these disorders. For the clinician, familiarity with the diseases and their molecular mechanisms will only increase in importance.

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