

Hypertrophic Cardiomyopathy and Related Disorders via *TNNI3* Gene Sequencing -- Test #178

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, most of which encode sarcomeric proteins. Defects in twelve genes, including *TNNI3* (Kimura et al. *Nat Genet* 16:379-382, 1997) accounted 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 occurred *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). To date, about 30 different *TNNI3* causative mutations have been reported in patients with HCM. Except for 2 small deletions and one 33 bp-deletion in exon 8, all mutations were missense resulting in amino acid changes. In addition to HCM, *TNNI3* mutations have been implicated in familial restrictive cardiomyopathy RCM (Mogensen et al. *J Clin Invest* 111:209-216, 2003) and dilated cardiomyopathy DCM (Carballo et al *Circ Res* 105:375-382, 2009).

Description of This Particular Test: The *TNNI3* gene encodes the troponin I subunit, which is one of the 3 subunits that form the troponin complex of the thin filaments of striated muscles. Troponin I is exclusively expressed in cardiac muscle. As required, this test involves bidirectional DNA sequencing of all 8 coding exons and splice sites of the *TNNI3* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced.

Reference Sequences: Genomic: **NC_000019.9** mRNA: **NM_000363.4** Protein: **NP_000354.4 (CCDS 42628.1)**

Indications for Test: Patients with symptoms suggestive of HCM (OMIM 192600), RCM (OMIM 612422), and DCM (OMIM 601494).

Sensitivity of Test: This test will detect mutations in ~5% of patients with HCM (Cirino and Ho, GeneReviews, 2009, www.genetests.org). Sensitivity of this test for RCM and DCM is not known.

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 *TNNI3* Gene, Exons 1-8 \$ 570

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x8	83898 \$ 150	Sequencing x8	83904 \$ 220
Separation x1	83894 \$ 50	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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