LAMA2 gene mutation update: Towards a more comprehensive picture of the laminin-α2 variome and its related phenotypes.

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Abstract

Congenital muscular dystrophy type 1A (MDC1A) is one of the main subtypes of early-onset muscle disease, caused by disease-associated variants in the laminin-α2 (LAMA2) gene. MDC1A usually presents as a severe neonatal hypotonia and failure to thrive. Muscle weakness compromises normal motor development, leading to the inability to sit unsupported or to walk independently. The phenotype associated with LAMA2 defects has been expanded to include milder and atypical cases, being now collectively known as LAMA2-related muscular dystrophies (LAMA2-MD). Through an international multicenter collaborative effort, 61 new LAMA2 disease-associated variants were identified in 86 patients, representing the largest number of patients and new disease-causing variants in a single report. The collaborative variant collection was supported by the LOVD-powered LAMA2 gene variant database (https://www.LOVD.nl/LAMA2), updated as part of this work. As of December 2017, the database contains 486 unique LAMA2 variants (309 disease-associated), obtained from direct submissions and literature reports. Database content was systematically reviewed and further insights concerning LAMA2-MD are presented. We focused on the impact of missense changes, especially the c.2461A > C (p.Thr821Pro) variant and its association with late-onset LAMA2-MD. Finally, we report diagnostically challenging cases, highlighting the relevance of modern genetic analysis in the characterization of clinically heterogeneous muscle diseases. This article is protected by copyright. All rights reserved.

KEYWORDS: LAMA2; congenital; laminin-α2; locus-specific database; muscular dystrophy; mutation update

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