Aortopathy Panel, Sequencing and Deletion/Duplication

Last Literature Review: March 2022 Last Update: January 2024

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.

Featured ARUP Testing

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
- If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information

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, or NGS) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for detection of large deletions and duplications.
- 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

[a]Genes 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).

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In 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
  - Deletions/duplications in *TGFB3*
  - Breakpoints of large deletions/duplications
  - SNVs and small deletions/insertions will not be called in the following exons 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 massively parallel sequencing
  - 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

Genes Tested

Gene	MIM #	Associated Disorder(s)	Inheritance
ACTA2	102620	Aortic aneurysm, familial thoracic 6 Multisystemic smooth muscle dysfunction syndrome	AD
BGN	301870	Meester-Loeys syndrome	XL
CBS	613381	Homocystinuria due to cystathionine beta-synthase deficiency (B6-responsive and nonresponsive types) Thrombosis (hyperhomocysteinemic)	AR

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

Gene	MIM #	Associated Disorder(s)	Inheritance
COL1A1	120150	Combined osteogenesis imperfecta and EDS 1 EDS arthrochalasia type, 1	AD
COL1A2	120160	Combined osteogenesis imperfecta and EDS 2 EDS arthrochalasia type 2	AD
		EDS cardiac valvular type	AR
COL3A1	120180	EDS, vascular type, type IV	AD
		Polymicrogyria with or without vascular-type EDS	AR
COL5A1	120215	EDS classic type 1 Multifocal fibromuscular dysplasia	AD
COL5A2	120190	EDS classic type 2	AD
EFEMP2	604633	Cutis laxa, autosomal recessive, type IB	AR
FBN1	134797	MFS Familial ectopia lentis MASS syndrome Marfan lipodystrophy syndrome	AD
FBN2	612570	Congenital contractural arachnodactyly (Beals syndrome)	AD
FLNA	300017	Cardiac valvular dysplasia Periventricular nodular heterotopia 1	XL
FOXE3	601094	Aortic aneurysm, familial thoracic 11	AD
LOX	153455	Aortic aneurysm, familial thoracic 10	AD
MFAP5	601103	Aortic aneurysm, familial thoracic 9	AD
MYH11	160745	Aortic aneurysm, familial thoracic 4	AD
MYLK	600922	Aortic aneurysm, familial thoracic 7	AD
NOTCH1	190198	Aortic valve disease Adams-Oliver syndrome 5	AD
PLOD1	153454	EDS kyphoscoliotic type VI	AR
PRKG1	176894	Aortic aneurysm, familial thoracic 8	AD
SKI	164780	Shprintzen-Goldberg craniosynostosis syndrome	AD
SLC2A10	606145	Arterial tortuosity syndrome	AR
SMAD2	601366	LDS 6	AD
SMAD3	603109	LDS 3	AD
SMAD4	600993	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome	AD

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Gene	MIM #	Associated Disorder(s)	Inheritance
		Myhre syndrome	
TGFB2	190220	LDS 4	AD
TGFB3	190230	LDS 5	AD
TGFBR1	190181	LDS 1	AD
TGFBR2	190182	LDS 2	AD

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

Related Information

Loeys-Dietz Syndrome Core Panel, Sequencing
Marfan Syndrome (FBN1) Sequencing and Deletion/Duplication

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