Hypertrophic Cardiomyopathy Panel, Sequencing

Hypertrophic cardiomyopathy (HCM) is a genetically heterogeneous disorder characterized by left ventricular hypertrophy (LVH) in the absence of loading conditions, such as hypertension. Although some individuals with HCM remain asymptomatic, symptoms, when present, can include shortness of breath, chest pain, palpitations, orthostasis, and syncope. Affected individuals are at risk for arrhythmias, outflow tract obstruction, thromboembolic complications, heart failure, and sudden cardiac death.

Onset of familial idiopathic HCM may range from infancy to adulthood, although it often occurs in adolescence or early adulthood, and the risk for developing HCM is reduced after 50 years of age. Syndromic forms of HCM include extracardiac manifestations; however, such disorders can present as isolated LVH. Identification of syndromic forms of HCM is important because such disorders often have specific extracardiac management recommendations. Molecular testing for individuals with HCM is recommended to determine if a genetic etiology can be identified, which can facilitate patient management and screening of at-risk relatives.

Disease Overview

Associated Disorders

Familial HCM

- Onset in adolescence or early adulthood is most common; risk for developing HCM after 50 years of age is reduced
- Most commonly implicated genes are those encoding sarcomeric proteins:
  - *MYBPC3* (50% of HCM cases)
  - *MYH7* (33% of HCM cases)

Select Syndromes Associated with HCM

Syndrome(s)	Gene(s)	Clinical Features
Danon disease	*LAMP2*	Skeletal myopathy Retinal dystrophy
Fabry disease	*GLA*	Periodic pain crises Agniokeratomas Hypohidrosis Ocular abnormalities Proteinuria/decreased renal function

CNS, central nervous system

Tests to Consider

Hypertrophic Cardiomyopathy Panel, Sequencing 3001579

Method: Massively Parallel Sequencing

- Use to determine etiology of hypertrophic cardiomyopathy (HCM) in symptomatic individuals.
- Useful for presymptomatic testing in individuals with a family history of HCM or sudden cardiac death.
- Test includes genes associated with familial HCM and common syndromic forms of HCM (including Noonan syndrome/RASopathy); mitochondrial genes are not interrogated.

Cardiomyopathy and Arrhythmia Panel, Sequencing and Deletion/Duplication 2010183

Method: Massively Parallel Sequencing

Preferred test to assess for hereditary forms of cardiomyopathy or arrhythmia.

Familial Targeted Sequencing 3005867

Method: Massively Parallel Sequencing

- Testing for a known familial sequence variant by sequencing gene of interest. A copy of the family member's test result documenting the familial gene variant is REQUIRED.
- To determine if the variant(s) of interest are detectable by this assay, contact an ARUP genetic counselor at 800-242-2787.

Syndrome(s)	Gene(s)	Clinical Features
Glycogen storage disease II	*GAA*	Poor feeding Macroglossia Motor delay/muscle weakness Respiratory difficulty
Glycogen storage disease of the heart, congenital	*PRKAG2*	Neonatal hypoglycemia Vacuolar myopathy Facial differences/macroglossia
Mitochondrial disease	mtDNA or nuclear genes associated with mitochondrial function	Up to 60% of individuals with a mitochondrial disorder may exhibit HCM
RASopathies	*BRAF*, *HRAS*, *KRAS*, *MAP2K1*, *MAP2K2*, *NRAS*, *PTPN11*, *RAF1*, *RIT1*, *SOS1*	20-30% of individuals with Noonan syndrome have HCM Other features include variable developmental delay, short stature, characteristic facial features, and cutaneous abnormalities
Transthyretin amyloidosis	*TTR*	Progressive peripheral sensorimotor neuropathy and autonomic neuropathy Vitreous opacities CNS amyloidosis

CNS, central nervous system

Genetics

Genes

See table of Genes Tested.

Etiology

- Pathogenic germline variants in sarcomeric genes or other genes associated with HCM[1]
- The most commonly implicated genes are those encoding sarcomeric proteins:
  - *MYBPC3*: 50% of HCM cases
  - *MYH7*: 33% of HCM cases

Penetrance

Variable; influenced by gene and age

Prevalence of HCM

1 in 500

Inheritance

- Familial HCM is typically autosomal dominant.
- Compound heterozygous or digenic heterozygous variants may result in severe and early onset disease.
- Genes with X-linked, autosomal recessive, or mitochondrial inheritance are also associated with HCM.
- De novo variation may be found in children or adults.
- Compound heterozygous or digenic heterozygous variants may result in severe and early onset disease.

Test Description

Clinical Sensitivity

50-60% for familial HCM, 20-30% for isolated HCM[2]

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	99.9	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	99.9	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Limitations

- A negative result does not exclude a heritable form of hypertrophic cardiomyopathy.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted gene(s)
  - Variants in the mitochondrial genome
  - Regulatory region and deep intronic variants
  - Large deletions/duplications in any of the tested genes (Large deletions/duplications account for ~1% of causative variants for familial HCM.[3])
  - Noncoding transcripts
  - The following exons are not sequenced due to technical limitations of the assay:
    - *BRAF* (NM_004333) exon(s) 5, 18
    - *FLNC* (NM_001458) exon(s) 47, 48
    - *PRKAG2* (NM_016203) exon(s) 10, 13
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing

- Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
- Low-level somatic variants

Genes Tested			
Gene	MIM #	Associated Disorder(s)	Inheritance
ACTC1	102540	HCM 11 DCM 1R Atrial septal defect 5	AD
ACTN2	102573	HCM 23 with or without LVNC DCM 1AA with or without LVNC	AD
AGL	610860	Glycogen storage disease III	AR
ALPK3	617608	HCM 27	AR
BRAF	164757	Cardiofaciocutaneous syndrome 1 Noonan syndrome 7	AD
CACNA1C	114205	Timothy syndrome LQTS 8	AD
CSRP3	600824	HCM 12	AD
DES	125660	Myofibrillar myopathy 1	AD/AR
		DCM 1I	AD
FHL1	300163	Emery-Dreifuss muscular dystrophy 6 Reducing body myopathy 1B Uruguay faciocardiomusculoskeletal syndrome	XL
FLNC	102565	HCM 26 Restrictive cardiomyopathy 5 Distal myopathy 4	AD
GAA	606800	Glycogen storage disease II (Pompe)	AR
GLA	300644	Fabry disease	XL
HRAS	190020	Costello syndrome	AD
JPH2	605267	HCM 17	AD
KRAS	190070	Cardiofaciocutaneous syndrome 2 Noonan syndrome 3	AD

AD, autosomal dominant; AR, autosomal recessive; DCM, dilated cardiomyopathy; LQTS, long QT syndrome; LVNC, left ventricular noncompaction; XL, X-linked

Gene	MIM #	Associated Disorder(s)	Inheritance
LAMP2	309060	Danon disease	XL
MAP2K1	176872	Cardiofaciocutaneous syndrome 3	AD
MAP2K2	601263	Cardiofaciocutaneous syndrome 4	AD
MYBPC3	600958	HCM 4 DCM 1MM	AD
MYH7	160760	HCM 1 DCM 1S	AD
		Myosin storage myopathy	AR
MYL2	160781	HCM 10	AD
MYL3	160790	HCM 8	AD
NRAS	164790	Noonan syndrome 6	AD
PLN	172405	HCM 18 DCM 1P	AD
PRKAG2	602743	Lethal congenital glycogen storage disease of heart HCM 6 Wolff-Parkinson-White syndrome	AD
PTPN11	176876	Noonan syndrome 1 LEOPARD syndrome 1	AD
RAF1	164760	Noonan syndrome 5 DCM 1NN LEOPARD syndrome 2	AD
RIT1	609591	Noonan syndrome 8	AD
SOS1	182530	Noonan Syndrome 4	AD
TNNC1	191040	HCM 13 DCM 1Z	AD
TNNI3	191044	HCM 7 Restrictive cardiomyopathy 1 DCM 1FF	AD

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Gene	MIM #	Associated Disorder(s)	Inheritance
		DCM 2A	AR
TNNT2	191045	HCM 2 Restrictive cardiomyopathy 3 DCM 1D	AD
TPM1	191010	HCM 3 DCM 1Y	AD
TTR	176300	Transthyretin-related amyloidosis	AD

AD, autosomal dominant; AR, autosomal recessive; DCM, dilated cardiomyopathy; LQTS, long QT syndrome; LVNC, left ventricular noncompaction; XL, X-linked

References

1. Ingles J, Goldstein J, Thaxton C, et al. Evaluating the clinical validity of hypertrophic cardiomyopathy genes. *Circ Genom Precis Med*. 2019;12(2):e002460.

2. Cirino AL, Ho C. Hypertrophic cardiomyopathy overview. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2022. [Updated: Jun 2021; Accessed: Mar 2022]

3. Lopes LR, Murphy C, Syrris P, et al. Use of high-throughput targeted exome-sequencing to screen for copy number variation in hypertrophic cardiomyopathy. *Eur J Med Gene*t. 2015;58(11):611-616.

Additional Resources

Hershberger RE, Givertz MM, Ho CY, et al. Genetic evaluation of cardiomyopathy–a Heart Failure Society of America practice guideline. *J Card Fail*. 2018;24(5):281-302.

Related Information

Dilated Cardiomyopathy Panel, Sequencing
Noonan Spectrum Disorders Panel
Cardiomyopathy and Arrhythmia Panel, Sequencing and Deletion/Duplication
Familial Transthyretin Amyloidosis (TTR) Sequencing

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