Cincinnati Children's
Heart Institute

Heart Institute Diagnostic Lab
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Shipping Instructions

Please enclose a test requisition form with sample. All information must be complete before sample can be processed. Samples may be shipped at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship To:

Cincinnati Children's
Hospital Medical Center
Attn: Heart Institute Diagnostic Lab
240 Albert Sabin Way,
Room S4.381
Cincinnati, OH 45229-3039

MYBPC3 - Hypertrophic Cardiomyopathy Testing

Hypertrophic Cardiomyopathy (HCM) is relatively common, with a prevalence of 1 in 500 adults (1). HCM is a primary disorder of heart muscle characterized by left ventricular hypertrophy. The most classic finding in HCM is asymmetric septal hypertrophy, with or without left ventricular outflow tract obstruction. The disease demonstrates extensive clinical variability with regard to age of onset, severity and progression of disease. HCM can affect infants and children although it is more typically identified in adolescence or adulthood (2,3). The *MYBPC3* gene codes for cardiac myosin binding protein C. Phosphorylation of this protein modulates contraction and is an important component of the sarcomere (4). The *MYBPC3* gene contains 35 exons and is located at chromosome 11p11.2.

Up to 40% of individuals with a clinical diagnosis of HCM have *MYBPC3* mutations (2). *MYBPC3* mutations are inherited in an autosomal dominant manner. The majority of individuals inherit the *MYBPC3* from a parent, although *de novo* mutations do occur.

Mutations in *MYBPC3* and *MYH7* genes are the most common causes of HCM. However, the disease is genetically heterogeneous and sequencing additional genes should be considered if familial HCM is suspected or the underlying etiology remains unknown. Approximately 50-65% of individuals with a known or suspected diagnosis of familial HCM have a mutation in one of a number of genes encoding components of the sarcomere and cytoskeleton (3). Compound heterozygous mutations have been reported in *MYBPC3* and other genes associated with HCM (5). Mutations in the *MYBPC3* gene have been primarily associated with HCM, but can also be associated with other types of heart muscle disease including dilated cardiomyopathy, restrictive cardiomyopathy and left-ventricular non-compaction (6).

Indication

MYBPC3 testing is utilized to confirm a diagnosis of HCM in patients with clinically evident disease. Genetic testing also allows for early identification and diagnosis of individuals at greatest risk prior to the expression of typical clinical manifestations. If a mutation is identified in an asymptomatic individual, regular and routine outpatient follow up is indicated. If clinically unaffected members of a family with an identified mutation for HCM are found not to carry that mutation, they can be definitely diagnosed as unaffected and reassured that neither they nor their children will be at higher risk compared to the general population to develop symptoms related to HCM. A negative test result in an individual with a known familial mutation also eliminates the need for routine follow up.

Methodology:

All 35 exons of the *MYBPC3* gene, as well as the exon/intron boundaries and a portion of untranslated regions of the gene are amplified by PCR. Genomic DNA sequences from both forward and reverse directions are obtained by automatic fluorescent detection using an *ABI PRISM® 3730 DNA Analyzer*. Sequence variants different from National Center for Biotechnology Information GenBank references are further evaluated for genetic significance. If a mutation is identified, a known familial mutation analysis will be available for additional family members.

Sensitivity & Accuracy:

Greater than 98.5% of the mutations in exon 1-35 of *MYBPC3* are detectable by sequence based methods. Sequencing does not detect deletions or duplications. Mutations in *MYBPC3* account for up to 40% of cases of idiopathic hypertrophic cardiomyopathy.

References:

1. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the cardia study. Coronary artery risk development in (young) adults. *Circulation*. 1995;92:785-789.

2. Kaski JP, Syrris P, Esteban MT, Jenkins S, Pantazis A, Deanfield JE, McKenna WJ, Elliott PM. Prevalence of sarcomere protein gene mutations in preadolescent children with hypertrophic cardiomyopathy. *Circulation Cardiovascular Genetics*. 2009;2:436-441.

3. Morita H, Rehm HL, Menesses A, McDonough B, Roberts AE, Kucherlapati R, Towbin JA, Seidman JG, Seidman CE. Shared genetic causes of cardiac hypertrophy in children and adults. *The New England Journal of Medicine*. 2008;358:1899-1908.

4. van Dijk SJ, Dooijes D, dos Remedios C, Michels M, Lamers JM, Winegrad S, Schlossarek S, Carrier L, ten Cate FJ, Stienen GJ, van der Velden J. Cardiac myosin-binding protein c mutations and hypertrophic cardiomyopathy: Haploinsufficiency, deranged phosphorylation, and cardiomyocyte dysfunction. *Circulation*. 2009;119:1473-1483.

5. Van Driest SL, Vasile VC, Ommen SR, Will ML, Tajik AJ, Gersh BJ, Ackerman MJ. Myosin binding protein c mutations and compound heterozygosity in hypertrophic cardiomyopathy. *Journal of the American College of Cardiology*. 2004;44:1903-1910.

6. Hershberger RE, Norton N, Morales A, Li DX, Siegfried JD, Gonzalez-Quintana J. Coding sequence rare variants identified in *MYBPC3, MYH6, TPM1, TNNC1*, and *TNNI3* from 312 patients with familial or idiopathic dilated cardiomyopathy. *Circulation-Cardiovascular Genetics*. 2010;3:155-161.

Specimen:

Peripheral blood in EDTA tube
Adult: 5-10mL
Child: 3-5mL
Infant: 1-3mL
For other specimen types, please contact Amy Shikany at 513-803-3317

Turnaround Time:

Full Mutation Analysis 4-6 weeks
Known Mutation Analysis 1-2 weeks

CPT Codes:

Full Gene Sequencing	81407
Additional Family Members	81403