Aortopathy disorders are characterized by progressive aortic dilation, dissection, and other vascular findings, and may involve multiple organ systems. If an individual meets clinical criteria for a specific disorder (eg, Marfan syndrome [MFS], Ehlers-Danlos syndrome [EDS]) or if a specific diagnosis is suspected, consider more targeted gene testing first.

### Disease Overview

#### Symptoms

- Aneurysm, dissection, and/or rupture of the aorta in any aortic section, including the aortic root or arch, ascending or descending aorta
- Cerebral, thoracic, and abdominal arterial aneurysms and/or dissections
- Skeletal manifestations, joint laxity, or craniofacial features

#### Etiology

Pathogenic variants in genes associated with aortopathy lead to structurally weakened cardiac, vascular, and/or connective tissues that become prone to progressive aneurysm, dissection, and/or rupture. Malformations of the heart, dysmorphic features, joint and skin laxity, and skeletal defects may also occur.

#### Prevalence

- MFS – 1/5,000-10,000
- Homocystinuria due to cystathionine beta-synthase deficiency (HCY) – 1/1,800-800,000
- EDS, type I/II (EDS I/II) – 1/20,000
- EDS, type IV (EDS IV) – at least 1/250,000
- Thoracic aortic aneurysm and dissection (TAAD) – 9 to 16/100,000 individuals/year; is familial in approximately 20 percent of cases

#### Inheritance

- Autosomal recessive for CBS, EFEMP2, PLOD1, and SLC2A10
- X-linked for FLNA
- Autosomal dominant for all other genes

#### Genotype-Phenotype Correlation

- Clinical phenotype may vary and overlap among disorders.
- Complete penetrance is seen in MFS, EDS IV, EDS VI, congenital contractual arachnodactyly (CCA), and Loeys-Dietz syndrome (LDS), with rare exceptions.
- Reduced penetrance is seen in TAAD and EDS I/II.
- May include previously undiagnosed Turner syndrome.

#### Test Description

See Genes Tested table for genes included in the panel.
Clinical Sensitivity

Variable, dependent on phenotype/condition

Indications for Ordering

- Clinical phenotype of aortic or vascular aneurysm, dissection, or rupture if no single specific diagnosis is strongly suspected
- If an individual meets clinical criteria for a specific disorder or if a specific diagnosis is suspected, consider more targeted gene testing first.

Limitations

- A negative result does not exclude a heritable form of MFS, HCY, EDS, TAAD, CCA, or LDS.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if the individual has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted gene(s)
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Deletions/duplications in LOX
  - Noncoding transcripts
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Deletions/duplications less than 1kb in the targeted genes by array
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants
  - Single exon deletions/duplications in the following exons:
    - COL3A1 (NM_000090) 6, 7, 9, 13; COL5A1 (NM_000093) 1, 16, 20; COL5A2 (NM_000393) 36; MYH11 (NM_001040113) 42; PRKG1 (NM_006258) 8, 17; TGFBR1 (NM_004612) 1

Analytical Sensitivity

For massively parallel sequencing:

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytical Sensitivity (PPA) Estimate (%)</th>
<th>Analytical Sensitivity (PPA) 95% Credibility Region (%)</th>
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</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>99.2</td>
<td>96.9-99.4</td>
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<tr>
<td>Deletions 1-10 bp</td>
<td>93.8</td>
<td>84.3-98.2</td>
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<tr>
<td>Deletions 11-44 bp</td>
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<td>87.8-100</td>
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<tr>
<td>Insertions 1-10 bp</td>
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<tr>
<td>Insertions 11-23 bp</td>
<td>100</td>
<td>62.1-100</td>
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</table>

*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

Genes Tested
<table>
<thead>
<tr>
<th>Gene</th>
<th>Alias Symbol(s)</th>
<th>MIM Number</th>
<th>Disorder</th>
<th>Inheritance</th>
</tr>
</thead>
</table>
| ACTA2 | ACTSA | 102620 | Aortic aneurysm, familial thoracic 6  
Multisystemic smooth muscle dysfunction syndrome  
Moyamoya disease 5 | AD |
| CBS | HIP4 | 613381 | Homocystinuria due to cystathionine beta-synthase deficiency  
Vitamin b6-responsive and vitamin b6-nonresponsive types of homocystinuria  
Thrombosis  
Hyperhomocysteinemic | AR |
| COL3A1 | EDS4A | 120180 | Ehlers-Danlos syndrome, vascular type, type IV | AD |
| COL5A1 | 120215 | Ehlers-Danlos syndrome, classic types, I/II | AD |
| COL5A2 | 120190 | Ehlers-Danlos syndrome, classic type, I | AD |
| EFEMP2 | FBLN4, UPH1 | 604633 | Cutis laxa, autosomal recessive, type IB | AR |
| FBN1 | FBN, MFS1, WMS, MASS, OCTD, SGS | 134797 | MFS  
Acromicric dysplasia  
Ectopia lentis 1, isolated, autosomal dominant  
MASS syndrome  
Weill-Marchesani syndrome 2  
Geleophysic dysplasia 2  
Marfan lipodystrophy syndrome | AD |
| FBN2 | CCA, DA9 | 612570 | Beals syndrome, congenital contractural arachnodactyly  
Arthrogryposis, distal, type 9 | AD |
| FLNA | FLN1, FLN, OPD2, OPD1, ABP-280 | 300017 | Cardiac valvular dysplasia, x-linked  
FG syndrome 2  
Frontometaphyseal dysplasia 1  
Periventricular nodular heterotopia 1 | XL |
| LOX | 153455 | Aortic aneurysm, familial thoracic 10 | AD |
| MYH11 | SMMHC, SMHC | 160745 | Aortic aneurysm, familial thoracic 4 | AD |
| MYLK | MLCK, smMLCK, MYLK1, MLCK1 | 600922 | Aortic aneurysm, familial thoracic 7 | AD |
| PLOD1 | LLH, PLOD, LH1 | 153454 | EDS  
Kyphoscoliotic type, VI | AR |

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked
<table>
<thead>
<tr>
<th>Gene</th>
<th>Alias Symbol(s)</th>
<th>MIM Number</th>
<th>Disorder</th>
<th>Inheritance</th>
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<tr>
<td>PRKG1</td>
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<td>SLC2A10</td>
<td>GLUT10</td>
<td>606145</td>
<td>Arterial tortuosity syndrome</td>
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<td>SMAD3</td>
<td>MADH3, JV15-2, HsT17436</td>
<td>603109</td>
<td>LDS 3</td>
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<td>SMAD4</td>
<td>MADH4, DPC4</td>
<td>600993</td>
<td>Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome</td>
<td>AD</td>
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<td>Juvenile polyposis syndrome</td>
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<td>Myhre syndrome</td>
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<td>ARVD1, ARVD</td>
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<td>Arrhythmogenic right ventricular dysplasia, familial, 1</td>
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<td>TGFBRI</td>
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<td>LDS 1, types 1B/2B</td>
<td>AD</td>
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<td>Aortic aneurysm, familial thoracic 5</td>
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<tr>
<td>TGFBRII</td>
<td>MFS2, TBRII, TBR-ii</td>
<td>190182</td>
<td>LDS 2, types 1B/2B</td>
<td>AD</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked

Additional Resources


Related Tests

Marfan Syndrome, FBN1 Sequencing 2005589
Method: Polymerase Chain Reaction/Sequencing

Marfan Syndrome (FBN1) Sequencing and Deletion/Duplication 2005584
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Loeys-Dietz Syndrome (TGFBR1 and TGFBR2) Sequencing 2002705
Method: Polymerase Chain Reaction/Sequencing

Familial Mutation, Targeted Sequencing 2001961
Method: Polymerase Chain Reaction/Sequencing