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

<table>
<thead>
<tr>
<th>Revised Ghent Nosology (Loeys, 2010)</th>
<th>Point Values for Specific Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>Point Value</td>
</tr>
<tr>
<td>Wrist AND thumb sign</td>
<td>3</td>
</tr>
<tr>
<td>Wrist OR thumb sign</td>
<td>1</td>
</tr>
<tr>
<td>Pectus carinatum</td>
<td>2</td>
</tr>
<tr>
<td>Pectus excavatum or chest asymmetry</td>
<td>1</td>
</tr>
<tr>
<td>Hindfoot deformity</td>
<td>2</td>
</tr>
<tr>
<td>Plain des planus</td>
<td>1</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>2</td>
</tr>
<tr>
<td>Dural ectasia</td>
<td>2</td>
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<tr>
<td>Acetabular protrusion</td>
<td>2</td>
</tr>
<tr>
<td>Reduced upper segment-to-lower segment (US/LS) ratio AND increased arm span-to-height ratio AND no severe scoliosis</td>
<td>1</td>
</tr>
<tr>
<td>Scoliosis or thoracolumbar kyphosis</td>
<td>1</td>
</tr>
<tr>
<td>Reduced elbow extension</td>
<td>1</td>
</tr>
<tr>
<td>Skin striae</td>
<td>1</td>
</tr>
<tr>
<td>Myopia &gt;3 diopters</td>
<td>1</td>
</tr>
<tr>
<td>Mitral valve prolapse (all types)</td>
<td>1</td>
</tr>
<tr>
<td>Characteristic facial features</td>
<td>1</td>
</tr>
</tbody>
</table>

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 dilatation or dissection
• Other disorders associated with \textit{FBN1} gene variants
  o Neonatal MFS – atrioventricular valve dysfunction, pulmonary emphysema, joint contractures, crumpled ears, and loose skin
  o MFS phenotype with severe congenital lipodystrophy and progeroid-like appearance
  o Mitral valve prolapse syndrome – mitral valve prolapse, pectus excavatum, scoliosis, mild arachnodactyly
  o Familial ectopia lentis – bilateral ectopia lentis, sometimes scoliosis
  o MASS syndrome – mitral valve prolapse, aortic enlargement, skin, skeletal findings
  o Weill-Marchesani syndrome type 2 – ectopia lentis, brachydactyly, joint stiffness, short stature
  o SGS – craniosynostosis, arachnodactyly, brachycephaly, pectus deformities, scoliosis, mental retardation, rarely aortic root dilatation
  o Aortic aneurysm, ascending and dissection
  o Acromicric dysplasia
  o Geleophysic dysplasia type 2
  o Stiff skin syndrome

\textbf{Test Interpretation}

\textbf{Sensitivity/specificity}

- Clinical sensitivity
  o Sequencing – ranges from 70-93%; dependent on accuracy of clinical diagnosis (Dietz, 2017; Korkko, 2002)
  o Deletion/duplication analysis – unknown

- Analytical sensitivity/specificity – 99%

\textbf{Results}

- Positive – known pathogenic \textit{FBN1} variant detected
  o Individual predicted to be affected with MFS or \textit{FBN1}-related disorder in a symptomatic individual

- Negative – no known pathogenic \textit{FBN1} variant detected
  o Reduces risk, but does not exclude the diagnosis of MFS

- Inconclusive – variant of uncertain clinical significance may be detected

\textbf{Limitations}

- Not determined or evaluated
  o Deep intronic pathogenic variants
  o Regulatory region pathogenic variants
  o Large deletions/duplications of exon 40 may or may not be detected, depending on the location of breakpoints
  o Breakpoints of large \textit{FBN1} deletions/duplications

- Variants in genes other than \textit{FBN1} Diagnostic errors can occur due to rare sequence variations

- Do not use for prenatal testing for an unknown \textit{FBN1} variant

\textbf{Pathogenic variants}

- The revised Ghent nosology defines causal \textit{FBN1} variants
- Variants segregate with disease in MFS families
- Few genotype/phenotype correlations
- MFS with \textit{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

\textbf{References}