



Test Information Sheet

Cardiology Genetics: Hypertrophic Cardiomyopathy (HCM) Panel

Also known as: Idiopathic Hypertrophic Subaortic Stenosis (IHSS), Hypertrophic Obstructive Cardiomyopathy (HOCM)

Mendelian Inheritance in Man Number: [192600](#)

Clinical Features:

Hypertrophic cardiomyopathy (HCM) is characterized by myocardial hypertrophy in the absence of other cardiac or systemic causes. It is the most common genetic cardiovascular disease, often caused by mutations in genes encoding for the sarcomeric proteins in the cardiac muscle.^{1,2} HCM has a variable clinical presentation; ranging from asymptomatic to sudden death. The prevalence of HCM in the general population is 0.2% or 1/500, affecting males and females equally.²

The initial presentation of HCM can be as benign as a heart murmur noted on a physical examination, while other patients may present with symptoms of palpitations, chest pain, heart failure or syncope. HCM is most commonly characterized by left ventricular hypertrophy (LVH) on echocardiogram.

Inheritance Pattern: Autosomal dominant; an affected individual with a disease-causing mutation has a 50% chance of transmitting this mutation to a child.

Genetics:

Approximately 50% of adult patients diagnosed with HCM have at least one relative with HCM or sudden death at a young age (e.g. < 30 years of age). However, a positive family history can be elicited only in 20% of children with early-onset HCM.³ With the help of molecular genetic studies it is possible to identify asymptomatic family members at risk for HCM. HCM is a genetically heterogeneous condition and to date, mutations in 17 genes have most commonly been identified in adult HCM patients: MYH7, TNNT2, MYBPC3, TNNI3, TPM1, ACTC, MYL3, MYL2, LAMP2, PRKAG2, GLA, CAV3, MTTG, MTTI, MTTK, TNNC1 and TTR.⁴

Etiology:

Hypertrophic cardiomyopathy can be caused by mutations in genes coding for sarcomeric proteins of the heart muscle, and their regulators and interaction partners. The sarcomere is formed by thick and thin filaments, which build a fundamental structural and functional, contractile unit of the heart muscle. Muscle contraction is achieved by sliding and interdigitating the thick and thin filaments. This mechanism is dependent on complex interactions between the sarcomeric proteins and is regulated by calcium via the troponin–tropomyosin complex.⁵ The following contractile proteins are involved: myosin-binding protein C (MYBPC3), regulatory and essential light chains (MYL2, MYL3), β -myosin heavy chain (MYH7) (thick filament), actin (ACTC), tropomyosin (TPM1), troponin I (TNNI3), and troponin T (TNNT2) (thin filament). Another important regulator and binding partner is caveolin 3 (CAV3). Other genes that can cause HCM through metabolic effects on the cardiac myocyte include noncatalytic AMP-activated protein kinase gamma 2 (PRKAG2), lysosome-associated membrane protein 2 (LAMP2), galactosidase alpha (GLA), mitochondrial transfer RNA glycine/isoleucine/lysine (MTTG, MTTI, MTTK), and transthyretin (TTR).

Reasons for Referral:

1. Confirmation of clinical diagnosis in symptomatic patients
2. Risk assessment of asymptomatic family members of a proband with HCM
3. Genetic counseling and recurrence risk calculation
4. Differentiation of hereditary HCM from heart disease due to other causes, such as Athlete's Heart
5. Differentiation of hereditary HCM associated with mutations in sarcomeric genes from phenocopies, such as Fabry Disease and Amyloidosis
6. Prenatal diagnosis in families with a known mutation

Test Method:

Using genomic DNA obtained from blood (2-5 mL in EDTA), approximately 150 exons of the 17 genes including their splice junctions are sequenced using a novel solid-state sequencing-by-synthesis process that allows sequencing a large number of amplicons in parallel.¹⁰ For analysis, DNA sequence is assembled and compared to the published genomic reference sequences. The presence of any potentially disease-associated sequence variant(s) is confirmed by conventional dideoxy DNA sequence analysis. A reference library of almost 800 alleles is used to evaluate the allele frequency of novel sequence variants if indicated. If appropriate, testing of one affected relative or, if not available, of both biological parents, is performed to clarify variants of unknown significance at no additional charge.

Test Sensitivity:

Approximately 60%-70% of individuals with a clinical diagnosis of HCM are expected to harbor a disease-causing mutation in one or more of the genes tested in this panel. The technical sensitivity of this test is estimated to be 98%.

Specimen Requirements and Shipping/Handling:

- **Blood:** A single tube with 2-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping.
- **Buccal Brushes: Not accepted**
- **Other Specimens:** Contact us for specific inquiries and specimen requests.
- **Prenatal Diagnosis:** Available only if a familial mutation has been identified. Contact us for more information.

Required Forms:

- Cardiology Sample Submission (Requisition) Form – complete all pages
- Payment Options Form or Institutional Billing Instructions
- We highly recommend submitting relevant clinical information (ECG/Echo/MRI Reports, etc) with specimens.

CPT Codes and Turn-Around-Times:

Test #	Description	CPT codes	Turnaround time
333	HCM panel in a new patient	83891x1, 83900x1, 83901x51, 83904x51, 83909x3, 83912x1	Approx. 8 weeks
901	DNA testing of a relative for a single known mutation	83891x2, 83898x2, 83894x2, 83904x4, 83892x2, 83912x2	Approx. 3 weeks
902	Prenatal diagnosis for a known mutation	83891x5, 83898x10, 83894x5, 83904x10, 83892x2, 83912x5	Approx. 2 weeks

Possible ICD9 Codes: Hypertrophic Cardiomyopathy, Idiopathic: 425.1
 Hypertrophic Cardiomyopathy, Familial: 425.4
 Metabolic Cardiomyopathy: 425.7
 Syndromic Cardiomyopathy: 425.8
 Family member is a carrier of a genetic disease: V18.9

References Cited:

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