Marfan Syndrome (FBN1) Sequencing and Deletion/Duplication

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.

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**
  - Ectopic 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 dilation (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

Source: Loeys, 2010[1]

Tests to Consider

Marfan Syndrome (FBN1) Sequencing and Deletion/Duplication 3004102

Method: Massively Parallel Sequencing/Multiplex Ligation-dependent Probe Amplification

Preferred test to confirm diagnosis of Marfan syndrome in individuals meeting consensus criteria

Related Tests

Aortopathy Panel, Sequencing and Deletion/Duplication 2006540

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

Preferred panel for individuals with clinical phenotype of aortic or vascular aneurysm, dissection, or rupture if no single specific diagnosis is strongly suspected

Loeys-Dietz Syndrome Core Panel, Sequencing 3003947

Method: Massively Parallel Sequencing

Preferred test to confirm diagnosis of Loey-Dietz syndrome in individuals meeting consensus criteria

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

- Preferred test when a pathogenic familial variant identifiable by sequencing is known
- A copy of affected family member's lab report documenting the pathogenic variant is required.

Deletion/Duplication Analysis by MLPA 3003144

Method: Multiplex Ligation-dependent Probe Amplification

- Useful for confirming a diagnosis when a pathogenic deletion/duplication variant has been identified in a family member
- A copy of the family member's lab report documenting the familial variant is required.

Characteristics	Point Value
Pectus excavatum or chest asymmetry	1
Hindfoot deformity	2
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.

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

Sensitivity/Specificity

Clinical Sensitivity

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

Analytical Sensitivity/Specificity

For multiplex ligation-dependent probe amplification (MLPA): 99%

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	99.9	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	99.9	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; 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
  - Noncoding transcripts

- Breakpoints of large deletions/duplications
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - 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. Marfan syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2021. [Last update: Oct 2017; Accessed: Feb 2020]

Additional Resources

Kumar A, Agarwal S. Marfan syndrome: an eyesight of syndrome. Meta Gene. 2014;2:96-105.

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