

Hypertrophic Cardiomyopathy via *MYBPC3* Gene Sequencing -- Test # 173

Brief Description of Clinical Features: Hypertrophic cardiomyopathy (HCM, OMIM # 192600) is a primary disease of the cardiac muscle characterized by idiopathic hypertrophy of the left ventricle, although hypertrophy of the right ventricle may occur occasionally (Fifer and Vlahakes *Circulation* 117:429-439, 2008). HCM is distinguished by an extensive clinical variability between individuals with regards to the age of onset, pattern and extent of hypertrophy, and prognosis. Symptoms include dyspnea, exercise intolerance, chest pain, palpitations, arrhythmia, atrial fibrillation, syncope and sudden death (Maron et al. *N Engl J Med* 316:780-789, 1987). Additional features include left ventricular outflow tract obstruction, which is associated with increased risk for heart failure and cardiovascular death (Ommen et al. *J Am Coll Cardiol* 46:470-476, 2005). HCM affects 1 in 500 people worldwide (Maron et al. *Circulation*, 92:785-789, 1995). See also the Hypertrophic Cardiomyopathy Association (<http://www.4hcm.org/>) and (Cirino and Ho, *GeneReviews*, 2009, www.genetests.org).

Genetics: HCM is a heterogeneous genetic disease that is inherited in an autosomal dominant manner. It is caused by mutations in various genes that encode sarcomeric proteins. Defects in twelve genes, including *MYBPC3* (Bonne et al. *Nat Genet* 11:438-440, 1995; Watkins *Nat Genet* 11:434-437, 1995), account for approximately 60% of all HCM cases. Mutations were identified in both familial and sporadic cases, with similar distribution. Mutations identified in sporadic cases were either nonpenetrant or *de novo*. Some patients with severe phenotype were shown to have more than one mutation, either in two different genes or in the same gene (Richard et al. *Circulation* 107:2227-2232, 2003). At least 220 different *MYBPC3* causative mutations were reported in patients with HCM. The vast majority of mutations consist of missense, nonsense and small deletions or insertions (<http://www.biobase-international.com>). Compound heterozygous mutations in the *MYBPC3* gene were reported in two unrelated patients with severe neonatal hypertrophic cardiomyopathy, who died in infancy (Lekanne-Deprez et al. *J Med Genet* 43:829-832, 2006).

Description of This Particular Test: The *MYBPC3* gene encodes the cardiac isoform of myosin binding protein-C that is expressed exclusively in heart. This test involves bidirectional DNA sequencing of all 34 coding exons and splice sites of the *MYBPC3* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced.

Reference Sequences: Genomic: NC_000011.9 mRNA: NM_000256.3 Protein: NP_000247.2

Indications for Test: All patients with symptoms suggestive of HCM (OMIM 192600) as described above.

Sensitivity of Test: This test allows the detection of mutations in roughly 25% of patients with HCM (~40% of patients with detectable mutations) (Richard et al. *Circulation* 107:2227-2232, 2003).

Turn Around Time: Maximum of 40 days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of *MYBPC3* Gene, Exons 1-34 \$ 1460

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x31	83898 \$ 480	Sequencing x31	83904 \$ 720
Separation x1	83894 \$ 90	Interpretation/Report x1	83912 \$ 100

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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