During the past decade, outstanding progress in the areas of congenital and limb-girdle muscular dystrophies has led to staggering clinical and genetic complexity. With the identification of an increasing number of genetic defects, individual entities have come into sharper focus and new pathogenic mechanisms for muscular dystrophies, like defects of posttranslational O-linked glycosylation, have been discovered. At the same time, this progress blurs the traditional boundaries between the categories of congenital and limb-girdle muscular dystrophies, as well as between limb-girdle muscular dystrophies and other clinical entities, as mutations in genes such as fukutin-related protein, dysferlin, caveolin-3 and lamin A/C can cause a striking variety of phenotypes. We reviewed the different groups of proteins currently recognized as being involved in congenital and limb-girdle muscular dystrophies, associated them with the clinical phenotypes, and determined some clinical and molecular clues that are helpful in the diagnostic approach to these patients.

Muscular dystrophies were first recognized as a disease entity with the detailed description of the clinical presentation of Duchenne muscular dystrophy in 1852 and thereafter.1,2 About 50 years later, Batten3 published the first case reports of a congenital form of muscular dystrophy (CMD). Unlike the Duchenne-Becker phenotype,2 in patients with CMD weakness and dystrophic changes in muscle biopsy specimens are present at birth, but they tend in many cases to be considerably less progressive than in patients with the Duchenne form. The term limb-girdle muscular dystrophy (LGMD) was introduced in the mid-20th century when it became obvious that there was an additional major group of non-congenital muscular dystrophies different from the X-linked Duchenne-Becker and autosomal dominant facioscapulohumeral forms.4 Accordingly, LGMD currently comprises clinical phenotypes with progressive weakness, onset in the limb-girdle muscles, and histologic evidence of a dystrophin-positive muscular dystrophy. The age at onset may range from early childhood to late adulthood.5

During the past decade, exciting progress has been made in the field of CMD and LGMD, emphasizing differences as well as commonalities between them. After further careful clinical delineation of phenotypes in particular within CMD, advances in genetic and histochemical characterization have led to the identification of numerous molecularly defined subtypes of muscular dystrophy based on the involved genes and proteins. This has brought individual clinical entities into sharper focus, but has also blurred the boundaries between the traditional categories of muscular dystrophy. For example, it has now been recognized that mutations in the same protein can give rise to very different phenotypes. Fukutin-related protein (FKRP) mutations can manifest with variable severity ranging from a severe CMD (including type 1C, CMD with cerebellar cysts, and Walker-Warburg syndrome) to a milder adult-onset LGMD (type 2I).6-11 Dysferlinopathies can present as a classic LGMD phenotype (type 2B), as a distal muscular dystrophy (Miyoshi type), or as mixed phe-
notypes. Mutations in lamin A/C have an even wider spectrum of phenotypes associated with them.

In this review, we will focus on entities within the scope of CMD and LGMD, as progress in these areas has led to staggering clinical and genetic complexity. We will briefly introduce the different groups of proteins currently recognized as being involved in CMD and LGMD before we associate them in a second step with the clinical phenotypes. Finally, we offer some clinical and molecular clues that are helpful in the diagnostic approach to these patients.

THE MOLECULAR PLAYERS

Dystrophin-Associated and Membrane-Based Proteins

The discovery of dystrophin as the protein deficient in Duchenne and Becker muscular dystrophy has led to the recognition of a multimeric protein complex associated with dystrophin (dystrophin-associated proteins) (for review see Blake et al). This complex can be subdivided further into 2 transmembrane (dystroglycan and sarcoglycan-sarcospan) and 1 intracellular (dystrobrevin-syntrophin) complex (Figure).

The dystroglycan complex forms an important link from the actin cytoskeleton via dystrophin to the basal lamina and extracellular matrix proteins, in muscle most importantly to laminin-2. Other ligands are known, such as neurexin, in the nervous system. Although mutations of dystroglycan itself in humans have not been found, alterations of its posttranslational modification as well as mutations in its main extracellular ligand laminin-2 give rise to diverse forms of LGMD and CMD. O-mannose-linked glycosylation is a rare form of posttranslational modification of mammalian proteins, but it seems to be specifically perturbed in dystroglycan in a number of disorders. Abnormal glycosylation appears to decrease or abolish dystroglycan's binding affinity for known interacting proteins of the extracellular matrix (eg, laminin and neurexin). So far, 3 different known or putative glycosyltransferases or proteins involved in these pathways have been shown to cause mainly CMDs in humans (for review see Michele and Campbell). Abnormal α-dystroglycan likely is responsible for most of the observed aspects of these disorders, but it is unclear whether other target proteins could also be underglycosylated and contribute to the pathogenesis of the disease.

In contrast, the sarcoglycan-sarcospan complex is mainly involved in the pathogenesis of LGMD phenotypes (LGMD2C-F). In muscle, the major sarcoglycan complex consists of the subunits α-, β-, γ-, and δ-sarcoglycan, all of which can be mutated in forms of LGMD. Additional sarcoglycans (ε, ζ) are also known to be expressed in other tissues. Mutations in e-sarcoglycan cause myoclonus-dystonia syndrome. Possible
functions of the complex are still speculative and range from structural support of the nearby dystroglycan complex to roles in signaling and cell survival. Sarcospan is a transmembrane protein intimately associated with signaling proteins and receptors. Although a mouse splicing factor fer-1 (from which the name is derived), dystrobrevin presumably is involved in calcium-dependent membrane fusion and repair by regulating vesicle formation.44,45 The impaired muscle mem-

Table 1. The Congenital Muscular Dystrophies (CMDs)

<table>
<thead>
<tr>
<th>Disease Entity</th>
<th>Locus, Protein Product</th>
<th>Helpful Clinical Features</th>
<th>CNS Involvement</th>
<th>Laboratory Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMD with primary laminin-2 (merosin) deficiency (MDC1A)</td>
<td>6q22-q23, Laminin-α2</td>
<td>Seating and standing with support as maximal motor ability if complete deficiency, neuropathy, epilepsy in about 30%, possible subclinical cardiomyopathy, generally normal mental development</td>
<td>Abnormal white-matter signal (T2 MR imaging), 5% occipital pachygyria or agyria</td>
<td>Mostly complete laminin-α2 deficiency on IH/WB, secondary reduction of integrin α7 possible, mutation analysis*</td>
</tr>
<tr>
<td>CMD with partial merosin deficiency (MDC1B)</td>
<td>1q42, Not known</td>
<td>Rare, variety of severity, delayed onset possible, proximal girdle weakness, generalized muscle hypertrophy, early respiratory failure possible</td>
<td>Abnormal white-matter and structural changes possible</td>
<td>Partial deficiency of laminin-α2 on IH/WB, α-DG significantly reduced on IH, linkage analysis</td>
</tr>
<tr>
<td>Fukutin-related proteinopathy (MDC1C)</td>
<td>19q13.3, Fukutin-related protein (FKRP, putative phospholipid transferase)</td>
<td>Often reminiscent of MDC 1A, but severity more variable, from severe CMD to LGMD (Table 2), generally normal mental development, rare cases with structural brain involvement and mental retardation</td>
<td>Generally normal, structural abnormalities with cerebellar cysts possible</td>
<td>α-DG with diminished MW on WB, or reduction of IH using antibodies against glycosylated isotypes, secondary reductions in laminin-α2 on IH/WB, mutation analysis*</td>
</tr>
<tr>
<td>LARGE-related CMD (MDC1D)</td>
<td>22q12.3, LARGE (putative glycosyltransferase)</td>
<td>So far only 1 patient described; congenital muscular dystrophy with profound mental retardation</td>
<td>White-matter changes, hypoplastic brainstem, mild pachygyria</td>
<td>IH/WB comparable with MDC1C, mutation analysis*</td>
</tr>
<tr>
<td>Ulrich CMD (UCMD)</td>
<td>21q22.3 And 2q37, α1/2 and α3 collagen VI</td>
<td>Distal joint hyperextensibility, proximal contractures, motor abilities variable, precludes independent ambulation in severe cases, soft palmar skin</td>
<td>No</td>
<td>IH for collagen VI with severe to mild deficiency, mutation analysis*</td>
</tr>
<tr>
<td>CMD with early spine rigidity (RSMD)</td>
<td>1p36-p35, Selene protein N†</td>
<td>Delayed walking, predominantly axial weakness with early development of rigidity of the spine, restrictive respiratory syndrome</td>
<td>No</td>
<td>Normal expression of laminin-α2, mutation analysis</td>
</tr>
<tr>
<td>Fukuyama CMD (FCMD)</td>
<td>9q31, Fukutin (putative phospholipid transferase)†</td>
<td>Frequent in Japanese population, never walk, mental retardation, epilepsy common</td>
<td>Lissencephaly type II/ pachygyria, cerebellar abnormalities</td>
<td>IH/WB comparable with MDC1C, mutation analysis</td>
</tr>
<tr>
<td>Muscle-eye-brain disease (MEB)</td>
<td>1q22-q34, Protein-O-linked mannose β1,2-M-acetylglucosaminyltransferase 1 (POMGnT1)†</td>
<td>Severe weakness and mental retardation, large head, prominent forehead, flat midface, walking rarely achieved, ocular involvement (eg, severe myopia, retinal hypoplasia), deterioration because of spasticity</td>
<td>Lissencephaly type II/ pachygyria, eye malformations, brainstem and cerebellar abnormalities</td>
<td>IH/WB comparable with MDC1C, mutation analysis</td>
</tr>
<tr>
<td>Walker-Warburg syndrome (WWS)</td>
<td>9q34.1, O-mannosyltransferase 1 (POMT1)†</td>
<td>Severe, lethal within first years of life because of severe CNS involvement</td>
<td>Lissencephaly type II, pachygyria, hydrocephalus, encephalocoele, eye malformations</td>
<td>IH/WB comparable with MDC1C, same phenotype can also be caused by fukutin or FKRP mutations, mutation analysis</td>
</tr>
<tr>
<td>Integrin α7</td>
<td>12q13, Integrin α7</td>
<td>Rare, delayed motor milestones, walking within 2-3 y</td>
<td>No</td>
<td>Absence of integrin α7 on IH (secondary reduction possible), mutation analysis*</td>
</tr>
</tbody>
</table>

(continued)
brane repair in the absence of dysferlin might be a key factor in the pathogenesis of dysferlinopathies (LGMD2B and Miyoshi muscular dystrophy). 51

**Extracellular Matrix**

As mentioned earlier, laminin-2 (merosin) is the most important extracellular ligand of α-dystroglycan in muscle. Posttranslational processing defects of α-dystroglycan disturbing this interaction have already been pointed out as an important cause of various forms of muscular dystrophy. Mutations in the gene encoding the laminin-α2 chain cause one of the most common single forms of CMD (type 1A, or CMD with primary merosin deficiency). 52-55 Collagen VI is a component of the extracellular matrix that does not directly belong to the group of dystrophin-associated proteins. It is unique among the collagens in that it forms beaded microfibrils 56 and is closely associated with cells and the basal lamina. 37 Mutations in collagen VI underlie both the milder Bethlem myopathy 58 and the more severe CMD type Ullrich. 59-62 Disturbed interactions of collagen VI with the basal lamina might be a possible pathomechanism, but the precise role and function of collagen VI are still unclear.

**Contractile Apparatus**

Several sarcomeric proteins, mostly associated with thin filaments, are known to be involved in nemaline myopathy. 63 whereas components of the thick filaments (myosin heavy-chain genes) are associated with hypertrophic cardiomyopathy, distal myopathy, and hyaline body myopathy. However, it has now become apparent that there is an important but rare group of “sarcomeric LGMDs” as well. So far, relevant molecules include the Z-disc-associated proteins telethonin (LGMD2G) 64 and myotilin (LGMD1A), 65 and the M-line–associated protein titin (LGMD2J). Heterozygous mutations in titin can cause a dominantly inherited late-onset distal muscular dystrophy. 66

**Nuclear Membrane**

Lamin A/C is a multifunctional intermediate filament of the inner nuclear membrane that has so far been shown to be involved in a range of quite divergent but also overlapping phenotypes, including Emery-Dreifuss muscular dystrophy (EDMD), 4 cardiac myopathy with conduction system disease, 15 autosomal recessive axonal polyneuropathy (CMT2), 7 mandibuloacral dysplasia, 16 Hutchinson-Gilford progeria syndrome, 18,19 and atypical Werner syndrome, 2 as well as rare cases of autosomal dominant LGMD. 67 It interacts with emerin and may regulate chromatin structure, thereby influencing gene expression. 68

**Enzymes and Others**

In addition to the known and putative enzymes involved in posttranslational glycosylation of α-dystroglycan, 2 additional enzymes, namely, the muscle-specific neutral protease calpain-3 59,70 and tripartite motif-containing protein 32 (TRIM32), an enzyme possibly involved in ubiquitination, 71 have been identified by positional cloning as causative of LGMD2A and LGMD2H, respectively. However, the exact pathway by which these mutations cause muscular dystrophies still has to be elucidated. Selenoprotein N (SEPN1), which causes rigid spine muscular dystrophy 72 and the classic form of multisystemic disease, 73 belongs to the family of selenoproteins, but no function has been assigned to it yet.

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**Table 1. The Congenital Muscular Dystrophies (CMDs) (cont)**

<table>
<thead>
<tr>
<th>Disease Entity</th>
<th>Locus, Protein Product</th>
<th>Helpful Clinical Features</th>
<th>CNS Involvement</th>
<th>Laboratory Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMD with microcephaly/calf hypertrophy</td>
<td>Not known</td>
<td>Joint contractures associated, severe psychomotor retardation, no walking, striking enlargement of calf and quadriceps muscles, CK grossly elevated</td>
<td>Megacisterna magna, cerebellar hypoplasia, white-matter changes</td>
<td>Mild to moderate partial deficiency of laminin-α2 on IH</td>
</tr>
<tr>
<td>CMD with adducted thumbs</td>
<td>Not known</td>
<td>Rare, adducted thumbs, toe contractures, generalized weakness, delayed walking, ptosis, external ophthalmoplegia, mild mental retardation</td>
<td>Mild cerebellar hypoplasia</td>
<td>Normal expression of laminin-α2 and α-DG on IH</td>
</tr>
<tr>
<td>CMD with mental retardation and microcephaly</td>
<td>Not known, FKRP not yet excluded</td>
<td>Microcephaly, delayed psychomotor development, generalized muscular wasting and weakness with mild facial involvement, calf pseudohypertrophy, joint contractures, severe mental retardation</td>
<td>Pontocerebellar hypoplasia, focal cortical dysplasia, white-matter changes, cerebellar cysts</td>
<td>Normal expression of laminin-α2</td>
</tr>
<tr>
<td>CMD with cerebellar atrophy</td>
<td>Not known</td>
<td>Delayed motor milestones, mild intellectual impairment</td>
<td>Moderate to severe cerebellar hypoplasia, no white-matter abnormalities</td>
<td>Normal expression of laminin-α2</td>
</tr>
</tbody>
</table>

Abbreviations: CK, creatine kinase; CNS, central nervous system; DG, dystroglycan; IH, immunohistochemistry; MR, magnetic resonance; MW, molecular weight; WB, Western blot.

*Currently not available as diagnostic testing; performed only on a research basis.
†Marked genetic heterogeneity for this phenotype.
THE PHENOTYPES: CMD

The CMDs are a group of genetic disorders in which weakness and abnormal muscle histologic features are present at birth. Muscle weakness tends to be more stable overall, depending on the individual disease, but complications of the dystrophy can become more prominent over time. To establish a diagnosis of CMD, a muscle biopsy is required. Pathological findings include variation in fiber size, internal nuclei, and increased endomysial and fatty tissue. Signs of ongoing degeneration and regeneration may be less prominent than in later-onset muscular dystrophies (eg, Duchenne-Becker or sarcoglycanopathies). Serum creatine kinase concentrations are variable and can also be normal. The mode of inheritance for most CMDs is autosomal recessive with significant genetic heterogeneity. The worldwide incidence of congenital muscular dystrophies is not known, but for northeast Italy it has been estimated at 4.7/100,000. Although the abbreviation CMD is widely used for congenital muscular dystrophies, in the HUGO (Human Genome Organisation) nomenclature this abbreviation has already been assigned to cardiomyopathy, dilated. Therefore, in the HUGO nomenclature MDC for muscular dystrophy, congenital is used instead.

For a useful clinical approach, CMD can be segregated in subgroups with normal mental development or mental retardation. Magnetic resonance imaging of the brain is indispensable in the clinical approach to CMD, as it may show abnormalities of brain formation and neuronal migration or changes in the white matter, or it may be completely normal. Although this clinical approach does not completely coincide with a classification according to the involved proteins, most of the forms with abnormalities of brain formation that have been defined on a molecular level show alterations of α-dystroglycan O-linked glycosylation, while mutations of laminin-2 and other proteins of the extracellular matrix generally allow normal mental development, even though abnormalities of the white matter are seen in laminin-2 mutations.

CMD With Normal Mental Development

The largest subgroup in this category consists of patients with a primary laminin-2 (merosin) deficiency due to mutations in the laminin-α2 chain (MDC1A). These patients mostly present at birth or during the first month of life with muscular hypotonia, contractures, and respiratory and feeding problems. Facial weakness is often prominent and motor development is markedly delayed, precluding independent ambulation. Most patients develop respiratory insufficiency requiring ventilatory support during the first decade of life. Although cognitive function is usually normal, T2-weighted magnetic resonance imaging of the brain by 6 months of age almost always shows abnormalities of the white matter. A small minority of patients show structural brain changes in the form of occipital pachygria or agryria, which is associated with mental retardation and epilepsy. However, epilepsy is also found in about one third of patients without such structural brain abnormalities. Electrophysiologically, most children show a demyelinating motor neuropathy, since laminin-α2 normally is also expressed in Schwann cells. Partial deficiency of laminin-α2 can lead to milder phenotypes up to a LGMD-like presentation. However, white-matter abnormalities and a mild demyelinating peripheral neuropathy are features even in mild cases of lamininopathy.

A related clinical phenotype is shared by a group of patients with mutations in FKRP, a putative glycosyltransferase involved in the posttranslational O-mannose-linked glycosylation of α-dystroglycan, leading to a variable secondary deficiency of laminin-2 (MDC1C). As mentioned before, mutations in the same gene can also cause an LGMD phenotype. Divergent and therefore useful clinical features in the CMD group include the presence of pseudohypertrophy of leg and other muscles and evidence of left ventricular dilative cardiomyopathy in many patients, as well as the absence of white-matter abnormalities and peripheral neuropathy. Very recently, the phenotypic spectrum of this entity has been widened with the identification of homozygous FKRP mutations in 2 unrelated patients with CMD who also had cerebellar cysts and mental retardation and 1 patient with the severe phenotype of Walker-Warburg syndrome.

Ullrich muscular dystrophy (UCMD) defines a distinct group of patients with CMD with normal brain development. Clinically it is characterized by generalized muscle weakness and striking hypermobility of distal joints in conjunction with variable contractures of more proximal joints. Additional findings may include kyphoscoliosis, protruded calcanei, and follicular hyperkeratosis. Although in the classic presentation the disease is severe, precluding or leading to early loss of ambulation, considerably milder presentations have now also been recognized. A number of patients with UCMD were shown to be deficient in collagen type VI on the basis of autosomal recessive mutations in all 3 α-chain genes. Autosomal dominant mutations of collagen VI are known to cause the milder phenotype of Bethlem myopathy. Recently, it has been shown that a dominant mutation may also underlie the severe phenotype of UCMD. In addition, there is evidence of further genetic heterogeneity underlying the phenotype of UCMD, as involvement of collagen VI was excluded by immunohistochemistry or linkage analysis in a number of patients with the clinical characteristics reminiscent of UCMD.

The category of CMD with rigid spine is characterized by early rigidity of the spine and a restrictive respiratory syndrome. These signs are often preceded by hypotonia in the first months of life and predominantly axial muscle weakness. However, independent ambulation is normally achieved before 18 months of age. A considerable number of patients with this phenotype show mutations of selenoprotein N. Selenoprotein N mutations have now also been described in patients with the classic form of multimimicore disease, indicating significant overlap with one of the classic congenital myopathies. Conversely, core-like structures can sometimes also be seen in biopsy specimens from patients with CMD with rigid spine. Thus, these disorders represent a morphologic spectrum with similar clinical phenotypes and are also referred to as selenoprotein N-related myopathies.
CMD With Abnormal Brain Development and Mental Retardation

The main phenotypes in this group have been delineated on clinical grounds and include Fukuyama CMD,82 muscle-eye-brain disease,83,84 and Walker-Warburg syndrome,85 but variations and overlap phenotypes are not uncommon. All 3 of these syndromes are caused by mutations in genes encoding distinct glycosyltransferases and related proteins involved in the posttranslational modification of α-dystroglycan25-27 (Table 1). Common characteristics include severe muscular dystrophy, neuronal migration defects including lissencephaly type II (cobblestone complex), pachygryria, cerebellar and brainstem abnormalities, and variable ocular anomalies.

Fukuyama CMD is mainly found in the Japanese population and is characterized by congenital weakness, profound delay of motor development mostly precluding independent ambulation, and severe mental retardation. Typical findings on cerebral imaging include abnormal gyral formation as outlined above, a flat brainstem, and cerebellar hypoplasia.82 A first non-Japanese case has now also been described.86

Muscle-eye-brain disease was first described in Finland, where it is most prevalent. In addition to severe congenital muscular dystrophy and brain malformation such as lissencephaly II–pachygryria and cerebellopontine hypoplasia, this syndrome presents with more severe ocular abnormalities including severe congenital myopia, congenital glaucoma, pallor of the optic discs, and retinal hypoplasia.83,84

Walker-Warburg syndrome generally presents the most severe brain involvement and is lethal either prenatally or within the first years of life. The morphologic features are altogether more severe than what is found in muscle-eye-brain disease and in addition may include congenital cataracts, microphthalmia, hydrocephalus, occipital encephalocoele, fusion of the hemispheres, and absence of the corpus callosum.85 However, with the identification of the involved genes in these 3 syndromes, it has also been recognized that the phenotypic spectrum and the regional distribution for individual genetic defects are probably wider than previously assumed, thus blurring the boundaries between the clinically defined entities.87 Muscle-eye-brain disease and Walker-Warburg syndrome in particular are genetically very heterogeneous.

Additional clinical phenotypes of congenital muscular dystrophy with mental retardation are coming to light, often on a single-family basis (Table 1). A number of these appear to show abnormalities in α-dystroglycan immunostaining and immunoblot, suggesting that they may also fall within the same pathway of O-mannose–linked glycosylation of α-dystroglycan.91

LIMB-GIRDLE MUSCULAR DYSTROPHY

The term LGMD is used for all noncongenital muscular dystrophies with progressive proximal weakness that are not caused by a primary dystrophin deficiency. Onset, progression, and distribution of weakness vary considerably among patients and genetic subtypes.2 As in CMD, a muscle biopsy usually is necessary to confirm the presence of dystrophic changes, including evidence of degeneration and regeneration, and also to differentiate LGMD from other causes of progressive proximal weakness that do not qualify as muscular dystrophies. To keep track of an increasing number of distinct forms of LGMD, a purely genetic nomenclature was introduced.88 This nomenclature chronologically assigned LGMD1A, 1B, 1C, and so on to the autosomal dominant forms, and 2A, 2B, 2C, and so on to autosomal recessive forms. Compared with the dominant forms, autosomal recessive forms are about 10 times more common.89 Within autosomal recessive LGMD, calpainopathy, sarcoglycanopathies, dysferlinopathy, and FKRP mutations are the most important entities. In addition, a number of other disorders not strictly subsumed under LGMD in this classification may present with LGMD-like phenotypes. Examples include facioscapulohumeral muscular dystrophy,90 late-onset EDMD,95 and Bethlem myopathy.94

In developing a clinical approach, age at onset and progression, the pattern of weakness and contractures, and the mode of inheritance are important clues to narrow down the differential diagnostic possibilities and pursue further directed histologic and genetic workup.

When larger numbers of patients with LGMD are compared, there seems to be a gradation according to the age at onset and clinical severity. While early-onset Duchenne-like phenotypes tend to be caused by either sarcoglycan or FKRP mutations, calpain mutations more commonly present with juvenile onset and dysferlin mutations in early adulthood.95,96 The autosomal dominant types often show milder phenotypes, with onset in the later teens or adulthood. However, later onset is also common in FKRP mutations and can indeed occur in any type of LGMD.

Sarcoglycanopathies

This group comprises defects of α-, β-, δ-, and γ-sarcoglycan (LGMD2D, E, F, and C, respectively) and is frequent in the severe forms of LGMD.37-41,90,97 The clinical picture, although more variable, resembles in many aspects that of Duchenne muscular dystrophy. The course is invariably progressive, with loss of ambulation often occurring during the second decade of life. However, especially in cases with later onset, ambulation may be preserved until adult life. Unlike Duchenne muscular dystrophy, there is no cognitive involvement and overt cardiomyopathy is less common. However, in about 30% of patients, subclinical findings on electrocardiography or echocardiography indicate dilative cardiomyopathy.38 Patients with β- and δ-sarcoglycan mutations may be at higher risk for cardiac manifestations that are clinically relevant.

Fukutin-Related Proteinopathy (LGMD2I)

As discussed earlier, mutations of the enzyme FKRP cause defects of the posttranslational O-mannose–linked glycosylation of α-dystroglycan, with phenotypic presentations ranging from severe CMD to mild forms of LGMD in late adulthood.90-91 The FKRP mutations are not in-
frequently a cause of LGMD, and juvenile onset seems to be the most prevalent. Characteristic features include early weakness, in particular of the upper arms, shoulders, and neck flexors. There may be mild facial weakness especially in early-onset cases. Intelligence and magnetic resonance images of the brain are normal, but dilative cardiomyopathy and respiratory failure are common and occur in more than one third of patients.\(^{10,11}\) Especially because of the cardiac involvement, there are clinical similarities to Becker muscular dystrophy. Respiratory failure may be imminent after loss of ambulation.

**Calpainopathy (LGMD2A)**

In this also relatively common type of LGMD, the age at onset lies in late childhood or adolescence for most patients, but can range from about 2 to 40 years. An initial scapular-humeral-pelvic distribution of muscle weakness and atrophy is characteristic and often allows for its clinical recognition. In general, calpainopathy is a more atrophic muscular dystrophy with a rather thin muscle profile and early development of contractures. Contractures can be so extensive as to mimic EDMD. Calf hypertrophy, as occurs in patients with dystrophin, sarcoglycan, or FKRP mutations, is rarely seen in these patients, but it can occur. The course is progressive, with loss of ambulation mostly in the second or third decade of life. Life expectancy, however, is close to normal.\(^99\)

**Dysferlinopathy (LGMD2B, Miyoshi Myopathy)**

Although the initial clinical presentation can be of various types, the time of onset in dysferlinopathies seems to cluster rather homogeneously around 20 years of age.\(^100,101\) Possible patterns of muscle involvement include a limb-girdle phenotype, a posterior distal presentation (gastrocnemius) as Miyoshi myopathy, an anterior distal presentation, and mixed presentations, even with identical mutations.\(^102\) In the LGMD phenotype, the periscapular muscles are relatively spared in the early course compared with other types of LGMD (eg, sarcoglycanopathies). Even in the LGMD presentation, there is often characteristic early involvement of the gastrocnemius and soleus muscles, which might lead to wasting and difficulties in walking on the toes and can also be noted by imaging.\(^99,101\) The weakness is slowly progressive, with loss of ambulation often in the fourth decade of life. The serum levels of creatine kinase tend to be very high, at least in early stages of the disease.

**Other Autosomal Recessive LGMDs**

These rare disorders include telethoninopathy (LGMD2G),\(^64,103\) TRIM32-related dystrophy (LGMD2H),\(^71,104\) and titinopathy (LGMD2J)\(^66,105\) and have so far been confined to specific pedigrees or populations.

**Autosomal Dominant LGMD**

Autosomal dominant LGMDs tend to have an altogether slower course and later onset, with less elevation of serum creatine kinase level compared with recessive LGMD. They are also clinically much more heterogeneous. Some characteristics of individual disorders are shown in Table 2. The LGMD1B (laminopathy) is allelic with autosomal dominant EDMD caused by lamin A/C mutations.\(^109\) Possible cardiac involvement with various degrees of conduction block is comparable to that of the EDMD phenotype and necessitates early diagnosis and close follow-up. The LGMD1D (no gene identified yet) is very similar in its cardiac involvement. The phenotypic spectrum of caveolinopathy has recently broadened considerably. In addition to the LGMD phenotype (1C), possible presentations include asymptomatic elevation of blood levels of creatine kinase,\(^110\) myalgias,\(^111\) rippling muscle disease,\(^99\) and distal myopathy.\(^112\) The latter phenotypes appear to be the more common presentations.

**TREATMENT OPTIONS AND PERSPECTIVES**

Unfortunately, there are still no curative treatment options for any of the disease entities discussed in this review. Although virus-mediated gene transfer has been demonstrated to be feasible in some animal models of muscular dystrophy, there remain major challenges before these therapies can be used in large-scale clinical trials. These include, among others, the need for an efficient, systemic delivery system and appropriate ways to control neutralizing immune responses against vector components as well as the therapeutic protein. The use of corticosteroids and creatine monohydrate as in patients with Duchenne muscular dystrophy has been reported only in individual patients or small groups with sarcoglycanopathies,\(^113,114\) and larger studies are needed to substantiate possible positive effects.

The principles applied to the care of patients with congenital or limb-girdle muscular dystrophies resemble in many ways those in other neuromuscular disorders such as Duchenne muscular dystrophy or spinal muscular atrophy and will not be discussed in detail here. They are best addressed by an interdisciplinary team including physical and occupational therapists, orthopedist, pulmonologist, cardiologist, and social worker in addition to the neuromuscular specialist. All therapeutic efforts have to be adjusted to the individual patient and his or her environment and should aim to maintain the patient's independence as long as possible. Relentless development of contractures and scoliosis can be a prominent problem, particularly in collagen VI–related CMD, and requires vigilant orthopedic supervision and intervention. Restrictive lung disease or weakness of respiratory muscles can occur early in some of the discussed disorders (eg, laminin-α2 deficiency, collagen VI disorders, CMD with rigid spine syndrome, and FKRP pathy) and have to be tested for specifically. This will often require a sleep study in addition to standard pulmonary function tests to recognize the possibility of nocturnal hypoventilation. The same is true for cardiac involvement, which is more prominent in patients with sarcoglycanopathies and mutations in FKRP or lamin A/C.

Through unraveling their molecular causes, the muscular dystrophies and their phenotypes have been brought into sharper focus. At the same time, it has become clear that the possible phenotypes associated with given genes...
Abbreviations: AD-EDMD, autosomal dominant Emery-Dreifuss muscular dystrophy; BMD, Becker muscular dystrophy; CK, creatine kinase; DMD, Duchenne muscular dystrophy; ECG, electrocardiogram; IH, immunohistochemistry; WB, Western blot.

*Currently not available as diagnostic testing; performed only on a research basis.
†From Messina et al.106
‡From Speer et al.107
§From Palenzuela et al.108

Table 2. The Limb-Girdle Muscular Dystropies (LGMDs)

<table>
<thead>
<tr>
<th>Disease Entity</th>
<th>Locus, Protein Product</th>
<th>Helpful Clinical Features</th>
<th>Laboratory Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGMD2A, calpainopathy</td>
<td>15q15, calpain-3</td>
<td>Onset around age 10 y, but variable, early periscapular and humeral weakness, in lower extremity hip abductors relatively spared and posterior compartment of thigh prominently affected</td>
<td>Imaging to confirm with selective posterior involvement, lobulated type I fibers, calpain-3 reduction only on WB, mutation analysis</td>
</tr>
<tr>
<td>LGMD2B, dysferlinopathy</td>
<td>2p13, dysferlin</td>
<td>Onset around age 18 y with proximal, proximal-distal, or distal (Miyoshi) weakness, periscapular muscles relatively spared, distal biceps involved, gastrocnemius involved early</td>
<td>CK excessively elevated, deficiency of dysferlin in IH/WB, secondary reduction of calpain-3 on WB possible, mutation analysis possible but laborious (55 exons), * dysferlin expression in lymphocytes*</td>
</tr>
<tr>
<td>LGMD2C, γ-SGopathy</td>
<td>13q12, γ-sarcoglycan (SG)</td>
<td>Onset around age 6-8 y, but great variability with much later onset, distribution of weakness reminiscent of DMD/BMD, but sometimes earlier scapular involvement, calf hypertrophy very common, mental development normal, significant cardiomyopathy possible in a subset</td>
<td>CK elevated to very high, IH pattern of primary and/or secondary reduction of all 4 SG antibodies helpful to direct mutation analysis, secondary reduction in IH of dystrophin possible but normal size on WB, mutation analysis mostly necessary for definitive diagnosis</td>
</tr>
<tr>
<td>LGMD2D, α-SGopathy</td>
<td>17q21, α-sarcoglycan</td>
<td>Wide spectrum of possible age at onset and severity, from DMD-like severity to mild late-onset presentation, often reminiscent of dystrophinopathies, including muscle pseudohypertrophy and cardiomyopathy, more weakness in upper extremities/shoulders relative to lower extremities</td>
<td>α-Dystroglycan with diminished MW on WB, or reduction of IH using antibodies against glycosylated isotopes, secondary reduction in laminin-α2 on IH/WB possible, mutation analysis*</td>
</tr>
<tr>
<td>LGMD2E, β-SGopathy</td>
<td>4q12, β-sarcoglycan</td>
<td>Variable clinical picture, may have initial anterior tibial weakness with foot drop, but may also present as pure LGMD picture</td>
<td>Rimmed vacuoles in some patients, reduction in IH/WB for telethonin, mutation analysis (2 exons)*</td>
</tr>
<tr>
<td>LGMD2F, δ-SGopathy</td>
<td>5q33-34, δ-sarcoglycan</td>
<td>Variable clinical picture, may have initial anterior tibial weakness with foot drop, but may also present as pure LGMD picture</td>
<td>Rimmed vacuoles in some patients, reduction in IH/WB for telethonin, mutation analysis (2 exons)*</td>
</tr>
<tr>
<td>LGMD2G, telethoninopathy</td>
<td>17q11-12, telethonin</td>
<td>Variable clinical picture, may have initial anterior tibial weakness with foot drop, but may also present as pure LGMD picture</td>
<td>Rimmed vacuoles in some patients, reduction in IH/WB for telethonin, mutation analysis (2 exons)*</td>
</tr>
<tr>
<td>LGMD2H</td>
<td>9q33.2, TRIM32</td>
<td>Onset usually mid 20s, somewhat slower progression, back pain, some evidence of cardiac involvement on ECG, so far only in Hutterites</td>
<td>CK levels 5- to 50-fold elevated, dystrophic picture on biopsy, mutation analysis*</td>
</tr>
<tr>
<td>LGMD2I, FKRPopathy</td>
<td>19q13.3, fukutin-related protein (FKRP)</td>
<td>Wide spectrum of possible age at onset and severity, from DMD-like severity to mild late-onset presentation, often reminiscent of dystrophinopathies, including muscle pseudohypertrophy and cardiomyopathy, more weakness in upper extremities/shoulders relative to lower extremities</td>
<td>α-Dystroglycan with diminished MW on WB, or reduction of IH using antibodies against glycosylated isotopes, secondary reduction in laminin-α2 on IH/WB possible, mutation analysis*</td>
</tr>
<tr>
<td>LGMD2J, titinopathy</td>
<td>2q24.3, titin</td>
<td>Heterozygous parents might present with tibial muscular dystrophy, proximal weakness before 10 y</td>
<td>Possibly secondary deficiency of calpain-3 on WB, mutation analysis*</td>
</tr>
<tr>
<td>LGMD1A, myotilinopathy</td>
<td>5q22-q34, myotilin</td>
<td>Onset in young adulthood, slowly progressive, nasal quality of speech, mildly raised CK values, no cardiac involvement</td>
<td>Biopsy with autophagic vacuoles and nemaline rodlike structures, IH normal, mutation analysis*</td>
</tr>
<tr>
<td>LGMD1B, laminopathy</td>
<td>1q11-21, lamin A/C</td>
<td>Onset in late teens or early adulthood, cardiac manifestation with conduction system disease, overlap with AD-EDMD</td>
<td>Antibody studies for lamin A/C normal in heterozygous mutations, mutation analysis</td>
</tr>
<tr>
<td>LGMD1C, caveolinopathy</td>
<td>3p25, caveolin-3</td>
<td>Onset in childhood, muscle cramping and calf hypertrophy possible, no cardiac involvement</td>
<td>Reduction in IH for caveolin-3, mutation analysis (2 exons)*</td>
</tr>
<tr>
<td>LGMD1D†</td>
<td>6q23</td>
<td>Onset early adulthood, slowly progressive, cardiomyopathy</td>
<td>Only by linkage analysis*</td>
</tr>
<tr>
<td>LGMD1E‡</td>
<td>7q</td>
<td>Onset in late adulthood, dysphagia possible, no cardiac involvement</td>
<td>Only by linkage analysis*</td>
</tr>
<tr>
<td>LGMD1F§</td>
<td>7q32 (distinct from LGMD1E locus)</td>
<td>Progressive weakness mainly affecting proximal muscle, age at onset ranging from &lt;1 y to 58 y</td>
<td>Only by linkage analysis*</td>
</tr>
</tbody>
</table>

Cross boundaries between clinical groupings such as LGMD, CMD, distal muscular dystrophies, congenital myopathies, and others. Nonetheless, in clinical practice the patient usually is seen first without any knowledge of the underlying genetic basis. Thus, proper recognition and delineation of clinical phenotypes remains the initial and
most important step in initiating a workup that will ultimately establish a genetic diagnosis.

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REFERENCES


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**Correction**

Error in Wording and Terminology. In the article titled “Magnetic Resonance Imaging Abnormalities in Familial Temporal Lobe Epilepsy With Auditory Auras” in the November issue of the ARCHIVES (2003;60:1546-1551), the last sentence of paragraph 3 in the “Results” section should have read, “An interictal electroencephalogram performed in 6 patients detected no abnormalities,” and “VIIIS7(-2)A-G” in the “Results” section of the Abstract and article should have been “IVS7-2A>G.” This correction was made previously to online versions of this article.