Exploring the Genetic Link between Clonal Hematopoiesis and Dilated Cardiomyopathy: Insights from a Polygenic Risk Score Analysis

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INTRODUCTION

Clonal hematopoiesis (CH) refers to the expansion of a blood stem cell and its descendants, driven by somatic driver mutations, and includes clinically relevant subsets such as clonal hematopoiesis of indeterminate potential (CHIP). CHIP, in particular, is increasingly recognized for its role in lymphoid malignancies. Although CH is a relatively common phenomenon—affecting over one-third of individuals and becoming more prevalent with age—it is linked to a heightened risk of hematological cancers, various non-hematological conditions and inflammation. Inflammation responses play a central role in cardiovascular diseases and heart failure and recent studies suggested CH as an important trigger for dilated cardiomyopathy (DCM) [1].

AIMS

Thanks to recent findings of a genome-wide association study (GWAS) that identified 42 independent genetic variants associated with the risk of developing CH [2], we conducted a study aimed at evaluating whether a polygenic risk score (PRS) for CH risk is related to the diagnosis and prognosis of DCM.

METHODS

The study analyzed a DCM cohort of 315 patients recruited in the Heart Muscle Disease Registry of Trieste (IT) and 718 healthy individuals from the same region. A PRS was derived based on 27 GWAS loci was calculated using imputed SNP-array data. PRS standardized levels were compared across groups using a generalized linear mixed-model that included a genomic relatedness matrix as random effect to account for familial relationships. As for the analysis of disease progression in the DCM cohort, two primary outcomes were investigated: (1) life-threatening arrhythmic events, and (2) heart failure–related events. Time-to-event analysis was performed using cause-specific Cox mixed-models.

RESULTS

The PRS was significantly higher in healthy individuals compared to DCM patients (OR=0.82 95% CI [0.69, 0.97] per SD increase, p=0.005). When differentiating between DCM patients who were carriers and non-carriers of pathogenic/likely pathogenic variants, the observed difference was primarily driven by the carrier group (mean difference=-0.22, 95% CI [-0.41, -0.04]). During a median follow-up of 109 months (IQR=[24,194]), 80 (25%) individuals experienced life-threatening arrhythmic events, 43 (14%) experienced heart failure–related events and 57 (18%) died. No association was observed between PRS and either arrhythmic outcome, neither with heart failure outcome.

CONCLUSIONS

These findings contribute to expanding the knowledge on the relationship between clonal hematopoiesis (CH) and cardiovascular diseases, specifically dilated cardiomyopathy (DCM), where current understanding remains limited. The observed association between lower CH PRS levels and higher DCM risk was unexpected. Further studies are needed to confirm these results and clarify their implications.

DOI: 10.54103/2282-0930/29519

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DOI: 10.54103/2282-0930/29519