Supplementary

Table S1 Classifications of pathogenicity and nucleotide and amino acid changes for all hypertrophic cardiomyopathy or hypertrophic cardiomyopathy phenocopy-positive variants

Variant	ACMG classification	Nucleotide change	Amino acid change	Novel HGMD®/ ClinVar	Number of cases	Countries
HCM variants (n=115)						
MYH7	Pathogenic	c.428G>A	Arg143Gln	–	1	Brazil[a]
MYH7	Likely pathogenic	c.431G>A	Gly144Asp	+/–	1	Mexico
MYH7	Pathogenic	c.655C>G	Gln219Glu	–	1	Mexico
MYH7	Pathogenic	c.715G>A	Asp239Asn	–	1	Colombia
MYH7	Pathogenic	c.727C>T	Arg243Cys	–	2	Colombia, 2
MYH7	Pathogenic	c.746G>A	Arg249Gln	–	4	Brazil, 4
MYH7	Pathogenic	c.751C>A	His251Asn	–	1	Colombia
MYH7	Pathogenic	c.788T>C	Ile263Thr	–	1	Brazil
MYH7	Pathogenic	c.1063G>A	Ala355Thr	–	1	Brazil
MYH7	Pathogenic	c.1207C>T	Arg403Trp	–	1	Colombia
MYH7	Pathogenic	c.1208G>A	Arg403Gln	–	2	Mexico, 2
MYH7	Pathogenic	c.1223A>G	Asn408Ser	+/+	2	Colombia, 2
MYH7	Pathogenic	c.1357C>T	Arg453Cys	–	6	Brazil, 6
MYH7	Likely pathogenic	c.1511A>G	Glu504Gly	+/+	1	Mexico
MYH7	Pathogenic	c.1750G>C	Gly584Arg	–	1	Brazil
MYH7	Pathogenic	c.1988G>A	Arg663His	–	3	Mexico, 1; Brazil, 1; Turkey, 1
MYH7	Pathogenic	c.2011C>T	Arg671Cys	–	2	Colombia, 1; Columbia: 1[e]
MYH7	Pathogenic	c.2012G>A	Arg671His	–	1	Mexico
MYH7	Pathogenic	c.2146G>A	Gly716Arg	–	1	Colombia
MYH7	Pathogenic	c.2155C>T	Arg719Trp	–	1	Brazil
MYH7	Pathogenic	c.2156G>A	Arg719Gln	–	1	Colombia
MYH7	Pathogenic	c.2167C>T	Arg723Cys	–	1	Turkey
MYH7	Pathogenic	c.2207T>C	Ile736Thr	–	1	Israel
MYH7	Pathogenic	c.2221G>C	Gly741Arg	–	1	Israel
MYH7	Pathogenic	c.2302G>A	Gly768Arg	–	1	Brazil[e]
MYH7	Pathogenic	c.2347C>T	Arg783Cys	–	1	Colombia
MYH7	Pathogenic	c.2389G>A	Ala797Thr	–	5	Brazil, 2; Colombia, 1; Mexico, 2
MYH7	Pathogenic	c.2466G>A	Met822Ile	+/–	2	Mexico, 2
MYH7	Likely pathogenic	c.2555T>G	Met852Arg	+/–	2	Turkey, 2
MYH7	Pathogenic	c.2602G>C	Ala868Pro	–	1	Mexico

Table S1 (*continued*)

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Table S1 (*continued*)

Variant	ACMG classification	Nucleotide change	Amino acid change	Novel HGMD®/ ClinVar	Number of cases	Countries
MYH7	Pathogenic	c.2633T>C	Val878Ala	–	3	Colombia, 3
MYH7	Pathogenic	c.2770G>A	Glu924Lys	–	1	Mexico
MYH7	Pathogenic	c.4499G>A	Arg1500Gln	–	1	Brazil
MYH7	Pathogenic	c.4954G>T	Asp1652Tyr	–	2	Brazil, 1; Colombia, 1
MYH7	Pathogenic	c.5342G>A	Arg1781His	–	1	Brazil[b]
MYH7	Likely pathogenic	c.2242_2243delTCinsAT	Ser748Ile	+/–	1	Colombia
MYH7	Pathogenic	c.2623_2625del	Glu875del	–	1	Brazil
MYBPC3	Pathogenic	c.622C>T	Gln208*	+/–	1	Turkey
MYBPC3	Pathogenic	c.772G>A	Glu258Lys	–	2	Brazil, 1; Colombia, 1
MYBPC3	Pathogenic	c.1483C>T	Arg495Trp	–	2	Turkey, 1[c]; Colombia, 1
MYBPC3	Pathogenic	c.1484G>A	Arg495Gln	–	2	Brazil, 2
MYBPC3	Likely pathogenic/VUS	c.1828G>A	Asp610Asn	–	1	Brazil
MYBPC3	Pathogenic	c.2429G>A	Arg810His	–	1	Brazil[a]
MYBPC3	Pathogenic	c.2670G>A	Trp890*	–	2	Brazil, 1; Colombia, 1
MYBPC3	Pathogenic	c.3641G>A	Trp1214*	+/–	1	Brazil
MYBPC3	Pathogenic	c.3694A>T	Lys1232*	–	1	Israel
MYBPC3	Pathogenic	c.3773T>G	Leu1258*	–	1	Turkey
MYBPC3	Pathogenic	c.1928-2A>G	Splicing	–	2	Mexico, 2
MYBPC3	Pathogenic	c.3491-2A>T	Splicing	–	1	Colombia
MYBPC3	Pathogenic	c.1800delA	Lys600Asnfs*2	–	3	Brazil, 2; Mexico, 1
MYBPC3	Pathogenic	c.2511delC	Ile837Metfs*42	+/–	1	Mexico
MYBPC3	Pathogenic	c.1351+2T>C	Splicing	–	1	Israel
MYBPC3	Pathogenic	c.2994+1G>A	Splicing		1	Turkey
MYBPC3	Pathogenic	c.3190+5G>A	Splicing	–	3	Mexico, 1; Turkey, 1; Colombia, 1
MYBPC3	Likely pathogenic	c.613_614insTGACC	Gln205Leufs*97	+/+	1	Turkey
MYBPC3	Pathogenic	c.560delC	Pro187Leufs*13	+/–	1	Turkey
MYBPC3	Pathogenic	c.913_914delTT	Phe305Profs*27	–	1	Brazil
MYBPC3	Pathogenic	c.1358delC	Pro453Leufs*13	–	2	Brazil, 2
MYBPC3	Pathogenic	c.1526_1527delGA	Arg509Thrfs*21	+/–	1	Brazil
MYBPC3	Pathogenic	c.2230_2233delGAAG	Glu744Metfs*9	+/–	2	Colombia, 2
MYBPC3	Pathogenic	c.2864_2865delCT	Pro955Argfs*95	–	1	Mexico
MYBPC3	Pathogenic	c.1838dupA	Asp613Glufs*25	–	2	Israel, 2
MYBPC3	Likely pathogenic	c.2418_2419dupCA	Ile807Thrfs*16	+/+	1	Colombia

Table S1 (*continued*)

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Table S1 (*continued*)

Variant	ACMG classification	Nucleotide change	Amino acid change	Novel HGMD®/ ClinVar	Number of cases	Countries
MYBPC3	Likely pathogenic	c.2556dupC	Gly853Argfs*31	+/+	1	Turkey
MYBPC3	Likely pathogenic	c.3758_3773dup16	Glu1261Hisfs*10	+/+	1	Mexico
MYBPC3	Likely pathogenic	c.3774dupA	Gln1259Thrfs*7	+/+	1	Colombia
TNNT2	Pathogenic	c.274C>T	Arg92Trp	–	1	Turkey
TNNT2	Pathogenic	c.305G>A	Arg102Gln	+/–	1	Brazil
TNNT2	Likely pathogenic	c.838A>C	Lys280Gln	+/–	1	Saudi Arabia
TNNT2	Pathogenic	c.881G>A	Trp294*	+/–	1	Brazil
TNNI3	Pathogenic	c.434G>A	Arg145Gln	–	2	Brazil, 1; Turkey, 1[c]
TNNI3	Pathogenic	c.470C>T	Ala157Val	–	1	Colombia
TNNI3	Pathogenic	c.485G>T	Arg162Leu	+/–	1	Colombia
TPM1	Pathogenic	c.523G>A	Asp175Asn	+/–	2	Brazil, 2[d]
MYL2	Pathogenic	c.401A>C	Glu134Ala	–	1	Mexico
MYL2	Likely pathogenic	c.53T>C	Phe18Ser	+/–	1	Mexico
MYL3	Pathogenic	c.517A>G	Met173Val	–	1	Colombia
TNNC1	Pathogenic	c.23C>T	Ala8Val	–	1	Colombia
HCM phenocopies (n=17)						
TTR	Pathogenic	c.148G>A	Val50Met	–	1	Brazil
TTR	Pathogenic	c.250T>C	Phe84Leu	–	1	Brazil
TTR	Pathogenic	c.325G>C	Glu109Gln	–	1	Turkey
TTR	Pathogenic	c.424G>A	Val142Ile	–	4	Brazil, 2[d]; Mexico, 1; Saudi Arabia, 1
LAMP2	Pathogenic	c.864+1G>A	Splicing	–	1	Brazil
LAMP2	Likely pathogenic	c.972_973insA	Leu325Thrfs*25	+	1	Brazil[b]
LAMP2	Pathogenic	c.973dupC	Leu325Profs*25	–	1	Brazil
GLA	Pathogenic	c.644A>G	Asn215Ser	–	1	Brazil
GLA	Likely pathogenic	c.413delG	Gly138Glufs*27	+/+	1	Brazil
PRKAG2	Pathogenic	c.905G>A	Arg302Gln	–	2	Brazil, 1; Mexico, 1
PTPN11	Pathogenic	c.1528C>G	Gln510Glu	–	1	Brazil
DES	Pathogenic	c.893C>T	Ser298Leu	–	1	Colombia
DES	Likely pathogenic	c.1219A>T	Lys407*	+/+	1	Colombia

Double variants were detected in 4 cases: [a], *MYH7* and MYBPC3; [b], *MYH7* and *LAMP2*; [c], *MYBPC3* and *TNNI3*; [d], *TPM1* and *TTR*. [e], age is unknown. ACMG, American College of Medical Genetics; ClinVar, public archive of interpretations of clinically relevant variants; HGMD®, Human Gene Mutation Database; HCM, hypertrophic cardiomyopathy; VUS, variant of uncertain significance; –, published variant listed in HGMD®; +/+, variant not reported either in HGMD® or ClinVar; +/–, variant not listed in HGMD® but listed in ClinVar; (*) marks stop codon.

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Table S2 Studies reporting the diagnostic yield of hypertrophic cardiomyopathy, transthyretin cardiac amyloidosis, and Fabry disease using an NGS screening method

Study no.	Author; country (year): study design	No. of genes in the panel	No. of patients included, M/F ratio	Inclusion criteria	Diagnostic yield of HCM, M/F ratio	Diagnostic yield of ATTR-CA, M/F ratio	Diagnostic yield of FD, M/F ratio
1	Current Cardio NGS study; Colombia, Brazil, Mexico, Turkey, Israel, and Saudi Arabia: Prospective study	17	N=535, M/F =1.4:1	LVWT ≥13 mm	21.5% (n=115) M/F =1:1	1.3% (n=7) M/F = 2.5:1	0.4% (n=2) M/F = 0:2
2	Jääskeläinen P, *et al.* (17); Finland (2019): Prospective study	59	N=382, M/F =1.6:1	LVH ≥15 mm in probands and ≥13 mm in relatives	38.2% All were pathogenic or likely pathogenic	0%	0.5% (n=2)
3	Tran Vu MT, *et al.* (18); Vietnam (2019): Prospective study	23	N=104 M/F =1.7:1	LV wall thickness ≥15 mm	42.3% (n=44) M/F =1.4:1	0%	0.9% (n=1)
4	Zhao Y, *et al.* (19); China (2017): Prospective study	19	N=18 M/F =1.5:1	LV septum and/or interventricular septal thickness ≥15 mm	66.7% (12/18) M/F =1:1	TTR gene was not included in the panel	5.6% (n=1)
5	Hayashi T, *et al.* (20); Japan (2018): Retrospective study	67	HCM patients (N=46) M/F =1.4:1 RCM patients (N=7) M/F ratio=6:1	LVH ≥15 mm in probands and ≥13 mm in relatives	In HCM patients, 78% (n=36/46) M: 88% In RCM patients, 71% (n=5/7)	0%	0%
6	Bonaventura J, *et al.* (21); Czech Republic (2020): Prospective study	229	HCM patients (N=336) M/F =1.4:1	LVH ≥15 mm	21% (n=70)	0%	0.6% (n=2)
7	Nagyova E, *et al.* (22); Bratislava, Slovakia (2019): Prospective study	46	Cardiomyopathy patients (N=16); dilated (DCM) (n=6); hypertrophic (HCM) (n=8); and noncompaction (NNCM) (n=2); cardiomyopathy M/F: 3:1	Patients with HCM, DCM, and NNCM	In HCM patients: 62.5% (n=5) M: 80% F: 20%	0%	0%
8	Norrish G, *et al.* (23); London, England (1994–2017): Retrospective study	NGS panels were available since 2011: small (≤21 genes) or expanded (>21 genes) panels	First-degree child relatives with HCM (N=57)	≤18 years of age; maximal LVWT, 13 mm	69% (n=27/39) Median age 6 years (IQR, 3.75–10 years)	No information on whether TTR was included in the panel	No information whether GLA was included in the panel
9	Rubattu S, *et al.* (24); Rome, Italy (2016): Prospective cohort study	17	HCM patients (N=70) with both early-onset (EO) (n=35) and later-onset (LO) (n=35) HCM; EO: M/F =3.3:1 LO: M/F =0.3:1	Age: EO HCM: ≤25 years and LO HCM: ≥65 years LVWT >15 mm in adults	Overall; 40% (n=28/70)	TTR was not included in the panel	0%
10	Cecconi M, *et al.* (25); Italy (2016): Retrospective study	19	19 DNA samples of HCM patients in the discovery set	LVWT ≥15 mm	79% (n=15/19)	TTR was not included in the panel	5.3% (n=1)
11	Maurizi N, *et al.* (26); Italy (2019): Prospective study	11	N=343, M: 58% F: 42% M/F =1.3:1	HCM patients at age ≥40 years	73% (n=251)	3.5% (n=12)	2% (n=6)

ATTR-CA, transthyretin cardiac amyloidosis; DCM, dilated cardiomyopathy; EO, early onset; F, females; FD, Fabry disease; *GLA*, α-galactosidase A gene; HCM, hypertrophic cardiomyopathy; LO, later onset; LV, left ventricle; LVH, left ventricular hypertrophy; LVWT, left ventricular wall thickness; M, males; NGS, next-generation sequencing; NNCM, noncompaction cardiomyopathy; N, number/sample size; RCM, restrictive cardiomyopathy; *TTR*, transthyretin gene.

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Table S3 Web-based databases

Name of the webpage	How to access	Information given
Population frequency		
Varsome	https://varsome.com/	A global genomics community of 500,000+ healthcare professionals and researchers who share their findings and expertise and look to establish collaborations. Varsome features as a knowledge database consisting of +140 data resources and a powerful variant search engine
Alamut® Visual	https://extranet.interactive-biosoftware.com/AlamutVisual-2.15_Documentation/SNPs.html	Provides convenient access to several databases of known variants, including NCBI (dbSNP), gnomAD, Swiss-Prot variants, NHLBI GO ESP, HGVD, and GoNL
dbSNP	http://www.ncbi.nlm.nih.gov/SNP/	dbSNP is a public-domain archive for a broad collection of simple genetic polymorphisms designed to support submissions and research into a broad range of biological problems, including physical mapping, functional analysis, pharmacogenomics, association studies, and evolutionary studies
gnomAD	https://gnomad.broadinstitute.org/	gnomAD is a collaborative effort by international researchers to gather and standardize exome and genome sequencing data from diverse large-scale projects, with the aim of providing accessible summary data to the broader scientific community
Mutation/Polymorphism and Novel/Published		
HGMD®	https://www.hgmd.cf.ac.uk/ac/index.php	HGMD® is a comprehensive compilation of (published) gene lesions associated with inherited human diseases
ClinVar	https://www.ncbi.nlm.nih.gov/clinvar/	ClinVar is a public archive of reports of the relationships among human variations and phenotypes, with supporting evidence, serving as a valuable resource for understanding the impact of genetic variations on human well-being
Pathogenic/Benign		
Franklin	https://franklin.genoox.com/clinical-db/home	Franklin is a connectivity hub across the medical genetics domain. The network effect generated by the Franklin community extends the actionable genomic information that impacts patients' care
PolyPhen-2	http://genetics.bwh.harvard.edu/pph2/	PolyPhen-2is a computational tool that employs physical and comparative assessments to predict the potential effects of an amino acid substitution on the structure and function of a human protein
SIFT	https://sift.bii.a-star.edu.sg/	SIFT utilizes sequence homology and the physical characteristics of amino acids to forecast the impact of an amino acid substitution on protein function, applicable to both naturally occurring nonsynonymous polymorphisms and experimentally induced missense mutations
MutationTaster	https://www.mutationtaster.org/	A web-based application that assesses the disease-causing potential of DNA sequence variants, utilizing a series of computational tests to estimate the impact of the variant on the gene product or protein
CADD	https://cadd.gs.washington.edu/	CADD is a tool utilized for evaluating the deleterious nature of single nucleotide variants and insertion/deletion variants in the human genome by assigning them scores
Related to a specific disorder/incidental		
OMIM®	https://www.omim.org/	OMIM®is a compendium providing comprehensive and authoritative information on human genes, genetic phenotypes, and Mendelian disorders, with over 16,000 genes covered

CADD, combined annotation-dependent depletion; ClinVAR, public archive of interpretations of clinically relevant variants; DbSNP, the single nucleotide polymorphism database; DNA, deoxyribonucleic acid; gnomAD, genome aggregation database; GoNL, the genome of the Netherlands consortium; HGMD®, the human gene mutation database; HGVD, the Japan human genetic variation database; NCBI, national center for biotechnology information; NHLBI GO ESP, national heart, lung, and blood Institute grand opportunity exome sequencing project; OMIM®, online mendelian inheritance in man; PolyPhen-2, polymorphism phenotyping v2; SIFT, sorting intolerant from tolerant; Swiss-prot, curated protein sequence database.

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