Cincinnati Children's
Heart Institute

Heart Institute Diagnostic Lab
CAP#: 7518730
CLIA#: 36D2003208
Phone: (513) 803-1751
Fax: (513) 803-1748
Email: HeartDx@cchmc.org

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

FBN1 – Marfan Syndrome

Marfan Syndrome (MS) is relatively common, with a prevalence of 1 in 5-10,000 individuals. The *FBN1* gene codes for fibrillin-1, a structural component of microfibrils. Microfibrils provide mechanical stability and elastic properties to connective tissues. Mutations in the *FBN1* gene can affect multiple organ systems with primary involvement of the skeletal, ocular and cardiovascular systems. The *FBN1* gene contains 65 exons and is located at chromosome 15q21.

Up to 90% of individuals with a clinical diagnosis of MS have *FBN1* mutations (1). *FBN1* mutations are inherited in an autosomal dominant manner. Approximately 75% of individuals with MS have an affected parent, and 25% have a *de novo* mutation.

Five to 21% of individuals with a known or suspected diagnosis of MS who did not have mutations in *FBN1* had mutations in *TGFBR2 (2,3)*. Loeys-Dietz syndrome (LDS) has been associated with mutations in both *TGFBR1* and *TGFBR2*. LDS is an autosomal dominant condition that has many vascular and skeletal features in common with MS. Craniofacial and cutaneous manifestations are also frequently present in individuals with LDS.

Indication

FBN1 testing is utilized to confirm a diagnosis of MS 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 and can be used for prenatal diagnosis. 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 MS are found not 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 MS. A negative test result in an individual with a known familial mutation also eliminates the need for routine follow up.

Methodology:

All 65 exons of the *FBN1* 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 member.

Sensitivity & Accuracy:

Greater than 98.5% of the mutations in exon 1-65 of *FBN1* are detectable by sequence based methods. Sequencing does not detect deletions or duplications. Mutations in *FBN1* account for up to 90% of cases of Marfan syndrome.

References:

1. Loeys B, De Backer J, Van Acker P, Wettinck K, Pals G, Nuytinck L, Coucke P, De Paepe A. Comprehensive molecular screening of the *FBN1* gene favors locus homogeneity of classical Marfan syndrome. *Human Mutation*. 2004;24:140-146.

2. Mizuguchi T, Collod-Beroud G, Akiyama T, Abifadel M, Harada N, Morisaki T, Allard D, Varret M, Claustres M, Morisaki H, Ihara M, Kinoshita A, Yoshiura K, Junien C, Kajii T, Jondeau G, Ohta T, Kishino T, Furukawa Y, Nakamura Y, Niikawa N, Boileau C, Matsumoto N. Heterozygous *TGFBR2* mutations in Marfan syndrome. *Nature Genetics*. 2004;36:855-860.

3. Sakai H, Visser R, Ikegawa S, Ito E, Numabe H, Watanabe Y, Mikami H, Kondoh T, Kitoh H, Sugiyama R, Okamoto N, Ogata T, Fodde R, Mizuno S, Takamura K, Egashira M, Sasaki N, Watanabe S, Nishimaki S, Takada F, Nagai T, Okada Y, Aoka Y, Yasuda K, Iwasa M, Kogaki S, Harada N, Mizuguchi T, Matsumoto N. Comprehensive genetic analysis of relevant four genes in 49 patients with Marfan syndrome or Marfan-related phenotypes. *American Journal of Medical Genetics A*. 2006;140:1719-1725.

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	81408
Additional Family Members	81403