Chapter 4

LAMA2 mutations in adult-onset muscular dystrophy with leukoencephalopathy

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LETTER TO THE EDITOR

In 1992, van Engelen et al. reported a familial, adult-onset muscular dystrophy with distal weakness and leukoencephalopathy. Apart from adult onset, the combination of muscle disease and leukoencephalopathy was reminiscent of congenital muscular dystrophies (CMD). The investigators suspected that this family may have an adult-onset variant of a subtype of CMD, probably with an allelic mutation at a CMD locus. The MRI findings (Figure 1, A-C) would be compatible with merosin (α2-chain of laminin-2) deficient congenital muscular dystrophy (now called MDC1A), but other variants would also be possible. Immunocytochemical staining of a muscle biopsy was performed using an anti-α2-chain antibody (clone Mer2/22B2; Novocastra), which probably recognizes the LG3 or LG4 domain of the laminin-α2 chain; normal staining was found (Figure 1, D and E). Because of lack of further information regarding the possible mutation, no DNA analysis was performed.

Figure 1. Brain MRI (A–C) shows diffuse cerebral white matter abnormalities with mild swelling of the abnormal white matter (C). The cerebellar white matter (A) and corpus callosum (B) are spared. Immunocytochemical labeling of spectrin as control and laminin-α2 in the muscle biopsy (collected in 2001) from a patient (D, E). Note the normal level of laminin α2 expression using an antibody directed against merosin (clone Mer2/22B2; Novocastra) (E) as compared with the control (D). Original magnification: x125.
Using whole-exome sequencing we recently identified 2 novel compound heterozygous mutations in the LAMA2 gene in the 3 affected siblings: 4516T>A missense mutation predicting p.Cys1506Ser located in exon 31 (protein domain IIIA) and 6466C>T nonsense mutation predicting p.Arg2156* located in exon 46 (protein domain I/G). Both mutations were not present in public control databases [dbSNP132 (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_summary.cgi?build_id=132), NHLBI GO Exome Sequencing Project (http://evs.gs.washington.edu/EVS/), and 1000 Genomes (http://www.1000genomes.org/home)], and the missense mutation was predicted to be deleterious by the Sorting Tolerant From Intolerant program (http://sift.jcvi.org/) and Polyphen-2 (http://genetics.bwh.harvard.edu/pph2/). These mutations were confirmed by Sanger sequencing.

LAMA2 mutations are the cause of MDC1A. Some mutations in LAMA2 result in complete deficiency of the laminin-α2 chain and are associated predominantly with a severe CMD.4 Other mutations result in partial laminin-α2 chain deficiency, a group that is clinically more heterogeneous.4,5 The latter group also contains a few patients with an adult-onset muscular dystrophy, mainly affecting the proximal muscles (limb-girdle distribution).5 Using the NCL-antibody we did not detect partial deficiency of laminin α2 in our family. However, we cannot exclude the possibility that we would detect partial deficiency of laminin-α2 using a more sensitive antibody, directed against the N-terminal 300-kDa fragment.6 The observed mild phenotype would be compatible with the compound heterozygosity between a nonsense and missense mutation that we found. The missense change results in loss of a conserved cysteine residue on the short arm of laminin-α2 that probably plays a role in disulfide cross-linking. The important G-domain of the protein that interacts with the membrane receptors alpha-dystroglycan and integrin α7β17 is not affected by the missense mutation, which could possibly explain the mild phenotype. The late onset of the disease and the predominantly distal muscle weakness in our patients extends the clinical spectrum associated with LAMA2 mutations.
REFERENCES
