Marfan Syndrome

Indications for Ordering

- Confirm diagnosis for individuals with suspected Marfan syndrome (MFS)
- Determine the specific *FBN1* gene variant in known affected individual
- Determine disease status in children or other at-risk family members of affected individuals

Test Description

- Sequencing
  - Polymerase chain reaction followed by bidirectional sequencing of *FBN1* coding regions and intron/exon boundaries
- Deletion/duplication analysis
  - Multiplex ligation-dependent probe amplification

Tests to Consider

Primary tests

Marfan Syndrome (*FBN1*) Sequencing and Deletion/Duplication 2005584

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

Marfan Syndrome, *FBN1* Sequencing 2005589

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

Related tests

Aortopathy Panel, Sequencing and Deletion/Duplication, 21 Genes 2006540

- 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

- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Prevalence – 1/5,000-10,000

Symptoms

- MFS is a connective tissue disorder
- A clinical diagnosis of MFS in an individual **without a family history** of MFS (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 7 points from the table below

Revised Ghent Nosology (Loeys, 2010) 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
Plain des 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
Characteristic facial features	1
Score ≥7 indicates systemic involvement	

- A clinical diagnosis of MFS in an individual **with a family history** of MFS (SGS, LDS, and EDS IV have been excluded) is based on the presence of any of the following
  - Ectopia lentis
  - Systemic findings scoring 7 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

Treatment issues

Early diagnosis is crucial for treatment of skeletal, orthopedic, and cardiovascular abnormalities

Genetics

Gene – *FBN1*

Inheritance – autosomal dominant

Penetrance – high variability; age dependent

De novo variants– 25% of cases
- Nonsense
- In- or out-of-frame deletions/insertions
- Splice-site variants
- Missense variants
  - Involve cysteine residues
  - Affect epidermal growth factor-like consensus sequences absent in 400 ethnically matched controls

Pathogenic 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 (Dietz, 2017; Korkko, 2002)
  - Deletion/duplication analysis – unknown
- Analytical sensitivity/specificity – 99%

Results
- Positive – known pathogenic *FBN1* variant detected
  - Individual predicted to be affected with 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

Limitations
- Not determined or evaluated
  - Deep intronic pathogenic variants
  - Regulatory region pathogenic 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
- Do not use for prenatal testing for an unknown *FBN1* variant

References

- Dietz HC. Marfan Syndrome. 2001 Apr 18 [Updated 2017 Feb 2]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. (www.ncbi.nlm.nih.gov/books/NBK1335/)
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