

Hypertrophic Cardiomyopathy via VCL Gene Sequencing -- Test #144

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 12 genes: *MYBPC3*, *MYH7*, *TNNT2*, *TNNI3*, *TPM1*, *MYL2*, *MYL3*, *ACTC1*, *CSRP3*, *TTN*, *MYH6* and *TCAP* account for approximately 90% of HCM cases that have detectable mutations (Cirino and Ho, *GeneReviews*, 2009, www.genetests.org). In addition to these 12 genes, several genes have been shown to be rarely mutated in HCM patients. These include the *VCL* gene. To date, one missense mutation in exon 7 of the *VCL* gene, p.Leu277Met, was reported in one patient with severely obstructive, mid-ventricular hypertrophy (Vasile et al. *Biochem Biophys Res Commun* 345:998-1003, 2006). *VCL* mutations were also reported in patients with dilated cardiomyopathy (DCM) (Olson et al. *Circulation* 105:431-437, 2002).

Description of This Particular Test: The *VCL* gene encodes vinculin, a cytoskeletal protein. As required, this test involves bidirectional DNA sequencing of all 22 coding exons and splice sites of the *VCL* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. We will perform targeted sequencing of exon 7 or any other single exon.

Reference Sequences: Genomic: NC_000010.10 mRNA: NM_014000.2 Protein: NP_054706.1 (CCDS 7341.1)

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 (Hershberger et al. *Circ Heart Fail* 2:253-261, 2009). The frequency of *VCL* mutations in DCM patients is unknown (Gordon et al. *GeneReviews*, 2009, www.genetests.org).

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 *VCL* Gene, Exons 1-22 \$ 1170

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x23	83898 \$ 360	Sequencing x23	83904 \$ 540
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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