

Hypertrophic Cardiomyopathy and Related Disorders *via ACTC1 Gene Sequencing -- Test #174*

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 inherited in an autosomal dominant manner. It is caused by mutations in various genes that encode sarcomeric proteins. Defects in twelve genes, including *ACTC1* (Mogensen et al. *J Clin Invest* 103:R39-43, 1999), 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 family members or *de novo*. Some patients were shown to have more than one mutation, either in two different genes or in the same gene. These patients presented with an early onset hypertrophy and severe phenotype (Richard et al. *Circulation* 107:2227-2232, 2003). To date, 10 different *ACTC1* missense mutations were reported in patients with HCM. In addition to HCM, *ACTC1* mutations have been implicated in dilated cardiomyopathy (DCM) (Olson et al. *Science* 280:750-752, 1998), childhood restrictive cardiomyopathy (RCM) (Kaski et al. *Heart* 94:1478-1484, 2008) and atrial septal defect (ASD5) (Matsson et al. *Hum Mol Genet* 17:256-265, 2008).

Description of This Particular Test: The *ACTC1* gene encodes alpha cardiac actin protein, a contractile element of the cardiac muscle fibers. This test involves bidirectional DNA sequencing of all 6 coding exons and splice sites of the *ACTC1* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced.

Reference Sequences: Genomic: **NC_000015.9** mRNA and Protein: **CCDS 10041.1**

Indications for Test: Patients with symptoms suggestive of HCM (OMIM 192600), RCM (OMIM 115210), DCM (OMIM 601494) and ASD5 (OMIM 612794).

Sensitivity of Test: *ACTC1* pathogenic mutations are rare. Perhaps 1% of HCM patients with known causative mutations have mutations in *ACTC1* (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 *ACTC1* Gene, Exons 2-7** **\$ 530**

CPT Codes:

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x7	83898	\$130	Sequencing x7	83904	\$190
Separation x1	83894	\$ 60	Interpretation/Report x1	83912	\$ 80

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

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