Identification of Candidate Protein Markers in Skeletal Muscle of Laminin-211-Deficient CMD Type 1A-Patients.

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Abstract

Laminin-211 deficiency leads to the most common form of congenital muscular dystrophy in childhood, MDC1A. The clinical picture is characterized by severe muscle weakness, brain abnormalities and delayed motor milestones defining MDC1A as one of the most severe forms of congenital muscular diseases. Although the molecular genetic basis of this neurological disease is well-known and molecular studies of mouse muscle and human cultured muscle cells allowed first insights into the underlying pathophysiology, the definition of marker proteins in human vulnerable tissue such as skeletal muscle is still lacking. To systematically address this need, we analyzed the proteomic signature of laminin-211-deficient vastus muscle derived from four patients and identified 86 proteins (35 were increased and 51 decreased) as skeletal muscle markers and verified paradigmatic findings in a total of two further MDC1A muscle biopsies. Functions of proteins suggests fibrosis but also hints at altered synaptic transmission and accords with central nervous system alterations as part of the clinical spectrum of MDC1A. In addition, a profound mitochondrial vulnerability of the laminin-211-deficient muscle is indicated and also altered abundances of other proteins support the concept that metabolic alterations could be novel mechanisms that underline MDC1A and might constitute therapeutic targets. Intersection of our data with the proteomic signature of murine laminin-211-deficient gastrocnemius and diaphragm allowed the definition of nine common vulnerable proteins representing potential tissue markers.

KEYWORDS: NudC domain-containing protein 2; agrin; congenital muscular dystrophy; laminin-211; laminin-α2; muscle proteomics

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