Polygenic risk score for hypertrophic cardiomyopathy predicts population disease risk, penetrance in sarcomeric rare variant carriers and survival in cases

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Background: Hypertrophic cardiomyopathy (HCM) is an important cause of mortality, caused by rare pathogenic variants (sarcomere-positive) in around one third of cases. Recent large genome-wide association studies (GWAS) highlight the important contributions of common genetic variation on HCM risk and heritability1-3. Polygenic scores (PGS) quantify the cumulative individual risk from common genetic variation, and may provide important clinical utility.

Purpose: The aim of this study is to generate PGS for HCM, and evaluate its performance in predicting HCM in the general population, HCM penetrance in sarcomere-positive carriers, and risk of adverse outcomes in individuals with HCM.

Methods: The PGS was generated using a Bayesian framework (PRS-CS) with individual SNP effect estimates derived from the largest published HCM GWAS (5900 cases and 68359 controls of European ancestry from 7 cohorts) and multi-trait analysis of GWAS (MTAG) (incorporating GWAS of genetically correlated cardiac magnetic resonance imaging (CMR) traits from 36203 White British individuals in the UK Biobank [UKB]1. Genome-wide PGS were calculated using an additive model for participants in two cohorts (UKB and 100,000 Genomes Project [GeL]). To evaluate the effect of PGS on penetrant HCM in sarcomere-positive carriers, we identified individuals with pathogenic or likely pathogenic variants in 8 definitive HCM-causing genes (MYBPC3, MYH7, TNNT2, TNNI3, TPM1, ACTC1, MYL3, and MYL2) in UKB and GeL.

Results: In 343,182 unrelated White British ancestry participants from the UK Biobank (UKB), PGS was associated with an increased risk of HCM (OR per PGS SD 2.3, P <2x10-16), with 75% of HCM cases having a PGS above the population mean (Figure 1A). Individuals with PGS in the top centile had a substantially increased risk of HCM compared with those in the median (OR 14.5, P <2x10-16) and bottom centile (OR 36.6, 3x10-25) (Figure 1B). PGS had significant effects on stratifying HCM penetrance in 640 sarcomere-positive carriers in the UKB (top vs. middle quintile HCM OR: 3.7, P 0.009), and risk of being a HCM case in 599 sarcomere-positive carriers in GeL (top vs. middle quintile HCM OR 9.5, P 4x10-5) (Figure 1C), highlighting the important interactive effect of common and rare genetic variants. Finally, PGS predicted risk of all-cause mortality and major adverse cardiovascular events (MACE) after HCM diagnosis in 382 cases in UKB (all-cause mortality: top vs. bottom quintile: HR 3.9, P 0.013; MACE: top vs. bottom quintile: HR 3.5, P 4.x10-4), and all-cause mortality in 683 cases in GeL (top vs. bottom quintile: HR 6.3, P 1x10-6) (Figure 1D).

Conclusions: We derive a PGS for HCM risk prediction, and demonstrate potential clinical utility in stratifying risk of penetrant HCM in sarcomere-positive carriers, and in predicting risk of adverse outcomes in individuals with HCM.