

## Hypertrophic Cardiomyopathy via MYL3 Gene Sequencing -- Test #176

**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](http://www.genetests.org)).

**Genetics:** HCM is inherited in an autosomal dominant manner. It is caused by mutations in various genes, most of which encode sarcomeric proteins. Defects in twelve genes, including *MYL3* (Poetter et al. *Nat Genet* 13:63-69, 1996), 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 in other family members or occurred *de novo* (Richard et al. *Circulation* 107:2227-2232, 2003). To date, about 10 *MYL3* mutations have been reported in patients with HCM. These were nearly all missense, although one splicing mutation was also reported. *MYL3* mutations were detected in HCM patients with diverse ethnic background and may result in various phenotypes, even within members of the same family. The first HCM patients identified with *MYL3* mutations resemble those with *MYL2* mutations. Both groups of patients presented with a distinct phenotype that involved mid-cavity obstruction. However, additional *MYL3* mutations were reported in patients with the classical form of HCM (Lee et al. *Am Heart J* 141:184-189, 2001).

**Description of This Particular Test:** The *MYL3* gene encodes the essential light chain of human cardiac myosin. This test involves bidirectional DNA sequencing of all 6 coding exons and splice sites of the *MYL3* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. The *MYL3* gene is also included within our HCM gene panel (see Test #190).

**Reference Sequences:** Genomic: **NC\_000003.11** mRNA and protein: **CCDS 2746.1**

**Indications for Test:** All patients with symptoms suggestive of HCM with or without mid-cavity obstruction.

**Sensitivity of Test:** About 1% of HCM patients who have known causative mutations have mutations in *MYL3* (Hershberger et al. *Circ Heart Fail* 2:253-261, 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 *MYL3* Gene, Exons 1- 6 \$ 450

**CPT Codes:**

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x 5	83898 \$ 120	Sequencing x 5	83904 \$ 170
Separation x1	83894 \$ 30	Interpretation/Report x1	83912 \$ 60

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

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