

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. 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. 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.

Genetics

Genes

See the [Genes Tested](#) table for genes included in the panel.

Prevalence

- MFS: 1/5,000-10,000
- Homocystinuria due to cystathionine beta-synthase deficiency (HCY): 1/1,800-335,000
- EDS, classic type (cEDS, type I/II): 1/20,000
- EDS, vascular type (vEDS, type IV): at least 1/200,000
- Thoracic aortic aneurysm and dissection (TAAD): 9-16/100,000 individuals/year; is familial in approximately 20% of cases

Inheritance

- Commonly autosomal dominant
- Autosomal recessive for *CBS*, *EFEMP2*, *PLOD1*, and *SLC2A10*
- X-linked for *BGN* and *FLNA*

Penetrance

- Complete penetrance is seen in MFS, vEDS, *PLOD1*-related kyphoscoliotic EDS (kEDS), congenital contractural arachnodactyly (CCA), and Loeys-Dietz syndrome (LDS), with rare exceptions.
- Reduced penetrance is seen in TAAD and cEDS.

Test Interpretation

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.

Tests to Consider

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

Method: Massively Parallel Sequencing

- Preferred panel for individuals with clinical phenotype of aortic or vascular aneurysm, dissection, or rupture if no single specific diagnosis is strongly suspected

[Familial Targeted Sequencing 3005867](#)

Method: Massively Parallel Sequencing

- Testing for a known familial sequence variant by sequencing gene of interest. A copy of the family member's test result documenting the familial gene variant is REQUIRED.
- To determine if the variant(s) of interest are detectable by this assay, contact an ARUP genetic counselor at 800-242-2787.

See [Related Tests](#)

- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Clinical Sensitivity

Variable, dependent on phenotype/condition

Analytic Sensitivity

For massively parallel sequencing:

Variant Class	Analytic Sensitivity (PPA) Estimate ^a (%) and 95% Credibility Region	Analytic Specificity (NPA)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp ^b	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp ^b	94.8 (86.8-98.5)	>99.9
Exon-level ^c deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [Single exon]	>99.9
Exon-level ^c duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

^aGenes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

^bVariants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

^cIn most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; PPA, positive percent agreement; NPA, negative percent agreement; SNVs, single nucleotide variants

Limitations

- A negative result does not exclude a heritable aortopathy disorder.
- 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 and deep intronic variants
 - Breakpoints of large deletions/duplications
 - Deletions/duplications in *TGFB3*
 - The following regions are not sequenced due to technical limitations of the assay:
 - *CBS* (NM_001321072) exon(s) 1
 - *COL5A1* (NM_000093) exon(s) 1
 - *COL5A1* (NM_001278074) exon(s) 1
 - *FOXE3* (NM_012186) partial exon(s) 1(Chr1:47882098-47882163)
- The following may not be detected:
 - Deletions/duplications/insertions of any size by MPS
 - Large duplications less than three exons in size
 - Noncoding transcripts
 - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
 - Low-level somatic variants
 - Single-exon deletions/duplication in the following exons:

Gene	Exon(s)
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Gene	Exon(s)
<i>CBS</i>	(NM_001321072) 1
<i>COL1A2</i>	(NM_000089) 3
<i>COL5A1</i>	(NM_000093) 1
<i>COL5A1</i>	(NM_001278074) 1
<i>MYLK</i>	(NM_053025) 13
<i>MYLK</i>	(NM_001321309) 12
<i>MYLK</i>	(NM_053026) 12
<i>MYLK</i>	(NM_053027) 13
<i>MYLK</i>	(NM_053028) 12
<i>NOTCH1</i>	(NM_017617) 1

Genes Tested

Gene	MIM #	Associated Disorder(s)	Inheritance
<i>ACTA2</i>	102620	Aortic aneurysm, familial thoracic 6 Multisystemic smooth muscle dysfunction syndrome	AD
<i>BGN</i>	301870	Meester-Loeys syndrome	XL
<i>CBS</i>	613381	Homocystinuria due to cystathionine beta-synthase deficiency (B6-responsive and nonresponsive types) Thrombosis (hyperhomocysteinemic)	AR
<i>COL1A1</i>	120150	Combined osteogenesis imperfecta and EDS 1 EDS arthrochalasia type, 1	AD
<i>COL1A2</i>	120160	Combined osteogenesis imperfecta and EDS 2 EDS arthrochalasia type 2	AD
		EDS cardiac valvular type	AR
<i>COL3A1</i>	120180	EDS, vascular type, type IV	AD
		Polymicrogyria with or without vascular-type EDS	AR
<i>COL5A1</i>	120215	EDS classic type 1 Multifocal fibromuscular dysplasia	AD
<i>COL5A2</i>	120190	EDS classic type 2	AD
<i>EFEMP2</i>	604633	Cutis laxa, autosomal recessive, type IB	AR

Gene	MIM #	Associated Disorder(s)	Inheritance
<i>FBN1</i>	134797	MFS Familial ectopia lentis MASS syndrome Marfan lipodystrophy syndrome	AD
<i>FBN2</i>	612570	Congenital contractural arachnodactyly (Beals syndrome)	AD
<i>FLNA</i>	300017	Cardiac valvular dysplasia Periventricular nodular heterotopia 1	XL
<i>FOXE3</i>	601094	Aortic aneurysm, familial thoracic 11	AD
<i>LOX</i>	153455	Aortic aneurysm, familial thoracic 10	AD
<i>MFAP5</i>	601103	Aortic aneurysm, familial thoracic 9	AD
<i>MYH11</i>	160745	Aortic aneurysm, familial thoracic 4	AD
<i>MYLK</i>	600922	Aortic aneurysm, familial thoracic 7	AD
<i>NOTCH1</i>	190198	Aortic valve disease Adams-Oliver syndrome 5	AD
<i>PLOD1</i>	153454	EDS kyphoscoliotic type VI	AR
<i>PRKG1</i>	176894	Aortic aneurysm, familial thoracic 8	AD
<i>SKI</i>	164780	Shprintzen-Goldberg craniosynostosis syndrome	AD
<i>SLC2A10</i>	606145	Arterial tortuosity syndrome	AR
<i>SMAD2</i>	601366	LDS 6	AD
<i>SMAD3</i>	603109	LDS 3	AD
<i>SMAD4</i>	600993	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome Myhre syndrome	AD
<i>TGFB2</i>	190220	LDS 4	AD
<i>TGFB3</i>	190230	LDS 5	AD
<i>TGFBR1</i>	190181	LDS 1	AD
<i>TGFBR2</i>	190182	LDS 2	AD

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

Additional Resources

Byers PH. [Vascular Ehlers-Danlos syndrome](#). In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2022. [Last Update: Feb 2019; Accessed: Mar 2022]

Dietz H. [FBN1-related Marfan syndrome](#). In: Adam MP, Everman DB, Mirzaa GM, et al, editors. GeneReviews, University of Washington; 1993-2022. [Last update: Feb 2022; Accessed: Mar 2022]

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; 1993-2022. [Last Update: Jul 2018; Accessed: Mar 2022]

Milewicz DM, Regalado E. [Heritable thoracic aortic disease overview](#). In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2022. [Last update: Dec 2017; Accessed: Mar 2022]

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; 1993-2022s. [Last Update: May 2017; Accessed: Apr 2022]

Related Tests

[Marfan Syndrome \(FBN1\) Sequencing and Deletion/Duplication 3004102](#)

Method: Massively Parallel Sequencing

[Loeys-Dietz Syndrome Core Panel, Sequencing 3003947](#)

Method: Massively Parallel Sequencing

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