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Amino Acid-level Signal-to-Noise Analysis Aids in Pathogenicity Prediction of Incidentally-identified TTN-Encoded Titin Truncating Variants

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Abstract

Background - TTN, the largest gene in the human body, encodes titin (TTN), a protein that plays key structural, developmental, and regulatory roles in skeletal and cardiac muscle. Variants in TTN, particularly truncating variants (TTNtv), have been implicated in the pathogenicity of cardiomyopathy (CM). Despite this link, there is also a high burden of TTNtv in the ostensibly healthy general population. This complicates the diagnostic interpretation of incidentally identified TTNtv which are of increasing abundance given expanding clinical exome sequencing (ES).

Methods - Incidentally identified TTNtv were obtained from a large referral database of clinical ES (Baylor Genetics) and compared to rare population variants from gnomAD and CM-associated variants from cohort studies in the literature. A subset of TTNtv-positive children evaluated for cardiomyopathy at Texas Children's Hospital (TCH) were retrospectively reviewed for clinical features of cardiomyopathy. Amino acid-level signal-to-noise analysis (S:N) was performed.

Results - Pathologic hotspots were identified within the A-band and N-terminal I-band that closely correlated with regions of high percent spliced in (PSI) of exons. Incidental TTNtv and population TTNtv did not localize to these regions. Variants were re-classified based on current ACMG criteria with incorporation of S:N analysis among TCH cases. Those re-classified as likely pathogenic or pathogenic were more likely to have evidence of CM on echocardiography than those re-classified as variants of unknown significance. Conclusions - Incidentally found TTNtv are common among clinical ES referrals. Pathologic hotspots within the A-band of TTN may be informative in determining variant pathogenicity when incorporated into current ACMG guidelines.

Keywords: Titin; TTN; incidental finding; variant of uncertain significance.

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