

Hypertrophic Cardiomyopathy Resequencing Array

TO DETERMINE THE ETIOLOGY OF HYPERTROPHIC CARDIOMYOPATHY (HCM) IN AFFECTED INDIVIDUALS

Disease Overview

- Hypertrophic cardiomyopathy (HCM) is a heterogeneous disorder of the myocardium characterized by left ventricular hypertrophy, predominantly involving the interventricular septum, in the absence of chamber expansion.
- Histopathologic findings include enlarged, disorganized myocytes, which die prematurely. This leads to cardiac fibrosis.
- Clinical symptoms are highly variable and may include: dyspnea, chest pain, palpitations, arrhythmias, and syncope.
- HCM is the most common cause of sudden death in healthy young individuals.
- Non-genetic factors such as lifestyle, sex, and age have a role in modulating clinical presentation.
- An abnormal electrocardiogram signal due to muscle thickening and disorganization is seen in the majority of HCM patients. Confirmation of a suspected diagnosis is achieved using echocardiogram.
- Establishing care with a cardiologist familiar with HCM is recommended for patients or presymptomatic mutation carriers.

Epidemiology

- Prevalence: one in 500 in the United States.
- Frequency of HCM is equal between sexes and among ethnic groups.
- Most common single-gene cardiac disorder.

Genetics

- Autosomal dominant.
- Sporadic occurrence is relatively rare.
- Genetic heterogeneity is present, as mutations in numerous genes encoding sarcomere proteins cause hypertrophic remodeling. Furthermore, gene mutations causing syndromic glycogen storage diseases may also be implicated.
- Many HCM mutations exert dominant-negative effects as the stable, but defective, polypeptides produced are incorporated into cardiac myofilaments that disrupt normal sarcomere function.
- Double heterozygosity for genes encoding sarcomere proteins has been reported and may be associated with more significant ventricular hypertrophy than in carriers of a single HCM gene mutation.
- The majority of HCM mutations (approximately 80 percent) occur in two genes: *MYH7* and *MYBPC3*.
- Several genotype/phenotype correlations for *MYH7*, *TNT2*, and *MYBPC3* have been established and may be helpful in predicting prognosis.
- The table (upper right) describes the genes included on the HCM resequencing array.

Gene Symbol	Gene Name	Locus	
Sarcomere protein encoding genes	<i>MYH7</i>	β-cardiac myosin-heavy chain	14q12
	<i>MYBPC3</i>	Cardiac myosin-binding protein C	11p11.2
	<i>TNT2</i>	Troponin T	1q32
	<i>TNI3</i>	Troponin I	19q13.4
	<i>TPM1</i>	α-tropomyosin	15q22.1
	<i>MYL2</i>	Myosin-regulatory light chain	12q23-q24.3
	<i>MYL3</i>	Myosin-regulatory light chain	3p
	<i>ACTC</i>	α-cardiac actin	15q14
Metabolic cardiomyopathy	<i>LAMP2</i>	Lysosomal-associated membrane protein 2	Xq24
	<i>PRKAG2</i>	5-AMP-activated protein kinase, gamma-2 subunit	7q35-q36
	<i>GLA</i>	α-galactosidase a	Xq22

Indications for Ordering

Diagnostic testing for patients with clinical features of HCM.

Contraindications

- Screening for an HCM-associated mutation previously identified in a family member.
- Prenatal testing.

Additional Ordering Notes

If there is a positive family history of HCM, please provide information on the relationship of the affected family member(s) to the individual being tested.

Interpretation

- Positive: At least one known deleterious gene mutation was detected predicting HCM.
- Negative: No known deleterious mutations were detected, reducing the possibility of a genetic cause of cardiomyopathy.
- Gene sequencing may reveal novel mutation(s); thus, the determination of clinical significance (benign or deleterious) may be unclear.

Limitations

- Mutations in genes not included on the sequencing array will not be detected.
- Large deletions, deep intronic mutations, and promoter mutations will not be detected.
- Analytical sensitivity may be compromised by rare primer-site mutations.

Methodology

- Oligonucleotide hybridization-based DNA sequencing of the coding regions and intron-exon boundaries of the *MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*, *TPM1*, *ACTC*, *MYL2*, *LAMP2*, *PRKAG2*, and *GLA* genes using an Affymetrix GeneChip platform. The chip includes probes specific for 760 known variants, largely indels, within the targeted genes. Additional sequencing of the coding regions and intron-exon boundaries of *MYBPC3* is performed on all samples due to the high rate of indels. Confirmatory sequencing is performed for positive and ambiguous results.

- Clinical sensitivity is 40 percent for isolated cases of HCM and 66 percent for cases with a positive family history of either HCM or sudden cardiac death.
- Analytic sensitivity is 98 percent.
- The test is performed by Harvard Medical School and Partners Healthcare Laboratory for Molecular Medicine.

Related Test

Hypertrophic Cardiomyopathy, Familial Mutation (0093482)

References

1. Morita H, et al. Genetic causes of human heart failure. *J Clin Invest* 2005;115:518–26.
2. Maron BJ, et al. Contemporary definitions and classification of the cardiomyopathies. *Circulation* 2006;113:1807–16.
3. Richard P, et al. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. *Circulation* 2003;17:2227–32.
4. Bashyam MD, et al. Molecular genetics of familial hypertrophic cardiomyopathy (FHC). *J Hum Genet* 2003;48:55–64.

Test Information

0093484

Hypertrophic Cardiomyopathy Microarray, 11 Genes

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.