Shared genetic pathways contribute to risk of hypertrophic and dilated cardiomyopathies with opposite directions of effect

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The heart muscle diseases hypertrophic (HCM) and dilated (DCM) cardiomyopathies are leading causes of sudden death and heart failure in young, otherwise healthy, individuals. We conducted genome-wide association studies and multi-trait analyses in HCM (1,733 cases), DCM (5,521 cases) and nine left ventricular (LV) traits (19,260 UK Biobank participants with structurally normal hearts). We identified 16 loci associated with HCM, 13 with DCM and 23 with LV traits. We show strong genetic correlations between LV traits and cardiomyopathies, with opposing effects in HCM and DCM. Two-sample Mendelian randomization supports a causal association linking increased LV contractility with HCM risk. A polygenic risk score explains a significant portion of phenotypic variability in carriers of HCM-causing rare variants. Our findings thus provide evidence that polygenic risk score may account for variability in Mendelian diseases. More broadly, we provide insights into how genetic pathways may lead to distinct disorders through opposing genetic effects.

Cardiomyopathies are heritable heterogeneous diseases characterized by changes in myocardial structure and function. We sought to better understand the genetic underpinnings of HCM and DCM as well as their relation to myocardial traits in the general population (Fig. 1). HCM has a prevalence of 0.2% (ref. 1) and has been classically considered a Mendelian disease. However, genetic testing identifies a causal rare variant in less than half of cases 2, and data from both families and population cohorts support reduced penetrance and variable expressivity3, suggesting a complex genetic architecture. Here, we performed a meta-analysis of three new genome-wide association studies (GWAS) comprising 1,733 unrelated HCM cases and 6,628 controls of European ancestry from the Netherlands, the United Kingdom and Canada (Supplementary Table 1). Of the cases, 642 (37%) carried pathogenic or likely pathogenic variants in established HCM disease genes (Supplementary Table 2). Analysis of SNP-based heritability ($h^2_{SNP}$) using generalized restricted maximum likelihood (GREML) 4 demonstrated that a significant portion of HCM liability is attributed to common genetic variation (Supplementary Table 3), with $h^2_{SNP}$ estimates in meta-analyses ranging from 0.12 (GREML, fixed-effects; $P=8 \times 10^{-6}$) to 0.29 (GREML with linkage disequilibrium (LD) and MAF stratification (GREML-LDMS), random effects; $P=9 \times 10^{-5}$). The GWAS summary meta-analysis results of 6,530,233 variants with a minor allele frequency (MAF) $\geq 0.01$ are shown as Manhattan and quantile–quantile (QQ) plots in Fig. 2a. The wide association signal observed on chromosome 11 tagging recurrent MYBPC3 founder variants disappeared when restricting the analysis to the 1,445 HCM cases without such variants (Supplementary Table 4).
Using a conservative threshold of $P < 1 \times 10^{-8}$ to account for multiple testing, a total of six loci were significantly associated with HCM (Table 1, Supplementary Table 4 and Supplementary Fig. 2), of which five are new and one, on chromosome 18 near FHOD3, has been previously published. Importantly, two of the new HCM loci (chromosome 1 near HSPB7 and chromosome 10 near BA3G) have been previously associated with DCM at genome-wide statistical significance, but with an opposite direction of effect. Specifically, the published DCM lead risk alleles at both loci (rs10927875-C and rs2234962-T) were protective for HCM in the present study (odds ratio, OR (95% confidence interval, CI), 0.80 (0.74–0.87) and 0.71 (0.64–0.77), respectively). Recently, both loci were also found to be correlated phenotypically (Supplementary Fig. 6). The Manhattan plots appear as panels in Fig. 2 and Extended Data Figs. 1–10. A total of three loci in the DCM (all previously published; Supplementary Table 7 and Supplementary Fig. 7) and 17 loci in any of the nine LV traits meta-analyses reached a $P$-value threshold of $1 \times 10^{-8}$ (Supplementary Table 8).

Genetic correlations between LV traits in the general population, HCM and DCM were assessed using LD score regression (Supplementary Table 9). The results highlight the divergent relationships of LV traits with DCM and HCM (Fig. 3). HCM showed a positive genetic correlation with meanWT ($r_g = 0.51, P = 9 \times 10^{-4}$), while DCM was positively correlated with LV end-diastolic (LVEDV) and end-systolic (LVESV) volumes ($r_g = 0.43, P = 2 \times 10^{-4}$ and $r_g = 0.46, P = 1 \times 10^{-4}$, respectively). Decreased LV contractility is a hallmark of DCM, and we observed a negative genetic correlation between DCM and LV contractility, whether assessed using a volumetric measure, LVEF ($r_g = -0.35, P = 9 \times 10^{-4}$), or using global LV strain measured in any direction: circumferential ($-\text{strain}^{c}$; $r_g = -0.48, P = 2 \times 10^{-4}$), radial ($\text{strain}^{r}$; $r_g = -0.42, P = 3 \times 10^{-4}$) and longitudinal ($\text{strain}^{l}$; $r_g = -0.27, P = 0.05$) (note that for strain$^{r}$ and strain$^{l}$, increasingly negative values reflect higher strain/contractility). Remarkably, all four of these contractility parameters were positively correlated with HCM; increases in contractility are correlated with increased HCM risk ($r_g$ ranging from 0.27 for $-\text{strain}^{c}$ ($P = 0.03$) to 0.62 for $\text{strain}^{l}$ ($P = 1 \times 10^{-7}$)).

We then performed multi-trait analysis of GWAS (MTAG) to increase power for discovery of novel loci. Two analyses were performed: (1) MTAG of nine LV traits (referred to as MTAG9) to uncover novel loci associated with LV traits and (2) MTAG of HCM, DCM and nine LV traits (henceforth MTAG11) to uncover loci associated with DCM and HCM. The corresponding Manhattan and QQ plots appear as panels b in Fig. 2 and Extended Data Figs. 1–10. MTAG9 uncovered six additional genetic loci associated with LV traits (Supplementary Table 8). MTAG11 uncovered an additional
10 HCM (Table 1, Supplementary Table 4 and Supplementary Fig. 2) and 10 DCM loci (Supplementary Table 7 and Supplementary Fig. 7). Supplementary Tables 4, 7 and 8 tabulate relationships for all traits with all HCM, DCM and LV trait lead SNPs, respectively, highlighting the cross-trait single SNP level correlation. In particular, 8 of the 16 HCM-associated loci also showed significant association with DCM using a Benjamini–Hochberg false discovery rate (FDR) < 0.05, where all 8 lead SNPs showed opposite directions of effect in HCM versus DCM (Supplementary Table 4). Similarly, all 13 DCM loci were also associated with HCM at an FDR < 0.05 (Supplementary Table 7), with all loci showing an opposite effect in HCM versus DCM except locus DCM4 near TTN. At this locus, the DCM risk allele also increases risk for HCM. We hypothesize that this unique concordant HCM/DCM effect may be attributable to pleiotropic effects of that locus on LV structure/function, where the HCM and DCM risk increasing allele reduces LV contractility parameters but also increases LV hypertrophy (LV mass and meanWT; Supplementary Table 7). Figure 4 displays a heatmap representation of the direction and strength of effect of all 16 HCM risk alleles and 13 DCM risk alleles in all nine LV traits, HCM and
Many HCM risk alleles are also associated with reduced risk of DCM and, in the general population, increased LV contractility (LVEF and strain) and decreased LV volumes.

Replication of HCM loci was tested in an independent dataset comprising 2,694 HCM cases included from the Hypertrophic Cardiomyopathy Registry (HCMR) or the National Institute for Health Research (NIHR) Biorepository for Rare Disease (BRRD)\(^1\), and 47,486 controls without HCM included from the UKBB or BRRD. Of the 16 HCM loci, 15 (all except HCM4) were replicated at \(P < 0.003\) (Table 1 and Supplementary Table 10).

The correlation between increased contractility and HCM risk led us to test the hypothesis that increased contractility is causally associated with HCM. We tested such potential causal relation between increased LV contractility and HCM using two-sample Mendelian randomization (MR), where the exposure variables were LV contractility measures \((-\text{strain}_{\text{circ}}, \text{strain}_{\text{long}}\) and \(\text{LVEF}\); all strongly correlated, opposite effects). Center values are the estimated genetic correlation \((r_g)\) and error bars indicate 95\% CI. Samples sizes for included GWAS are as follows: 1,733 cases and 6,628 controls for HCM; 5,521 cases and 397,323 controls for DCM and nine quantitative LV traits. Asterisks identify significant odds ratio for each risk allele in the single-trait HCM analysis; \(P\), single-trait analysis \(P\) value; \(P\) (MTAG11), multi-trait analysis \(P\) value for HCM; \(P_{\text{replication}}\), \(P\) value in the replication dataset; RA, risk allele; RA, nonrisk allele; OR, odds ratio. Supplementary Table 9. Since \(\text{strain}_{\text{circ}}\) and \(\text{strain}_{\text{long}}\) are always negative values, \(\text{strain}_{\text{circ}}\) and \(\text{strain}_{\text{long}}\) are plotted to facilitate interpretation of effect direction.

### Table 1 | Lead SNPs and effect estimates for genome-wide significant loci (\(P < 1 \times 10^{-8}\)) in the HCM single-trait and multi-trait analyses

| Locus | Lead SNP | GRCh37 | Nearest gene | RA | NRA | RA% | OR | 95% CI | \(P\) | \(P\) (MTAG11) | \(P_{\text{replication}}\) |
|-------|----------|--------|--------------|----|-----|------|----|--------|------|-------------|-----------------|
| HCM1  | rs10927886 | 1:6339313 | HSPB7        | G  | C   | 0.41 | 1.28 | 1.18–1.38 | 1.8 \times 10^{-9} | 7.4 \times 10^{-13} | 2.5 \times 10^{-13} |
| HCM2  | rs12212795 | 6:118654308 | SLC35F1      | C  | G   | 0.06 | 1.69 | 1.43–2.01 | 1.6 \times 10^{-9} | 1.7 \times 10^{-12} | 6.7 \times 10^{-11} |
| HCM3  | rs17099139 | 10:12194487 | BAG3         | G  | C   | 0.29 | 1.46 | 1.34–1.59 | 7.2 \times 10^{-10} | 1.0 \times 10^{-11} | 1.3 \times 10^{-12} |
| HCM4* | rs9928278 | 16:2152651 | PKD1         | C  | T   | 0.18 | 1.45 | 1.28–1.65 | 9.5 \times 10^{-9} | 5.9 \times 10^{-7} | 2.7 \times 10^{-7} |
| HCM5  | rs1378358 | 17:44783712 | NSF          | T  | C   | 0.23 | 1.34 | 1.22–1.47 | 1.5 \times 10^{-9} | 4.7 \times 10^{-13} | 4.7 \times 10^{-14} |
| HCM6  | rs503279  | 18:34253745 | FHOD3        | C  | T   | 0.31 | 1.52 | 1.40–1.66 | 1.7 \times 10^{-10} | 2.4 \times 10^{-11} | 4.3 \times 10^{-11} |
| HCM7 (MTAG11) | rs9647379 | 3:171785168 | FND3C        | C  | G   | 0.42 | 1.22 | 1.12–1.33 | 6.8 \times 10^{-5} | 9.5 \times 10^{-6} | 2.4 \times 10^{-6} |
| HCM8 (MTAG11) | rs2191445 | 5:57011469 | ACTBL2       | T  | A   | 0.78 | 1.29 | 1.17–1.43 | 8.0 \times 10^{-7} | 3.5 \times 10^{-8} | 2.6 \times 10^{-9} |
| HCM9 (MTAG11) | rs4385202 | 5:138743256 | DNAJC18      | A  | G   | 0.31 | 1.25 | 1.15–1.37 | 6.0 \times 10^{-6} | 3.0 \times 10^{-8} | 7.3 \times 10^{-7} |
| HCM10 (MTAG11) | rs66761782 | 6:36636080 | CDKN1A       | C  | T   | 0.26 | 1.29 | 1.18–1.41 | 3.4 \times 10^{-9} | 2.1 \times 10^{-9} | 1.3 \times 10^{-9} |
| HCM11 (MTAG11) | rs60871386 | 7:128430437 | CCDC136      | T  | G   | 0.10 | 1.43 | 1.12–1.54 | 3.4 \times 10^{-10} | 2.2 \times 10^{-10} | 1.4 \times 10^{-11} |
| HCM12 (MTAG11) | rs3740293 | 10:75406141 | SYNPO2L      | C  | A   | 0.15 | 1.33 | 1.19–1.49 | 4.8 \times 10^{-7} | 4.6 \times 10^{-8} | 8.5 \times 10^{-9} |
| HCM13 (MTAG11) | rs11966078 | 10:114487812 | VTI1A        | A  | G   | 0.26 | 1.26 | 1.15–1.38 | 5.2 \times 10^{-7} | 1.6 \times 10^{-10} | 6.7 \times 10^{-8} |
| HCM14 (MTAG11) | rs11073729 | 15:85350081 | ZNF592       | C  | T   | 0.46 | 1.20 | 1.11–1.30 | 4.2 \times 10^{-6} | 9.9 \times 10^{-7} | 3.6 \times 10^{-7} |
| HCM15 (MTAG11) | rs9892651 | 17:64303793 | PRKCA        | T  | C   | 0.59 | 1.25 | 1.16–1.36 | 2.8 \times 10^{-6} | 3.0 \times 10^{-10} | 2.4 \times 10^{-9} |
| HCM16 (MTAG11) | rs2186370 | 22:24171305 | SMARC81      | A  | G   | 0.22 | 1.21 | 1.09–1.34 | 3.5 \times 10^{-7} | 2.5 \times 10^{-9} | 5.5 \times 10^{-10} |

* Locus HCM4 is not replicated. GRCh37, genomic position in GRCh37; MTAG11, multi-trait analysis of GWAS summary statistics from HCM, DCM and nine quantitative LV traits; NRA, nonrisk allele; OR, odds ratio for each risk allele in the single-trait HCM analysis; \(P\), single-trait analysis \(P\) value; \(P\) (MTAG11), multi-trait analysis \(P\) value for HCM; \(P_{\text{replication}}\), \(P\) value in the replication dataset; RA, risk allele; RA, nonrisk allele; OR, odds ratio.

| Fig. 3 | Genetic correlation between LV traits, HCM and DCM. HCM (red bars) and DCM (blue bars) show strong genetic correlations with quantitative cardiac LV traits measured in the general population, but with opposite effects. Center values are the estimated genetic correlation \((r_g)\) and error bars indicate 95\% CI. Samples sizes for included GWAS are as follows: 1,733 cases and 6,628 controls for HCM; 5,521 cases and 397,323 controls for DCM and 9,160 for LV traits. Asterisks identify significant genetic correlations with a Benjamini–Hochberg FDR < 0.05. Data shown correspond to that in Supplementary Table 9. Since \(\text{strain}_{\text{circ}}\) and \(\text{strain}_{\text{long}}\) are always negative values, \(\text{strain}_{\text{circ}}\) and \(\text{strain}_{\text{long}}\) are plotted to facilitate interpretation of effect direction.

increase in LVEF and \(\text{strain}_{\text{circ}}\) increases the risk of HCM by 37\% and 89\%, respectively (Supplementary Table 12). To place this in context, the standard deviations of LVEF and \(\text{strain}_{\text{circ}}\) in the UKBB are 5.5\% and 3.1\%, respectively.
Fig. 4 | Cross-trait associations of HCM and DCM loci. Heatmap of cross-trait associations of the 16 HCM (left side) and 13 DCM (right) risk variants in HCM, DCM and nine LV traits in the general population. The dbSNP ID and risk alleles are shown on the x-axis, with the corresponding locus number in parenthesis (corresponding to numbering in Fig. 2, Table 1 and Supplementary Table 4 for HCM, and Extended Data Fig. 1 and Supplementary Table 7 for DCM). Variants sorted along the x-axis using Euclidean distance and complete hierarchical clustering (dendrogram on top). Effect of the HCM or DCM risk alleles shown as a colormap of $Z$-scores (legend), where positive values (concordant effect) are in shades of blue and negative values (discordant effect) are in shades of red. Only associations with FDR $< 0.05$ are shown. HCM and DCM loci show many and reciprocal cross-trait associations. Since strain$^{circ}$ and strain$^{long}$ are negative values, we show -strain$^{circ}$ and -strain$^{long}$ to facilitate interpretation of effect direction. Lookup in DCM was performed using SNP proxies to maximize sample size, as shown in Supplementary Table 4. Note that the DCM risk allele rs2042995-T also increases risk of HCM, potentially through pleiotropic effects (decreased contractility and increased LV wall thickness).

We performed MAGMA$^\text{v}$ gene-based analyses using the HCM and DCM MTAG11 summary statistics. Not surprisingly, gene property analysis for tissue specificity identified muscle (heart and skeletal) as significantly associated with both HCM and DCM (Supplementary Fig. 10). Similarly, MAGMA gene-set analysis identified significantly associated gene sets related to muscle contraction for cellular components (for example, 1 Band, contractile fiber), biological processes (for example, myofibril assembly and sarcosome organization) and molecular functions (actin binding) (Supplementary Tables 13 and 14). Individual HCM, DCM and LV traits loci were annotated with proxy coding variants, significant expression (eQTL) and splice (sQTL) quantitative trait loci (QTL) in skeletal and heart muscle, and chromatin interactions using Hi-C data obtained in LV tissue (Supplementary Tables 15–18). The established Mendelian cardiomyopathy genes BAG3 (in loci HCM3, DCM3 and LV10), ALPK3 (HCM14, DCM10 and LV13), FHOD3 (HCM6 and DCM12), TTN (DCM4 and LV4), FLNC (HCM11 and DCM2) and PLN (HCM2 and LV8), which directly overlap associated loci (defined with $r^2 > 0.6$ from the lead SNP), are highly plausible candidates for the functional effects of variation at the corresponding loci. The involvement of FHOD3 and FLNC is further supported by eQTL effects, and involvement of PLN, ALPK3 and TTN is supported by evidence for Hi-C chromatin interactions between the association loci and the gene promoter. Notably, two loci overlap genes that play key roles in cardiomyocyte calcium handling related with muscle contraction (PLN and CASQ2; each supported by eQTL effects). Other candidate genes that emerge based on annotation and prior knowledge include GATA4 (DCM7 and LV19)$\text{v}$, PRKCA (HCM15 and DCM11)$\text{v}$, HSPB7 (HCM1, DCM1 and LV1)$\text{v}$ and TMEM43 (DCM5)$\text{v}$. In aggregate, candidate genes at associated loci suggest susceptibility mechanisms involving regulation of sarcomere assembly, homeostasis and calcium handling in cardiomyocytes.

HCM attributed to rare disease-causing sarcomeric variants is characterized by variable disease severity. We investigated whether common variants could explain such phenotypic variability. We first derived a polygenic risk score (PRS$\text{HCM}$; Supplementary Table 19) from an HCM GWAS meta-analysis excluding a hold-out cohort of cases with sarcomeric variants from a single (Dutch) center. We then assessed the association of PRS$\text{HCM}$ with HCM expression and severity in the hold-out cohort and their family members (368 carriers of pathogenic or likely pathogenic sarcomeric variants, Supplementary Table 20). The results are shown in Supplementary Table 21. PRS$\text{HCM}$ was associated with maximal LV wall thickness (maxLVWT) indexed to body surface area (BSA), where each standard deviation (SD) increase in the PRS$\text{HCM}$ is associated with a 0.7 mm m$^{-2}$ increase in maxLVWT ($P = 1 \times 10^{-5}$), corresponding to a clinically relevant 1.4 mm absolute increase in maxLVWT for an average BSA of 1.95 m$^2$ (cohort mean, Dutch population). PRS$\text{HCM}$ was also associated with adverse clinical events (a composite of septal reduction therapy, cardiac transplantation, sustained ventricular arrhythmia, sudden cardiac death, appropriate defibrillator therapy
or atrial fibrillation/flutter), where each SD increase in PRS_{HCM} was associated with a 28% relative risk increase in adverse clinical events (hazard ratio 1.28, 95% CI 1.06–1.54; \( P = 9 \times 10^{-3} \); see Supplementary Table 21).

Several new observations emerge from this work: (1) by conducting the first fully powered GWAS in HCM and the largest GWAS meta-analysis in DCM, we identified 15 novel loci associated with HCM, of which 14 replicate in an independent cohort, and 7 novel loci for DCM, bringing the total number of loci to 16 and 13, respectively; (2) we identified a total of 23 loci for LV traits and extended the study of these traits to include LV strain (13 loci) and LV wall thickness (6 loci); (3) we demonstrate for the first time a direct genetic correlation between LV traits and susceptibility to HCM and DCM with opposing direction of effect, indicating shared pathways for these disorders; (4) by using MR, we demonstrate that increased cardiac contractility plays an etiologic role in HCM. The demonstration of causal common variant effects on HCM through increased contractility broadens the applicability of therapeutic strategies targeting contractility as has been proposed for rare variants in sarcomere genes; and (5) we provide the first evidence that a polygenic score based on common HCM susceptibility variants may explain interindividual differences in HCM disease severity among carriers of rare disease-causing variants. This work constitutes a proof of principle for potential use of PRS in HCM risk stratification, to be assessed in future purposely designed and adequately powered studies. More broadly, this work demonstrates that the same genetic pathways may lead to distinct disorders through opposing genetic effects.

Online content
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Letters

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GWAS of HCM. Case inclusion. Unrelated people with HCM were included from cardiovascular genetics referral centers (Supplementary Table 1). Cases were included if they had a clinical diagnosis of HCM according to current diagnostic criteria: maximum LVWT of ≥ 25 mm, ≥ 13 mm in presence of family history of HCM, or Z-score > 2 in children, where LV hypertrophy is not solely explained by loading conditions. Cases were excluded if they had syndromic HCM (for example, Noonan syndrome spectrum), metabolic disease (for example Fabry) or had >1 sarcomeric pathogenic or likely pathogenic variants (homozygous, compound heterozygous or digenic). The maximum LVWT was collected from chart review of cases using the most recent cardiac imaging report available, before septal reduction therapy or cardiac transplantation, if performed. Because cases were referred from multiple centers for cardiogenetic evaluation, imaging data were not available for standardized remeasurements in most cases. Cases underwent targeted sequencing of genes associated with HCM, as per local practice at the time of analysis. Rare variants detected through sequencing in each of the contributing cohorts of this study were assessed centrally for pathogenicity according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) guidelines, using an adapted version of the CardioClassifier resource (details provided in the Supplementary Note, and classification results in Supplementary Table 2).

GWAS analysis design. Quality control (QC) and case–control association analysis were performed in three strata (Netherlands, NL; Royal Brompton and Harefield Hospitals, RBH; and Canada, CAN) followed by meta-analysis. See Supplementary Note for details regarding each stratum, including enrolling centers, DNA genotyping, QC and imputation.

Association analysis. The association of alternate allele dosage with HCM was performed for each of the three strata using a frequentist test in an additive model implemented in SNPTEST (v.2.5.2 for the CAN and NL strata, v.2.5.4 for the RBH stratum), correcting for the first three genotypic principal components. The results of the three strata were then combined using an IVW fixed-effect meta-analysis, performing meta-analysis heterogeneity analysis, implemented in METAL2 (version released on 25 March 2011). SNPs that were missing in any of the strata were excluded from the meta-analysis. A founder variant was defined as a rare variant classified as pathogenic or likely pathogenic that was observed at least 10 times in the population of parents of the study cohort. Multiple Europeanancestry-defined founder variants were included as follows in each stratum: HCM-Causing Pathogenic variants for (as defined below) approximated to normal distributions for all phenotypes. The distributions of raw measures of these nine phenotypes are shown in Supplementary Table 6. The results of the DCM meta-analysis are shown in Supplementary Fig. 1. The results of the main HCM case–control meta-analysis are shown in Fig. 2, Table 1 and Supplementary Table 4. QQ plots of each stratum and forest plots for lead SNPs at all significant loci are shown in Supplementary Fig. 2.

Analysis of heritability attributable to common variants. We used the GREML approach of GCTA (v.1.9.24 beta) to estimate how much of the variance in HCM susceptibility could be attributed to common genetic variants (SNP-based heritability, h^2_SNP). The analysis was performed by stratum (NL, RBH, CAN), followed by a fixed-effects and random effects meta-analysis using the meta-package (v.4.9-9) in R v.3.6.0. Before heritability analyses, we performed additional stringent postmutation QC as suggested, using hard call genotypes (genotype probability, GP >0.9), including SNPs with missing rate >0.1, MAF <0.05, Hardy–Weinberg test P <0.05 and phenotype biased missingness P <0.05, as well as samples with missing rate >0.01, and excluded regions in the genome that tag founder HCM-causing rare variants in HCM (chr1:42008264–65380094 (MYBPC3) in NL and CAN, and chr1:196816127–204926859 (TNNT2) in CAN). In all strata, we calculated the genetic relationship matrix (GRM) and excluded family members with minor allele frequency >0.1.

<h4>GWAS of CMR-derived LV traits. UKBB study population. The UKBB is an open-access population cohort resource that has recruited half a million participants in its initial recruitment phase, from 2006 to 2010. At the time of analysis, robust CMR imaging data were available from 26,523 individuals in the imaging substudy. The UKBB CMR acquisition protocol has been described previously. In brief, images were acquired according to a basic cardiac imaging protocol using clinical 1.5 Tesla–wide bore scanners (MAGNETOM Aera, Syno Platform VD13A, Siemens Healthcare, Erlangen, Germany) in three separate imaging centers. Extensive clinical and questionnaire data and genotypes are available for these individuals. Clinical data were obtained at the time of the imaging visit. These included sex (31), age (21,003), weight (21,002), height (50), systolic blood pressure (SBP) (2,521), diastolic blood pressure (DBP) (1,072), self-reported noncancer illness codes (20,002) and ICD-10 codes (41,270). The mean age at the time of CMR image acquisition was 63 ± 9 years (range: 20–100 years). All participants were male. Cohort anthropometrics, demographics and comorbidities are reported in Supplementary Table 6. Exclusion criteria for the UKBB imaging substudy included childhood disease, pregnancy and contraindications to magnetic resonance imaging scanning. For the current analysis, we also excluded, by ICD-10 code and/or self-reported diagnoses, any participants with heart failure, cardiomyopathy, a previous myocardial infarction or structural heart disease. We also excluded those with uncontrolled hypertension (defined by SBP or DBP >180 mmHg or >110 mmHg, respectively, at time of imaging visit) or with extremes of body mass index (BMI <16 or >40). We restricted our analysis to individuals of European ancestry defined by genotype as described (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4910276/). All participants provided informed consent (https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/Consent.pdf). The present study was conducted under terms of UKBB access approval 18545.

LV trait phenotyping. A description of CMR image analysis appears in the Supplementary Note and Supplementary Fig. 3. We included nine LV phenotypes for GWAS analyses: LVEDV, LVEDW, LVEF, LVMI, concentricity (LVconc = LVEV/LIVEDV) and meanWT, as well as mean waist circumference strain (strain^2)) and circumferential strain (strain^2) for each region. The mean and SD of all nine LV phenotypes overall and stratified by sex are shown in Supplementary Table 6. The distributions of raw measures of these nine phenotypes are shown in Supplementary Fig. 4. Despite non-normal distribution of some of the raw LV phenotypes, the residuals from our regression model including covariates (as defined below) approximated to normal distributions for all phenotypes (Supplementary Fig. 5). Therefore, the primary analysis was conducted using raw, non-normalized phenotypes.

LV trait genome-wide association analyses. A description of genotyping, imputation and QC appears in the Supplementary Note. The GWAS model included age, sex, height, weight and mean arterial pressure (MAP) as covariates. We performed a meta-analysis comprising two strata. Participants recruited and imaged in the North of England (Cheadle, Newcastle) were treated as the first stratum (n = 15,215 after QC) and the second stratum and those recruited and imaged in the remaining of the England (Reading) comprised the second stratum (n = 4,045). For each stratum, BOLT–LMM^2 (v.2.3.2) was used to construct mixed models for association with around 9.5 million directly

Lambda estimation using GREML, using the same QC and prevalence described for h^2_SNP. The genome was partitioned into three segments (FHOD3 locus, 15 novel loci and rest of genome). Loci were defined based on the lead SNP ± 500 kb. Analysis was also performed by stratum, followed by an IVW meta-analysis using fixed-effects and random effects models. The results of h^2_Lambda estimation are shown in Supplementary Table 3.

HCW GWAS replication dataset. Replication of HCM loci reaching the significance threshold was tested in an independent dataset comprising 2,694 HCM cases included from the HCMR^1 or the NIHR BRRD^2, and 47,486 controls without HCM included from the UKBB or BRRD. The detailed methodology is described in Harper et al.^11. Of the 2,780 HCM cases included in Harper et al.^11, 86 were overlapping with the present discovery dataset and have been excluded from the replication dataset. The results of this replication analysis and a fixed-effects model meta-analysis combining the discovery and replication results are shown in Supplementary Table 10.

Meta-analysis of association studies in DCM. A meta-analysis of three published case–control association studies^8 of DCM was performed. The included studies are described in the Supplementary Note and in Supplementary Table 5. A fixed-effects meta-analysis was performed using METAL^2 (version released on 25 March 2011). Study weighting was performed using the case sample size. The results of the DCM meta-analysis are shown in Extended Data Fig. 1 and Supplementary Table 7. QQ plots for each stratum and forest plots for lead SNPs at all significant loci are shown in Supplementary Fig. 7.
Multi-trait analysis of GWAS. We performed multi-trait analysis of GWAS (Supplementary Table 8 and Extended Data Figs. 2–10).

GWAS statistical significance threshold. We accounted for multiple testing to define the P-value threshold for genome-wide statistical significance in the HCM, DCM and LV traits GWAS. As expected, LV trait pairs are phenotypically correlated (Supplementary Table 9). We performed multi-trait analysis of GWAS based on myocardial tissue deformation. We used two approaches for instrument discovery for HCM and DCM. Only SNPs included in all meta-analyses (that is, HCM, DCM and LV traits) were used in MTAG. The coded/noncoded alleles were aligned for all 11 studies before MTAG, and multi-allelic SNPs were removed. All variants were centrally curated as described above. Lead SNPs reaching the genome-wide significance threshold (P < 5 × 10⁻⁸) were included in the PRS_HCM, and their corresponding weights were shown in Supplementary Table 19 using Plink 2.0, followed by scaling to a mean of 0 and postimputation QC were performed also as described for the GW AS in the Erasmus Medical Center (EMC). All variants were centrally curated as described above. Lead SNPs reaching the genome-wide significance threshold were included (see list in Supplementary Table 2). Homozygous carriers and those carrying multiple pathogenic or likely pathogenic variants were excluded. Clinical data including maxLVWT on cardiac imaging and time of clinical events were retrieved from an ongoing registry (EMC), including all patients with HCM. lead risk allele dosage by the corresponding regression coefficient in the derivation study (Supplementary Table 19) using Plink 2.0, followed by scaling to a mean of 0 and SD of 1.

Derivation of PRS_HCM. The PRS_HCM was derived from an independent GWAS, excluding HCM cases with (likely) pathogenic variants from EMC. This was done to ensure that the PRS is derived from an independent cohort. Specifically, a Dutch HCM case–control GWAS was repeated after excluding 161 cases from EMC cases that carry (likely) pathogenic variants, followed by a meta-analysis combined with the RH HCM GWAS and the CAN HCM GWAS, followed by MTAG11 as described above. Lead SNPs reaching the genome-wide significance threshold (P < 5 × 10⁻⁸) were included in the PRS_HCM. Those SNPs included in the PRS_HCM and their corresponding weights are shown in Supplementary Table 19.

Calculation of PRS_HCM. All EMC samples that carry pathogenic or likely pathogenic HCM variants underwent array genotyping on the Illumina GSA. QC was performed as described in the Supplementary Note for the Dutch HCM GWAS, except for IBD analysis, where only duplicate (or twin) samples were excluded. No sample was excluded for relatedness, which was accounted for using a GRM as described in the statistical analyses paragraph below. Imputation and postimputation QC were performed also as described for the GWAS in the Supplementary Note. PRS_HCM was calculated by summing the products of each lead risk allele dosage by the corresponding regression coefficient in the derivation study (Supplementary Table 19) using Plink 2.0, followed by scaling to a mean of 0 and SD of 1.

Study endpoints. Two primary endpoints were predefined. The first primary endpoint was maxLVWT at last available transthoracic echocardiogram (TTE) or
CMR. MaxLVWT is routinely assessed in clinical practice as a measure of HCM severity and for risk stratification of life-threatening ventricular arrhythmias. For participants who had cardiac transplantation and/or septal reduction therapy to relieve LV obstruction, the last available CMR or TTE before cardiac transplantation and/or septal reduction therapy was used. Considering the higher accuracy of CMR to assess wall thickness in all LV segments, maxLVWT from CMR was used whenever available unless TTE was performed more than 5 years after last CMR. To account for body size, a determinant of wall thickness in the general population, in the current cohort with HCM, maxLVWT was indexed to BSA calculated using the DuBois formula ($0.007184 \times \text{height}^{0.725} \times \text{weight}^{0.425}$). The second primary endpoint was time to first adverse clinical event (a composite of invasive septal reduction therapy, cardiac transplantation, sustained ventricular arrhythmia, sudden cardiac death, appropriate defibrillator therapy or atrial fibrillation/flutter). The components of this composite endpoint were also assessed as secondary endpoints. As a sensitivity analysis, we also performed an analysis for the primary outcomes restricted to nonprobands.

Statistical analyses. A GRM was estimated using GCTA (v.1.92.4 beta) and used to account for between-sample relatedness. The association of PRSHCM with maxLVWT was performed using a mixed linear model integrating the GRM as a random effect. Neither sex nor rare variant type (MYBPC3 truncation versus others) were associated with maxLVWT and were therefore not included as covariates. The association of PRSHCM with the primary composite clinical events endpoint and secondary endpoints were assessed using a Cox proportional hazards mixed effects model integrating the GRM as a random effect. Since biological male sex was significantly associated with increased risk for clinical events, it was added as a fixed-effect covariate. Time 0 was set to birth in the Cox model to maximize statistical power by including events that occurred at the time of first medical encounter. Given the genetic nature of our exposure factor, all study participants are exposed since birth. Nevertheless, there is a possibility of selection bias in our cohort, since study participants have to reach the age of inclusion. Study participants were censored at the time of last clinical follow up. For analyses of secondary endpoints that do not include cardiac transplantation, study participants were also censored at the time of cardiac transplantation. In addition to PRSHCM, we also assessed the association of a genome-wide score (PRSHCM) derived from a large atrial fibrillation meta-analysis and validated by Khra et al. with atrial fibrillation within the study population. Mixed effects analyses of PRSHCM with maxLVWT was performed using the lme4in and mixed effects analyses of PRSHCM and PRSHCM with clinical events was performed using the lme4n function, both from the lme4 package v.2.2-14 in R v.3.6.0. The statistical significance threshold was set to $P < 0.05$ for hypothesis-generating secondary endpoints and $P < 0.05$ for hypothesis-generating primary endpoints. The results of the primary, secondary and sensitivity analyses are shown in Supplementary Table 21. Kaplan–Meier curves stratified by PRSHCM above or below the median are shown in Fig. 5.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability
Data from the Genome Aggregation Database (gnomAD, v.2.1) are available at https://gnomad.broadinstitute.org. Data from the UKB participants can be requested from the UKBB Access Management System (https://biobsm.ndph.ox.ac.uk). Data from the GTEX consortium are available at the GTEX portal (https://gtxportal.org). Other datasets generated during and/or analyzed during the current study can be made available upon reasonable request to the corresponding authors. Individual level data sharing is subject to restrictions imposed by patient consent and local ethics review boards. Results from meta-analyses of GWAS reported in this article are available at https://www.human-phenome.org/gwas and https://data.hpc.imperial.ac.uk (https://doi.org/10.14469/hpc/7468).

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Author contributions
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Competing interests
M.-P.D. is author on a patent pertaining to pharmacogenomics-guided CETP inhibition (US20170233812A1), has a minor equity interest in DalCor and has received honoraria from Dalcor and Servier and research support (access to samples and data) from AstraZeneca, Pfizer, Servier, Sanofi and GlaxoSmithKline. J.-C.T. has received research grants from Amarin, AstraZeneca, DalCor, Esperion, Ionis, Sanofi and Servier; honoraria from AstraZeneca, DalCor, HLS, Sanofi and Servier; holds minor equity interest in DalCor; and is an author of a patent on pharmacogenomics-guided CETP inhibition (US20170233812A1). B.M. has received research funding from Siemens Healteneers, Daiichi Sankyo. The UMCG, which employs R.A.d.B., has received research grants and/or fees from AstraZeneca, Abbott, Bristol-Myers Squibb, Novartis, Novo Nordisk and Roche. R.A.d.B. received speaker fees from Abbott, AstraZeneca, Novartis and Roche. HW is a consultant for Cytokinetics. P.M.M. receives an honorarium as Chair of the UKRI Medical Research Council Neuroscience and Mental Health Board. He acknowledges consultancy fees from Adelphi Communications, MedScape, Neurodiem, Nodthera, Biogen, Celgene and Roche. He has received speakers’ honoraria from Celgene, Biogen, Novartis and Roche, and has received research or educational funds from Biogen, GlaxoSmithKline and Novartis. He is paid as a member of the Scientific Advisory Board for Ipsen Pharmaceuticals. J.S.W. has received research support and consultancy fees from Myokardia, Inc.

Additional information
Extended data is available for this paper at https://doi.org/10.1038/s41588-020-00762-2. Supplementary information is available for this paper at https://doi.org/10.1038/s41588-020-00762-2.

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Extended Data Fig. 1 | Manhattan and QQ plots of DCM GWAS and MTAG. **a,b.** Summary results of the dilated cardiomyopathy (DCM) GWAS meta-analysis of 5,521 cases and 397,323 controls shown as Manhattan plots for the single-trait (**a**) and the multi-trait analyses (MTAG; **b**). Single-trait analysis (**a**) consisted of a fixed-effects meta-analysis of case–control GWAS using summary statistics of three previously published DCM GWAS, and multi-trait analysis results (**b**) were obtained using MTAG for DCM, including GWAS for hypertrophic cardiomyopathy (HCM) and nine left ventricular (LV) traits. Red dashed line shows the significance threshold of $P=1 \times 10^{-8}$. Quantile-quantile (QQ) plots shown as inserts in corresponding panels. Genomic inflation ($\lambda$) = 1.028 (single-trait) and 1.049 (MTAG). Numbering of signals as shown in Supplementary Table 7. Black numbers refer to loci reaching the statistical significance threshold in single-trait analysis, while red numbers refer to loci only reaching statistical significance in the multi-trait analysis. The low density of association signals in the single-trait analysis (**a**) is attributable to the inclusion of a large sample size study that used a low density array (Illumina Infinium HumanExome BeadChip; Supplementary Table 5).
Extended Data Fig. 2 | Manhattan and QQ plots of LV ejection fraction GWAS and MTAG. a,b. Summary results of the left ventricular ejection fraction (LVEF) GWAS in the UK Biobank (n = 19,260) shown as Manhattan plots for the single-trait (a) and the multi-trait analyses (MTAG; b). Single-trait analysis (a) consisted of a fixed-effects meta-analysis of case–control GWAS using a linear mixed model (BOLT-LMM), and multi-trait analysis results (b) were obtained using MTAG including summary statistics for all nine left ventricular (LV) traits. Red dashed line shows the significance threshold of $P = 1 \times 10^{-8}$. Quantile-quantile (QQ) plots shown as inserts in corresponding panels. Genomic inflation ($\lambda$) = 1.041 (single-trait) and 1.049 (MTAG). Numbering of loci as shown in Supplementary Table 8. Black numbers refer to loci reaching the statistical significance threshold in any single-trait analysis, while red numbers refer to loci only reaching statistical significance in the multi-trait analysis.
Extended Data Fig. 3 | Manhattan and QQ plots of LV concentricity GWAS and MTAG. a,b. Summary results of the left ventricular concentricity index (LVconc) GWAS in the UK Biobank (n = 19,260) shown as Manhattan plots for the single-trait (a) and the multi-trait analyses (MTAG; b). LVconc is defined as the ratio of left ventricular mass to the left ventricular end-diastolic volume. Single-trait analysis (a) consisted of a fixed-effects meta-analysis of case-control GWAS using a linear mixed model (BOLT-LMM), and multi-trait analysis results (b) were obtained using MTAG including summary statistics for all nine left ventricular (LV) traits. Red dashed line shows the significance threshold of \( P = 1 \times 10^{-8} \). Quantile-quantile (QQ) plots shown as inserts in corresponding panels. Genomic inflation (\( \lambda \)) = 1.06 (single-trait) and 1.084 (MTAG). Numbering of signals as shown in Supplementary Table 8. Black numbers refer to loci reaching the statistical significance threshold in any single-trait analysis, while red numbers refer to loci only reaching statistical significance in the multi-trait analysis.
Extended Data Fig. 4 | Manhattan and QQ plots of LV mass GWAS and MTAG. a, b, Summary results of the left ventricular mass (LVM) GWAS in the UK Biobank (n = 19,260) shown as Manhattan plots for the single-trait (a) and the multi-trait analyses (MTAG, b). Single-trait analysis (a) consisted of a fixed-effects meta-analysis of case–control GWAS using a linear mixed model (BOLT-LMM), and multi-trait analysis results (b) were obtained using MTAG including summary statistics for all nine left ventricular (LV) traits. Red dashed line shows the significance threshold of $P = 1 \times 10^{-8}$. Quantile-quantile (QQ) plots shown as inserts in corresponding panels. Genomic inflation ($\lambda$) = 1.081 (single-trait) and 1.071 (MTAG). Numbering of signals as shown in Supplementary Table 8.
Extended Data Fig. 5 | Manhattan and QQ plots of LV end-diastolic volume GWAS and MTAG.  

**a, b.** Summary results of the left ventricular end-diastolic volume (LVEDV) GWAS in the UK Biobank (N=19,260) shown as Manhattan plots for the single-trait (a) and the multi-trait analyses (MTAG; b). Single-trait analysis (a) consisted of a fixed-effects meta-analysis of case-control GWAS using a linear mixed model (BOLT-LMM), and multi-trait analysis results (b) were obtained using MTAG including summary statistics for all nine left ventricular (LV) traits. Red dashed line shows the significance threshold of \( P = 1 \times 10^{-8} \). Quantile-quantile (QQ) plots shown as inserts in corresponding panels. Genomic inflation \( \lambda = 1.076 \) (single-trait) and 1.078 (MTAG). Numbering of signals as shown in Supplementary Table 8. Black numbers refer to loci reaching the statistical significance threshold in any single-trait analysis, while red numbers refer to loci only reaching statistical significance in the multi-trait analysis.

**A** Left ventricular end-diastolic volume (LVEDV)

**B** LVEDV (MTAG9)
Extended Data Fig. 6 | Manhattan and QQ plots of LV end-systolic volume GWAS and MTAG. Summary results of the left ventricular end-systolic volume (LVESV) GWAS in the UK Biobank (n = 19,260) shown as Manhattan plots for the single-trait (a) and the multi-trait analyses (MTAG; b). Single-trait analysis (a) consisted of a fixed-effects meta-analysis of case–control GWAS using a linear mixed model (BOLT-LMM), and multi-trait analysis results (b) were obtained using MTAG including summary statistics for all nine left ventricular (LV) traits. Red dashed line shows the significance threshold of $P = 1 \times 10^{-8}$. Quantile-quantile (QQ) plots shown as inserts in corresponding panels. Genomic inflation ($\lambda$) = 1.069 (single-trait) and 1.081 (MTAG). Numbering of signals as shown in Supplementary Table 8.
Extended Data Fig. 7 | Manhattan and QQ plots of LV global circumferential strain GWAS and MTAG. 

**A**

Global circumferential strain ($\text{strain}^{\text{circ}}$)

Summary results of the left ventricular global circumferential strain ($\text{strain}^{\text{circ}}$) GWAS in the UK Biobank ($N=19,260$) shown as Manhattan plots for the single-trait (a) and the multi-trait analyses (MTAG, b). Single-trait analysis (a) consisted of a fixed-effects meta-analysis of case–control GWAS using a linear mixed model (BOLT-LMM), and multi-trait analysis results (b) were obtained using MTAG including summary statistics for all nine left ventricular (LV) traits. Red dashed line shows the significance threshold of $P=1\times 10^{-8}$. Quantile-quantile (QQ) plots shown as inserts in corresponding panels. Genomic inflation ($\lambda$) = 1.046 (single-trait) and 1.061 (MTAG). Numbering of signals as shown in Supplementary Table 8.

**B**

$\text{strain}^{\text{circ}}$ (MTAG9)$_{10}$

The same analysis as described in **A** but for a different set of signals.
Extended Data Fig. 8 | Manhattan and QQ plots of LV global radial strain GWAS and MTAG. a, b. Summary results of the left ventricular global radial strain (strain\textsuperscript{rad}) GWAS in the UK Biobank (n=19,260) shown as Manhattan plots for the single-trait (a) and the multi-trait analyses (MTAG; b). Single-trait analysis (a) consisted of a fixed-effects meta-analysis of case-control GWAS using a linear mixed model (BOLT-LMM), and multi-trait analysis results (b) were obtained using MTAG including summary statistics for all nine left ventricular (LV) traits. Red dashed line shows the significance threshold of $P=1 \times 10^{-8}$. Quantile-quantile (QQ) plots shown as inserts in corresponding panels. Genomic inflation ($\lambda$) = 1.049 (single-trait) and 1.057 (MTAG). Numbering of signals as shown in Supplementary Table 8. Black numbers refer to loci reaching the statistical significance threshold in any single-trait analysis, while red numbers refer to loci only reaching statistical significance in the multi-trait analysis.
Extended Data Fig. 9 | Manhattan and QQ plots of LV global longitudinal strain GWAS and MTAG. a, b, Summary results of the left ventricular global longitudinal strain (strain$^{\text{long}}$) GWAS in the UK Biobank ($n=19,260$) shown as Manhattan plots for the single-trait (a) and the multi-trait analyses (MTAG; b). Single-trait analysis (a) consisted of a fixed-effects meta-analysis of case-control GWAS using a linear mixed model (BOLT-LMM), and multi-trait analysis results (b) were obtained using MTAG including summary statistics for all nine left ventricular (LV) traits. Red dashed line shows the significance threshold of $P=1 \times 10^{-8}$. Quantile-quantile (QQ) plots shown as inserts in corresponding panels. Genomic inflation ($\lambda$) = 1.040 (single-trait) and 1.059 (MTAG). Numbering of signals as shown in Supplementary Table 8.
Extended Data Fig. 10 | Manhattan and QQ plots of LV mean wall thickness GWAS and MTAG. a,b. Summary results of the mean left ventricular wall thickness (meanWT) GWAS in the UK Biobank (n=19,260) shown as Manhattan plots for the single-trait (a) and the multi-trait analysis (MTAG; b). Single-trait analysis (a) consisted of a fixed-effects meta-analysis of case-control GWAS using a linear mixed model (BOLT-LMM), and multi-trait analysis results (b) were obtained using MTAG including summary statistics for all nine left ventricular (LV) traits. Red dashed line shows the significance threshold of $P=1 \times 10^{-8}$. Quantile-quantile (QQ) plots shown as inserts in corresponding panels. Genomic inflation ($\lambda$) = 1.065 (single-trait) and 1.072 (MTAG). Numbering of signals as shown in Supplementary Table 8.
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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection  No software was used.

Data analysis  CardioClassifier v0.2.0, PLINK v1.9 and v2.0, Michigan Imputation Server v1.0.2 and v1.2.1, SHAPEIT v2.790, IMPUTE2 v2.3.2, SNPV TEST v2.5.2 and v2.5.4, METAL v2011-03-25, GCTA v1.92.4, R v3.6.0, R package meta v4.9-9, MIRTK toolkit r2.0.0, BOLT-LMM v2.3.2, LDSC v1.0.1, MTAG v1.0.8, R package TwoSampleMR v0.4.25, FUMA v1.3.5, MAGMA v1.07, LDlink v3.3, R package covxme v2.2-14

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Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Data from the Genome Aggregation Database (gnomAD, v2.1) are available at https://gnomad.broadinstitute.org. Data from the UK Biobank participants can be requested from the UK Biobank Access Management System (https://bbams.ndph.ox.ac.uk). Data from the Genotype Tissue Expression (GTEx) consortium are available at the GTEx portal (https://gtexportal.org). Other datasets generated during and/or analyzed during the current study can be made available upon reasonable request to the corresponding authors. Individual level data sharing is subject to restrictions imposed by patient consent and local ethics review boards. Results from meta-analyses of genome-wide association studies reported in this article are available at https://www.heart-institute.ni/gwas and https://data.hpc.imperial.ac.uk [doi.org/10.14469/hpc/7468].
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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size

For hypertrophic cardiomyopathy (HCM), we analyzed the largest sample size available from the Dutch, Royal Brompton and Canadian HCM cohorts, including 1,733 unrelated HCM cases and 6,626 ancestry-matched controls. For left ventricular (LV) traits, we analyzed the largest sample size with available cardiac magnetic resonance imaging studies from the UK Biobank at the time of analysis, consisting of 19,260 individuals. For the study of polygenic risk scores in sarcomeric variant carriers, the largest sample size with available clinical data was used, consisting of 368 carriers of pathogenic or likely pathogenic sarcomeric variants. No method was applied to predetermine sample size.

Data exclusions

HCM case-control GWAS: Samples excluded if genotype missingness rate >0.03, inbreeding coefficient |F|>0.1, sex mismatch, cryptic relatedness up to 3rd degree or are population outliers using genotypic principal component analysis. Following imputation, SNPs were excluded if minor allele frequency (MAF) <0.01, or poor imputation quality (INFO<0.4 for the Royal Brompton stratum, or Minimac R2<0.5 for Dutch and Canadian strata). More stringent quality control was performed for heritability analyses.

HCM polygenic risk score (PRS) analyses in sarcomeric variant carriers: PRS was derived from a GWAS excluding sarcomeric variant carriers from the Erasmus Medical Center. We then tested for the association of PRS with disease expression in sarcomeric variant carriers (probands and non-probands) from the Erasmus Medical Center.

LV traits GWAS: Exclusion criteria for the UK Biobank imaging substudy included childhood disease, pregnancy and contraindications to MRI scanning. For the LV traits GWAS, we also excluded, by ICD-10 code and/or self-reported diagnoses, any subjects with heart failure, cardiomyopathy, a previous myocardial infarction, or structural heart disease. We also excluded those with uncontrolled hypertension (defined by systolic or diastolic blood pressure >180mmHg or >110mmHg, respectively, at time of imaging visit) or with extremes of body mass index (BMI <16 or >40). We restricted our analysis to Caucasians, defined by genotype. After phenotyping, we also excluded subjects with mean wall thickness >13mm in any of the 16 American Heart Association (AHA) left ventricular (LV) segments, and subjects with outlying (>3 SD from mean) LV mass, LV volumes or LV ejection fraction. We excluded samples with outlying heterozygosity or missingness rates, and those with mismatches between the genotypic and recorded sex. We also excluded subjects with outlying heterozygosity or missingness rates, and those with mismatches between the genotypic and recorded sex. We excluded SNPs failing UK Biobank protocols (filtered per batch by Hardy-Weinberg equilibrium and missingness), those with imputation INFO score <0.3 or MAF <0.01, or with missingness >0.1.

Replication

Replication of HCM loci reaching the significance threshold was tested in an independent dataset comprised of 2,694 cases with HCM included from the Hypertrophic Cardiomyopathy Registry (HCMR) or the NIHR Bioresource for Rare Disease (BRRD), and 47,486 controls without HCM included from the UK Biobank or BRRD. All loci reaching P<1e-8 in the multi-trait analysis were successfully replicated.

Randomization

The main study design is a case control genome-wide association study. HCM cases: participants with a clinical diagnosis of hypertrophic cardiomyopathy. Controls: participants free of HCM.

Blinding

Analysts were not blinded because linking the genotype and phenotype data was necessary for quality control and analyses. Blinding was not relevant to our study. The participants from the included studies were sampled by multiple different research centers. The meta-analyses were conducted centrally on summary level results from each study.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

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- [x] Palaeontology and archaeology
- [x] Animals and other organisms
- [x] Human research participants
- [ ] Clinical data
- [x] Dual use research of concern

Methods

- n/a Involved in the study

- [x] ChIP-seq
- [x] Flow cytometry
- [x] MRI-based neuroimaging
# Human research participants

Policy information about **studies involving human research participants**

| Population characteristics | Population characteristics are described in Supplementary Tables 1 (HCM GWAS), 6 (LV traits GWAS) and 20 (PRS analyses). |
|-----------------------------|---------------------------------------------------------------------------------------------------------------|
| Recruitment                 | HCM cases were recruited from Amsterdam University Medical Center (location AMC, Netherlands), University Medical Center Groningen (Netherlands), Erasmus Medical Center (Netherlands), Royal Brompton & Harefield Hospitals (United Kingdom), Montreal Heart Institute (Canada) and London Health Sciences Center (Canada). The LV trait GWAS was performed in participants of the UK Biobank. |
| Ethics oversight            | All components of the study were approved by ethics review boards at corresponding institutions: |
|                             | - Dutch HCM GWAS: Approved by the Medisch Ethische Toetsingscommissie (METC) of the Amsterdam University Medical Center. |
|                             | - UK HCM GWAS: Healthy volunteers were recruited as part of the Digital Heart Project (approved by Hammersmith & Queen Charlotte’s Research Ethics Committee). HCM cases came from the Royal Brompton & Harefield Hospital Biobank (Approved by South Central - Hampshire B Research Ethics Committee). |
|                             | - Canadian HCM GWAS approved by the Research Ethics and New Technology Development Committee of the Montreal Heart Institute. |
|                             | - HCM GWAS replication: HCMR approved by South Central - Oxford A Research Ethics Committee. BRRD approved by East of England - Cambridge South Research Ethics Committee. |
|                             | - UK Biobank approved by the UK Research Ethics Committee. Reported analyses conducted under application 18545. |

Note that full information on the approval of the study protocol must also be provided in the manuscript.