Titin mutations and muscle disease.

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Abstract

The introduction of next-generation sequencing technology has revealed that mutations in the gene that encodes titin (TTN) are linked to multiple skeletal and cardiac myopathies. The most prominent of these myopathies is dilated cardiomyopathy (DCM). Over 60 genes are linked to the etiology of DCM, but by far, the leading cause of DCM is mutations in TTN with truncating variants in TTN (TTNtv\textsubscript{s}) associated with familial DCM in \(~20\%) of the cases. Titin is a large (3-4 MDa) and abundant protein that forms the third myofilament type of striated muscle where it spans half the sarcomere, from the Z-disk to the M-line. The underlying mechanisms by which titin mutations induce disease are poorly understood and targeted therapies are not available. Here, we review what is known about TTN mutations in muscle disease, with a major focus on DCM. We highlight that exon skipping might provide a possible therapeutic avenue to address diseases that arise from TTNtv\textsubscript{s}.

KEYWORDS: Dilated cardiomyopathy; Exon skipping; Mutations; TTNtv; Titin

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