

## Aortopathy Panel, Sequencing and Deletion/Duplication

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 contractural arachnodactyly (CCA), and Loews-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.

#### Tests to Consider

##### [Aortopathy Panel, Sequencing and Deletion/Duplication 2006540](#)

**Method:** Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

- 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 (see [Related Tests](#)).

## 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, TAAO, 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:

Variant Class	Analytical Sensitivity (PPA) Estimate <sup>a</sup> (%)	Analytical Sensitivity (PPA) 95% Credibility Region <sup>a</sup> (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	100	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	100	62.1-100

<sup>a</sup>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

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

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

Gene	Alias Symbol(s)	MIM Number	Disorder	Inheritance
<i>PRKG1</i>	PRKGR1B, PRKG1B, PGK, PKG, PKG1	176894	Aortic aneurysm, familial thoracic 8	AD
<i>SKI</i>		164780	Shprintzen-Goldberg craniosynostosis syndrome	AD
<i>SLC2A10</i>	GLUT10	606145	Arterial tortuosity syndrome	AR
<i>SMAD3</i>	MADH3, JV15-2, HsT17436	603109	LDS 3	AD
<i>SMAD4</i>	MADH4, DPC4	600993	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome Juvenile polyposis syndrome Myhre syndrome	AD
<i>TGFB2</i>		190220	LDS 4	AD
<i>TGFB3</i>	ARVD1, ARVD	190230	LDS 5 Arrhythmogenic right ventricular dysplasia, familial, 1	AD
<i>TGFB1</i>	MSSE, ESS1, ALK-5, ACVRLK4, ALK5, TBRI, TBR-i	190181	LDS 1, types 1B/2B Aortic aneurysm, familial thoracic 5	AD
<i>TGFB2</i>	MFS2, TBRII, TBR-ii	190182	LDS 2, types 1B/2B	AD

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

## Additional Resources

Dietz H. [Marfan Syndrome](#). In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: Oct 2017; Accessed: Feb 2020]

Sacharow SJ, Picker JD, Levy HL. [Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency](#). In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: May 2017; Accessed: Feb 2020]

Malfait F, Wenstrup R, De Paepe A. [Classic Ehlers-Danlos Syndrome](#). In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: Jul 2018; Accessed: Feb 2020]

Byers PH. [Vascular Ehlers-Danlos Syndrome](#). In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: Feb 2019; Accessed: Feb 2020]

Milewicz DM, Regalado E. [Heritable Thoracic Aortic Disease Overview](#). In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Revision: Dec 2017; Accessed: Feb 2020]

## 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

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