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Congenital Muscular Dystrophies and the Extracellular Matrix

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During the past decade, considerable progress in the field of congenital muscular dystrophies (*CMD*s) 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 (*CMD*s) 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-α2 (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 multiminicore 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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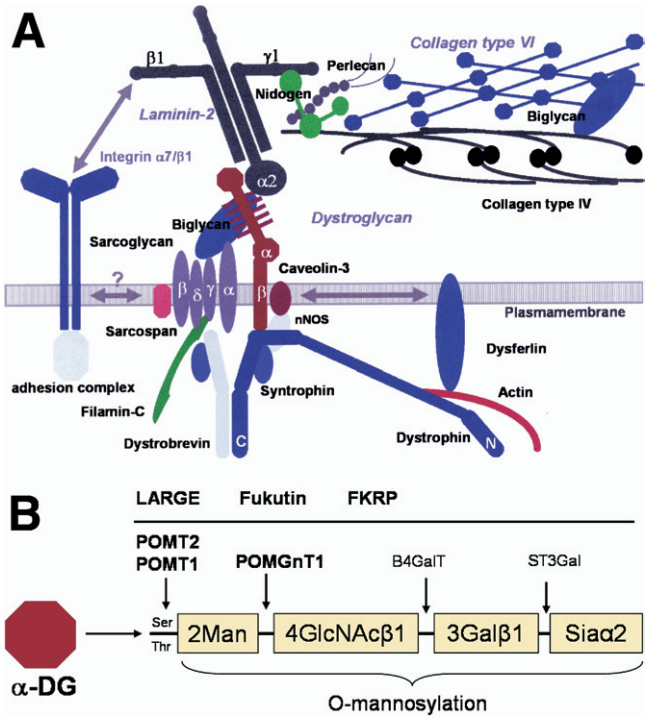

Figure 1 (A) Schematic representation of dystroglycan (DG) connecting the cytoskeleton of muscle cells with the extracellular matrix. (B) This binding is disrupted by defects in the posttranslational modification of α-dystroglycan (α-DG), causing congenital muscular dystrophy. Disease associated genes 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 *CMD*s, 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 β1,2-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 neurexin 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 proecess.[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,