

## Hypertrophic Cardiomyopathy via ACTN2 Gene Sequencing -- Test #198

**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/>).

**Genetics:** HCM is a heterogeneous genetic disease that 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: *MYBPC3*, *MYH7*, *TNNT2*, *TNNI3*, *TPM1*, *MYL2*, *MYL3*, *ACTC1*, *CSRP3*, *TTN*, *MYH6* and *TCAP* account for approximately 90% of HCM cases with detectable mutations (Cirino and Ho, *GeneReviews*, 2009, [www.genetests.org](http://www.genetests.org)). In addition to these 12 genes, several genes have been shown to be rarely mutated in HCM patients. These include the *ACTN2* gene. To date, four different *ACTN2* missense mutations, within various domains of the protein, have been reported in familial HCM (Chiu et al., published online ahead of print December 29 2009, *J Am Coll Cardiol*). Additionally, one missense mutation, Gln9Arg, has been previously reported in a patient with dilated cardiomyopathy (Mohapatra et al. *Mol Genet Metab* 80:207-215, 2003).

**Description of This Particular Test:** The *ACTN2* gene encodes alpha-actinin-2, a component of the sarcomere Z-disc. As required, this test involves bidirectional DNA sequencing of all 21 coding exons and splice sites of the *ACTN2* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced.

**Reference Sequences:** Genomic: **\_000001.10** mRNA: **\_001103.2** Protein: **NP\_001094.1 (CCDS 1613.1)**

**Indications for Test:** Patients with symptoms suggestive of HCM and no mutations in the primary HCM genes, and patients with DCM.

**Sensitivity of Test:** This test allows the detection of mutations in rare cases of HCM patients and in less than 1% of patients with DCM (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 Requisition Form.

**Price:                      Sequencing of ACTN2 Gene, Exons 1-21                      \$1090**

**CPT Codes:**

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x21	83898 \$ 330	Sequencing x21	83904 \$ 490
Separation x1	83894 \$ 90	Interpretation/Report x1	83912 \$ 110

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

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