The Giant Protein Titin's Role in Cardiomyopathy: Genetic, Transcriptional, and Post-translational Modifications of TTN and Their Contribution to Cardiac Disease.

Tharp CA¹, Haywood ME¹, Sbaizero O², Taylor MRG¹, Mestroni L¹.

Author information

1 Adult Medical Genetics Program and Cardiovascular Institute, University of Colorado Anschutz Medical Campus, Aurora, CO, United States.
2 Department of Engineering and Architecture, University of Trieste, Trieste, Italy.

Abstract

Dilated cardiomyopathy (DCM) is a leading cause of heart failure, sudden cardiac death and heart transplant. DCM is inherited in approximately 50% of cases, in which the most frequent genetic defects are truncation variants of the titin gene (TTNtv). TTN encodes titin, which is the largest protein in the body and is an essential component of the sarcomere. Titin serves as a biological spring, spanning half of the sarcomere and connecting the Z-disk to the M-line, with scaffold and signaling functions. Truncations of titin are believed to lead to either haploinsufficiency and loss-of-function, or to a "poison peptide" effect. However, other titin mechanisms are postulated to influence cardiac function including post-translational modifications, in particular changes in titin phosphorylation that alters the stiffness of the protein, and diversity of alternative splicing that generates different titin isoforms. In this article, we review the role of TTN mutations in development of DCM, how differential expression of titin isoforms relate to DCM pathophysiology, and discuss how post-translational modifications of titin can affect cardiomyocyte function. Current research efforts aim to elucidate the contribution of titin to myofibril assembly, stability, and signal transduction, and how mutant titin leads to cardiac dysfunction and human disease. Future research will need to translate this knowledge toward novel therapeutic approaches that can modulate titin transcriptional and post-translational defects to treat DCM and heart failure.

HIGHLIGHTS: - Titin (TTN) truncation variants are the most frequent cause of dilated cardiomyopathy, one of the main causes of heart failure and heart transplant. Titin is a giant protein, and the mechanisms causing the disease are both complex and still incompletely understood. - This
The Giant Protein Titin’s Role in Cardiomyopathy: Genetic, Transcript...l Modifications of TTN and Their Contribution to C... - PubMed - NCBI

The Giant Protein Titin’s Role in Cardiomyopathy: Genetic, Transcript...l Modifications of TTN and Their Contribution to C... - PubMed - NCBI

12/22/19, 2:10 PM

The Giant Protein Titin’s Role in Cardiomyopathy: Genetic, Transcript...l Modifications of TTN and Their Contribution to C... - PubMed - NCBI

The Giant Protein Titin’s Role in Cardiomyopathy: Genetic, Transcript...l Modifications of TTN and Their Contribution to C... - PubMed - NCBI

review discusses the role of titin in myocardial function and in disease. In particular, we discuss TTN gene structure, the complexity of genotype-phenotype correlation in human disease, the physiology of TTN and the role of post-translation modification. Additional studies will be required to clarify whether missense variants are associated with cardiac disease. While initial studies suggested a role of non-synonymous variants in arrhythmogenic cardiomyopathy, confirmatory investigations have been hampered by the complexity of the protein structure and function.

Copyright © 2019 Tharp, Haywood, Sbaizer, Taylor and Mestroni.

KEYWORDS: RBM20; dilated cardiomyopathy; phosphorylation; phosphosites; proportion-spliced-in; sarcomere; titin; truncation variants

PMID: 31849696  PMCID: PMC6892752  DOI: 10.3389/fphys.2019.01436

Free PMC Article

Images from this publication. See all images

(2) Free text

Publication type

LinkOut - more resources