

Congenital Muscular Dystrophies and the Extracellular Matrix

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During the past decade, considerable progress in the field of congenital muscular dystrophies (CMDs) had led to the identification of a growing number of causative genes. This genetic progress has uncovered crucial pathophysiological concepts and has been instrumental in redefining clinical phenotypes. Important new pathogenic mechanisms include the disorders of O-mannosyl-linked glycosylation of α -dystroglycan as well as the involvement of a collagen type VI in the pathogenesis of congenital disorders of muscle. Thus, an emerging theme among gene products involved in the pathogenesis of congenital muscular dystrophy is their intimate connection to the extracellular matrix. In this review, we focus on the clinical phenotypes that we are correlating with the novel genetic and biochemical findings encountered within CMD. This correlation will frequently lead to a considerably expanded clinical spectrum associated with a given CMD gene.

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Congenital muscular dystrophies (CMDs) constitute a heterogeneous group of genetic neuromuscular disorders with clinical manifestations evident at birth or in infancy. The muscle biopsy in CMD should be consistent with a myopathy, often but not invariably including evidence for degeneration and regeneration, whereas the biopsy more importantly does not suggest an alternate diagnosis such as a congenital myopathy that is defined by characteristic histologic and ultrastructural features. The identification of an increasing number of the genes mutated in patients with CMD has allowed for the better definition of molecular subgroups and their associated clinical phenotypes. However, it is frequently not possible to maintain a one-to-one relationship between a given gene and a defined phenotype. The most striking example of this broadening genotype-phenotype relationship is the clinical spectrum associated with mutations in the *FKRP* (Fukutin-related protein) gene, ranging from Walker-Warburg syndrome to late adult-onset limb-girdle muscular dystrophy (LGMD).¹⁻⁴ However, 2 major themes have

emerged concerning the molecular and clinical aspects of CMD. On the molecular side, it is striking that the majority of the genetic defects discovered either affect the post-translational processing of α -dystroglycan, a major extracellular matrix receptor on muscle, or more directly involve molecules of the extracellular matrix itself, notably laminin- α 2 (the heavy chain of laminin-2/merosin), and the three alpha chains making up collagen type VI. On the clinical side, important themes include the potential involvement of muscle, eyes, and brain in the disorders of α -dystroglycan glycosylation and the combined involvement of muscle, tendon, and skin in the disorders of collagen VI.

Thus, CMD shows considerable clinical as well as molecular heterogeneity, yet it seems that the majority of defined conditions involve a disturbed connection of muscle to its extracellular matrix.⁵ The focus of this review is on the CMD forms for which the molecular basis is to be found in this muscle/matrix interaction (Table 1). Mutations in the endoplasmic reticulum component selenoprotein N are one exception to this observation since they are found in patients with congenital muscular dystrophy with rigidity of the spine.⁶ However, this condition may in fact be more closely related to a congenital myopathy referred to as multimincore disease, which can also be caused by mutations in the same gene.⁷ This condition and mutations in the integrin alpha7 (ITAG7) gene, which appear to be exceedingly rare, will not be covered in this review.⁸

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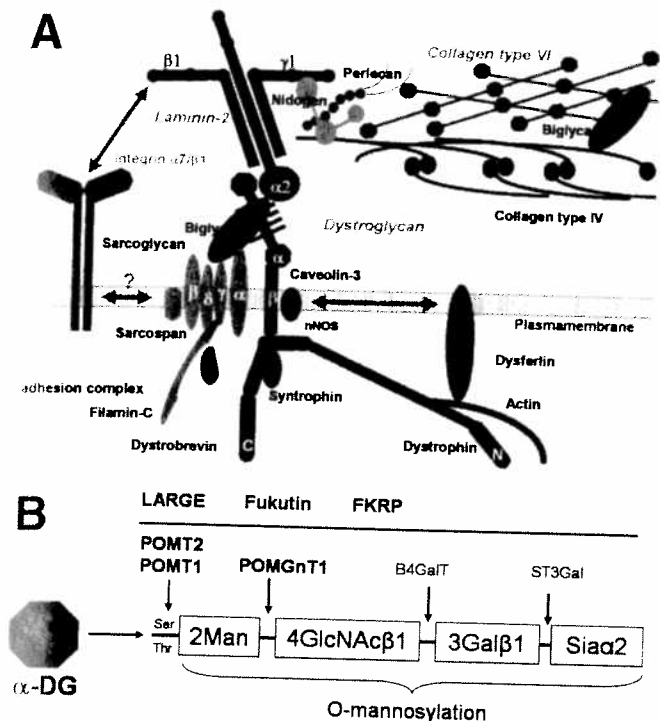


Figure 1 (A) Schematic representation of dystroglycan (DG) connecting the cytoskeleton of muscle cells with the extracellular matrix. (B) This binding is disrupted by defects in the posttranslational modification of α -dystroglycan (α -DG), causing congenital muscular dystrophy. Disease associated genes are in bold. (Modified with permission.¹⁵) (Color version of figure is available online.)

CMD With Abnormal α -Dystroglycan Glycosylation

One of the protein complexes on the sarcolemma mediating this connection from muscle cell to the extracellular matrix is the complex of dystrophin-associated proteins (DAPs), linking cytoskeletal actin via dystrophin to the extracellular matrix, most notably to the basement membrane component laminin-2 (merosin) (Fig 1A). This link across the plasma membrane is mediated by the transmembrane components of the DAP complex, in particular the dystroglycan and sarcoglycan subcomplexes. The major receptor within this complex appears to be α -dystroglycan, situated on the extracellular site attached to the transmembrane β -dystroglycan (both dystroglycans are transcribed from the same gene but are posttranslationally processed as independent proteins). Alpha-dystroglycan undergoes extensive O-mannosyl-linked glycosylation, giving it mucin-like characteristics and also conveying ligand binding activity to the molecule. In an increasing number of CMDs, α -dystroglycan O-mannosyl-linked glycosylation is disturbed specifically at a number of steps, including actual glycosyltransferases (POMT1 and POMT2 = protein O-mannosyl transferase 1 and 2, POMGnT1 = protein O-mannose β 1,2-N-acetylglucosaminyltransferase 1) as well as proteins that are probably collaborating in this process (Fukutin, Fukutin-related protein [FKRP], and LARGE).⁹⁻¹³ For an excellent recent review of

the biochemistry of these disorders, see Jimenez-Mallebrera and coworkers.⁵ Mutations in all of these genes affect the O-mannosyl-linked glycosyl side chains attached to α -dystroglycan resulting in a decrease or loss of the binding affinity to its extracellular ligands (such as laminin-2 in muscle and nerve or neuexin in the brain) (Fig 1B).^{14,15} Animal models suggest that underglycosylation of α -dystroglycan specifically is causative for the clinical and pathological features of this CMD group, although other proteins could conceivably also be affected by this faulty glycosylation process.¹⁶ Because α -dystroglycan is widely expressed and the defective glycosylation is not restricted to just muscle but has effects also in the brain and eye, the typical clinical constellations resulting from these defects affect all three of these organs (muscle-eye-brain disease [MEB] spectrum). The immunohistologic hallmark in muscle in all of these conditions is a significant reduction or absence of staining with antibodies against glycosylated α -dystroglycan as well as a secondary reduction of laminin-2 (merosin). Although very helpful when present, these findings can sometimes be less than obvious.

Even though there are a number of classic phenotypes that were initially associated with just a single-gene defect, it has now become apparent that there really is a spectrum of phenotypes extending from the most severe Walker-Warburg syndrome via MEB and Fukuyama CMD (FCMD) to CMD with and without mental retardation and all the way to LGMD. FKRP currently exhibits the widest known spectrum (Fig 2), but it would be altogether not surprising if the other genes involved in this pathway expanded their associated clinical phenotypes significantly as well. We will nevertheless proceed by introducing the classic phenotypes together with the gene defects currently associated with them, well aware that the number of genes associated with each one of these phenotypes will expand. The typical central nervous system involvement common to all the disorders of α -dystroglycan glycosylation includes various degrees of lissencephaly type II (also known as cobblestone complex), pachygyria, neuronal heterotopias, pontocerebellar hypoplasia, and cerebellar cysts.¹⁷ Accumulations of tau protein have been seen in a number of postnatal FCMD brains.¹⁸

FCMD

Clinical Features

Initially, this condition was almost exclusively recognized in Japan, where it is the second most common childhood muscular dystrophy after Duchenne muscular dystrophy.^{19,20} FCMD presents with congenital onset of muscle weakness, hypotonia, and severe delay in motor development with immobilization within the first decade of life in most children.^{19,20} Cerebral imaging is variable but may reveal lissencephaly type II (cobblestone complex), pachygyria, flat brain stem, cerebellar hypoplasia, and cerebellar cysts.²¹ Mental retardation generally is severe, more than 50% do not acquire language while seizures are common.^{19,22} About 60% to 70% of the children present with mostly mild eye abnormalities,

Table 1 The Congenital Muscular Dystrophies (CMD)

| Disease entity | Locus protein product gene symbol | Helpful clinical features | CNS involvement | Laboratory testing |
|--|---|--|--|---|
| Primary merosin/laminin 2 deficiency CMD with primary laminin-2 (merosin) deficiency (MDC1A) Alpha-dystroglycanopathies-secondary merosin/laminin2 deficiency | 6q22-q23 Laminin- α 2 LAMA2 | Sitting and standing with support as maximal motor ability if complete deficiency, neuropathy, epilepsy in about 30%, possible subclinical cardiomyopathy, generally normal mental development. | Abnormal white matter signal (T2MRI), 5% occipital pachy- or agyria, pontocerebellar atrophy (rare) | Mostly complete laminin- α 2 deficiency on IH/WB, secondary reduction of integrin α 7 possible, mutation analysis.* |
| CMD with partial merosin deficiency (MDC1B) Fukutin related proteinopathy (MDC1C) | 1q42 Not known 19q13.3 Fukutin related protein FKRP | Rare, variety of severity, delayed onset possible, proximal girdle weakness, generalized muscle hypertrophy, early respiratory failure possible. Often reminiscent of MDC1A, but severity more variable, from severe CMD to LGMD as well as to WWS (see there), in the absence of structural brain involvement normal mental development, cases with structural brain involvement and mental retardation increasingly recognized, including MEB and WWS. So far only one patient described. Congenital muscular dystrophy with profound mental retardation may eventually blend with the MEB/WWS spectrum. Frequent in Japanese population, never walk, mental retardation, epilepsy common—clinical overlap to MEB—see there. | Range from normal to significant structural abnormalities, ranging from cerebellar cysts to typical MEB and WWS | Partial deficiency of laminin- α 2 on IH/WB, α -DG significantly reduced on IH, linkage analysis. α -DG with diminished MW on WB, or reduction of IH using antibodies against glycosylated isotopes, secondary reductions in laminin- α 2 on IH/WB, mutation analysis.* |
| LARGE related CMD (MDC1D) Fukuyama CMD (FCMD) | 22q12.3 Acetylglucosaminyltransferase-like protein LARGE 9q31 Fukutin FCMD | Severe weakness and mental retardation, large head, prominent forehead, flat midface, walking rarely achieved, ocular involvement (e.g. severe myopia, retinal hypoplasia), deterioration because of spasticity. | White matter changes, hypoplastic brainstem, mild pachygyria (similar to MEB). Lissencephaly type II/pachygyria, hypoplastic brainstem cerebellar abnormalities | IH/WB comparable to MDC1C, mutation analysis.* IH/WB comparable to MDC1C, mutation analysis. |
| Muscle-eye-brain disease (MEB) | 1q32-q34 Protein-O-linked mannose β 1,2-N-acetylglucosaminyltransferase 1 POMGnT1 (FKRP, Fukutin). 9q34.1 O-Mannosyltransferase 1 POMT1 (POMT2, FKRP, Fukutin) | Severe weakness and mental retardation, large head, prominent forehead, flat midface, walking rarely achieved, ocular involvement (e.g. severe myopia, retinal hypoplasia), deterioration because of spasticity. | Lissencephaly type II/pachygyria, eye malformations, brain stem and cerebellar abnormalities | IH/WB comparable to MDC1C, mutation analysis (genetic heterogeneity!). |
| Walker-Warburg syndrome (WWS) | | Severe, lethal within first years of life because of severe CNS involvement | Lissencephaly type II, pachygyria, hydrocephalus, encephalocele, hypoplastic brainstem, cerebellar abnormalities, eye malformations | IH/WB comparable to MDC1C, mutation analysis (genetic heterogeneity!). |

Table 1 Continued.

| Disease entity | Locus protein product gene symbol | Helpful clinical features | CNS involvement | Laboratory testing |
|--|---|--|--|--|
| Other matrix disorders (merosin/laminin2 positive) | | | | |
| Ullrich CMD (UCMD) | 21q22.3 and 2q37 $\alpha 1/2$ and $\alpha 3$ collagen VI COL6A1, COL6A2, COL6A3 | Distal joint hyperextensibility, proximal contractures, motor abilities variable, precludes independent ambulation in severe cases, soft palmar skin. Very rare, delayed motor milestones, walking with 2-3 years | No | IH for collagen VI with severe to mild deficiency, mutation analysis.* |
| Integrin $\alpha 7^8$ | 12q13 Integrin $\alpha 7$ ITGA7 | Delayed walking, predominantly axial weakness with early development of rigidity of the spine, restrictive respiratory syndrome. | No | Absence of integrin $\alpha 7$ on IH (secondary reduction possible), mutation analysis.* |
| Other CMD | | | | |
| Rigid spine muscular dystrophy (RSM D) | 1p36-p35 Selenoprotein N SEPN1 | Severe muscle weakness of trunk and shoulder girdle muscles, and mild to moderate involvement of facial, neck and proximal limb muscles. Normal intelligence. Joint contractures associated, severe psychomotor retardation, no walking, striking enlargement of the calf and quadriceps muscles, CK grossly elevated. | No | Normal expression of laminin $\alpha 2$, mutation analysis. |
| CMD merosin-positive ⁸⁴ | 4p16.3 | | | |
| CMD with microcephaly/ calf hypertrophy ⁸⁵ | Not known | Rare, adducted thumbs, toe contractures, generalized weakness, delayed walking, ptosis, external ophthalmoplegia, mild mental retardation. | Megacisterma magna, cerebellar hypoplasia, white matter changes | Normal expression of laminins, dystrophin, sarcoglycans and β -dystroglycan. |
| CMD with adducted thumbs ⁸⁶ | Not known | | | |
| CMD with mental retardation and microcephaly ⁸⁷ | Not known, FKRP not yet excluded | Microcephaly, delayed psychomotor development, generalized muscular wasting and weakness with mild facial involvement, calf pseudohypertrophy, joint contractures, and severe mental retardation. Delayed motor milestones, mild intellectual impairment. | Mild cerebellar hypoplasia | Mild to moderate partial deficiency of laminin $\alpha 2$ on IH. |
| CMD with cerebellar atrophy ⁸⁸ | Not known | | | |
| CMD with joint hyperlaxity ⁸⁹ | 3p23-21 | Clinical overlap with UCMD with distal joint hyperextensibility, proximal contractures, cervical spine hypermobility. Pulmonary vital capacity diminished on average by 50%. Normal intelligence or mildly impaired. | Pontocerebellar hypoplasia, focal cortical dysplasia, white matter changes, cerebellar cysts Moderate to severe cerebellar hypoplasia, no white matter abnormalities. No | Normal expression of laminin $\alpha 2$. Normal expression of laminin $\alpha 2$. Normal expression of laminin $\alpha 2$. Variation in fibre sizes, the presence of central nuclei and increased endomysial connective tissue, mutation analysis* |

Abbreviations: CK, creatine kinase; DG, dystroglycan; IH, immunohistochemistry; MW, molecular weight; WB, Western blot. *currently not available as diagnostic testing, only performed on a research basis (modified Kirschner⁴⁹).

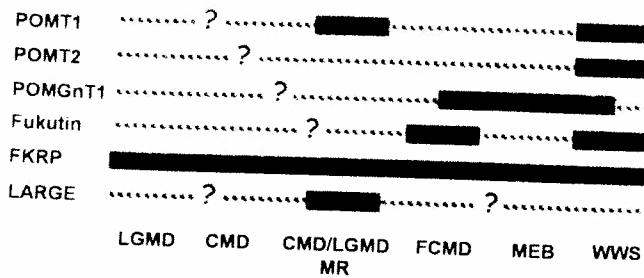


Figure 2 Genotype/phenotype spectrum in CMD. Each known gene appears to be widening its associated clinical spectrum. Fukutin-related protein (FKRP) has currently the widest known spectrum. Other genes may be involved in this pathway expanding their associated clinical phenotypes to a similar range. (Color version of figure is available online.)

including significant myopia.²³ Serum creatinine kinase (CK) levels are elevated. Immunohistochemistry in muscle reveals substantial reduction to absence of glycosylated α -dystroglycan staining as well as a secondary reduction of laminin-2 (merosin).²⁰

Genetics

The locus for the *FCMD* gene on chromosome 9q31-33 encodes the putative glycosyltransferase fukutin.^{14,24} In Japan, the disorder is mostly caused by homozygosity for an ancestral retrotransposon in the 3' untranslated region (UTR) of the fukutin gene, but fukutin mutations have now been found outside of Japan as well. Other mutations such as nonsense mutations have now been seen in the *FCMD* gene, including in association with the more severe phenotype of Walker-Warburg syndrome (WWS), but the full phenotypic spectrum is probably not yet known.²⁵

MEB

Clinical Features

This disorder was initially delineated in Finland, where it is most prevalent. However, MEB clearly does occur outside of Finland and is now recognized worldwide.²⁵ Patients present at birth or shortly thereafter with muscle weakness, hypotonia, and findings of eye and brain involvement. Motor development is severely delayed, whereas signs indicative of central nervous system involvement such as spasticity are becoming increasingly evident.^{26,27} Seizures are common. Affected children may have characteristic facial features including a large head, a prominent forehead, and a flat midface. Brain imaging reveals lissencephaly type II (cobblestone complex) or pachygyria and typically hypoplasia of the pons and cerebellum, which often shows abnormalities of foliation and small cysts (Fig 3). Typically, there are also significant ocular malformations present, including congenital myopia and glaucoma as well as retinal hypoplasia and optic disc abnormalities. CK is elevated to a variable degree. Muscle biopsy displays dystrophic findings with fiber-size variation and increased connective tissue. There also is reduced stain-

ing of glycosylated α -dystroglycan and of laminin-2 (merosin).²⁰

Genetics

The original gene for MEB has been linked to chromosome 1p32-p34, encoding the glycosyltransferase POMGnT1 (protein-O-mannose beta1,2-N-acetylglucosaminyltransferase).^{9,28} Mutations located toward the 5' end of the gene seem to cause more severe phenotypes.²⁵ However, the MEB phenotype can also be caused by mutations in other genes in this group of disorders, including FKRP and POMT1 and 2.^{29,30}

WWS

Clinical Features

WWS is the clinical phenotype with the most severe brain abnormalities. It occurs worldwide without clear predilec-

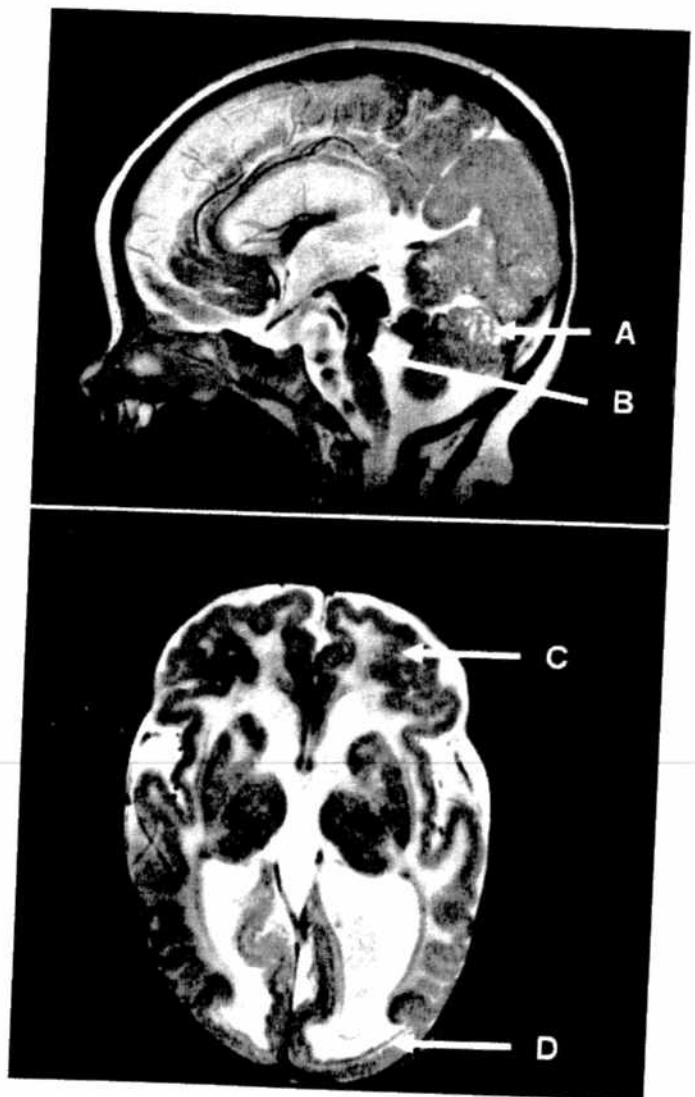


Figure 3 Magnetic resonance imaging of a muscle-eye-brain disease patient. (A) Typical features are cysts and hypoplasia of the cerebellum and (B) of the pons, (C) pachygyria, and (D) abnormal cortical layering. (Courtesy of M. Baumann, Kassel).

tion for a particular country. Most patients with the full WWS phenotype die prenatally or within the first year of life as a result of the severe brain malformations. Only 5% to 10% of patients reach an age older than 5 years.³¹ All patients have profound mental retardation, severely reduced motor function, and frequently develop epilepsy. Compared with the other CMD phenotypes, the brain malformations in WWS are altogether more severe. In addition to the widespread lissencephaly type II (cobblestone complex) and striking pontocerebellar hypoplasia, there may be hydrocephalus, meningoencephaloceles, hemispheric fusion as a result of the overmigration of neurons into the subarachnoid space, and absence of corpus callosum.³² The associated eye abnormalities also tend to be more severe including microphthalmia, glaucoma, severe retinal dysplasia, anterior chamber malformations, and cataracts.³³ CK is usually elevated but can, on occasion, be normal in newborns. Muscle pathology commonly reveals dystrophic features and an immunohistochemical profile comparable to the other disorders in this group, but it may look quite inconspicuous in infants within the first months of life.^{31,34,36}

Genetics

POMT1, encoding the glycosyltransferase protein O-mannosyltransferase 1, has been identified in about 20% of all WWS patients as the causative gene.^{13,25,37,38} In 3 patients, mutations in *POMT2* were detected.³⁹ But WWS phenotypes are also described with *FCMD* or *FKRP* gene mutations.^{40,41} Likely there are as-yet-undiscovered additional genes involved with the α -dystroglycan glycosylation machinery, which may underlie some of the phenotypes outlined here.

Congenital MD Type 1C

Clinical Features

Congenital MD type 1C (MDC1C) is caused by mutations in *FKRP* (fukutin-related protein), another putative glycosyltransferase involved in the pathway of α -dystroglycan O-mannosyl glycosylation, although its precise role in the pathway is not yet known.⁴² Mutations in *FKRP* are capable of giving rise to a vast spectrum of clinical severity ranging from WWS to late-onset limb-girdle muscular dystrophy. However, the initial description of MDC1C referred specifically to a phenotype of congenital/early infantile onset of weakness but without brain or eye involvement. Patients may have conspicuous muscle hypertrophy of lower-limb muscles in contrast to muscle wasting in the upper extremities; considerable tongue hypertrophy may also develop. Contractures are common but are usually mild. After an initial presentation with hypotonia and feeding problems, there is severe motor retardation often precluding ambulation, as well as considerable risk for respiratory insufficiency and dilated cardiomyopathy.^{12,20} Serum CK is significantly elevated. Similar to the other disorders in this group, muscle pathology shows a deficiency of glycosylated α -dystroglycan staining as well as reduced laminin-2 (merosin) staining, although this can be variable.²⁰

Genetics

Mutations in the *FKRP* gene on chromosome 19q13, were identified in the original phenotype of MDC1C.⁴² As noted earlier, mutations in *FKRP* are now found in an extraordinarily wide spectrum of clinical severities, ranging from severe CMD with profound brain malformations, mental retardation, and eye abnormalities (MEB and WWS spectrum), via the original MDC1C phenotype and LGMD2I with Duchenne or Becker-like severity to an adult-onset form of LGMD2I with very mild clinical symptoms.^{1,3,4,42-44} Severity of central nervous system involvement in patients with CMD and *FKRP* gene mutations seems to correlate with disruption of α -dystroglycan glycosylation.⁴⁵

Additional CMD Types With Abnormal α -Dystroglycan Glycosylation

CMD Type 1B (MDC1B)

This type appears to be rare presenting with variable severity but generally milder up to LGMD like symptoms.⁴⁷ Most patients present with proximal muscle weakness as well as some muscle hypertrophy. Delayed onset is possible as is the development of respiratory failure. Brain imaging is usually normal. Muscle immunohistochemistry again shows a reduction of glycosylated α -dystroglycan, suggesting that this condition may be another α -dystroglycan glycosylation disorder. Linkage to chromosome 1q42 has been established, but the primary molecular defect remains unknown at the time of writing.⁴⁷

CMD Type 1D (MDC1D)

This type is defined by mutations in *LARGE*, causing a type of CMD with lissencephaly type II (cobblestone complex) presenting with severe mental retardation. Mutations in the *LARGE* gene on chromosome 22q12.3-q13.1 have been identified in 1 patient so far, but again it is likely that more are going to be identified with a wider clinical spectrum.⁴⁸ Recent results indicate that *LARGE* interacts with α -dystroglycan in the Golgi apparatus to facilitate subsequent O-mannosyl-linked α -dystroglycan glycosylation and in addition functions as glycosyltransferase in its own right.^{49,50}

CMD With Laminin2/Merosin Deficiency

The most important ligand of α -dystroglycan in muscle is laminin-2, also referred to as merosin. It interacts with α -dystroglycan predominantly in muscle and peripheral nerve in a glycosylation-dependent manner, its other receptor being integrin $\alpha7/\beta1$.^{51,52} Some series estimate that about 30% of CMD is caused by mutations in the *LAMA2* gene, but regional variations in the frequency are described.^{5,53,54}

CMD With Primary Laminin2/Merosin Deficiency

Clinical Features

CMD with primary laminin-2 (merosin) deficiency, also referred to as congenital MD type 1A (MDC1A), is mostly a severe congenital disease. Patients usually present with severe muscular hypotonia and weakness, multiple contractures may be present at birth while respiratory and feeding problems may become apparent during infancy or early childhood.^{20,53-55} In the typical case, independent ambulation is not achieved; sitting and standing with support usually is the maximal motor development possible. Within the first 10 years of life, most patients require ventilatory support for respiratory insufficiency and nocturnal hypoventilation. T2-weighted magnetic resonance imaging reveals abnormal signal prolongation in the white-matter signals, sparing the compacted fiber tracts such as the corpus callosum or the internal capsule. The nature of these white matter alterations is not known, but they are different on magnetic resonance spectroscopy from hypomyelination or from a leukodystrophy, suggesting a higher free water content in the white-matter instead.⁵⁶ These findings also do not impair cognitive functions if the white-matter changes are isolated.⁵⁷ Additional structural brain changes may be identified in a minority of patients, including cortical dysplasia or cerebellar hypoplasia.⁵⁸⁻⁶⁰ When present, the cortical dysplasia has a posterior predilection as opposed to the anterior predilection that can be seen in the α -dystroglycan disorders. Epilepsy develops in approximately 30% of all children, even in the absence of structurally visible brain abnormalities.⁶¹ A demyelinating motor neuropathy is common, consistent with laminin- α 2 expression in Schwann cells.⁶² Muscle biopsy typically shows complete laminin- α 2 deficiency and possible reduction of integrin α 7.⁵ Partial laminin- α 2 deficiency can be seen with milder clinical presentations.

Genetics

Primary merosin-deficient CMD is caused by mutations in the *LAMA2* gene, mapped to 6q22-q23, encoding laminin- α 2, the heavy chain of laminin-2, also referred to as merosin.^{34,63,64} Milder cases are reported because of a homozygous out-of-frame deletion and homozygous missense mutation.⁶⁴

CMD With Collagen VI Mutations

A clinically and physiologically separate group of CMD is caused by mutations in the genes encoding the extracellular matrix component collagen type VI and encompasses a spectrum ranging from the severe CMD type Ullrich to the milder Bethlem form.⁶⁵ Collagen VI is composed of 3 alpha chains encoded by 3 genes: *COL6A1* and *COL6A2* gene on chromosome 21q22 or *COL6A3* gene on chromosome 2q37.^{66,67} It undergoes a complex assembly process in which all three alpha chains are required for a heterotrimeric monomer, which in the cell undergoes higher-order assembly via a

dimer state to a tetramer. Tetramers are then secreted and assemble in the extracellular matrix to form beaded microfibrils.⁵

It is still unclear how collagen VI links or relates to the DAP complex if at all. However, the molecular basis and consequences of this disorder appear to be different from the α -dystroglycanopathies in that the disease is less overtly "dystrophic" but still leads to significant weakness and disability. Collagen VI is a prominent component of most extracellular matrices where it forms beaded microfibrils that are found in close connection with cells and basement membranes as well as in the interstitial space in many tissues, including muscle, tendon, skin, cartilage, and intervertebral disks, among others.^{68,69} Thus, collagen VI mutations present as a combination of disorders of both muscle and connective tissue in that joint hyperlaxity and contractures as well as abnormal skin are important aspects of the clinical phenotype in addition to the weakness.

Congenital Muscular Dystrophy Type Ullrich

Clinical Features

Congenital muscular dystrophy type Ullrich (UCMD) is the more severe congenital clinical expression of collagen VI disorders; the later-onset milder form is referred to as Bethlem myopathy.⁷⁰ Typical clinical features of UCMD include generalized congenital muscle weakness with coexisting striking hypermobility of the distal small joints in conjunction with variable contractures in more proximal joints (knees and elbows in particular) and the spine (kyphoscoliosis and spinal rigidity) (Fig 4).⁷¹ The joint hyperlaxity is reminiscent of Ehlers-Danlos syndrome, a frequent initial diagnostic consideration in these children. Additional helpful clinical findings include prominent calcanei and skin findings including follicular hyperkeratosis as well as a predisposition to keloid scar formation, but these are not obligatory.^{65,72} The severity is quite variable ranging from weakness and contractures precluding ambulation via transient ambulation to milder phenotypes that are blending in with the Bethlem spectrum. The weakness and in particular the contractures can show progression. Intelligence and brain imaging are always normal. The diagnosis is supported by abnormal amount and localization of collagen VI immunoreactivity on muscle biopsies and in dermal fibroblast cultures.⁷³ Ultrastructural evidence in skin biopsies suggests that the clinical overlap between UCMD and Ehlers-Danlos syndrome as far as the laxity is concerned has a physiological basis in similar-appearing abnormalities of the large fibrillar collagen complement.⁷⁴

Genetics

UCMD is caused by mutations in all three alpha chain genes of collagen VI. It was initially thought to be an exclusively recessive disease; however, it has become clear now that a significant number of sporadic patients carry de novo dominant negative mutations in the triple helical domains of all 3 genes.⁷⁵⁻⁷⁹ It is likely that there is a degree of further genetic

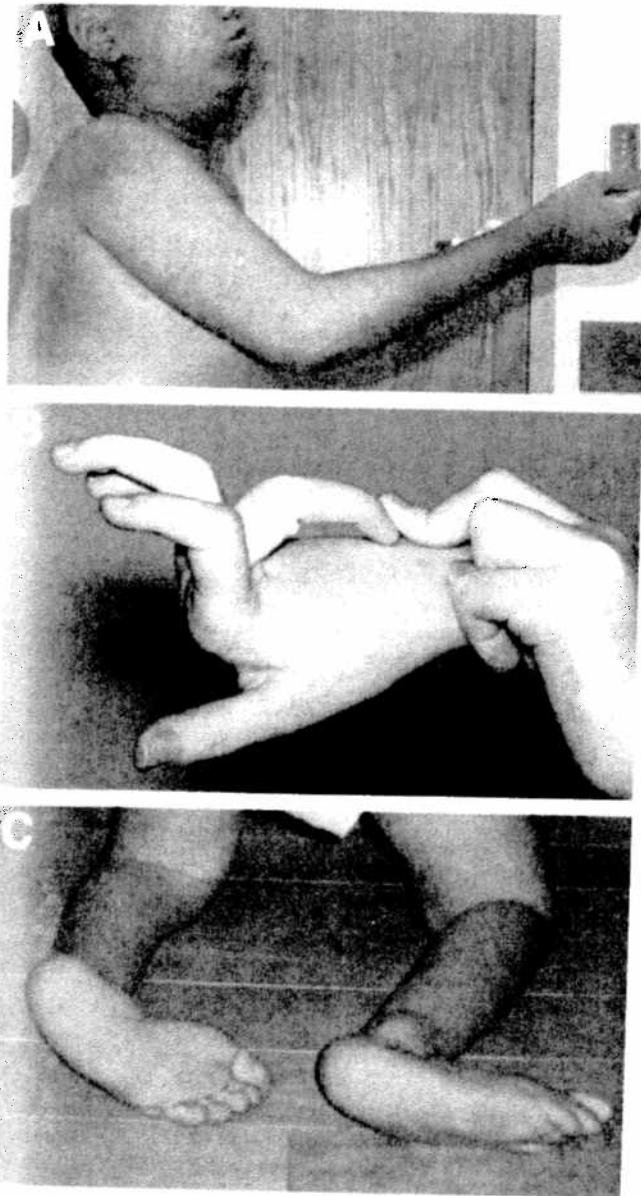


Figure 4 Ullrich congenital muscular dystrophy (UCMD). (A) Note prominent contractures of the elbows; also note keratosis pilaris on the upper arm, (B) extreme hyperlaxity of the distal joints, including distal interphalangeal joints, (C) prominent calcanei, and soft plantar skin. (B, courtesy of M. van der Knaap, Amsterdam, and C, courtesy G. Schreiber, Kassel). (Color version of figure is available online.)

heterogeneity causing the phenotype of UCMD; however, this is probably not common so that most patients with the typical clinical phenotype will have mutations in the collagen VI genes.^{72,79}

Bethlem Myopathy

Clinical Features

This condition presents with moderate congenital hypotonia and weakness of a milder degree compared with UCMD, or there may be later onset of mild generalized, proximal, or

distally pronounced weakness.^{73,79} After some initial joint hypermobility, which is less dramatic compared with UCMD, there is early development of typical contractures in the finger flexors, elbows, pectoralis, Achilles' tendons, and elsewhere. Loss of ambulation occurs in about 50% of patients after very slow progression at about 60 years of age.⁸⁰ Cardiac involvement is not known to occur. As mentioned before, it is becoming clear now that there is a spectrum with overlap phenotypes between UCMD and Bethlem. Considerable phenotypic variability may even occur in the same family.

Genetics

Mutations in Bethlem myopathy are familial or de novo dominant mutations in all 3 collagen VI genes; however, their effects on collagen VI deposition and function seem to be milder compared with the dominant mutations observed in UCMD.⁷⁹

Therapeutic Strategies

Unfortunately, thus far, there are no curative treatment options available for patients with CMD. Approaches such as the use of prednisone as used in Duchenne muscular dystrophy have not been sufficiently evaluated in the various CMD forms. Much research is dedicated to finding treatment solutions that may apply to specific forms of CMD, mostly based on the work in appropriate mouse models.^{5,25} One example would be the use of cyclosporine in collagen VI deficiency based on findings in a mouse model of the disorder that suggest that cyclosporine A blockage of the mitochondrial permeability transition pore may stop a mitochondrial apoptosis cascade that could be part of the pathophysiology of collagen VI deficiency.⁸¹ Other examples would be the use of an agrin minigene in a mouse model of merosin/laminin2-deficient CMD to compensate for the lack of laminin2, as well as the notion that hyperglycosylation of α -dystroglycan using a LARGE transgene may be able to compensate for other defects along the pathway.^{82,83} Less disease-specific approaches that are under development for other muscle disorders may ultimately find applications in CMD as well, including the use of myostatin blockade, interference with muscle atrophy pathways, or stem-cell-based approaches. The clinical care of patients with CMD has to be managed by an interdisciplinary team. Long-term physical and occupational therapy should be prescribed to maintain the patient's independence as long as possible. Orthopedic monitoring is essential, especially concerning the development of contractures and scoliosis, which may require surgical intervention. Regular sleep studies and pulmonary function testing are important early to reveal nocturnal hypoventilation, resulting from restrictive lung disease and weakness of respiratory muscles including the diaphragm. Noninvasive bilevel positive-airway pressure treatment usually is highly effective in this situation. Possible cardiac involvement in particular in the α -dystroglycan disorders requires regular cardiac monitoring. In addition, social workers help to adjust the patient's individuality and his/her own environment.

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