Hypertrophic cardiomyopathy (HCM) epidemiology and genetic background - 2021

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HCM is the most common monogenic cardiovascular disorder.

Prevalence: in the general population around the world is 0.2% (1 in 500 adults), 1 case per 200 to 500 persons, ***Atteya G, Lampert R.* Sudden Cardiac Death in Genetic Cardiomyopathies.** ***Card Electrophysiol Clin. 2017 Dec; 9(4):581-603***.

Sex ratio: M/F ratio 1:1. Genetic inheritance does not follow sex predilection as consequence of AD pattern of inheritance**.** It is a way a genetic trait or condition can be passed down from parent to child.
One copy of a mutated (changed) gene from one parent can cause the genetic condition.
A child who has a parent with the mutated gene has a 50% chance of inheriting that mutated gene.
Men and women are equally likely to have these mutations and sons and daughters are equally likely to inherit them.

Age presentation: The most common presentation is in the third decade of life but may be present at any age, from newborns to elderly patients.
The morphologic evidence is found in »25% of first-degree relatives of patients with HCM.

Global distribution: So far it has been described in 122 countries, 20 million peoples affected worldwide, accounting for 88% of world population.

Clinically identified individuals: only 10%, Unidentified: 90%; Symptomatic: 6%, Asymptomatic: 4%

Inherited pattern: AD inheritance pattern.[4]

Genes mutations: HCM is caused by mutations in genes encoding the tree different myofilament contractile components of the sarcomere: The thin **(» 5%)**, thick **(» 45%)** and Z disk **(» 1%)** with 11 mutations or more genes sarcomere genes mutations, with β-myosin heavy chain and myosin-binding protein C genes most commonly involved. (**Alfares AA, et al. Results of clinical genetic testing of 2,912 probands with hypertrophic cardiomyopathy: expanded panels offer limited additional sensitivity. Genet Med 2015;17: 880-8**.) (**Cirino AL, Harris S, Lakdawala NK, et al. Role of genetic testing in inherited cardiovascular disease: a review. JAMA Cardiol 2017;2:1153-60**), (**Fourey D, , et al. Prevalence and clinical implication of double mutations in hypertrophic cardiomyopathy: revisiting the gene-dose effect. Circ Cardiovasc Genet 2017;10(2): e001685.**)
There are more than 2000 sarcomere pathogenic or with uncertain pathogenicity mutations. Many mutations are confined to single families (**Richards S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015; 17:405-24.)()(Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. J Am Coll Cardiol 2012;60:705-15.)**
The main sarcomere gene mutation locations in HCM in thin, thick contractile myofilaments and Z disk protein.

I. **Thin contractile myofilament proteins (» 5%): ACT1 gene (Actin), TPM1(Tropomyosin 1), TNNI3, TNNC1, TNNT2**
II. **Thick contractile myofilament proteins (» 45%): MYBPC3 (20%), MYH7(20%), MYL2(<1%), MYL3(<1%).**
III. **Z disk protein (» 1%) CRSP3, MYZ02.**

HCM is caused by a mutation in a group of related genes that make up the cardiac sarcomere. More than 2000 mutations in any of at least 11 genes encoding the molecular components of the sarcomere can lead to development of HCM. One or more of these genetic mutations are found in up to 60% of individuals with a family history of HCM and 30% of those without a family history.

Table x Genes Implicated in HCM

Gene	Protein	Function	Tolerance to Variation	
			Missense (*Z* Score)	**LoF (pLI)**
Established causal gene HCM (large families)				
MYH7	β-Myosin heavy chain	ATPase activity, force generation	6.54	0.00
MYBPC3	Myosin-binding protein C	Cardiac contraction	0.69	0.00
TNNT2	Cardiac troponin T	Regulator of actomyosin interaction	1.54	0.01
TNNI3	Cardiac troponin I	Inhibitor of actomyosin interaction	1.88	0.17
TPM1	α-Tropomyosin	Places the troponin complex on cardiac actin	3.42	0.80
ACTC1	Cardiac α-actin	Actomyosin interaction	5.25	0.95
MYL2	Regulatory myosin light chain	Myosin heavy chain 7–binding protein	0.86	0.02
MYL3	Essential myosin light chain	Myosin heavy chain 7–binding protein	0.75	0.89
CSRP3	Cysteine- and glycine-rich protein 3	Muscle LIM protein (MLP), a Z disk protein	−0.66	0.00
Likely causal genes for HCM (small families)				
FHL1	Four-and-a-half LIM domains 1	Muscle development and hypertrophy	1.29	0.92
MYOZ2	Myozenin 2 (calsarcin 1)	Z disk protein	0.03	0.02

PLN	Phospholamban	Regulator of sarcoplasmic reticulum calcium	0.57	0.11
TCAP	Tcap (telethonin)	Titin capping protein	0.45	0.08
TRIM63	Muscle ring finger protein 1	E3 ligase of proteasome ubiquitin system	0.02	0.00
TTN	Titin	Sarcomere function	−5.48	0.00
Genes associated with HCM (small families and sporadic cases)				
ACTN2	Actinin, α2	Z disk protein	1.76	1.0
ANKRD1	Ankyrin repeat domain 1	A negative regulator of cardiac genes	−0.01	0.00
CASQ2	Calsequestrin 2	Calcium-binding protein	−1.08	0.00
CAV3	Caveolin 3	A caveolae protein	1.19	0.34
JPH2	Junctophilin-2	Intracellular calcium signaling	3.93	0.01
LDB3	Lim domain binding 3	Z disk protein	0.32	0.00
MYH6	Myosin heavy chain α	Sarcomere protein expressed at low levels in the adult human heart	2.87	0.00
MYLK2	Myosin light chain kinase 2	Phosphorylate myosin light chain 2	0.73	0.22
NEXN	Nexilin	Z disc protein	−1.32	0.00
TNNC1	Cardiac troponin C	Calcium-sensitive regulator of myofilament function	2.22	0.51
VCL	Vinculin	Z disk protein	3.11	0.99

Table 1. Genes Implicated in HCM

The Z score for each gene reflects deviation of the observed variants in the ExAC database from the expected number. A higher positive *Z* score indicates that the gene is intolerant to variation. Likewise, pLI indicates probability of intolerance to LoF variants with 1 indicating total

intolerance. HCM indicates hypertrophic cardiomyopathy; and LoF, loss of function.

Table 2. Hypertrophic Cardiomyopathy Genes

Gene 1	MOI	% of HCM Caused by Pathogenic Variants in This Gene 2	ClinGen Gene Validity Classification 3	Allelic Disorders 4	References / OMIM Gene Entry
MYBPC3	AD	50 %	Definitive	DCM	600958
MYH7	AD	33 %	Definitive	Laing distal myopathy Myosin storage myopathy Left ventricular non- compaction Scapuloperoneal myopathy	160760
TNNI3	AD	5 %	Definitive	DCM Restrictive cardiomyopathy	191044
TNNT2	AD	4 %	Definitive	DCM Left ventricular non- compaction Familial restrictive cardiomyopathy	191045
ACTC1	AD	<3%	Definitive	DCM	102540
MYL2	AD	<3%	Definitive		160781
MYL3	AD AR	<3%	Definitive		160790
TPM1	AD	<3%	Definitive	DCM	191010
PLN	AD	<3%	Definitive 5	DCM	172405
ALPK3	AR	Rare	Strong		617608

ACTN2	AD	<1%	Moderate 5	DCM	102573
CSRP3	AD	<1%	Moderate	DCM	600824
TNNC1	AD	<1%	Moderate	DCM	191040
JPH2	AD	Rare	Moderate		605267
MYOZ2	AD	<1%	Limited		605602
NEXN	AD	<1%	Limited	DCM	613121
ANKRD 1	AD	Rare	Limited		
CALR3	AD	Rare	Limited		611414
KLF10	AD	Rare	Limited		601878
MYH6	AD	Rare	Limited	DCM	160710
MYLK2	Dige nic	Rare	Limited		606566
MYOM 1	AD	Rare	Limited		603508
MYPN	AD	Rare	Limited	DCM Nemaline myopathy	608517
OBSCN	AD	Rare	Limited		608616
PDLIM3	AD	Rare	Limited		605889
RYR2	AD	Rare	Limited	ARVD2 CPVT1	180902
TCAP	AD	Rare	Limited	DCM LGMD2G	604488
TRIM63	AD	Rare	Limited		606131
TTN	AD	Rare	Limited	DCM Hereditary myopathy w/ early respiratory failure LGMD2J Salih myopathy Udd distal myopathy	613765
VCL	AD	Rare	Limited	DCM	193065

AD = autosomal dominant; AR = autosomal recessive; DCM = dilated cardiomyopathy; LGMD2G = limb-girdle muscular dystrophy type 2G;

LGMD2J = limb-girdle muscular dystrophy type 2J; MOI = mode of inheritance

1. Genes are ordered first by validity classification, then frequency of causation of HCM, and then alphabetically.
   Prevalence data list for genes included in Alfares et al.[5] "Rare" denotes genes not included in this paper. The Clin Gen Gene Curation working group developed a framework to evaluate the clinical validity of a gene-disease relationship. The classification reflects the strength of evidence that a variant in that gene can cause a particular phenotype, in this case HCM www.clinicalgenome.org.
2. Allelic disorders = other phenotypes caused by pathogenic variants in the same gene
3. PLN and ACTN2 were curated for intrinsic cardiomyopathy given their association with a spectrum of cardiac phenotypes, including isolated LVH and HCM.

The etiology may range from physiological adaptation in the athlete to myocardial involvement, isolated or integrated as part of a global neuromuscular involvement; metabolic or mitochondrial disease to deposition disease (phenocopies). As cardiac signs are non-specific, the clinical examination should focus on looking for a syndromic entity.