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Observational Study Am J Cardiol. 2020 Dec 15;137:97-102.

Discovery of TITIN Gene Truncating Variant Mutations and 5-Year Outcomes in Patients With Nonischemic Dilated Cardiomyopathy

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PMID: 32998006 DOI: 10.1016/j.amjcard.2020.09.026

Abstract

Genetic factors play an important role in nonischemic dilated cardiomyopathy (NIDC). However, prime opportunities remain for genetic discovery and prognostic understanding. TITIN gene truncating variant mutations (TTNtv) are of interest because of their frequent appearance in NIDC series. We sought to discover known and novel TTNtv mutations in a NIDC cohort and assess 5-year outcomes. Patients with NIDC entered into the INSPIRE Registry with ≥3 years of follow-up were studied. Whole exome sequencing (WES) was performed using an Illumina Novaseq platform. Genetic analysis used Sentience software and the GRCh38 human reference genome. Variant calls were annotated with ClinVar. Five-year outcomes were determined by functional assessment and ejection fraction (EF) as recovered (EF ≥50%), persistent (EF 21% to 49%), or progressive (left ventricular assist device, transplant, heart failure [HF] or arrhythmic death, or EF ≤20%). The study comprised 229 NIDC patients (age = 50 ± 15 years, 58% men). TTNtv's were discovered in 27 patients with 22 unique mutations; (7 known, 15 novel). TTNtv+ patients more frequently presented with severe NIDC (EF ≤20%) (p = 0.032). By 5-year, outcomes were worse in TTNtv+ patients (p = 0.027), and patients less often recovered (11% vs. 30%). Prognosis was similar with known and novel mutations. Nongenetic (e.g., environmental) cocausal risk factors for HF were frequently present, and these factors frequently appeared to act in concert with genetic variants to precipitate clinical HF. In conclusion, our study expands the library of likely pathogenic TTN mutations and increases our understanding of their clinical impact in association with other HF risk factors.

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