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Format: Abstract


New intronic splicing mutation in the LMNA gene causing progressive cardiac conduction defects and variable myopathy.

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Abstract

BACKGROUND: Most of mutations in the LMNA gene are unique and have been found in only a few unrelated families. The clinical interpretation of new genetic variants, especially beyond the coding area and canonical splice sites, is proving to be difficult and requires advanced investigation.

METHODS: This study included patients with progressive cardiac conduction defects with neuromuscular involvement. The clinical evaluation included medical history and 24-h Holter monitoring. The genetic evaluation included mutation screening in the LMNA gene by the Sanger sequence. Sanger sequencing was followed by RT-PCR of the target fragment of cDNA. In silico modeling was performed with CCBulder and Modeller software.

RESULTS: The diagnosis of limb-girdle muscular dystrophy type 1B (LGMD1B) was established. The new intronic variant c.513+45T>G was found in the LMNA gene in the proband and affected daughter. The insertion of 45bp was confirmed in the proband's cDNA. The structural and possible functional effects of the aberrant protein were predicted.

CONCLUSIONS: Variant c.513+45T>G in the LMNA gene likely translates into the longer lamin A/C proteins with additional 15 amino acids. This variant is thought to be pathogenic. Intronic variants in the LMNA gene located beside canonic splice sites may be responsible for some genotype-negative cases with clinical phenotype of laminopathies.

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KEYWORDS: Deep intronic mutation; Defect splice site mutation; Lamin; Lamin A/C-dependent limb-girdle muscular dystrophy type 1B

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