Congenital muscular dystrophies (CMDs) are overall clinically and genetically heterogeneous neuromuscular disorders with onset at birth or in infancy and in which the muscle biopsy is compatible with the presence of a dystrophic myopathy. In early stages the muscle biopsy may just reveal a myopathic picture without clear dystrophic features, but the clinical context and morphology are able to suggest a diagnosis different from that of a specific congenital myopathy, a metabolic myopathy, or a neurogenic disorder. During the past 10 years, our knowledge of neuromuscular disorders has increased dramatically, in particular with regard to the exponential boost in disclosing the genetic background of CMDs.

Information on incidence and prevalence of CMDs is scanty because of the lack of diagnostic genetic confirmation in the past 10 years. Few studies are limited to epidemiologic figures of prevalence ranging from 0.68 to 2.5 per 100,000, which are probably underestimated. Moreover, similarly to other rare autosomal recessive disorders, founder mutations are known to occur among CMDs, such as the founder mutation in fukutin (FKTN) reported in Japan in (FKTN-related) Fukuyama-type CMD (FCMD), representing the most common CMD in that country followed by collagen VI (COL6)-deficient CMD. However, these epidemiologic data provide only a relative frequency of a diagnosed subtype of CMD in a given country rather than a real figure of incidence or prevalence.

The diagnosis of CMDs requires the concurrence of expertise in multiple specialties (neurology, morphology, genetics, neuroradiology) available in a few centers worldwide that have gained sufficient experience with the different CMD subtypes. Currently, the achievement of a molecular diagnosis is of paramount importance not only for phenotype-genotype correlations, genetic and prenatal counseling, and prognosis and aspects of management, but also concerning the imminent availability of clinical trials and treatments.

**Common Clinical Aspects of CMD**

Overall differential diagnosis of CMD has to take into account congenital myopathies, ie, myopathies with typical structural or ultrastructural features on the muscle biopsy, congenital myotonic dystrophy, congenital myasthenic syndromes, early-onset metabolic myopathies, Marinese–Sjögren syn-
drome, and other subtypes of congenital ataxia, congenital disorders of the motor neuron and the peripheral nerve, and other genetic syndromes such as Prader–Willi syndrome, and the more frequently acquired conditions leading to profound hypotonia, such as acute hypoxic ischemic encephalopathy and neonatal sepsis.

The most important tools to address these differential diagnostic possibilities, beyond a careful family history and the physical examination, are creatine kinase (CK) determination searching for persistent increased CK in plasma, nerve conduction velocity (NCV) studies with repetitive stimulation to recognize neurogenic conditions and abnormalities of neuromuscular transmission, magnetic resonance imaging (MRI) of the brain, muscle biopsy, and specific genetic or metabolic testing. Physical examination will have to focus on clinical clues for subtyping CMDs, such as congenital contractures, hip dislocation, excessive laxity and externally visible malformations of the head, cleft lip and/or palate, as well as eye abnormalities (retinal dysplasia, anterior chamber malformation, Peter anomaly, and congenital cataract).

A great number of patients with CMD have onset of symptoms at birth or in infancy, manifesting hypotonia and weakness, and some of them show delay in walking unassistedly. The typical presentation of a “floppy baby” can be observed; however, in other patients with milder symptoms, antigravity movements of limbs may be preserved and axial muscles of the spine are more involved with pronounced head lag, as often happens in *selenoprotein 1* (*SEPN1*)-and *lamin A/C* (*LMNA*)-related CMDs. Some symptoms are unlikely in CMD, such as marked facial weakness which is generally known to occur in patients with congenital myopathies, like nemaline myopathy, myotubular myopathy, centronuclear myopathy, or congenital myotonic dystrophy, as well as non-neuromuscular conditions, such as the Möbius syndrome. It is unlikely to observe ophthalmoplegia in CMD although it is often observed in CMD. The distribution of weakness may be predominantly axial, leading to pronounced head drop as described in *SEPN1*- and *LMNA*-associated CMD, or principally limb-girdle related, or more diffuse as in adGpathy and COL6-related CMD, or scapuloperoneal as in *LMNA*-related CMD. A predominant distal distribution is unlikely in CMD but common in peripheral neuropathies, motor neuron disease or distal myopathy.

Rapid progression of symptoms is not common in CMDs and should direct attention toward a congenital myasthenic syndrome, a channelopathy or a mitochondrial disorder. However, rapid progression has been observed in *LMNA*- and *LAMA2*-related CMD and in some patients with *FKRP*—and *FKTN* mutations with an LGMD phenotype, which were responsive to steroids. Selective muscle hypertrophy of calves and tongue is mostly seen in the aDGpathies. Joint contractures of shoulders, elbows, knees, and Achilles tendons often with associated prominent distal joint laxity but long finger flexor stiffness, can be a prominent part of the picture in *COL6*-associated myopathies and in *LAMA2* - and *LMNA*-associated CMD, but are limited to the spine in *SEPN1*-related CMD. In particular rigid spine is a prominent finding in neuromuscular diseases which, among the CMDs, is characteristically seen in *SEPN1* - and *LMNA*-related CMDs, but partially also in *LAMA2* deficiency and *COL6*-related CMD. Apart from this group, rigid spine is a prominent feature in other Emery–Dreifuss myopathies, including those associated with *LMNA*, *emerin* or *FHL1* mutations. Exclusively distal contractures are unlikely in CMD and are suggestive of one of the distal arthrogryposis syndromes, acquired congenital myasthenia, and neurogenic disorders, including congenital Charcot–Marie–Tooth disease.

Excessive joint laxity is typically seen in the *COL6*-related disorders, but is also detected in *LAMA2* deficiency and other connective tissue disorders, such as the Ehlers–Danlos syndrome group of disorders.
Diagnostic Procedures

Diagnostic procedures for CMDs are based on clinical findings, brain and muscle MRI, muscle biopsy histology and immunohistochemistry, skin biopsy and cultured immunohistochemical staining, as well as molecular genetic testing. Electromyography can be dispensed with as a preliminary examination but perhaps NCV testing is useful to rule out a peripheral neuropathy.

Determination of CK levels is an important preliminary examination together with brain and muscle MRI and a muscle biopsy in the diagnosis of CMD. Most CMDs show even mildly elevated CK values which, however, is not a rule because CK levels are generally normal in SEPN1-related CMD and frequently normal in COL6-related CMD.

MRI of the brain can be particularly helpful in the diagnosis of the aDGopathies and in LAMA2-related CMD.

Muscle MRI

MRI of the muscle is particularly useful when suspecting a COL6-, SEPN1- or LMNA-related CMD\(^{10-12}\) showing specific or preferential involvement of certain muscle groups for each condition. In COL6-related disorders, the muscle MRI shows a characteristic pattern with diffuse fatty infiltration within thigh muscles taking the form of a rim of hypodensity at the periphery of muscles, particularly in vasti muscles, with a relative sparing of the central part and with relative sparing of the sartorius, gracilis, and adductor longus muscles. Particularly in the mild phenotypes of Bethlem myopathy (BM), MRI shows a systematic fatty infiltration in the rectus femoris muscle and specifically takes the form of a central hypodensity described as a “central shadow sign.”\(^{1011}\) In selenoproteinopathies, selective involvement of sartorius and adductor longus muscles but sparing of the gracilis muscle is highly suggestive of the diagnosis.\(^{11-13}\)

Electromyography/NCV testing can be useful to rule out a peripheral neuropathy that may be associated particularly in LAMA2-related CMD.\(^{14}\)

Muscle Pathology

Careful evaluation of the muscle biopsy offers a key to reach a correct genetic diagnosis. Moreover, the pathologic evaluation always has to consider that clinical features are essential to direct the interpretation of the pathologic findings. First of all, the muscle biopsy is useful to exclude other disorders that are not CDM-related, such as neurogenic changes (clear fiber-type grouping with oxidative stains as well as ATPase stains), typical findings of defined congenital myopathies (nemaline rods, central cores, central nuclei), or other aspects indicative of a metabolic myopathy, such as mitochondrial myopathy or a lipid and glycogen storage myopathy. Lack of any morphologic changes may suggest a Prader–Willi syndrome or congenital myasthenia.

In CMD, the muscle biopsy generally shows abnormal variation in fiber size with the histologic hematoxylin and eosin stain and the modified Gomori trichrome (GT) stain, associated with whorled and/or split fibers, and rare hypercontracted fibers. There is a frequent increase in internal nuclei with a variable increase in endomysial connective and adipose tissues. Prominent muscle necrosis is infrequent and frequently absent in CMD. In addition, the GT stain is useful to rule out nemaline bodies, ragged red fibers and features of myofibrillar myopathy that may occur in SEPN1-related CMD.

Cores can be diagnosed if observed with both COX and NADH-TR stains. The presence of large and longitudinally extended cores would exclude a diagnosis of CMD and suggests a ryanodine receptor 1 (RYRI)-related myopathy.

The presence of minicores with oxidative stains and NADH-TR stains may suggest either a SEPN1- or RYRI-related myopathy.

The immunohistochemical examination is of utmost importance in the pathologic workup of a biopsy from a patient suspected of being affected by a form of CMD, and the use of antibodies for merosin, COL6, and glycosylated α-dystroglycan (αDG) is particularly helpful.

Diagnosis and Genotype-Phenotype Correlation of the Specific Forms of CMD

LAMA2-Related CMD Deficiency (CMD with Merosin Deficiency/MDC1A)

Diagnosis

LAMA2-related CMD is caused by mutations in the LAMA2 gene, encoding the heavy α2 chain of the laminin 211 isoform (α2/β1/γ1).\(^{15-18}\) LAMA2 is also called merosin and this form of CMD is denominated as primary LAMA2 or merosin deficiency and in the genetic nomenclature, it is also defined as MDC1A. A complete deficiency in muscle is always caused by mutations in LAMA2, but some primary merosin deficiency may also show a partial deficiency that should be distinguished from the secondary merosin deficiency forms, mostly as the result of abnormal O-mannosylation of αDG, as seen in the aDGopathies. Complete absence of LAMA2 is generally associated with a more severe phenotype compared with a partial deficiency.

Patients with the most frequent severe phenotype present with weakness and hypotonia at birth and some can manifest contractures in their hands and feet. The CK level is elevated more than 5 times, particularly in the first 2 years of life. Patients with the severe form are generally unable to walk independently.\(^{19}\) MRI findings show typical involvement of the white matter in all patients, typically presenting with a high signal in the white matter of the brain on T2-weighted and fluid attenuation inversion recovery (FLAIR) images. The internal capsule, corpus callosum, cerebellum and other dense fiber tracts are usually spared. A small percentage (ie, 5%) of patients show more obvious abnormalities of brain formation, in particular occipital cortical dysgenesis and cerebellar hypoplasia.\(^{20}\) Seizures occur in about 30% of all patients with merosin-deficient CMD although the majority of
merosin-deficient CMD patients with seizures do not reveal any obvious evidence for a cortical malformation on MRI.

Progressive respiratory insufficiency is a constant finding in the course of the disease in nonambulatory patients and becomes fully manifest in the second or third decade of life. Development of a clinically relevant cardiomyopathy is unusual, although up to one-third of the patients show abnormal cardiac testing, but only a small subgroup turns out to be symptomatic.

Mutations in LAMA2 can also be related to partial LAMA2 deficiency in immunohistology of muscle, and in most cases this pattern is related to milder phenotypes, although some patients may have manifestations as severe as in the complete deficiency form. Patients with LAMA2 mutations and milder manifestations may present with features of LGMD weakness, associated with brain white matter changes on MRI and elevated CK levels, as well as with contractures of the elbows and rigidity of the spine. In one recent series of patients with partial LAMA2 deficiency, 5 of 13 patients achieved unassisted ambulation, and a further 3 of 13 walked with aid.

Genotype-Phenotype Correlations

Most mutations in typical complete LAMA2 deficiency are stop mutations or they predict a pretermination codon mutation leading to absence of the protein on immunostains, associated with a more severe phenotype. In a recent review series 55% of mutations were located in exons 14, 25, 26, and 27. Compound heterozygosity for a null mutation and an in-frame deletion or exon-skipping mutation may lead to a milder phenotype with partial deficiency of LAMA2. By contrast, in-frame deletions affecting the G-domain, which is important for binding to aDG and integrin, affect the function of this molecule profoundly, leading to a severe phenotype, even though merosin may be partially present in the basement membrane on immunohistologic examination. Rarely, a homozygous missense mutation has been associated with obvious LAMA2 deficiency such as pHis2627Gln. It is of note that there can be intrafamilial variability for the clinical manifestations and also for the degree of LAMA2 deficiency noted on immunostaining in the muscle biopsy.

α-Dystroglycanopathies

Diagnosis

The group of CMDs are characterized by abnormal glycosylation of aDG (aDGopathies) and include the FCMD (Online Mendelian Inheritance in Man [OMIM]: 253800), muscle-eye-brain disease (MEB; OMIM: 253280), Walker–Warburg syndrome (WWS; OMIM: 236670), congenital muscular dystrophy 1C (FKRP-related or MDC1C; OMIM: 606612), and congenital muscular dystrophy 1D (LARGE-related or MDC1D; OMIM: 608840) as well as the allelic LGMD presentations for most of these genes. All the classical clinical phenotypes along this spectrum are genetically heterogeneous with mutations residing in the known 6 genes encoding for proven or putative glycosyltransferases. In addition, a number of patients have similar clinical patterns but their genes are not known thus far. The underlying genetic defects in this group of disorders are mutations either in known or putative glycosyltransferase enzymes and cooperating proteins involving aDG-O-mannosyl-linked glycosylation or subsequent LARGE-dependent glycosylation, aDGpathies. Thus, all these conditions are characterized by an apparent deficiency of immunolabeling for aDG using antibodies directed against glycosylated aDG with preserved staining for the aDG core protein by immunohistochemistry in the muscle sarcolemma (monoclonal I1H6 and V1A4-1). A gross correlation between reduced aDG staining in the muscle biopsy and the clinical course was observed in a study of 24 patients with mutations in POMT1, protein-O-mannosyl transferase 2 (POMT2) and protein O-mannose β-1,2-n-acetylglucosaminyltransferase (POMGnT1), which, however, was not always the case in patients with mutations in FKTN and FKRP, in whom mild limb-girdle phenotypes without brain involvement may show profound depletion of glycosylated aDG. The reverse may also occur, that is a severe clinical phenotype associated with an only mild deficiency of aDG.

The anatomical abnormalities of the CNS that are apparent on MRI can be helpful for a preliminary diagnosis, including cortical malformations in the form of lissencephaly type II (cobblestone complex), ranging from complete lissencephaly to more focal pachygyria, or polymicrogyria with frontal predominance. Infratentorial changes are characteristic in many patients with midbrain hypoplasia with relatively thick tectum, pontocerebellar hypoplasia, and abnormalities of cerebellar foliation and cerebellar cysts. There may also be hydrocephalus, and occipital encephalocele in extreme cases. The white matter hypersignal on FLAIR or T2-weighted MRI is often abnormal and, in contrast with the situation in LAMA2-related CMD, has been reported to regress with time, at least for FKTN and FKRP-related CMD. In its typical appearance, the pattern of CNS involvement on imaging can be highly characteristic of these conditions and, therefore, of great diagnostic help. Cerebellar cysts, in particular, are frequently observed in POMGnT1, FKTN and FKRP mutations and have recently been described in POMT2- and LARGE-related patients. Notably a similar MRI pattern, associating lissencephaly type II with midbrain hypoplasia and the white matter hypersignal on FLAIR or T2-weighted MRI, has also been reported in patients with GPR56 mutations who do not have abnormal glycosylation of aDG and are not affected by a CMD. GPR56 is a G protein–coupled receptor family that plays a role in the development of neural progenitor cells.

According to the clinical phenotype, the priority for genetic testing can be summarized as follows: (a) in case of a WWS or in a patient with or without MR and microcephaly but normal brain MRI: POMT1, POMT2; (b) in case of a MEB-like picture with cerebellar cysts and with or without macrocephaly: POMGnT1, FKRP, FKTN, LARGE; (c) in case of a CMD/LGMD with normal intelligence, with or without cardiomyopathy: FKRP, FKTN (non-Japanese mutation).

Genotype-Phenotype Correlations

The mutation frequency in the 6 genes known for all patients with aDGopathies (ie, evidence for a deficiency of glycosylated
aDG immunoreactivity on the muscle biopsy) has been examined in 2 different large published series\(^{37,38}\) and ranges from 34% to 53% (although the study with the lowest mutation rate did not include the FKRP gene, which had been reported separately)\(^{39}\) indicating that approximately half of the patients with an aDG pathway harbor mutations in still undiscovered genes. For WWS patients alone, this number amounts to 50% to 60%\(^{37,38,40,41}\) [Van Broeckhoven, personal communication]. This and other data suggest that in patients presenting with a WWS phenotype based on POMT1 and POMT2, mutations should be analyzed first, then followed by analysis of FKRP, FKTN, LARGE and, finally, also POMGnT1 as the phenotypic spectrum is expanding.\(^{39}\) In the POMT1 and POMT2 genes, mutations leading to severe functional defects (eg, prematurely truncated protein, involvement of residues crucial for the enzymatic activity) appear to be associated with severe MEB or WWS phenotypes\(^{41}\) whereas missense changes distant from crucial protein domains or affecting not highly conserved amino acids result in milder phenotypes, such as CMD with MR and normal MRI\(^{27,42,43}\) or even LGMD without MR, as in one case, each with mutations in POMT2\(^{44}\) and POMGnTI.\(^{32}\) In addition, mutations in POMGnT1 showed the highest correlation with the typical MEB phenotype\(^{37,38}\) accounting for approximately 25% to 30% of all MEB cases. The Finnish MEB founder mutation\(^{28}\) has also frequently been reported in other series of patients with comparable severe clinical presentations consistent with the Finnish disease.\(^{40}\) Patients with milder clinical presentation most often exhibit a mutation located toward the 3’ end of the POMGnT1 gene.\(^{32,45}\)

Patients who are homozygous for the ancestral Japanese mutation (insertion of a retrotransposon) in FKTN have a comparatively milder phenotype (FCMD), whereas the disease severity increases in patients who are compound heterozygous for this ancestral mutation and reveal a more severe loss-of-function mutation on the other allele.\(^{46}\) Homozygous null mutations in the human FKTN gene have been characterized in 2 patients of Turkish origin with a severe WWS-like phenotype.\(^{47}\) The spectrum of phenotypes associated with FKRP mutations now also extends to the mild side into the LGMD range with normal brain imaging and cognition although significant cardiomyopathy may develop in some patients.\(^{31}\)

For the FKRP gene, the c.826C>A (p. Leu276Ile) mutation is particularly common in LGMD2I patients and appears to confer a relatively mild phenotype when present in the homozygous state, but can be more variable in the compound heterozygous state depending on the second mutation.\(^{39,46}\) By contrast, most of the other FKRP mutations associated with CMD are private. FKRP mutations are currently associated with the broadest clinical spectrum\(^{30,46}\) ranging from a Becker-like limb-girdle muscular dystrophy to a congenital muscular dystrophy (referred to as MDC1C) with presentation at birth and severe weakness or severely progressive weakness after walking acquisition.\(^{49}\) The spectrum further extends to patients with isolated cerebellar cysts and MR with or without posterior fossa- or supratentorial abnormalities (focal unilateral periventricular nodular heterotopias) to marked cerebellar dysplasia and pontine hypoplasia.\(^{30,50}\) Finally, some rare patients with a WWS phenotype caused by FKRP mutations have been reported.\(^{23}\) Cardiomyopathy has been observed in all of these severities, including—and even particularly—in the LGMD presentation.

So far, patients with normal cognition have been demonstrated for FKRP and FKTN mutations while any evidence for POMGnT1, POMT1, POMT2 and LARGE mutations remains unconfirmed.

Rare genomic deletions or deletion-insertion have been reported in POMT2 and LARGE.\(^{31,52}\)

Finally, patients with reduced aDG but without evident mutations in the 6 genes have been recognized. Within this group, some patients present with evidence of both aDG pathway and a congenital disorder of glycosylation and in whom mutations in the dolichol phosphate mannose 1, 2 and 3 genes are now being recognized.\(^{53}\) These patients may present with cognitive impairment, microcephaly, cerebellar hypoplasia, feeding difficulties and severe myoclonus epilepsy.\(^{54}\) Further broadening of the genetic and phenotypic spectrum of the aDG pathways is to be expected.

**COL6-Related Myopathies**

**Diagnosis**

COL6 is broadly expressed in several tissues, including skin and skeletal muscle, and it is able to form a beaded microfibrillar network that anchors the surface of cells with the interstitial connective tissue,\(^{55}\) playing an important role in mediating cell matrix interactions. COL6 is abundantly synthesized and secreted by cells organizing an extracellular matrix (ECM), such as skin fibroblasts and myofibroblasts, smooth muscle cells and endothelial cells. In skeletal and heart muscles, it localizes in the reticular layer of the basement membrane around each fiber, the perimysium and endomysium. In skin, it is particularly concentrated in the papillary dermis, as well as in the basal lamina of glands, hair follicles, blood vessels, peripheral nerves and erector pili muscles.

The COL6 protein is composed of 3 different subunit \(\alpha\)-chains encoded by the 3 genetically distinct genes \(\alpha\)COL6A1 (21q22.3), \(\alpha\)COL6A2 (22q23.3) and \(\alpha\)COL6A3 (2q37). Each \(\alpha\)-(VI) chain contains a relatively short triple-helical domain and N- and C-terminal globular regions. COL6 chains generally occur in a stoichiometric ratio\(^{39}\) and show a peculiar pattern of assembly. Owing to antiparallel aggregation, monomers assemble intracellularly into dimers and, subsequently, into trimers that are secreted in the ECM. Finally, trimers associate end-to-end to form the beaded filaments.\(^{56}\)

COL6 filaments are believed to play a pivotal role in ECM assembly due to their interactions with several matrix proteins, such as the fibrillar collagens I and II\(^{57,58}\) fibronectin,\(^{59}\) decorin and biglycan.\(^{57,61}\) In the basal lamina, COL6 interacts with several important components such as collagen IV and perlecan,\(^{62}\) suggesting its role in anchoring the basement membrane to the underlying connective tissue.

In addition, in the plasma membrane, COL6 also interacts with cell transmembrane receptors, such as NG2 proteogly-
can, syndecans and integrins, and, in this way, it may serve as a signal transmitter from the pericellular to the intracellular space.

The tight association of COL6 with collagen IV, the main basal lamina component, suggests that one of the major functions of COL6 is to anchor the basement membrane to the underlying connective tissue. A further possible role of the COL6 microfibrillar network is to act as a scaffold for the formation of the fibrillar collagen networks and, by interconnection with the fibronectin microfibrillar system, for the development of the matrix supramolecular structure. In addition, in vitro experiments suggest that COL6 is involved in cell cycle signaling, induces DNA synthesis and proliferation as well as spreading of fibroblasts, promotes survival, inhibits apoptosis, and contributes to the maintenance of tissue homeostasis. In this way, the COL6 network could have a pivotal role in repair processes, such as wound healing, as well as in tissue development and architecture.

Mutations in COL6 genes may cause 3 muscle diseases: Ullrich congenital muscular dystrophy (UCMD), BM and autosomal recessive myosclerosis myopathy. The UCMD syndrome is a severe muscle disease presenting in the newborn period with marked distal joint laxity and frequently provides evidence for more proximal contractures as, for example, in the knees and elbows. There may be congenital hip dislocation and talipes equinovarus although laxity of the ankles with dorsiflexion of the feet against the shin is probably more common. Congenital kyphoscoliosis and torticollis are frequent causing respiratory failure and death between the first and third decades of life due to a steady decline in forced vital capacity leading to predominantly night-time respiratory insufficiency.

UCMD was initially regarded as an exclusively autosomal-recessive condition, however, a few years later, patients were reported harboring heterozygous mutations in the COL6A1 and COL6A2 genes, not carrying any other mutations in the 3 COL6 genes.

BM is a relatively mild autosomal-dominant disorder linked to all 3 COL6 genes, characterized by slowly progressive muscle weakness and wasting with distal joint contractures affecting most frequently the long finger flexors, elbows, and ankles. Moreover, recent studies have pointed out the association of the BM phenotype with recessive mutations in the COL6A2 gene. The disorder shows a wide range of clinical symptoms, from mild myopathy to more severe cases with features of progressive muscular dystrophy although most patients have symptoms from birth. By immunofluorescence, COL6 reveals a normal or mildly reduced expression pattern in the endomysium of most patients, but it may be significantly reduced in the secreted ECM by cultured BM fibroblasts. Currently, it is recognized that UCMD and BM cannot be considered as separate entities, but they rather represent a clinical continuum ranging from severe UCMD to mild BM phenotypes in which patients showing intermediate phenotypes could be considered to have either “mild UCMD” or “severe BM.”

Autosomal-recessive myosclerosis myopathy is characterized by toe walking and progressive calf contractures in childhood, and progressive contractures of all joints in the adult life. Recently, a homozygous nonsense COL6A2 mutation was found in the siblings of a consanguineous family in whom COL6 immunofluorescence revealed a discontinuous distribution at the basal lamina of myofibers.

In UCMD, marked hyperlaxity associates with contractures that frequently appear at birth, particularly in the spine (kyphosis), elbows and knees, but decrease to some degree over time only to return progressively later. The most severe cases of UCMD never achieve the ability to walk. More frequently, UCMD children walk in time or later on and lose the ability to walk by the end of the first decade or by the early second decade of life due to the progression of contractures and weakness. Respiratory function steadily declines over time, leading to night-time respiratory failure by the end of the first decade of life in most patients. In the mildest forms of UCMD and in the intermediate forms between UCMD and BM, respiratory insufficiency can occur before loss of ambulation.

In BM, contractures and joint abnormalities are not rare at birth, manifesting as congenital torticollis and hip dysplasia. Children with BM may have some distal hyperlaxity, but motor difficulties can improve in the first decade in some patients. Later, contractures of Achilles tendons, elbows and long finger flexors develop with slowly progressive weakness, requiring the use of devices for maintaining ambulation in adulthood. Respiratory impairment is generally mild but may be critical in some patients.

The patients have normal cognition. Their CK value is frequently normal or only mildly elevated which is important for the differential diagnosis concerning the Emery–Dreifuss syndrome (EDS) and laminopathy, because some patients with BM can resemble those with an EDS. Dermatologic features include abnormal scar formation in the form of keloids or atrophic scars, keratosis pilaris particularly on the extensor surfaces of the limbs, and velvety and soft skin.

The muscle biopsy generally shows moderate myopathic changes to severe dystrophic features depending on the type of severity and duration of the disease. Staining of a muscle biopsy for COL6 is useful and requires double staining with another basal membrane marker (perlecan, collagen IV). The COL6 expression analysis in UCMD muscles, performed by immunofluorescence, shows absence or marked or subtle reduction around skeletal myofibers. Complete absence of staining suggests recessive UCMD whereas a reduction is suggestive of dominant UCMD or recessive missense mutations. Normal appearance does not exclude BM. Moreover, staining for COL6 in dermal fibroblast cultures is of greater sensitivity and the availability of cultured fibroblasts also allows for genetic testing and confirmation of splice mutations on fibroblast-derived cDNA.

Muscle imaging can be useful to suggest a diagnosis with the typical finding on various types of muscle. Imaging shows a characteristic outside-in pattern of degeneration in which most of the abnormal signal will be at the outer edges of muscle and around fascia. Even if this pattern is not clearly visible, this diagnosis is not excluded.
Genotype-Phenotype Correlations

Mutations spanning the 3 COL6A1-3 genes have been identified in patients, manifesting a spectrum ranging from the most severe UCMD to the mildest BM. Some genotype-phenotype correlations have been established in large series of patients.6,71,72,82,83 Mutations underlying the severe end of the spectrum are, in general, recessive loss of function mutations as well as certain de novo dominant-negative mutations. The severe recessive mutations are generally mutations that have a null effect on the chain, including stop codon mutations and larger genomic deletions, but there may be some exceptions, including occasional severe missense mutations.69 Other recessively acting mutations equivalent to null mutations are those that render the mutant chain assembly incompetent, such as preventing its incorporation into the basic COL6 heterotrimer and, thereby, effectively and completely excluding it from all the synthesized COL6.72 Such mutations generally consist of in-frame exon skipping mutations at the C-terminal end of the triple helical domain. In contrast with the recessive mutations, dominantly negative acting mutations cause in-frame skipping of exons at the N-terminal end of the triple helical domain, resulting in chains that are able to assemble into the basic heterotrimeric monomer and which are secreted in the tetrameric state of COL6.71,72 In case this inclusion is incorporated all the way to the tetrameric state, as in the case of exon 16 in COL6A3, the biochemical and clinical consequences will increase severity, with only 1/16 trimeric being completely composed of wild-type COL6.69 Conversely, if the mutation corresponds to the common skipping of exon 14 in COL6A1, one of the triple helical cysteines responsible for higher-order assembly is included in the skipped exon, with the effect that the mutated chain will reduce the probability to assemble, resulting in a milder clinical and biochemical phenotype.69,71

BM is generally caused by dominantly acting mutations, including missense mutations at the level of the triple helical glycine residues that are the invariant part of the Gly-X-Y basic collagenous motif.83 Notably, some of these dominant glycine mutations can be associated with more severe phenotypes extending into the UCMD and are responsible for a large part of patients in the intermediate severity group described before.82,83 Recently, it has become clear that BM can be caused by recessive mutations combining a functional null mutation on one allele with a milder missense mutation on the other allele.74,75 Currently, genetic testing in the COL6 genes is based on the direct sequencing of all exons of the 3 COL6 chains in most laboratories. It is important to realize that this analysis is not able to diagnose larger exonic or multixonic deletions in the genes that can be detected by the CGH array.84,85

The main differential diagnosis for COL6-related disorders at the milder end of the spectrum includes the Emery–Dreifuss muscular dystrophies when patients manifest prominent contractures. However, the COL6-related disorders do not have any cardiac involvement compared with the Emery–Dreifuss muscular dystrophies, and the CK blood levels are more frequently lower and can even be normal. In addition, Ehlers–Danlos syndromes can also manifest prominent laxity like UCMD, in particular the EDS type VI and the hypermobile type caused by mutations in tenascin X.86

SEPN1-Related CMD

SEPN1-related CMD (SEPN1-CMD) is a congenital muscle disorder due to recessive mutations of the SEPN1 gene that encode selenoprotein N (SelN). This selenoprotein has a key role in protecting human cells against oxidative stress87 and shows functional and physical interaction with the RYR1 in zebrafish.88 The clinical phenotype of SEPN1-CMD is homogenous and distinctive, representing—together with the molecular defect—the hallmark of the disorder. Clinical features are characterized by severe weakness of axial neck and trunk muscles, which typically leads to major scoliosis and life-threatening respiratory insufficiency in the second and third decades of life and contrasts with relatively preserved limb strength and ambulation. By contrast, the morphologic spectrum of SEPN1-CMD is large, encompassing at least 4 different myopathic patterns: SEPN1 mutations have been found (1) in patients defined as having rigid spine muscular dystrophy (RSMD1) with nonspecific muscle findings,89 (2) in classic multiminicore disease,90 (3) in desmin-related myopathy with Mallory body-like inclusions,91 and (4) in a small number of patients with congenital fiber-type disproportion (CFTD).92 This heterogeneity of morphologic features, together with the lack of immunohistochemical markers, can delay early diagnosis of SEPN1-CMD. Symptoms are generally not evident during the neonatal period. Delayed and poor head control is the most common presenting sign; head lag or dropped head are virtually constant and noticeable from the age of 3 months, whereas other motor milestones are relatively normal. Most patients achieve the ability to walk at the normal age but are never able to lift their head from the supine position, ie, they get up from the supine position to sitting by rolling over and pushing on their arms. The patients frequently have a nasal, high-pitched voice and a variable degree of facial weakness. During the follow-up, muscle weakness and slenderness remain more marked in axial groups, particularly in the neck flexors,93,94 and spinal rigidity, involving mainly the cervical and axial spine, can be present from 5 to 6 years of age. By contrast, walking ability is usually well preserved, although patients usually complain of difficulties in climbing stairs or walking long distances. The full phenotype develops usually at the end of the first decade of life, with the occurrence of severe respiratory failure and scoliosis. Typically, scoliosis begins in the cervical region and is associated with dorsal lordosis and a lateral trunk deviation, frequently requiring spinal fusion. Restrictive respiratory failure is mainly determined by diaphragmatic dysfunction and not correlated to the degree of general weakness; most patients require noninvasive ventilation while still ambulant. Polysomnographic studies should be performed—even in young children—as soon as the diagnosis is suspected because during daytime vital capacity can be preserved without signs of respiratory failure.95 Contractures are normally limited to the spine. However, if there are limb joint contractures, they are generally mild and
### Table 1 Summary of CMD

| Disease OMIM Entry | Protein Gene Symbol/OMIM Entry | Clinical Aspects | Brain MRI | Immunohistochemistry of Muscle Biopsy |
|--------------------|--------------------------------|------------------|-----------|--------------------------------------|
| CMD with primary laminin-α2 deficiency | Laminin-α2 (LAMA2)/156225 | Complete deficiency: maximal functional ability is sitting or standing with support. Partial deficiency: milder presentations. Generally normal mental development, epilepsy in about 30%. | Abnormal white matter signal (T2 weighted MR); rare occurrence of occipital pachygryia or agryria, or pontocerebellar atrophy. | Complete or partial deficiency of laminin-α2 |
| CMD with partial laminin-α2 deficiency (OMIM1B) | Locus: 1q42 | Variable severity, proximal limb girdle weakness, muscle hypertrophy, early respiratory failure reported. | Abnormal white matter and structural gray matter changes possible. Expanding spectrum. | Variable deficiency of glycosylated aDG, secondary reduction of laminin-α2 |
| LARGE related CMD (OMIM12) | Like-glycosyl transferase LARGE/603590 | Variable, CMD with significant mental retardation, may eventually blend with the MEB/WWS spectrum. | White matter changes, mild pachygyria, hypoplastic brainstem, cerebellar abnormalities, including cysts. | Variable deficiency of glycosylated aDG, secondary reduction of laminin-α2 |
| Fukuyama CMD (FCMD) | Fukutin FKTN/607440 | Frequent in the Japanese population, walking not achieved, mental retardation, epilepsy common, more limited eye findings but clinical overlap with MEB. | Lissencephaly type II/pachygyria, hypoplastic brainstem, cerebellar abnormalities, including cysts. | Variable deficiency of glycosylated aDG, secondary reduction of laminin-α2 |
| Muscle-eye-brain disease (MEB) | POMGnTI/606822, FKRP/606596 FKTN/607440 | Significant congenital weakness, walking is rarely achieved, motor deterioration because of spasticity. Mental retardation, significant ocular involvement (eg, severe myopia, retinal hypoplasia) | Lissencephaly type II/pachygyria, hydrocephalus, occipital encephalocele, hypoplastic brainstem, cerebellar atrophy. | Variable deficiency of glycosylated aDG, secondary reduction of laminin-α2 |
| Walker–Warburg syndrome (WWS) | POMT1/607423, POMT2/607429 FKRP/606596 FKTN/607440 | Often lethal within first years of life because of severe structural CNS involvement. Congenital weakness may be less apparent in the setting of the brain involvement. | Significant ocular involvement possible | Lissencephaly type II/pachygyria, hydrocephalus, occipital encephalocele, hypoplastic brainstem, cerebellar atrophy. | Variable deficiency of glycosylated aDG, secondary reduction of laminin-α2 |
| CMD/LGMD with MR | FKRP/606596 FKTN/607440 | Early-onset weakness, but ambulation is often achieved, or early-onset LGMD phenotype, with mental retardation, some patients with microcephaly. | May be normal, or with cerebellar and/or dystrophic abnormalities. Microcephaly without any other obvious structural changes. | Variable deficiency of glycosylated aDG, secondary reduction of laminin-α2 |
| CMD/LGMD without MR (including MDC1C) | FKRP/606596 FKTN/607440 | Early-onset weakness, but ambulation is often achieved, or early-onset LGMD phenotype, without mental retardation, may have steroid-responsive progression of weakness, cardiomyopathy. | None | Variable deficiency of glycosylated aDG, secondary reduction of laminin-α2 |

### Disorders of glycosylation (ICDG) associated with defects of α-dystroglycan glycosylation

| Disease OMIM Entry | Protein Gene Symbol/OMIM Entry | Clinical Aspects | Brain MRI | Immunohistochemistry of Muscle Biopsy |
|--------------------|--------------------------------|------------------|-----------|--------------------------------------|
| CDG I (DPM3) | Dolichol-phosphate-mannose synthase-3 DPM3/605951 | One patient: CMD/LGMD with elevated CK, cardiomyopathy and stroke-like episode, mild developmental disability. | Reduction in glycosylated aDG, variable laminin-α2 reduction | Reduction in glycosylated aDG, variable laminin-α2 reduction |
| CDG I (DPM2) | Dolichol-phosphate-mannose synthase-2 DPM2/603564 | CMD with MR and severe myoclonus epilepsy, evaluated CK. | Cerebellar vermis hypoplasia, microcephaly. | Reduction in glycosylated aDG, variable laminin-α2 reduction |
| CDG Ile (DPM1) | Dolichol-phosphate-mannose synthase-1 DPM1/603503 | Initially described as CDG, ie, now emerging evidence of the presence of a dystrophic myopathy with abnormal aDG | Reduction in glycosylated aDG, variable laminin-α2 reduction | Reduction in glycosylated aDG, variable laminin-α2 reduction |
| Collagen VI related Ullrich (Bethlem) spectrum | α1/2 and α3 COL6 COL6A1/120220 COL6A2/120240 COL6A3/120250 | Distal joint hyperextensibility, proximal contractures, motor abilities variable, precluding independent ambulation in severe cases; soft palmar skin. | No abnormalities. | Variable deficiency of COL6 immunoreactivity |
| Integrin α7 | Integrin α7 ITGA7/600536 | Rare, delayed motor milestones, walking with 2-3 years | No abnormalities. | Information not available |

### Other forms of CMD

| Disease OMIM Entry | Protein Gene Symbol/OMIM Entry | Clinical Aspects | Brain MRI | Immunohistochemistry of Muscle Biopsy |
|--------------------|--------------------------------|------------------|-----------|--------------------------------------|
| Rigid spine muscular dystrophy (RSMD) | Selenoprotein N SEPN1 602610 | Delayed walking, predominantly axial weakness with early development of rigidity of the spine, restrictive respiratory syndrome. | No abnormalities. | No diagnostic immunohistochemical deficiency |
| Lamin A/C-related CMD | Lamin A/C LMNA 613205 | Absent motor development in severe cases, more typical: “dropped head” and axial weakness/rigidity, proximal upper and more distal lower extremity weakness, may show early phase of progression. | No abnormalities. | No diagnostic immunohistochemical deficiency |
| CMD merosin-positive | 4p16.3 | Severe muscle weakness of trunk and shoulder girdle muscles, and mild-to-moderate involvement of facial, neck, and proximal limb muscles. Normal intelligence. | No abnormalities. | No diagnostic immunohistochemical deficiency |
| CMD with adducted thumbs | Nesprin 1 SYNE1 608441 | Rare, adducted thumbs, toe contractures, generalized weakness, delayed walking, ptosis, external ophthalmoplegia, mild MR. | Mild cerebellar hypoplasia. | No diagnostic immunohistochemical deficiency |
| CMD with cerebellar atrophy | Not known | Delayed motor milestones, mild intellectual impairment. | Moderate-to-severe cerebellar hypoplasia, no white matter abnormalities. | No diagnostic immunohistochemical deficiency |
can coexist with mild hyperlaxity of the hands and wrists. Mild ophthalmoparesis is uncommon, but can be seen in severe cases. Involvement of the skin, brain or heart does not occur. Motor weakness usually remains stable or is slowly progressive although a more marked progression is observed after the fourth decade of life. There have been some reports of insulin resistance. \(^9^3\) CK is generally normal or mildly elevated.

Muscle MRI shows typical findings on imaging of the thigh muscles, including selective involvement of the sartorius and adductor longus muscles with sparing of the gracilis muscle which is a suggestive diagnostic feature of SEPN1-related CMD in young children (<3 years) who show a disproportionately appearing neck weakness with much better extremity strength allowing for ambulation.

### Genotype-Phenotype Correlations

There is no key so far for genotype-phenotype correlation. Mutations are distributed along the whole gene, except exon 3. Most of them are nonsense mutations, microdeletions or insertions leading to framematches, as well as splice-site mutations leading to aberrant pre-mRNA splicing.\(^8^7,^9^6\) Missense mutations are relatively more common around or at the potential catalytic site encoded by exon 10. Interestingly, several mutations affect the cis sequences (3’ UTR SECIS element) and Sec codon redefinition element required for selenocysteine insertion.\(^9^7,^9^9\)

Differential diagnosis between SEPN1-RM and other conditions with prominent spinal rigidity should particularly consider Emery–Dreifuss muscular dystrophy, FHL-1-related myopathies, Pompe disease, collagenopathies (UCMD, BM) and some cases of RYR1-related central core disease.

Growing experience has demonstrated that patients with recessively acting mutations in the RYRI gene may clinically present with ophthalmoplegia and other features suggestive of an SEPN1-related CMD without histologic evidence of cores in the muscle biopsy. In fact, now there is evidence to suggest that the 2 gene products interact.\(^8^8\)

These patients with the CMD-like presentation of RYRI mutations may show significant congenital weakness, including facial weakness and early-onset scoliosis, as well as ophthalmoplegia/paresis as also seen in the centronuclear presentation of RYRI mutations, and suggesting a clinical and histologic overlap between these 2 RYRI-related conditions. Thus, it is now becoming clear that some patients with RYRI-related congenital myopathy are clinically and histologically indistinguishable from a patient presenting with CMD.

### LMNA-Related CMD

It is well known that mutations in LMNA cause a wide range of genetic disorders in humans.\(^1^0^0\) The typical neuromuscular syndrome associated with LMNA mutations is Emery–Dreifuss muscular dystrophy, characterized by the presence of scapulo-poroneal muscle weakness, typical contractures and cardiomypathy. More recently, mutations in LMNA have been associated with an early-onset CMD presentation of muscle disease.\(^1^0^1\) The weakness becomes evident in infancy and may show a phase of more rapid progression early on during the course of disease. Weakness predominated in axial and distal muscles, characteristically involving neck muscles (flexors and extensors) which results in the clinical phenomenon of “head-drop” caused by weak neck extensors. There is pronounced lumbar hyperlordosis, arm and hand weakness, as well as peroneal weakness. Characteristically, hip flexors appear to be preserved early on, with good anti-gravity strength. Contractures manifest early in the spine with considerable spinal rigidity, in the Achilles tendons, knees and hips, as well as in the elbows and finger flexors or extensors reminiscent of what is observed in the classic Emery–Dreifuss phenotype or in the COL6-related myopathies. In the most severe cases, sitting may not be achieved, and there is early respiratory failure. In the more typical expression of the condition, sitting is achieved but walking may be possible for only a limited period in some patients. Night-time respiratory insufficiency generally manifests early and, similarly to the classical Emery–Dreifuss phenotype, cardiac involvement may take the form of an initially atrial arrhythmogenic cardiomyopathy with conduction block, and also tachyarrhythmias, necessitating the use of an ICD (intracardiac defibrillator device). Cognition is unaffected.

The histologic appearance of the muscle biopsy does not show any peculiar key diagnostic and morphologic aspects, which are variable ranging from a myopathic-appearing biopsy with atrophic fibers, mostly of type I, to more obvious dystrophic findings. Seldom, myofibrillar abnormalities can be observed. Inflammation with conspicuous cellular infiltration can be found in some rare cases. Immunohistochemical examination and Western blot analysis of LMNA in the biopsy are normal and muscle MRI can be pivotal for diagnostic orientation.

### Genotype-Phenotype Correlations

So far, all identified mutations are heterozygous de novo mutations that act in a dominant negative way.\(^1^0^1\) There is no key for genotype-phenotype correlation. Some mutations observed in a large series of LMNA-related CMD patients\(^1^0^1\) have also been observed in patients with the more typical Emery–Dreifuss phenotype although with a slightly more severe presentation. It is known that the same mutations may be seen in severe and milder LMNA-related CMD as well as in typical Emery–Dreifuss muscular dystrophies, suggesting that there must be other modifiers of disease severity. Mutation analysis in LMNA is readily available. On identification of a sequence change of potential pathogenicity in LMNA in a proband with unaffected parents, the parents should subsequently be analyzed to confirm whether the mutation is indeed de novo as would be expected for a pathogenic change in this situation. (Table 1).

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