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Interpreting pathogenic variants in TTN for dilated cardiomyopathy

In this era of expanding gene panels and whole-exome and whole-genome sequencing for rare disease molecular diagnostics, it remains a challenge to filter numerous resulting variants from these sequencing assays, assign functional consequences of a variant in the resulting protein, and then determine potential pathogenicity. Inherited cardiac conditions such as cardiomyopathies and channelopathies highlight the challenges in implicating variants as being pathogenic in the respective disease phenotype. The authors present data to assist in the interpretation of variant data in the gene *titin (TTN)*, which encodes the largest human protein comprised of multiple isoforms ranging in size from 5,604 to 34,350 amino acids. Truncating variants in TTN (TTNtv) occur in approximately 25 percent of cases of severe and familial dilated cardiomyopathy (DCM). However, interpreting these variants has been challenging because they also occur in approximately two percent of people without overt disease. The authors conducted a study that surveyed the distribution of truncating mutations in more than 5,000 people with various stages of cardiac disorders, as well as in healthy control subjects, and incorporated transcriptome and protein analyses of human heart tissues. They observed that TTNtv were nonuniformly distributed between DCM and control study groups and that these mutations were more commonly located in the A-band region of the protein in the DCM group than in the controls. The A-band in TTN is responsible for binding myosin and myosin-binding protein. TTNtv were also compared among different isoforms, and those mutations that altered N2BA and N2B isoforms were strongly enriched in DCM patients, whereas TTNtv found in controls were enriched in exons that were not incorporated into N2BA and N2B transcripts. These data suggest that many TTNtv in controls may be tolerated because they do not occur in cardiac-expressed transcripts. The study also sought to determine the effect of the truncating mutation on DCM by measuring transcript levels in patients with and without TTNtv, as well as the abundance of N2BA and N2B protein isoforms in DCM patients with and without TTNtv. Both lines of evidence suggest that TTNtv might cause DCM by a dominant negative effect. The authors concluded that the study sheds light on TTNtv characteristics associated with DCM that will aid in interpreting variant data in this important gene for both DCM molecular diagnostic testing as well as reporting incidental findings in DCM low-risk individuals undergoing whole-exome and whole-genome sequence-based testing.

Roberts AM, Ware JS, Herman DS, et al. Integrated allelic, transcriptional, and phenomic dissection of the cardiac effects of titin truncations in health and disease [published online ahead of print January 14, 2015]. *Sci Transl Med.* doi:10.1126/scitranslmed.3010134.

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