



## Hypertrophic Cardiomyopathy Overview

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### Summary

The purpose of this overview is to increase clinician awareness of the genetic basis of hypertrophic cardiomyopathy (HCM) and the benefits of early diagnosis and management to individuals with genetic HCM. The following are the goals of this overview.

#### Goal 1

Define HCM.

#### Goal 2

Identify the categories of HCM.

#### Goal 3

Provide the evaluation strategy for a proband with HCM to establish (when possible) the specific genetic cause.

#### Goal 4

Provide a basic view of genetic risk assessment of at-risk asymptomatic relatives of a proband with HCM to inform cardiac surveillance and to allow early detection and treatment of HCM to improve long-term outcome.

## 1. Hypertrophic Cardiomyopathy: Definition

Hypertrophic cardiomyopathy (HCM) is typically defined by the presence of unexplained left ventricular hypertrophy (LVH) with a maximum wall thickness  $\geq 15$  mm in adults or a z-score  $>3$  in children [Gersh et al 2011, Elliott et al 2014]. If there is a family history of HCM, or if genetic testing confirms that a relative has inherited the family's pathogenic sarcomere variant, a maximum LV wall thickness  $\geq 13$  mm supports diagnosis. Such LVH occurs in a non-dilated ventricle in the absence of other cardiac or systemic disease capable of

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producing the observed magnitude of increased LV wall thickness, such as pressure overload or storage/infiltrative disorders.

The diagnosis of HCM is most often established with noninvasive cardiac imaging, including echocardiography and/or cardiac magnetic resonance imaging (cardiac MRI).

- While asymmetric septal hypertrophy is the most common pattern of hypertrophy, the degree and location of hypertrophy vary. LVH can be concentric, or confined to other walls or the LV apex.
- Findings on transthoracic echocardiography may also include:
  - Systolic anterior motion (SAM) of the mitral valve with associated left ventricular outflow tract obstruction and mitral regurgitation;
  - Mid-ventricular obstruction as a result of systolic cavity obliteration;
  - Diastolic dysfunction, including restrictive physiology. Of note, impaired LV relaxation can be detected in individuals with a pathogenic variant in a gene that encodes a component of the sarcomere (see Nonsyndromic HCM) who have normal LV wall thickness [Nagueh et al 2001, Ho et al 2002], suggesting that diastolic dysfunction is an early phenotype of HCM rather than a secondary consequence of LVH.

Although LVH and a clinical diagnosis of HCM often become apparent during adolescence around the onset of puberty or during young adulthood, onset can be earlier (in infancy and childhood) or later in life [Niimura et al 2002]. Common symptoms include shortness of breath (particularly with exertion), chest pain, palpitations, orthostasis, presyncope, and syncope.

**Variability and progression.** The clinical manifestations of HCM are highly variable, ranging from asymptomatic LVH to arrhythmias (atrial fibrillation as well as malignant ventricular arrhythmias) to refractory heart failure. Moreover, manifestations can vary even within the same family.

Approximately one third of persons with HCM have detectable intracavitary obstruction at rest, and another third of persons with HCM can develop outflow tract obstruction with provocation (e.g., reduction of preload or afterload) [Maron et al 2003, Elliott et al 2014]. The degree of obstruction does not strictly correlate with the severity of symptoms or risk for sudden cardiac death. Observational studies have reported that persons with HCM with outflow tract obstruction may be at higher risk for symptom progression and death than those without outflow tract obstruction [Maron et al 2003, Sorajja et al 2009]; high gradients may also be well tolerated over long periods of time.

Individuals with HCM are at an increased risk for atrial fibrillation (AF), which can have significant morbidity due to increased risk of thromboembolism and symptomatic deterioration. The prevalence of AF increases with age and duration of disease. The overall prevalence of AF in individuals with HCM is ~20%, but prevalence is ~60% by age 60 years for individuals diagnosed with HCM by age 40 years [Elliott et al 2014, Ho et al 2018]. In individuals with HCM and AF the prevalence of thromboembolic complications has been estimated at 27% [Elliott et al 2014].

Approximately 5%-10% of individuals with HCM progress to end-stage disease with impaired systolic function and, in some cases, left ventricular dilatation and regression of LVH. The annual mortality rate in individuals with end-stage disease is estimated at 11% [Harris et al 2006] and cardiac transplantation may be required.

Sudden cardiac death (SCD), most likely related to ventricular tachycardia / ventricular fibrillation, is an important but relatively rare consequence of HCM.

- In a large cohort of individuals with HCM, 6% experienced sudden death, resuscitated cardiac arrest, or appropriate ICD therapy [Ho et al 2018].
- SCD may be the first manifestation of disease [Maron et al 2000, Finocchiaro et al 2019].

- HCM is a well-described cause of SCD in competitive athletes in the US [Maron 2003], although more recent studies report a decline in prevalence (~5%-14%) [Eckart et al 2011, Harmon et al 2014, Bagnall et al 2016].
- Whereas sudden death occurs most often in adolescents or young adults, it may occur at any age and the risk persists throughout life.

**Life span.** Compared to the US general population, the mortality rate in individuals with HCM is approximately threefold higher, but the mortality rate in younger individuals with HCM, ages 20-29, is as much as fourfold higher than expected. Sudden death accounts for 16% of deaths [Ho et al 2018].

## 2. Hypertrophic Cardiomyopathy: Categories

The differential diagnosis for HCM includes increased left ventricular wall thickness due to acquired, syndromic (with other systemic involvement), and nonsyndromic (without other systemic involvement) disorders.

### Acquired (Secondary) Left Ventricular Hypertrophy

Secondary left ventricular hypertrophy (LVH) can be pathologic, occurring in response to pressure overload (e.g., systemic hypertension, aortic stenosis). This type of adverse remodeling can lead to diastolic abnormalities and heart failure. Physiologic hypertrophy (athlete's heart) may result from rigorous athletic training. Such training may result in increased left ventricular wall thickness accompanied by increased LV cavity size. This type of remodeling is thought to be adaptive and not associated with adverse consequences. Both pathologic and physiologic forms of secondary hypertrophy can regress if the underlying stimulus is removed (e.g., by adequate treatment of high blood pressure or a period of detraining for an athlete).

### Syndromic HCM (with Other Systemic Involvement)

In *GeneReviews*, "syndromic" refers to a disorder characterized by a constellation of phenotypic features that either (a) specifically suggests the diagnosis (which can be confirmed by molecular genetic testing) or (b) allows diagnosis of the disorder in the absence of confirmatory molecular genetic findings. A selected list of syndromic HCM is provided in Table 1. Syndromic HCM will not be discussed further in this overview.

**Table 1.** Syndromic Hypertrophic Cardiomyopathy – A Selected List

Disorder <sup>1</sup>	Gene(s)	MOI	Additional Clinical Features
Danon disease	<i>LAMP2</i>	XL	<ul style="list-style-type: none"> <li>• Skeletal myopathy</li> <li>• Retinal dystrophy</li> </ul>
Fabry disease	<i>GLA</i>	XL	<ul style="list-style-type: none"> <li>• Periodic crises of pain in extremities</li> <li>• Agniokeratomas</li> <li>• Hypohidrosis</li> <li>• Ocular abnormalities</li> <li>• Proteinuria &amp; deterioration of renal function</li> </ul>
Friedreich ataxia	<i>FXN</i>	AR	<ul style="list-style-type: none"> <li>• Slowly progressive ataxia before age 25 years</li> <li>• Dysarthria</li> <li>• Muscle weakness</li> </ul>
Glycogen storage disease of the heart, lethal congenital (OMIM 261740)	<i>PRKAG2</i>	AD	<ul style="list-style-type: none"> <li>• Neonatal hypoglycemia</li> <li>• Vacuolar myopathy</li> <li>• Mild facial dysmorphism &amp;/or macroglossia in some</li> </ul>
Hereditary transthyretin amyloidosis	<i>TTR</i>	AD	<ul style="list-style-type: none"> <li>• Slowly progressive peripheral sensorimotor neuropathy &amp; autonomic neuropathy</li> <li>• Vitreous opacities</li> <li>• CNS amyloidosis</li> </ul>

Table 1. continued from previous page.

Disorder <sup>1</sup>	Gene(s)	MOI	Additional Clinical Features
Pompe disease	<i>GAA</i>	AR	<ul style="list-style-type: none"> <li>Poor feeding</li> <li>Macroglossia</li> <li>Motor delay / muscle weakness</li> <li>Respiratory difficulty</li> </ul>
RASopathies <sup>2</sup> incl: <ul style="list-style-type: none"> <li>Noonan syndrome</li> <li>Cardiofaciocutaneous syndrome</li> <li>Costello syndrome</li> <li>Noonan syndrome with multiple lentiginos</li> </ul>	<i>BRAF</i> <i>HRAS</i> <i>KRAS</i> <i>LZTR1</i> <i>MAP2K1</i> <i>MAP2K2</i> <i>NRAS</i> <i>PTPN11</i> <i>RAF1</i> <i>RASA2</i> <i>RRAS2</i> <i>RIT1</i> <i>SOS1</i> <i>SOS2</i>	AD	<ul style="list-style-type: none"> <li>Characteristic facies</li> <li>Short stature</li> <li>Variable developmental delay</li> <li>Broad, webbed neck</li> <li>Unusual chest shape</li> </ul>

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked

1. Disorders are in alphabetic order.

2. The RASopathies are a group of syndromes that have overlapping clinical features resulting from a common pathogenetic mechanism [Tidyman & Rauen 2009].

## Nonsyndromic HCM (HCM without Other Systemic Involvement)

Individuals with HCM who do not have acquired (secondary) HCM or syndromic HCM (Table 1) have nonsyndromic hypertrophic cardiomyopathy (defined in this *GeneReview* as HCM with no other systemic involvement). For the remainder of this *GeneReview*, genes causing HCM without other systemic involvement will be referred to as HCM genes. See Table 2 for a current list of known HCM genes; the strength of the evidence associating each gene with HCM varies significantly [Ingles et al 2019]. The genes with the strongest clinical validity encode different components of the sarcomere [Ingles et al 2019].

Pathogenic variants in one of the genes encoding a component of the sarcomere are found in approximately 50%-60% of probands (adults and children) with a family history of HCM, and approximately 20%-30% of probands without a family history of HCM [Alfares et al 2015]. Approximately 3%-5% of affected individuals have more than one sarcomere gene variant (either biallelic variants in 1 gene or heterozygous variants in >1 gene) although fewer than 1% will have more than one pathogenic or likely pathogenic variant [Alfares et al 2015, Burns et al 2017].

The [Clinical Genome Resource \(ClinGen\) HCM Gene Curation Expert Panel](#) has classified HCM genes using the ClinGen framework for the strength of their relationship with monogenic, nonsyndromic HCM. A summary of the data curated for each gene can be accessed via the links provided in the ClinGen Classification column (see also Ingles et al [2019]).

**Table 2.** Hypertrophic Cardiomyopathy Genes

Gene <sup>1</sup>	MOI	% of HCM Caused by Pathogenic Variants in Gene <sup>2</sup>	ClinGen Gene Validity Classification	Allelic Disorders <sup>3</sup>	References / OMIM Gene Entry
<i>MYBPC3</i>	AD	50%	Definitive	DCM	600958

Table 2. continued from previous page.

Gene <sup>1</sup>	MOI	% of HCM Caused by Pathogenic Variants in Gene <sup>2</sup>	ClinGen Gene Validity Classification	Allelic Disorders <sup>3</sup>	References / OMIM Gene Entry
<i>MYH7</i>	AD	33%	Definitive	<ul style="list-style-type: none"> <li>• Laing distal myopathy</li> <li>• Myosin storage myopathy</li> <li>• Left ventricular non-compaction</li> <li>• Scapuloperoneal myopathy</li> <li>• DCM</li> </ul>	160760
<i>TNNI3</i>	AD	5%	Definitive	<ul style="list-style-type: none"> <li>• DCM</li> <li>• Restrictive cardiomyopathy</li> </ul>	191044
<i>TNNT2</i>	AD	4%	Definitive	<ul style="list-style-type: none"> <li>• DCM</li> <li>• Left ventricular non-compaction</li> <li>• Familial restrictive cardiomyopathy</li> </ul>	191045
<i>ACTC1</i>	AD	<3%	Definitive	DCM	102540
<i>MYL2</i>	AD	<3%	Definitive	DCM	160781
<i>MYL3</i>	AD AR	<3%	Definitive		160790
<i>PLN</i>	AD	<3%	Definitive <sup>4</sup>	DCM, ARVC	172405
<i>TPM1</i>	AD	<3%	Definitive	DCM	191010
<i>ALPK3</i>	AR	Rare	Strong		617608
<i>ACTN2</i>	AD	<1%	Moderate <sup>4</sup>	DCM	102573
<i>CSRP3</i>	AD	<1%	Moderate	DCM	600824
<i>TNNC1</i>	AD	<1%	Moderate	DCM	191040
<i>JPH2</i>	AD	Rare	Moderate	DCM	605267
<i>MYOZ2</i>	AD	<1%	Limited		605602
<i>NEXN</i>	AD	<1%	Limited	DCM	613121
<i>ANKRD1</i>	AD	Rare	Limited	DCM	
<i>CALR3</i>	AD	Rare	Limited		611414
<i>KLF10</i>	AD	Rare	Limited		601878
<i>MYH6</i>	AD	Rare	Limited	DCM	160710
<i>MYLK2</i>	Digenic	Rare	Limited		606566
<i>MYOM1</i>	AD	Rare	Limited		603508
<i>MYPN</i>	AD	Rare	Limited	<ul style="list-style-type: none"> <li>• DCM</li> <li>• Nemaline myopathy</li> </ul>	608517
<i>PDLIM3</i>	AD	Rare	Limited		605889
<i>RYR2</i>	AD	Rare	Limited	<ul style="list-style-type: none"> <li>• CPVT1</li> </ul>	180902
<i>TCAP</i>	AD	Rare	Limited	<ul style="list-style-type: none"> <li>• DCM</li> <li>• LGMD2G</li> </ul>	604488

Table 2. continued from previous page.

Gene <sup>1</sup>	MOI	% of HCM Caused by Pathogenic Variants in Gene <sup>2</sup>	ClinGen Gene Validity Classification	Allelic Disorders <sup>3</sup>	References / OMIM Gene Entry
<i>TRIM63</i>	AD	Rare	Limited		606131
<i>TTN</i>	AD	Rare	Limited	<ul style="list-style-type: none"> <li>• DCM</li> <li>• Hereditary myopathy w/ early respiratory failure</li> <li>• LGMD2J</li> <li>• Salih myopathy</li> <li>• Udd distal myopathy</li> </ul>	613765
<i>VCL</i>	AD	Rare	Limited	DCM	193065

AD = autosomal dominant; AR = autosomal recessive; ARVC = arrhythmogenic right ventricular cardiomyopathy; 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.

2. Prevalence data list for genes included in Alfares et al [2015]. "Rare" denotes genes not included in this paper.

3. Allelic disorders = other phenotypes caused by pathogenic variants in the same gene

4. *PLN* and *ACTN2* were curated for intrinsic cardiomyopathy given their association with a spectrum of cardiac phenotypes, including isolated LVH and HCM.

### 3. Establishing (when Possible) the Specific Genetic Cause of Hypertrophic Cardiomyopathy

Genetic testing is recommended (1) in individuals fulfilling diagnostic criteria for HCM to enable cascade screening of relatives and (2) to confirm the diagnosis in individuals with clinical evidence that is suggestive of HCM [Elliott et al 2014].

The purposes of establishing a molecular diagnosis of HCM are to (1) identify syndromic HCM (see Table 1) that could have different treatment and/or management and (2) inform risk assessment of relatives of a proband (see Genetic Risk Assessment and Cardiac Surveillance). Elements of the personal and family history (i.e., family history of HCM, septal morphology, younger age at diagnosis) have been associated with a higher likelihood of a positive genetic test result [Ingles et al 2013, Bos et al 2014].

A general approach to identifying the specific genetic cause in individuals with hypertrophic cardiomyopathy (HCM) is summarized in Figure 1. Genetic testing for HCM is best viewed as a family test rather than a test of an individual since results are most accurately interpreted after integrating genetic and medical test (echocardiogram, EKG) results from multiple family members. In this manner, a cohesive understanding of the family's phenotype can be used to determine if variants segregate with the disorder within the family (the suspected pathogenic variant should be present in affected family members, but not in unaffected family members).

**Initial evaluation should always include the following.**

**Family history.** Effort should be made to obtain a three-generation family history with attention to other relatives with a history of any of the following: heart failure, HCM, cardiac transplantation, unexplained or sudden death (particularly in relatives age <40 years), cardiac conduction system disease and/or arrhythmia, or unexplained stroke or other thromboembolic disease. Note: The family member who will undergo molecular genetic testing should have an unequivocal diagnosis of HCM and is, ideally, the most severely affected person in the family.

Note: (1) Confirming the absence of other affected relatives can be complicated by various medical issues (e.g., failure to undergo appropriate cardiac screening, reduced penetrance, early death from other causes before onset of HCM) and/or social issues (e.g., isolation from family members, undisclosed adoption, and alternate paternity or maternity). Thus, it may not be possible to distinguish whether the proband with HCM is truly a simplex case (i.e., a single occurrence in the family). (2) Clinical evaluation of family members can provide valuable information about the family history (e.g., diagnosis of a family member with previously unrecognized HCM). (3) Family history should be reviewed and updated periodically.

**Genetic counseling** is recommended for all individuals with HCM, whether or not genetic testing will be used [Elliott et al 2014].

**Molecular genetic testing** for HCM relies on use of multigene panels, which are comprehensive (i.e., comprising genes known to be associated with HCM and genes associated with a variety of genetic cardiomyopathies). See Table 2 for a current list of known HCM genes.

An HCM multigene panel that includes the genes with established clinical validity listed in Table 2 is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 2).

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

When an HCM multigene panel is not diagnostic, exome (or genome) sequencing is another possible testing method, though the anticipated incremental yield is low [Cirino et al 2017b]. If exome sequencing is not diagnostic, exome array (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

Health care providers ordering genetic testing should be familiar with the genetics of HCM. Given the complexity of interpreting genetic test results and their implications for surveillance and management, health care providers should consider referral to a cardiovascular genetics center or a genetic counselor specializing in cardiac genetics (see these search tools: [NSGC - Find a Genetic Counselor](#) or [ABGC Find a Certified Genetic Counselor](#)). Basic guidance on the clinical implications of different variant classification categories can be found in Table 3.



**Table 3.** Variant Classification Categories and Clinical Implications

	Variant Classification				
	Benign or No Variant Found	Likely Benign	Of Uncertain Significance	Likely Pathogenic	Pathogenic
	<b>NEGATIVE</b>		<b>UNCERTAIN</b>	<b>POSITIVE</b>	
<b>Meaning</b>	No important variants detected. Genetic disease cannot be excluded.	Variant detected is likely harmless. Genetic disease cannot be excluded.	Ambiguous result; insufficient data re variant pathogenicity. Segregation studies may provide additional data.	Likely cause of HCM; segregation studies may provide additional evidence for causality.	Responsible for causing HCM
<b>Utility for proband</b>	None	None	Unknown	Suggests HCM diagnosis; may inform mgmt or lead to additional diagnostic studies.	Establishes HCM diagnosis. May inform mgmt.
<b>Utility for family</b>	No option for predictive genetic testing; rely on longitudinal phenotypic eval.	No option for predictive genetic testing; rely on longitudinal phenotypic eval.	Predictive genetic not recommended; rely on longitudinal phenotypic eval. Consider segregation testing in affected relatives.	Predictive genetic testing should be approached carefully & may be combined w/phenotypic eval & surveillance.	Can be used for predictive genetic testing.

Adapted from Cirino et al [2017a]

## 4. Genetic Risk Assessment and Cardiac Surveillance of At-Risk Relatives for Detection of Early Treatable Manifestations of Hypertrophic Cardiomyopathy

Practice guidelines recommend construction of a three- (or more) generation family history in all persons with HCM to help identify at-risk family members [Hershberger et al 2018]. At-risk family members should seek clinical evaluation according to the guidelines listed in Table 4 and be offered genetic testing if a pathogenic variant has been identified in an affected family member. Consideration should be given to the timing of testing in unaffected children and the potential benefits and harms to the child should be weighed [Elliott et al 2014].

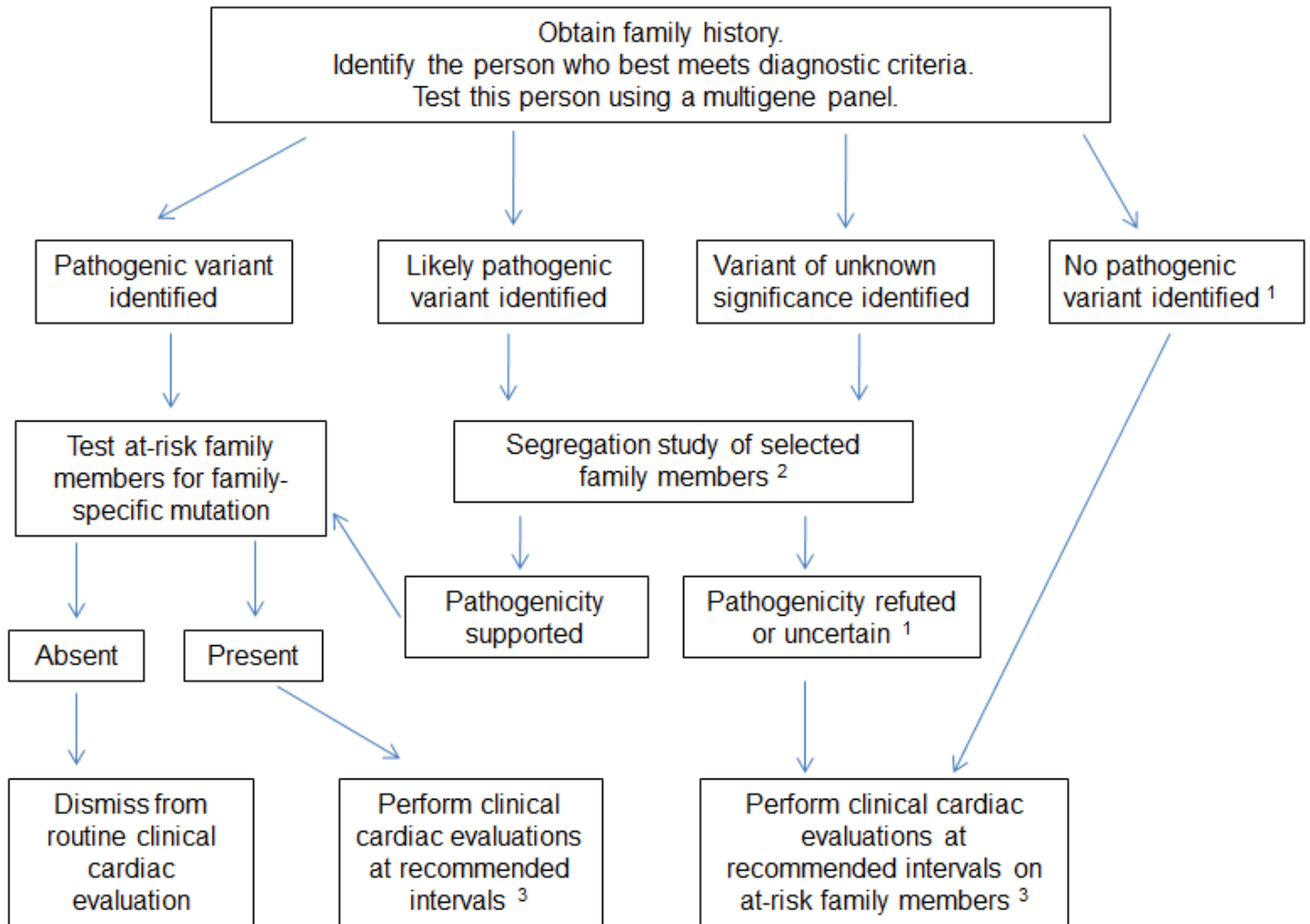
If the pathogenicity of the variant identified in the affected family member is uncertain (i.e., likely pathogenic or of unknown significance), testing other affected family members as part of a segregation analysis can help in variant interpretation; observation that the variant occurs with HCM in other affected family members (and does not occur in those with a normal phenotype) provides further support for pathogenicity.

The number of relatives tested is an important consideration, as the a priori chance that the variant is present in first-degree relatives is 50%. In contrast, the absence of the variant in a single affected individual provides strong evidence that the variant is not pathogenic.

- It is appropriate to combine genetic testing with clinical evaluation in at-risk relatives to provide more comprehensive information about the disease and variant transmission in the family.
- When pathogenicity of a variant is refuted by segregation analysis, this information should be relayed back to the genetic testing laboratory.

If the variant identified in the tested family member is of uncertain significance, testing of unaffected at-risk family members for the variant is not helpful, as this information will not aid in interpretation of the variant and will not reliably modify the a priori risk to that relative of developing HCM.





**Figure 1.** Familial hypertrophic cardiomyopathy: Algorithm for genetic testing and clinical cardiac screening

Notes:

1. No important variants detected. Genetic disease cannot be excluded. Consider retesting the person who best meets diagnostic criteria when new genes/tests are available.
2. Provide feedback to genetic testing laboratory regarding results of segregation study.
3. See Table 4. Guidelines for Clinical Screening of Healthy At-Risk Family Members (Note: These guidelines apply both to relatives in whom a pathogenic variant has been identified and to asymptomatic first-degree relatives (adults and children) of an individual with primary HCM in whom a pathogenic variant has not been identified.

If no variant is identified in the tested family member, no further genetic testing can be pursued (at this time) to clarify the genetic status of at-risk family members.

## Genetic Risk Assessment

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.*

Hypertrophic cardiomyopathy (HCM) is typically inherited in an autosomal dominant manner; pathogenic variants in genes associated with autosomal recessive inheritance have been reported in rare families.

In rare instances, more than one pathogenic variant in a gene encoding a sarcomere protein has been identified in a single individual (i.e., double heterozygosity) [Alfares et al 2015, Burns et al 2017]. Therefore, determining the pattern of inheritance for each variant in an individual is critical for accurate risk assessment of other family members.

## Autosomal Dominant Inheritance – Risk to Family Members

### Parents of a proband

- Some individuals diagnosed as having HCM have an affected parent.
- A proband with HCM may also have the disorder as the result of a *de novo* pathogenic variant. The proportion of cases caused by *de novo* pathogenic variants is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include molecular genetic testing for the pathogenic variant identified in the proband, echocardiogram, EKG, and physical examination by a cardiologist familiar with HCM.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the pathogenic variant most likely occurred *de novo* in the proband. Another possible explanation is that the proband inherited a pathogenic variant from a parent with germline mosaicism. A case of germline mosaicism has been reported [Forissier et al 2000] but the incidence is unknown.
- Note: Although some individuals diagnosed with HCM have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in asymptomatic or mildly symptomatic family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.

**Sibs of a proband.** The risk to sibs depends on the genetic status of the proband's parents:

- If a parent of the proband has the pathogenic variant, the risk to the sibs of inheriting the allele is 50%. However, clinical severity and age of onset cannot be predicted in sibs who inherit a familial HCM-related pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be ~1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

**Offspring of a proband.** Each child of an individual with HCM has a 50% chance of inheriting the pathogenic variant and therefore being at risk for developing HCM. However, penetrance may be reduced and clinical severity and age of onset cannot be predicted in offspring who inherit a familial HCM-related pathogenic variant.

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or has an HCM-related pathogenic variant, the parent's family members may be at risk.

## Autosomal Recessive Inheritance – Risk to Family Members

### Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one HCM-related pathogenic variant).

- Typically, risk of disease in heterozygotes (carriers) is not increased over that of the general population; however, *ALPK3* carriers may be at risk of developing cardiomyopathy in adulthood [Almomani et al 2016].

### Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of not being a carrier.
- Typically, risk of disease in heterozygotes (carriers) is not increased over that of the general population; however, *ALPK3* carriers may be at risk of developing cardiomyopathy in adulthood [Almomani et al 2016].

**Offspring of a proband.** The offspring of an individual with autosomal recessive HCM are obligate heterozygotes (carriers) for an HCM-related pathogenic variant.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of an HCM-related pathogenic variant.

## Cardiac Surveillance

It is appropriate to clarify the clinical and genetic status of asymptomatic family members at risk for HCM prior to the onset of manifestations to identify those with asymptomatic HCM and allow early diagnosis for those yet to develop disease.

**Family members of an affected individual who has a known pathogenic variant in an HCM-related gene.** If a definitive pathogenic variant is identified in the affected individual, predictive molecular genetic testing can be performed in at-risk relatives to clarify their genetic risk. Those identified as heterozygous for the pathogenic variant present in the affected family member (and thus at high risk for developing HCM) should undergo clinical cardiovascular screening by physical examination, EKG, and echocardiography performed in accordance with published recommendations [Ommen et al 2020] (see Table 4a).

**Table 4a.** Guidelines for Clinical Screening of Asymptomatic Family Members of a Proband With a Known HCM-Related Pathogenic Variant

Genetic Status	Age of Asymptomatic Relative <sup>1</sup>	Risk for Developing HCM	When To Initiate Screening	Repeat EKG & 2D Echo <sup>2</sup>
Heterozygous for the familial HCM-related pathogenic variant	Children & adolescents	High <sup>3</sup>	At the time HCM is diagnosed in another family member	Every 1-2 yrs
	Adults			Every 3-5 yrs
Not heterozygous for the familial HCM-related pathogenic variant	Children & adolescents	Not at ↑ risk	May be discharged from cardiac surveillance	NA
	Adults			

Adapted from Ommen et al [2020]

Echo = echocardiography; EKG = electrocardiogram; NA = not applicable

1. Includes first-degree relatives. May include more distant relatives based on clinical judgment.

2. Screening interval may be modified based on symptom development and/or family history

3. Lorenzini et al [2020] found ~50% penetrance over 15 years of follow up in at-risk relatives who were heterozygous for the familial HCM-related pathogenic variant.

**Family members of an affected individual in whom the specific genetic cause of HCM has not been identified.** Clinical cardiovascular screening by physical examination, EKG, and echocardiography should be performed in accordance with published recommendations [Ommen et al 2020] in all asymptomatic first-degree

relatives (adults and children) of an individual with HCM in whom a pathogenic variant has not been identified (see Table 4b).

**Table 4b.** Guidelines for Clinical Screening of Asymptomatic Family Members of a Proband in Whom the Specific Genetic Cause of HCM Has Not Been Identified

Age of Asymptomatic Relative <sup>1</sup>	Age of Onset in Affected Family Member(s)	When To Initiate Screening	Repeat EKG & 2D Echo <sup>2</sup>
Children & adolescents	Early onset (i.e., onset in infancy &/or childhood)	At the time HCM is diagnosed in another family member	Every 1-2 years
	Onset during or after puberty	At the time HCM is diagnosed in another family member <b>but no later than puberty</b>	Every 2-3 years
Adults	Any age	At the time HCM is diagnosed in another family member	Every 3 to 5 years

Adapted from Ommen et al [2020]

Echo = echocardiography; EKG = electrocardiogram

1. Includes first-degree relatives. May include more distant relatives based on clinical judgment.

2. Screening interval may be modified based on symptom development and/or family history.

Because penetrance of diagnostic features (i.e., LVH) is age dependent, a single unremarkable evaluation does not exclude the possibility of future development of HCM. Diagnostic clinical manifestations are often not present in infancy / early childhood; they commonly develop during adolescence and early adulthood, but may also develop late in life. Therefore, longitudinal follow up is required at a frequency based on the individual's age and family history and physician discretion. Screening should be performed in response to any symptoms that develop or any change in clinical status.

Note: As understanding of human DNA variation evolves, it is possible that the classification of a variant will change, potentially affecting the recommendations made to a person/family. It is recommended that families of individuals with HCM follow up with a cardiovascular genetics clinic and/or genetic counselor on a regular basis as genetic testing methods improve.

## Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- Children's Cardiomyopathy Foundation**  
**Phone:** 866-808-2873 (toll-free)  
**Fax:** 201-227-7016  
**Email:** [info@childrenscardiomyopathy.org](mailto:info@childrenscardiomyopathy.org)  
[www.childrenscardiomyopathy.org](http://www.childrenscardiomyopathy.org)
- Hypertrophic Cardiomyopathy Association (HCMA)**  
 328 Green Pond Road  
 PO Box 306  
 Hibernia NJ 07842  
**Phone:** 973-983-7429  
**Fax:** 973-983-7870  
**Email:** [support@4hcm.org](mailto:support@4hcm.org)

[www.4hcm.org](http://www.4hcm.org)

- **American Heart Association (AHA)**  
7272 Greenville Avenue  
Dallas TX 75231  
**Phone:** 800-242-8721 (toll-free)  
**Email:** [review.personal.info@heart.org](mailto:review.personal.info@heart.org)  
[Hypertrophic Cardiomyopathy](#)
- **Cardiomyopathy UK**  
United Kingdom  
**Phone:** 0800 018 1024 (UK only)  
**Email:** [contact@cardiomyopathy.org](mailto:contact@cardiomyopathy.org)  
[www.cardiomyopathy.org](http://www.cardiomyopathy.org)

## Chapter Notes

### Author Notes

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### Revision History

- 8 July 2021 (aa/ha) Revision: in Table 2 – added ClinGen gene validity hyperlinks, updated allelic disorders information, removed *OBSCN*
- 11 February 2021 (aa/ha) Revision: added 2020 AHA/ACC Guidelines and revised screening guidelines provided (Table 4a, Table 4b) for consistency with 2020 AHA/ACC Guidelines
- 6 June 2019 (ha) Comprehensive update posted live
- 16 January 2014 (me) Comprehensive update posted live
- 17 May 2011 (cd) Revision: testing available on a clinical basis for *ACTN2* and *CSRP3*
- 26 May 2009 (cd) Revision: sequence analysis and prenatal testing available clinically for *TNNC1*-related familial hypertrophic cardiomyopathy.
- 5 August 2008 (me) Review posted live
- 11 June 2007 (ac) Original submission

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