Overview

Useful For
Aiding in the diagnosis of:

- *FBN1*-associated Marfan syndrome
- Autosomal dominant ectopia lentis
- Isolated ascending aortic aneurysm and dissection
- Isolated skeletal features of Marfan syndrome
- MASS phenotype (mitral valve prolapse, aortic diameter increased, stretch marks, skeletal features of MFS)-Shprintzen-Goldberg syndrome
- Autosomal dominant Weill-Marchesani syndrome

Genetics Test Information

This test uses next-generation sequencing (NGS) to evaluate for the presence of *FBN1* variants associated with Marfan syndrome (MFS) or other *FBN1*-associated conditions. Additionally, NGS is used to test for the presence of large deletions and duplications.

Prior Authorization is available for this assay; see Special Instructions.

Highlights

Pathogenic *FBN1* variants are most commonly associated with Marfan syndrome (MFS), but have also been reported in other rare phenotypes with variable overlap with classic MFS.

Approximately 25% to 33% of individuals with a pathogenic *FBN1* variant have no family history of disease due to the variant being de novo.

Genetic testing for pathogenic *FBN1* variants aids in the diagnosis of *FBN1*-associated MFS and other *FBN1*-associated conditions. Confirmation of 1 of these conditions allows for proper treatment, management, and genetic counseling.

Special Instructions

- Informed Consent for Genetic Testing
- Marfan and Related Disorders Patient Information
- FBN1. Full Gene Sequence Prior Authorization Ordering Instructions
- Informed Consent for Genetic Testing (Spanish)

Method Name

Custom Sequence Capture and Targeted Next-Generation Sequencing

NY State Available

Yes

Specimen
Specimen Type
Varies

Advisory Information
In cases where there are hallmark features of Marfan syndrome, in particular the combination of ectopia lentis and aortic aneurysm or dissection in a patient or their family, FBN1 analysis (this assay) may be an appropriate first step in testing. In cases with more nonspecific features, such as isolated ascending aortic aneurysm or isolated skeletal features of Marfan syndrome, MFRGP / Marfan Syndrome and Related Disorders Multi-Gene Panel, Varies may be the more appropriate test to choose. Professional clinical judgment should be used by the ordering clinician. A genetic consultation may be helpful in determining the appropriate testing strategy for your patient.

Targeted testing for familial variants (also called site-specific or known mutation testing) is available for this gene. See:

- KVAR1 / Known Variant Analysis-1 Variant, Varies
- KVAR2 / Known Variant Analysis-2 Variants, Varies
- KVAR3 / Known Variant Analysis-3+ Variants, Varies

Call 800-533-1710 to confirm the appropriate test for targeted testing.

Shipping Instructions
Specimen preferred to arrive within 96 hours of collection.

Necessary Information
1. Marfan and Related Disorders Patient Information (T636) is required, see Special Instructions. Testing may proceed without the patient information however it aids in providing a more thorough interpretation. Ordering providers are strongly encouraged to complete the form and send it with the specimen.

2. Include physician name and phone number with specimen.

Specimen Required
Prior Authorization is available for this test. Submit the required form with the specimen.

Submit only 1 of the following specimens:

Specimen Type: Whole blood

Container/Tube: Lavender top (EDTA)

Specimen Volume: 3 mL

Collection Instructions:
1. Invert several times to mix blood.
2. Send specimen in original tube.

Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated 14 days
Specimen Type: DNA

Container/Tube: 2 mL screw top tube

Specimen Volume: 100mcL (microliters)

Collection Instructions:

1. The preferred volume is 100 mcL at a concentration of 250 ng/mcL.

2. Include concentration and volume on tube.

Specimen Stability Information: Frozen (preferred)/Ambient/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 in Special Instructions:
   - Informed Consent for Genetic Testing (T576)
   - Informed Consent for Genetic Testing-Spanish (T826)

2. FBN1, Full Gene Sequence Prior Authorization Ordering Instructions in Special Instructions.

3. 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

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<tr>
<th>Specimen Type</th>
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<th>Time</th>
<th>Special Container</th>
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<tbody>
<tr>
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Clinical and Interpretive

Clinical Information

Fibrillin-1 is a 320-kD 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.

Pathogenic FBN1 variants are most commonly associated with Marfan syndrome (MFS), an autosomal dominant
connective tissue disorder involving the ocular, skeletal, and cardiovascular systems. Ocular MFS manifestations most commonly include myopia and lens displacement. Skeletal manifestations can include arachnodactyly (abnormally long and slender fingers and toes), doliostenomelia (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. There is significant inter- and intrafamilial variability in the MFS phenotype.

Pathogenic FBN1 variants have also been reported in several other rare phenotypes with variable overlap with classic MFS. 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), familial thoracic aortic aneurysm and dissection, isolated skeletal features of MFS, MASS phenotype (mitral valve prolapse, aortic diameter increased, stretch marks, skeletal features of MFS), Shprintzen-Goldberg syndrome (Marfanoid-craniosynostosis; premature ossification and closure of sutures of the skull), and autosomal dominant Weill-Marchesani syndrome (short stature, short fingers, ectopia lentis).

Hundreds of pathogenic 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 pathogenic FBN1 variants. Approximately two-thirds of pathogenic FBN1 variants are missense changes, with the majority of these being cysteine substitutions. Approximately 25% to 33% of pathogenic FBN1 variants are de novo, in which an individual has no family history of disease. Pathogenic 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, and ectopia lentis, and severe, early onset MFS and variants in exons 24 through 32.

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 is caused by pathogenic variants in different genes (TGFBR1, TGFBR2, SMAD3, and TGFB2). 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. Confirmation of the genetic diagnosis also allows for preconception, prenatal, and family counseling.

Reference Values

An interpretive report will be provided.

Interpretation

Evaluation and categorization of variants is performed using American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline.

Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

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 predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Unless reported or predicted to impact splicing, alterations found deep in the intron or alterations that do not result in an amino acid substitution are not reported.

Cautions

Absence of a pathogenic variant does not preclude the diagnosis of Marfan syndrome or other FBN1-associated
condition unless a specific pathogenic variant has already been identified in an affected family member.

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 family history of Marfan syndrome or a related disorder, it is often useful to first test an affected family member. Identification of a pathogenic variant in an affected individual would allow for more informative testing of at risk individuals.

Technical Limitations:

Next-generation sequencing may not detect all types of genetic variants. Additionally, rare polymorphisms may be present that could lead to false-negative or false-positive results. If results do not match clinical findings, consider alternative methods for analyzing these genes, such as Sanger sequencing or large deletion/duplication analysis. Please contact a genetic counselor, call 800-533-1710 to discuss alternative testing methods. If the patient has had an allogeneic blood or marrow transplant or a recent (ie, <6 weeks from time of sample collection) heterologous blood transfusion these results may be inaccurate due to the presence of donor DNA.

Reclassification of variants policy:

At this time, it is not standard practice for the laboratory to systematically review likely pathogenic variants or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

Contact the laboratory if additional information is required regarding the transcript or human genome assembly used for the analysis of the patient's results.

Clinical Reference


Performance
**Method Description**

Next-generation sequencing (NGS) is performed using an Illumina instrument with paired-end reads. The DNA is prepared for NGS using a custom Agilent SureSelect Target Enrichment System. Data is analyzed with a bioinformatics software pipeline for sequence variants and the presence of large intragenic deletions and duplications. Supplemental Sanger sequencing or qPCR may be performed occasionally in regions where NGS is insufficient for data capture or not specific enough to correctly identify a variant. Sanger sequencing or qPCR may also be used for confirmatory testing. (Unpublished Mayo method)

**PDF Report**

No

**Day(s) and Time(s) Test Performed**

Wednesday; Varies

**Analytic Time**

2 weeks (after prior authorization is granted)

**Maximum Laboratory Time**

4 weeks

**Specimen Retention Time**

Extracted DNA: 2 months

**Performing Laboratory Location**

Rochester

**Fees and 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 Regional Manager. 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. This test has not been cleared or approved by the U.S. Food and Drug Administration.

**CPT Code Information**

81408

**LOINC® Information**

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<th>Order LOINC Value</th>
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Prior Authorization

Insurance preauthorization is available for this testing; forms are available in Special Instructions.

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.