Aortopathy Panel, 21 Genes

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 contractural 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
- Deletion/duplication analysis
  - Exonic oligonucleotide-based comparative genomic hybridization (CGH) microarray

Tests to Consider

Primary tests

Aortopathy Panel Sequencing and Deletion/Duplication, 21 Genes 2006540
- Preferred panel for individuals with clinical phenotype of aortic or vascular aneurysm, 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 whenMFS 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, TGFB2, 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

Gene Symbol	Gene Description	NM#	OMIM #	Condition	Inh.	Prevalence/ Incidence	Percentage of Associated Disorder(s) Attributed to Variants in this Gene	Other Conditions Caused by Variants in the Same Gene
ACTA2	Actin, alpha 2, smooth muscle, aorta	001613	102620	Familial aortic aneurysm, thoracic 6	AD	Unknown	~10-14%	Moyamoya disease 5; multisystemic smooth muscle dysfunction syndrome
CBS	Cystathionine beta synthase	000071	613381	Homocystinuria due to cystathionine beta-synthase deficiency	AR	1/1,800 in Qatar 1/65,000 in Ireland 1/17,800 in Germany 1/6,400 estimated in Norway	>95%	Vitamin B6-responsive and vitamin B6-nonresponsive types of homocystinuria; thrombosis; hyperhomocysteinemia
COL3A1	Collagen III alpha 1	000090	120180	Ehlers-Danlos syndrome (EDS), type IV	AD	Minimum estimate 1/200,000	~95%	
COL5A1	Collagen V alpha 1	000093	120215	EDS, types I/II	AD	Estimated 1/20,000 for EDS type I	~50-90%	
COL5A2	Collagen, type V, alpha 2	000393	120190	EDS, type I	AD			
EFEMP2	EGF containing fibulin-like extracellular matrix protein 2	016938	604633	Cutis laxa, autosomal recessive, type IB	AR	~1/4,000,000	~95%	
FBN1	Fibrillin 1	000138	134797	Marfan syndrome; ascending aortic aneurysm; aortic dissection	AD	1/5,000-10,000	~70-93%	Acromicric dysplasia; familial ectopia lentis; geleophysic dysplasia 2; MASS syndrome; stiff skin syndrome; Weill-Marchesani syndrome 2, dominant
FBN2	Fibrillin 2	001999	612570	Congenital contractural arachnodactyly	AD	Unknown	Up to 75%	
FLNA	Filamin A, alpha	001456	300017	Cardiac valvular dysplasia, X-linked	XL	Unknown	~49%	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
MYH11	Myosin, heavy polypeptide 11, smooth muscle	002474	160745	Familial aortic aneurysm, thoracic 4	AD	Unknown	~1%	
MYLK	Myosin light chain kinase	053025	600922	Familial aortic aneurysm, thoracic 7	AD	Unknown	~1%	
PLOD1	Procollagen-lysine, 2-oxoglutarate 5-dioxygenase (lysyl hydroxylase)	000302	153454	EDS, type VI	AR	Rare Incidence estimated ~1/100,000	~95%	

Gene Symbol	Gene Description	NM#	OMIM #	Condition	Inh.	Prevalence/ Incidence	Percentage of Associated Disorder(s) Attributed to Variants in this Gene	Other Conditions Caused by Variants in the Same Gene
PLOD3	Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3	001084	603066	Lysyl hydroxylase 3 deficiency	AR	Unknown	~95%	
PRKG1	Protein kinase, cGMP-dependent, type I	006258	176894	Aortic aneurysm, familial thoracic 8	AD	Unknown	Unknown	
SKI	V-ski sarcoma viral oncogene homologue (avian)	003036	164780	Shprintzen-Goldberg syndrome	AD	Very rare	Unknown	
SLC2A10	Solute carrier family 2 (facilitated glucose transporter), member 10	030777	606145	Arterial tortuosity syndrome	AR	Very rare	Unknown	
SMAD3	SMAD, mothers against DPP homologue 3 (Drosophila) MADH3	005902	603109	Loeys-Dietz syndrome (LDS), type 3	AD	Unknown	~5%	
SMAD4	SMAD, mothers against DPP homologue 4 (Drosophila) MADH4	005359	600993	Juvenile polyposis/ hereditary hemorrhagic telangiectasia syndrome (JPS/HHT)	AD	Unknown for JPS/HHT	Unknown	Myhre syndrome; pancreatic cancer; juvenile intestinal polyposis
TGFB2	Transforming growth factor, beta 2	003238	190220	LDS, type 4	AD	Unknown	~1%	
TGFBR1	Transforming growth factor, beta receptor I (activin A receptor type II-like kinase, 53kDa)	004612	190181	LDS, types 1A/2A	AD	Unknown	~20%	Susceptibility to multiple self-healing squamous epithelioma; abdominal aortic aneurysm
TGFBR2	Transforming growth factor, beta receptor 2 (70-80kDa)	003242	190182	LDS, types 1B/2B	AD	Unknown	~70%	Colorectal cancer; hereditary nonpolyposis, type 6; somatic esophageal cancer
Inh. = inheritance; AD = autosomal dominant; AR = autosomal recessive; XL = X-linked								