Titin-truncating Variants Are Associated with Heart Failure Events in Patients with Left Ventricular Noncompaction Cardiomyopathy

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Abstract

Background

Titin-truncating variants (TTNtv) have been recognized as the most prevalent genetic cause of dilated cardiomyopathy. However, their effects on phenotypes of left ventricular noncompaction cardiomyopathy (LVNC) remain largely unknown.

Hypothesis
The presence of TTNtv may have an effect on the phenotype of LVNC.

Methods

TTN was comprehensively screened by targeted sequencing in a cohort of 83 adult patients with LVNC. Baseline and follow-up data of all participants were collected. The primary endpoint was a composite of death and heart transplantation. The secondary endpoint was heart failure (HF) events, a composite of HF-related death, heart transplantation, and HF hospitalization.

Results

Overall, 13 TTNtv were identified in 13 patients, with 9 TTNtv located in the A-band of titin. There was no significant difference in baseline characteristics between patients with and without TTNtv. During a median follow-up of 4.4 years, no significant difference in death and heart transplantation between the two groups was observed. However, more heart failure events occurred in TTNtv carriers than in noncarriers ($P=0.006$). Multivariable analyses showed that TTNtv were associated with an increased risk of heart failure events independent of sex, age, and baseline cardiac function (hazard ratio: 3.25, 95% confidence interval: 1.50–7.01, $P=0.003$). Sensitivity analysis excluding non-A-band TTNtv yielded similar results, but with less strength.

Conclusions

The presence of TTNtv may be a genetic modifier of LVNC and confer a higher risk of heart failure events among adult patients. Studies of larger cohorts are needed to confirm our findings.

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Supporting Information

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<td>Titin-truncating variants detected in patients with left ventricular noncompaction cardiomyopathy Genotypic background and clinical characteristics of patients with TTNtv Baseline characteristics of patients with and without A-band TTNtv Incidence of primary and secondary endpoints in patients with and without A-band TTNtv Univariable and multivariable analysis for outcomes in patients with and without A-band TTNtv</td>
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