Large scale genome-wide association analyses identify novel genetic loci and mechanisms in hypertrophic cardiomyopathy

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Funding Acknowledgements: Type of funding sources: Public Institution(s). Main funding source(s): British Heart Foundation
Dutch Heart Foundation

Background: Hypertrophic cardiomyopathy (HCM) is an important cause of morbidity and mortality with both monogenic and polygenic components. Prior genome-wide association studies (GWAS) identified few genomic loci and disease genes due to limited sample size.

Purpose: To discover novel genetic loci, genes and mechanisms implicated in HCM using a large scale GWAS and multi-trait analysis of GWAS (MTAG).

Methods and results: We performed the largest HCM GWAS meta-analysis and MTAG to date including 5,900 HCM cases, 68,359 controls, and 36,083 UK Biobank (UKB) participants with cardiac magnetic resonance (CMR) imaging. We estimated the heritability of HCM attributable to common genetic variation (h²SNP) to be 0.25±0.02 using genome-based restricted maximum likelihood (GREML), with higher h²SNP in non-sarcomeric (0.29±0.02) compared to sarcomeric HCM (0.16±0.04). We identified a total of 70 loci (50 novel) associated with HCM (Figure 1), and 62 loci (32 novel) associated with relevant left ventricular (LV) structural or functional traits. Amongst the common variant HCM loci, we identify a novel HCM disease gene, SVIL, which encodes the actin-binding protein supervillin. We performed rare variant burden analysis including 1,845 clinically-diagnosed unrelated HCM cases and 37,481 controls and demonstrated a 10.5-fold (95% CI: 4.1-26.8; P=0.0000002) excess burden of SVIL loss of function (LoF) variants in HCM cases. Two-sample mendelian randomization analyses using LV contractility as exposure and obstructive (oHCM) and non-obstructive HCM (nHCM) as outcomes support a causal role of increased LV contractility in both oHCM and nHCM (Figure 2), suggesting common disease mechanisms and anticipating shared response to therapy.

Conclusion: We identify 50 novel genomic loci associated with HCM. Our data suggest that LoF variants in SVIL are a cause of HCM, and that increased contractility mediate both nHCM and oHCM. Taken together, the findings significantly increase our understanding of the genetic basis and molecular mechanisms of HCM, with potential implications for disease management.

Figure 1. Circular Manhattan plot of HCM summary statistics from MTAG analysis. Previously published loci are identified in black (N=201), novel loci discovered by single trait all-variant GWAS meta-analysis are identified in blue (N=15) and additional novel loci from MTAG are identified in green (N=32). Two other loci reaching EWAS significance threshold in the single trait HCM GWAS meta-analysis but not reaching significance in MTAG are not shown.
Figure 2: Mendelian randomization (MR) analysis of LV contractility on risk of obstructive (oHCM) and non-obstructive (nHCM) hypertrophic cardiomyopathy (HCM). Odds ratio (OR) represented are those inferred from the inverse variance weighted (IVW) two-sample MR per standard deviation increase (SD). The error bars represent the 95% confidence interval of the OR. MR suggests causal association of LV contractility (exposure) with HCM, oHCM and nHCM (outcomes), where increased contractility increases disease risk. Genetic instruments for LV contractility were selected from the present GWAS of left ventricular ejection fraction (LVEF), and strain in the radial (strain_rad), longitudinal (strain_long) and circumferential (strain_circ) directions in 36,083 participants of the UKB without cardiomyopathy and with available CMR.