Marfan Syndrome

Marfan syndrome (MFS) is a connective tissue disorder that exhibits a high degree of clinical variability. Clinical symptoms typically involve the cardiovascular, ocular, and skeletal systems. Early diagnosis is crucial for treatment of skeletal, orthopedic, and cardiovascular abnormalities. The diagnosis of MFS can be made or suspected based on established clinical criteria (see below). MFS 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

Symptoms

- A clinical diagnosis of MFS in an individual **without a family history** of MFS (when Shprintzen-Goldberg syndrome [SGS], Loeys-Dietz syndrome [LDS], and Ehlers-Danlos syndrome type IV [EDS IV] have been excluded) is based on the presence of any of the following:
  - Aortic root dilatation or dissection and ectopia lentis
  - Aortic root dilatation or dissection and pathogenic *FBN1* variant
  - Ectopia lentis and an *FBN1* gene variant previously reported to be associated with cardiovascular disease
  - Aortic root dilatation or dissection and at least seven points from the table below

Revised Ghent Nosology Point Values for Specific Characteristics

Characteristics	Point Value[a]
Wrist AND thumb sign	3
Wrist OR thumb sign	1
Pectus carinatum	2
Pectus excavatum or chest asymmetry	1
Hindfoot deformity	2
Plain des planus	1
Pneumothorax	2

[a]Score ≥7 indicates systemic involvement

Source: Loeys, 2010[1]

Tests to Consider

Marfan Syndrome (FBN1) Sequencing and Deletion/Duplication 2005584

Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Preferred test to confirm diagnosis when MFS is strongly suspected by consensus criteria

Marfan Syndrome, FBN1 Sequencing 2005589

Method: Polymerase Chain Reaction/Sequencing

Acceptable test to confirm diagnosis for individuals with clinical phenotype of MFS

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

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

Useful when a pathogenic familial variant identifiable by sequencing is known

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 family member
- A copy of the family member's lab report documenting the familial variant is REQUIRED

Characteristics	Point Value[a]
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
Characteristic facial features	1

[a]Score ≥7 indicates systemic involvement

Source: Loeys, 2010[1]

- A clinical diagnosis of MFS in an individual **with a family history** of MFS (when SGS, LDS, and EDS IV have been excluded) is based on the presence of any of the following:
  - Ectopia lentis
  - Systemic findings scoring seven points or higher (refer to table of point values, above)
  - Aortic root dilation or dissection
- Other disorders associated with *FBN1* gene variants:
  - Neonatal MFS: atrioventricular valve dysfunction, pulmonary emphysema, joint contractures, crumpled ears, and loose skin
  - MFS phenotype with severe congenital lipodystrophy and progeroid-like appearance
  - Mitral valve prolapse syndrome: mitral valve prolapse, pectus excavatum, scoliosis, mild arachnodactyly
  - Familial ectopia lentis: bilateral ectopia lentis, sometimes scoliosis
  - MASS syndrome: **m**itral valve prolapse, **a**ortic enlargement, **s**kin, **s**keletal findings
  - Weill-Marchesani syndrome type 2: ectopia lentis, brachydactyly, joint stiffness, short stature
  - SGS: craniosynostosis, arachnodactyly, brachycephaly, pectus deformities, scoliosis, mental retardation, rarely aortic root dilatation
  - Aortic aneurysm, ascending and dissection
  - Acromicric dysplasia
  - Geleophysic dysplasia type 2
  - Stiff skin syndrome

Genetics

Gene

FBN1

Inheritance

Autosomal dominant

- 25% of cases are de novo

Penetrance

High variability; age dependent

Variants

- The revised Ghent nosology defines causal *FBN1* variants
- Variants segregate with disease in MFS families
- Few genotype/phenotype correlations
- MFS with *FBN1* variants identified in exons 24-32 generally have a severe prognosis
- Exon 64 frameshift variants reported in individuals with Marfan phenotype, generalized lipodystrophy, and progeroid facial appearance
- Large genomic deletions of regulatory elements have been reported in individuals with MFS or MFS spectrum disorders, including MASS phenotype

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity
  - Sequencing: ranges from ~70-93%; dependent on accuracy of clinical diagnosis[2,3]
  - Deletion/duplication analysis: ~5%[2]
- Analytical sensitivity/specificity: 99%

Results

- Positive: pathogenic *FBN1* variant detected
  - Consistent with diagnosis of MFS or *FBN1*-related disorder in a symptomatic individual
- Negative: no known pathogenic *FBN1* variant detected
  - Reduces risk, but does not exclude the diagnosis of MFS
- Inconclusive: variant of uncertain clinical significance may be detected
  - Unclear if variant is disease causing or benign

Limitations

- Not determined or evaluated:
  - Deep intronic and regulatory region variants
  - Large deletions/duplications of exon 40 may or may not be detected, depending on the location of breakpoints
  - Breakpoints of large *FBN1* deletions/duplications
- Variants in genes other than *FBN1*
- Diagnostic errors can occur due to:
  - Rare sequence variations or repeat element insertions
  - Primer- or probe-site variants
- Do not use for prenatal testing for an unknown *FBN1* variant

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. PubMed

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]

3. Körkkö J, Kaitila I, Lönnqvist L, et al. Sensitivity of conformation sensitive gel electrophoresis in detecting mutations in Marfan syndrome and related conditions. J Med Genet. 2002;39(1):34-41. PubMed

Additional Resources

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

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