Marfan Syndrome (FBN1) Sequencing and Deletion/Duplication

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Marfan syndrome (MFS) is a connective tissue disorder that exhibits a high degree of clinical variability. Symptoms typically involve the cardiovascular, ocular, and skeletal systems. Early diagnosis is crucial for treatment of skeletal, orthopedic, and cardiovascular abnormalities to enable affected individuals to approach a normal lifespan. The diagnosis of MFS can be made based on established clinical criteria (see below). It is caused by pathogenic variants in the *FBN1* gene; however, there is significant overlap of the clinical features with syndromes caused by pathogenic variants in other genes.

Featured ARUP Testing

Marfan Syndrome (FBN1) Sequencing and Deletion/Duplication 3004102

Method: Massively Parallel Sequencing

Use to confirm diagnosis of Marfan syndrome in individuals meeting consensus criteria

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Disease Overview

Prevalence

1/5,000-10,000

Diagnostic Criteria

A clinical diagnosis of MFS can be made in an individual **without a family history** based on the presence of **either**:

- An *FBN1* gene known pathogenic variant **and either**
  - Aortic root dilatation (z-score of ≥2.0)
    or
  - Ectopia lentis
- Aortic root dilatation (z-score of ≥2.0) **and either**
  - Ectopia lentis
    or
  - ≥7 points on the revised Ghent nosology scale

A clinical diagnosis of MFS can be made in an individual **with a family history** based on the presence of any of the following:

- Ectopia lentis
- ≥7 points on the revised Ghent nosology scale
- Aortic root dissection or dilatation (z-score ≥3.0 for those <20 years of age or ≥2.0 for those ≥20 years of age)

Revised Ghent Nosology Point Values for Specific Characteristics

Characteristics	Point Value
Wrist AND thumb sign	3
Wrist OR thumb sign	1
Pectus carinatum	2
Pectus excavatum or chest asymmetry	1
Hindfoot deformity	2

Source: Loeys, 2010[1]

Characteristics	Point Value
Pes planus	1
Pneumothorax	2
Dural ectasia	2
Acetabular protrusion	2
Reduced upper segment-to-lower segment (US/LS) ratio AND increased arm span-to-height ratio AND no severe scoliosis	1
Scoliosis or thoracolumbar kyphosis	1
Reduced elbow extension	1
Skin striae	1
Myopia >3 diopters	1
Mitral valve prolapse (all types)	1
3 of 5 characteristic facial features	1

Source: Loeys, 2010[1]

Genetics

Gene

FBN1

See the Phenotypes Associated With *FBN1* Gene table.

Inheritance

Autosomal dominant; 25% of cases are de novo

Penetrance

High

Variants

Large gene deletions are causative for 5% of MFS, and large genomic deletions of regulatory elements have been reported in individuals with MFS or MFS spectrum disorders, including the MASS (**m**itral valve prolapse, **a**ortic root dilation, **s**kin striae, and **s**keletal features) phenotype. The following variants have associations with a particular syndrome or phenotype:

- Pathogenic *FBN1* variants in exons 24-32 generally cause a severe phenotype.
- Pathogenic missense variants in fourth 8-cysteine domain (exon 38 of *FBN1*) cause stiff skin syndrome.
- Heterozygous pathogenic variants in fifth 8-cysteine domain of *FBN1* cause geleophysic dysplasia 2 and acromicric dysplasia.
- Frameshift variants in exon 64 reported may cause lipodystrophy and progeroid facial appearance.

Test Interpretation

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Sensitivity/Specificity

Clinical Sensitivity

Approximately 95-98% depending on accuracy of clinical diagnosis[2]

Analytic Sensitivity/Specificity

For massively parallel sequencing:

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region	Analytic Specificity (NPA)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] Deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [Single exon]	>99.9
Exon-level[c] Duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

Results

Result	Variant(s) Detected	Clinical Significance
Positive	Pathogenic *FBN1* variant detected	Confirms diagnosis of MFS or *FBN1*-related disorder in a symptomatic individual
Negative	No known pathogenic *FBN1* variant detected	Reduces possibility of, but does not exclude, a diagnosis of MFS
Inconclusive	Variant of uncertain clinical significance detected	Unclear if variant is disease causing or benign

Limitations

A negative result does not exclude a diagnosis of MFS or other *FBN1*-related disorders.
Diagnostic errors can occur due to rare sequence variations.
Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
The following will not be evaluated:

- Variants outside the coding regions and intron-exon boundaries of the *FBN1* gene

- Regulatory region and deep intronic variants
- Breakpoints of large deletions/duplications

- The following may not be detected:
  - Deletions/duplications/insertions of any size by MPS
  - Large duplications less than 3 exons in size
  - Noncoding transcripts
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants

Phenotypes Associated With *FBN1* Gene		
OMIM Number	**Phenotype**	**Inheritance**
102370	Acromicric dysplasia	AD
129600	Ectopia lentis, familial	AD
614185	Geleophysic dysplasia	AD
616914	Marfan lipodystrophy syndrome	AD
154700	Marfan syndrome	AD
604308	MASS syndrome	AD
184900	Stiff skin syndrome	AD
608328	Weill-Marchesani syndrome 2	AD

References

1. Loeys BL, Dietz HC, Braverman AC, et al. The revised Ghent nosology for the Marfan syndrome. *J Med Genet*. 2010;47(7):476-485.

2. Dietz H. *FBN1*-related Marfan syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. *GeneReviews.* University of Washington, Seattle. Last update Feb 2022; accessed Mar 2022.

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