Aortopathy Panel, Sequencing and Deletion/Duplication

Indications for Ordering

Confirm a clinical diagnosis of an aortopathy
- Marfan syndrome (MFS)
- Loeys-Dietz syndrome (LDS)
- Ehlers-Danlos syndrome (EDS) types I/II, IV, VI
- Thoracic aortic aneurysm and dissections (familial)
- Congenital contractual arachnodactyly
- Arterial tortuosity syndrome
- Homocystinuria due to cystathionine beta-synthase deficiency
- Lysyl hydroxylase 3 deficiency
- Cutis laxa type IB
- Cardiac valvular dysplasia, X-linked
- Shprintzen-Goldberg syndrome

Test Description

- Next generation sequencing
  - Targeted capture of all coding exons and exon/intron junctions followed by massively parallel sequencing
  - Sanger sequencing is performed as necessary to fill in regions of low coverage and confirm reported variants
- Deletion/duplication analysis
  - Exonic oligonucleotide-based comparative genomic hybridization (CGH) microarray

Tests to Consider

Primary tests
Aortopathy Panel, Sequencing and Deletion/Duplication 2006540
- Preferred panel for individuals with clinical phenotype of aortic or vascular aneurism, dissection, or rupture if no single specific diagnosis is strongly suspected

Related tests
Loeys-Dietz Syndrome (TGFBR1 & TGFBR2) Sequencing 2002705
- Confirm clinical diagnosis of LDS
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

Familial Mutation, Targeted Sequencing 2001961
- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Symptoms
- Disease can affect any of the aortic sections
  - Aortic root
  - Ascending aorta
  - Aortic arch
  - Descending aorta
- Causes aneurysm, dissection, and/or rupture of the aorta
- Clinical phenotype may vary and overlap among disorders
  - May include previously undiagnosed Turner syndrome

Genetics

Genes – see table

Test Interpretation

Clinical sensitivity – disease dependent

Results
- Positive
  - One pathogenic variant was detected in ACTA2, COL3A1, COL5A1, COL5A2, FBN1, FBN2, FLNA (in a male), MYH11, MYLK, PRKG1, SKI, SMAD3, SMAD4, TGFBR2, TGFBR1, or TGFBR2 gene
    - Predicts aortopathy
  - Two pathogenic variants were detected in CBS, EFEMP2, PLOD1, PLOD3, or SLC2A10 gene
    - Predicts aortopathy
  - One pathogenic variant was detected in CBS, EFEMP2, FLNA (in a female), PLOD1, PLOD3, or SLC2A10 gene
    - Predicts carrier status
- Negative
  - No pathogenic variant was detected in any of the tested genes
    - Reduces, but does not exclude, a diagnosis of aortopathy
- Inconclusive
  - Variants of uncertain clinical significance may be identified in any of the 21 tested genes
Limitations

- Not determined or evaluated
- Variants in genes not listed
- Deep intronic or regulatory region variants
- Breakpoints of large deletions/duplications
- Small deletions or insertions may not be detected by massively parallel sequencing
- Mosaic Turner syndrome may not be detected
- Diagnostic errors can occur due to rare sequence variations

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene Description</th>
<th>NM#</th>
<th>OMIM #</th>
<th>Condition</th>
<th>Inh.</th>
<th>Prevalence/Incidence</th>
<th>Percentage of Associated Disorder(s) Attributed to Variants in this Gene</th>
<th>Other Conditions Caused by Variants in the Same Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTA2</td>
<td>Actin, alpha 2, smooth muscle, aorta</td>
<td>001613</td>
<td>102620</td>
<td>Familial aortic aneurysm, thoracic 6</td>
<td>AD</td>
<td>Unknown</td>
<td>~10-14%</td>
<td>Moyamoya disease; multisystemic smooth muscle dysfunction syndrome</td>
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<tr>
<td>CBS</td>
<td>Cystathionine beta synthase</td>
<td>000071</td>
<td>613381</td>
<td>Homocystinuria due to cystathionine beta-synthase deficiency</td>
<td>AR</td>
<td>1/1,800 in Qatar; 1/65,000 in Ireland; 1/17,800 in Germany; 1/6,400 estimated in Norway</td>
<td>&gt;95%</td>
<td>Vitamin B6-responsive and vitamin B6-nonresponsive types of homocystinuria; thrombosis; hyperhomocysteinemia</td>
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<tr>
<td>COL3A1</td>
<td>Collagen III alpha 1</td>
<td>000090</td>
<td>120180</td>
<td>Ehlers-Danlos syndrome (EDS), type IV</td>
<td>AD</td>
<td>Minimum estimate 1/200,000</td>
<td>~95%</td>
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<tr>
<td>COL5A1</td>
<td>Collagen V alpha 1</td>
<td>000093</td>
<td>120215</td>
<td>EDS, types I/II</td>
<td>AD</td>
<td>Estimated 1/20,000 for EDS type I</td>
<td>~50-90%</td>
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<tr>
<td>COL5A2</td>
<td>Collagen, type V, alpha 2</td>
<td>000393</td>
<td>120190</td>
<td>EDS, type I</td>
<td>AD</td>
<td></td>
<td></td>
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<tr>
<td>EFEMP2</td>
<td>EGF containing fibulin-like extracellular matrix protein 2</td>
<td>016938</td>
<td>604633</td>
<td>Cutis laxa, autosomal recessive, type IB</td>
<td>AR</td>
<td>~1/4,000,000</td>
<td>~95%</td>
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<tr>
<td>FBN1</td>
<td>Fibrillin 1</td>
<td>000138</td>
<td>134797</td>
<td>Marfan syndrome; ascending aortic aneurysm; aortic dissection</td>
<td>AD</td>
<td>1/5,000-10,000</td>
<td>~70-93%</td>
<td>Acromicric dysplasia; familial ectopia lentis; geleophysic dysplasia 2; MASS syndrome; stiff skin syndrome; Weill-Marchesani syndrome 2, dominant</td>
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<tr>
<td>FBN2</td>
<td>Fibrillin 2</td>
<td>001999</td>
<td>612570</td>
<td>Congenital contractural arachnodactyly</td>
<td>AD</td>
<td>Unknown</td>
<td>Up to 75%</td>
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<tr>
<td>FLNA</td>
<td>Filamin A, alpha</td>
<td>001456</td>
<td>300017</td>
<td>Cardiac valvular dysplasia, X-linked</td>
<td>XL</td>
<td>Unknown</td>
<td>~49%</td>
<td>Congenital short bowel syndrome; FG syndrome 2; frontometaphyseal dysplasia; heterotopia, periventricular; heterotopia, periventricular, ED variant; intestinal pseudo-obstruction, neuronal; Melnick-Needles syndrome; otopalatodigital syndrome, type I; otopalatodigital syndrome, type II; terminal osseous dysplasia</td>
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<tr>
<td>MYH11</td>
<td>Myosin, heavy polypeptide 11, smooth muscle</td>
<td>002474</td>
<td>160745</td>
<td>Familial aortic aneurysm, thoracic 4</td>
<td>AD</td>
<td>Unknown</td>
<td>~1%</td>
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<td>MYLK</td>
<td>Myosin light chain kinase</td>
<td>053025</td>
<td>600922</td>
<td>Familial aortic aneurysm, thoracic 7</td>
<td>AD</td>
<td>Unknown</td>
<td>~1%</td>
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<tr>
<td>PLOD1</td>
<td>Procollagen-lysine, 2-oxoglutarate 5-dioxygenase (lysyl hydroxylase)</td>
<td>000302</td>
<td>153454</td>
<td>EDS, type VI</td>
<td>AR</td>
<td>Rare incidence estimated 1/100,000</td>
<td>~95%</td>
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<td>Gene Symbol</td>
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<td>PLOD3</td>
<td>Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3</td>
<td>001084</td>
<td>603066</td>
<td>Lysyl hydroxylase 3 deficiency</td>
<td>AR</td>
<td>Unknown</td>
<td>~95%</td>
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<td>PRKG1</td>
<td>Protein kinase, cGMP-dependent, type I</td>
<td>006258</td>
<td>176894</td>
<td>Aortic aneurysm, familial thoracic 8</td>
<td>AD</td>
<td>Unknown</td>
<td>Unknown</td>
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<td>SKI</td>
<td>V-ski sarcoma viral oncogene homologue (avian)</td>
<td>003036</td>
<td>164780</td>
<td>Shprintzen-Goldberg syndrome</td>
<td>AD</td>
<td>Very rare</td>
<td>Unknown</td>
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<tr>
<td>SLC2A10</td>
<td>Solute carrier family 2 (facilitated glucose transporter), member 10</td>
<td>030777</td>
<td>606145</td>
<td>Arterial tortuosity syndrome</td>
<td>AR</td>
<td>Very rare</td>
<td>Unknown</td>
<td></td>
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<tr>
<td>SMAD3</td>
<td>SMAD, mothers against DPP homologue 3 (Drosophila) MADH3</td>
<td>005902</td>
<td>603109</td>
<td>Loeys-Dietz syndrome (LDS), type 3</td>
<td>AD</td>
<td>Unknown</td>
<td>~5%</td>
<td>Myhre syndrome; pancreatic cancer; juvenile intestinal polyposis</td>
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<tr>
<td>SMAD4</td>
<td>SMAD, mothers against DPP homologue 4 (Drosophila) MADH4</td>
<td>005359</td>
<td>600993</td>
<td>Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome (JPS/HHT)</td>
<td>AD</td>
<td>Unknown for JPS/HHT</td>
<td>Unknown</td>
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<td>TGFB2</td>
<td>Transforming growth factor, beta 2</td>
<td>003238</td>
<td>190220</td>
<td>LDS, type 4</td>
<td>AD</td>
<td>Unknown</td>
<td>~1%</td>
<td>Susceptibility to multiple self-healing squamous epithelioma; abdominal aortic aneurysm</td>
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<td>TGFB1</td>
<td>Transforming growth factor, beta receptor I (activin A receptor type II-like kinase, 53kDa)</td>
<td>004612</td>
<td>190181</td>
<td>LDS, types 1A/2A</td>
<td>AD</td>
<td>Unknown</td>
<td>~20%</td>
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<tr>
<td>TGFB2</td>
<td>Transforming growth factor, beta receptor 2 (70-80kDa)</td>
<td>003242</td>
<td>190182</td>
<td>LDS, types 1B/2B</td>
<td>AD</td>
<td>Unknown</td>
<td>~70%</td>
<td>Colorectal cancer; hereditary nonpolyposis, type 6; somatic esophageal cancer</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive; Inh., inheritance; XL = X-linked