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Format: Abstract

Neuromuscul Disord. 2019 May;29(5):350-357. doi: 10.1016/j.nmd.2019.03.007. Epub 2019 Mar 14.

Recessive mutations in proximal I-band of TTN gene cause severe congenital multi-minicore disease without cardiac involvement.

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Abstract

Titin, encoded by the gene TTN, is one of the main sarcomere components. It is involved in not only maintaining the structure of cardiac and skeletal muscles, but also in their development, extensibility, elasticity, and signaling events. Congenital titinopathy increasingly appears an important and common form of axial predominant congenital myopathy. The pathophysiological role of TTN in congenital titinopathy and pediatric heart diseases is yet to be explored. Here, we delineate the phenotype of two female siblings who developed severe congenital multi-minicore disease without cardiac involvement. Genetic investigation by whole exome sequencing demonstrated compound heterozygous TTN mutations (c.15496+1G>A, p.5166_5258del; c.18597_18598insC, p.Thr6200Hisfs*15), corresponding to the Ig domain of the proximal I-band. Aberrant splicing causing exon skipping was verified by in vitro minigene analysis. Our results suggest that TTN mutations affecting the Ig domain of the proximal I-band may be a cause of severe congenital defect in skeletal muscles without severe cardiac involvement, thereby providing evidence for the hypothesis that congenital titinopathy patients carrying biallelic N2BA only mutations are at lower cardiac risk than those with other combinations of mutations. Meanwhile, this study confirm the hypothesis on recessive truncating variants of TTN experimentally and thus support earlier reported genotype-phenotype correlations.

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KEYWORDS: Congenital titinopathy; Electron microscopy study; Histochemical staining; Minigene; Multi-minicore disease; TTN

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Publication types, MeSH terms, Substances, Supplementary concept

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