Test Definition: MFBNG

FBN1 Full Gene Sequencing with Deletion/Duplication, Varies

Overview

Useful For

Providing a genetic evaluation for patients with a personal or family history suggestive of Marfan syndrome and other *FBN1*-related conditions

Establishing a diagnosis for Marfan syndrome and other *FBN1*-related conditions

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in the *FBN1* gene. See Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for Marfan syndrome or other *FBN1*-related conditions.

Prior Authorization is available for this assay.

Special Instructions

- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- Connective Tissue/Cerebrovascular Disease Genetic Testing Patient Information
- FBN1 Full Gene Analysis (MFBNG) Prior Authorization Ordering Instructions

Method Name

Sequence Capture and Targeted Next-Generation Sequencing followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing.

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

This is a single gene test for the *FBN1* gene. The *FBN1* gene is also included on multi-gene panels. If testing for multiple overlapping clinical presentations is desired, see MFRGG Marfan, Loeys-Dietz, and Aortopathy Gene Panel, Varies or CAORG / Comprehensive Marfan, Loeys-Dietz, Ehlers-Danlos, and Aortopathy Gene Panel, Varies.

Customization of this panel and single gene analysis for any gene present on this panel are available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Necessary Information

Prior Authorization is available, **but not required**, for this test. If proceeding with the prior authorization process, submit the required form with the specimen.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Any anticoagulant
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**
Specimen Stability Information: Ambient (preferred)/Refrigerated

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing (Spanish) (T826)
2. Connective Tissue/Cerebrovascular Disease Genetic Testing Patient Information
3. FBN1 Full Gene Analysis (MFBNG) Prior Authorization Ordering Instructions
4. If not ordering electronically, complete, print, and send a Cardiovascular Test Request Form (T724) with the specimen.

Specimen Minimum Volume

1 mL

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information

Fibrillin-1 is a 320 kDa, cysteine-rich glycoprotein found in the extracellular matrix. Monomers of fibrillin-1 associate to form microfibrils that provide mechanical stability and elastic properties to connective tissues. Fibrillin-1 is encoded by the *FBN1* gene, which contains 65 exons and is located at chromosome 15q21.

Disease-causing *FBN1* variants are most commonly associated with Marfan syndrome (MFS), an autosomal dominant connective tissue disease involving the ocular, skeletal, and cardiovascular systems. Ocular MFS manifestations most commonly include myopia and ectopia lentis (lens displacement). Skeletal manifestations can include arachnodactyly (abnormally long and slender fingers and toes), dolichostenomelia (long limbs), pectus (chest wall) deformity, and scoliosis. Cardiovascular manifestations, which are the major cause of early morbidity and mortality in MFS, include aortic aneurysm and dissection, as well as mitral valve and tricuspid valve prolapse.(1) The clinical diagnosis of Marfan syndrome is based on the revised Ghent nosology for the Marfan syndrome.(2) There may be significant inter- and intrafamilial variability in the MFS phenotype.

Disease-causing *FBN1* variants have also been reported in several other rare phenotypes with variable overlap with classic MFS.(3) In some cases, MFS may present in the neonatal period with severe, rapidly progressive disease (previously termed "neonatal Marfan syndrome"). Other *FBN1*-associated conditions include autosomal dominant ectopia lentis (displacement of the lens of the eye), isolated skeletal features of MFS, MASS phenotype (mitral valve prolapse, aortic diameter increased, stretch marks, skeletal features of MFS), autosomal dominant Weill-Marchesani syndrome (short stature, short fingers, ectopia lentis), Marfan lipodystrophy syndrome, and stiff skin syndrome.

Hundreds of disease-causing variants have been identified in *FBN1*, many of them unique to individual families. There is a wide range of variability, including intrafamilial variability, in expressivity among disease-causing *FBN1* variants. Approximately two-thirds of disease-causing *FBN1* variants are missense changes, with the majority of these being cysteine substitutions. Approximately 25% to 33% of disease-causing *FBN1* variants are *de novo*, in which an individual has no family history of disease. Disease-causing FBN1 variants have been shown to occur across the gene. Some genotype-phenotype correlations have been observed, including the association with truncating and splicing variants with risk for aortic dissection, cysteine-based variants associated with ectopia lentis, and severe, early onset MFS associated with variants in exons 24 through 32.(4-6)

Marfan syndrome has significant clinical overlap with a condition called Loeys-Dietz syndrome (LDS); however, the vascular phenotype of LDS can be more severe, and LDS has disease-causing variants in different genes (*TGFBR1, TGFBR2, SMAD2, SMAD3, TGFB2* and *TGFB3*). When the diagnosis of MFS, LDS, or a related disorder is suspected, the use of genetic testing is important to verify the diagnosis and provide appropriate clinical management. Single gene analysis of the *FBN1* gene may be appropriate when there is a very high index of suspicion for Marfan syndrome based on clinical presentation and Ghent diagnostic criteria, while multigene panel-based testing can be more appropriate when the differential diagnosis includes Marfan syndrome and additional, overlapping phenotypes. Confirmation of the genetic diagnosis also allows for preconception, prenatal, and family counseling.

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:
Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact the Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/Duplication Analysis:
This analysis targets single and multi-exon deletions/duplications; however, in some instances single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

Deletion/duplication events that extend past the genes included on the panel may occur. In these instances, genes included in the ordered test are provided on the report and interpreted, and genomic breakpoints are reported if they are confirmed. However, copy number variants for genes not listed in the Method Description are typically not reported or interpreted for haploinsufficiency/triplosensitivity. CMACB / Chromosomal Microarray, Congenital, Blood; WESPR /

Panel to Whole Exome Sequencing Reflex Test, Varies; or WGSDX / Whole Genome Sequencing for Hereditary Disorders, Varies is recommended for a full interpretation of deletions/duplications predicted to extend past the genes included on the panel.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants:
At this time, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time.

Variant Evaluation:
Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(7) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. Incidental findings may include, but are not limited to, results related to the sex chromosomes. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1 Dietz H: *FBN1*-related Marfan syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2001. Updated February 17, 2022. Accessed August 1, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1335/
2. Loeys BL, Dietz HC, Braverman AC, et al: The revised Ghent nosology for the Marfan syndrome. J Med Genet. 2010 Jul;47(7):476-485
3. OMIM. 134797 Fibrillin 1; FBN1. Johns Hopkins University; 1991. Updated November 12, 2020. Accessed August 1, 2022. Available at https://omim.org/entry/134797

4. Baudhuin LM, Kotzer KE, Lagerstedt SA: Increased frequency of FBN1 truncating and splicing variants in Marfan syndrome patients with aortic events. Genet Med. 2015 Mar;17(3):177-187. doi: 10.1038/gim.2014.91
5. Baudhuin LM, Kotzer KE, Lagerstedt SA: Decreased frequency of FBN1 missense variants in Ghent criteria-positive Marfan syndrome and characterization of novel FBN1 variants. J Hum Genet. 2015 May;60(5):241-252. doi: 10.1038/jhg.2015.10
6. Faivre L, Collod-Beroud G, Loeys BL, et al: Effect of mutation type and location on clinical outcome of 1,013 probands with Marfan syndrome or related phenotypes and FBN1 mutations: an international study. Am J Hum Genet. 2007;81(3):454-466. doi: 10.1086/520125
7. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May;17(5):405-424.

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of *FBN1*, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletion-insertions (delins) less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction-based quantitative method is performed to test for the presence of deletions and duplications in *FBN1*.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine content, and repetitive sequences.(Unpublished Mayo method)

The reference transcript for *FBN1* gene is NM_000138.4. Reference transcript numbers may be updated due to transcript re-versioning. Always refer to the final patient report for gene transcript information referenced at the time of testing. Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

PDF Report

Supplemental

Day(s) Performed

Varies

Report Available

28 to 42 days

Specimen Retention Time

Whole blood: 2 weeks (if available); Extracted DNA: 3 months

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

81408

Prior Auhtorization

Insurance preauthorization is available for this testing; forms are available.

Patient financial assistance may be available to those who qualify. Patients who receive a bill from Mayo Clinic Laboratories will receive information on eligibility and how to apply.

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
MFBNG	FBN1 Full Gene Analysis	77114-7

Result ID	Test Result Name	Result LOINC® Value
617366	Test Description	62364-5
617367	Specimen	31208-2
617368	Source	31208-2
617369	Result Summary	50397-9
617370	Result	82939-0
617371	Interpretation	69047-9
617372	Additional Results	82939-0
617373	Resources	99622-3
617374	Additional Information	48767-8
617375	Method	85069-3
617376	Genes Analyzed	48018-6
617377	Disclaimer	62364-5

617378	Released By	18771-6