Exome sequencing detects compound heterozygous nonsense LAMA2 mutations in two siblings with atypical phenotype and nearly normal brain MRI.

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Abstract

LAMA2 mutations cause the most frequent congenital muscular dystrophy subtype MDC1A and a variety of milder phenotypes, characterized by total or partial laminin-α2 deficiency. In both severe and milder cases brain MRI invariably shows abnormal white matter signal intensity. We report clinical, histopathological, imaging and genetic data on two siblings with very subtle, and at first undetected, reduction in laminin-α2 expression, and brain MRI showing minor non-specific abnormalities. Clinical features in the female proband were characterized by muscle weakness involving neck and axial muscles, and pelvic girdle and distal lower limb muscles, reduced tendon reflexes and pes cavus. Clinical features in a younger brother were similar, and remained stable in both siblings during the follow up. Whole exome sequencing (WES) detected two heterozygous truncating LAMA2 mutations. Brain MRI in combination with laminin-α2 immunohistochemistry might not be sufficient and WES might be the only means to reach a diagnosis.

KEYWORDS: Congenital muscular dystrophy type 1A; LAMA2; Laminin-α2; WES

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