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Titin–Truncating Mutations Associated With Dilated Cardiomyopathy Alter Length–Dependent Activation And Its Modulation Via Phosphorylation

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Abstract

**Aims:** Dilated cardiomyopathy (DCM) is associated with mutations in many genes encoding sarcomere proteins. Truncating mutations in the titin gene TTN are the most frequent. Proteomic and functional characterisations are required to elucidate the origin of the disease and the pathogenic mechanisms of TTN-truncating variants.

**Methods and results:** We isolated myofibrils from DCM hearts carrying truncating TTN mutations and measured the Ca2+ sensitivity of force and its length dependence. Simultaneous measurement of force and adenosine triphosphate (ATP) consumption in skinned cardiomyocytes was also performed. Phosphorylation levels of troponin I (TnI) and myosin binding protein-C (MyBP-C) were manipulated using protein kinase A and λ phosphatase. mRNA sequencing was employed to overview gene expression profiles. We found that Ca2+ sensitivity of myofibrils carrying TTN mutations was significantly higher than in myofibrils from donor hearts. The length dependence of the Ca2+ sensitivity was absent in DCM myofibrils with TTN-truncating variants. No significant difference was found in the expression level of TTN mRNA between the DCM and donor groups. TTN exon usage and splicing were also similar. However, we identified downregulation of genes encoding Z-disk proteins, while the atrial-specific regulatory myosin light chain gene, MYL7, was upregulated in DCM patients with TTN-truncating variants.

**Conclusion:** Titin-truncating mutations lead to decreased length-dependent activation and increased elasticity of myofibrils. Phosphorylation levels of TnI and MyBP-C seen in the left ventricles are essential for the length-dependent changes in Ca2+ sensitivity in healthy donors, but they are reduced in DCM patients with TTN-truncating variants. A decrease in expression of Z-disk proteins may explain the observed decrease in myofibril passive stiffness and length-dependent activation.

**Translational perspective:** Our findings may have implications in the development of new strategies for DCM treatment in patients with TTN-truncating variants as well as in the development of new drugs.

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