

Hypertrophic Cardiomyopathy and other MYH7-Related Disorders via MYH7 Gene Sequencing -- Test # 172

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 1/500 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 *MYH7* (Geisterfer-Lowrance et al. *Cell* 62:999-1006, 1990), 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* (Richard et al. *Circulation* 107:2227-2232, 2003). Over 230 different *MYH7* causative mutations were reported in patients with HCM. Although over 90% of mutations are missense resulting in amino acid changes, rare cases of splice mutations, small deletions, indels, gross deletions and rearrangements have been reported. In addition to HCM, heterozygous *MYH7* mutations were found in patients with dilated cardiomyopathy (DCM1S) (Kamisago et al. *N Engl J Med* 343:1688-1696, 2000), noncompaction cardiomyopathy (NCCM) (Hoedemaekers et al. *Eur Heart J* 28:2732-2737, 2007), distal myopathy (MPD1) (Meredith et al. *Am J Hum Genet* 75:703-708, 2004), myosin storage myopathy/hyaline body myopathy (Tajsharghi et al. *Ann Neurol* 54:494-500, 2003), scapuloperoneal myopathy (SPMM) (Pegoraro et al. *Neuromuscul Disord* 17:321-329, 2007) and patients with distal myopathy and cardiomyopathy (Darin et al. *Neurology* 68:2041-2042, 2007).

Description of This Particular Test: The *MYH7* gene encodes the beta-myosin heavy chain. This test involves bidirectional DNA sequencing of all 38 coding exons and splice sites of the *MYH7* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced.

Reference Sequences: Genomic: NC_000014.8 mRNA and protein: CCDS 9601.1

Indications for Test: Patients with symptoms suggestive of HCM (OMIM 192600), DCM1S (OMIM 160760), (NCCM), MPD1 (OMIM 160500), myosin storage myopathy (OMIM 608358), SPMM (OMIM 181430) and patients with distal myopathy and cardiomyopathy (<http://www.ncbi.nlm.nih.gov/omim/>).

Sensitivity of Test: This test will detect mutations in roughly 25% of patients with HCM (~40% of patients with detectable mutations) (Richard et al. 2003) and 5%-8% of patients with DCM (Hershberger et al. *GeneReviews*, 2009).

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 *MYH7* Gene, Exons 3-40 **\$ 1640**

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x36	83898 \$ 550	Sequencing x36	83904 \$ 830
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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