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.

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).

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): 9-16/100,000 individuals/year; is familial in approximately 20% 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 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 1 kb in the targeted genes by array
  - Some variants due to technical limitations in the presence of pseudogenes, or 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[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
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

[a]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

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

Gene	Alias Symbol(s)	MIM Number	Disorder	Inheritance
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
PRKG1	PRKGR1B, PRKG1B, PGK, PKG, PKG1	176894	Aortic aneurysm, familial thoracic 8	AD
SKI		164780	Shprintzen-Goldberg craniosynostosis syndrome	AD

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

Gene	Alias Symbol(s)	MIM Number	Disorder	Inheritance
SLC2A10	GLUT10	606145	Arterial tortuosity syndrome	AR
SMAD3	MADH3, JV15-2, HsT17436	603109	LDS 3	AD
SMAD4	MADH4, DPC4	600993	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome Juvenile polyposis syndrome Myhre syndrome	AD
TGFB2		190220	LDS 4	AD
TGFB3	ARVD1, ARVD	190230	LDS 5 Arrhythmogenic right ventricular dysplasia, familial, 1	AD
TGFBR1	MSSE, ESS1, ALK-5, ACVRLK4, ALK5, TBRI, TBR-i	190181	LDS 1, types 1B/2B Aortic aneurysm, familial thoracic 5	AD
TGFBR2	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; 1993-2021. [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 Core Panel, Sequencing 3003947

Method: Massively Parallel Sequencing

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

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