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
  o Polymerase chain reaction followed by bidirectional sequencing of FBN1 coding regions and intron/exon boundaries
• Deletion/duplication analysis
  o 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 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
  o Aortic root dilatation or dissection and ectopia lentis
  o Aortic root dilatation or dissection and pathogenic FBN1 variant
  o Ectopia lentis and an FBN1 gene variant previously reported to be associated with cardiovascular disease
  o Aortic root dilatation or dissection and at least seven points from the table below

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Point Value</th>
</tr>
</thead>
<tbody>
<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>
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<tr>
<td>Dural ectasia</td>
<td>2</td>
</tr>
<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
  o Ectopia lentis
  o Systemic findings scoring seven points or higher (refer to table of point values, above)
  o Aortic root dilatation or dissection

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           |
Mitrval valve prolapse (all types)                    | 1           |
Characteristic facial features                        | 1           |

Score ≥7 indicates systemic involvement

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Other disorders associated with \textit{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 – mitral valve prolapse, aortic enlargement, skin, skeletal 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

\textbf{Test Interpretation}

\textbf{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%

\textbf{Results}

- Positive – known pathogenic \textit{FBN1} variant detected
  - Individual predicted to be affected with MFS or \textit{FBN1}-related disorder in a symptomatic individual
- Negative – no known pathogenic \textit{FBN1} variant detected
  - 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
  - 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 \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{References}