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THE INTERPLAY BETWEEN TITIN, POLYGENIC RISK AND MODIFIABLE CARDIOVASCULAR RISK FACTORS IN ATRIAL FIBRILLATION

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Abstract

Background: Common and rare variants, including those in the cardiac structural gene titin (TTN), have been implicated in the risk of developing atrial fibrillation (AF). However, the effect of genetic variants on risk of AF compared to established modifiable risk factors is unclear. The objective of this study was to evaluate the risk of AF and associated cardiovascular complications in TTN variant carriers and examine interactions between TTN variants or common variants and modifiable AF risk factors.

Methods: We used whole exome sequencing data of 49,881 individuals and genotyping data of 408,572 individuals from the UK Biobank to examine the associations of TTN variants, polygenic risk, and four risk factors (hypertension, diabetes, obesity, and smoking) with AF. Adjusted hazard ratios (aHR) were calculated using Cox proportional hazards models.

Results: TTN variant carrier status was associated with a higher risk of AF (aHR, 2.10 [95% CI, 1.59–2.79]; P = 2.54x10⁻⁷) and higher risk of DCM in AF patients (aHR, 10.39 [95% CI, 5.31–20.33]; P = 8.37x10⁻¹²). We identified additive effects between TTN variants and polygenic risk with hypertension, diabetes, obesity, and smoking on the risk of AF.

Conclusion: Genetic and modifiable cardiovascular risk factors contribute to the probability of developing AF. Our findings highlight the potential utility of incorporating data from targeted sequencing or genotyping of common variants to further inform AF risk stratification and aggressive management of modifiable cardiovascular risk factors.

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