

Marfan Syndrome/Thoracic Aortic Aneurysm and Dissection and Related Disorders Panel

Panel Gene List: *ACTA2, BGN, CBS, COL3A1, COL5A1, COL5A2, FBN1, FBN2, FLNA, LOX, MAT2A, MED12, MFAP5, MYH11, MYLK, NOTCH1, PRKG1, SKI, SLC2A10, SMAD2, SMAD3, SMAD4, TGFB2, TGFB3, TGFBR1, TGFBR2*

Additional genes from our cardiology test menu may be added to this panel by selecting test code 883C.

Clinical Features:

Familial thoracic aortic aneurysm and dissection (TAAD) is a genetically heterogeneous disorder that accounts for approximately 20% of all cases of thoracic aortic aneurysms and dissections.¹ Increased risk for aortopathy can occur in conjunction with other syndromic features or as a primarily isolated feature.² When syndromic features are absent or non-specific, genetic testing aids in diagnosis, management and establishing recurrence risk for family members.

Syndromic TAAD includes Marfan syndrome, Loeys-Dietz syndrome, Meester-Loeys syndrome, and Shprintzen-Goldberg syndrome. Marfan syndrome is a heritable connective tissue disorder caused by variants in the *FBN1* gene, and clinical diagnosis is based on the presence of major and minor criteria, as established by the Ghent nosology.³ Features of Loeys-Dietz syndrome (LDS) overlap with those of Marfan syndrome, and may also include extensive arteriopathy and craniofacial features such as hypertelorism, craniosynostosis, cleft palate/bifid uvula.⁴ LDS is due to a pathogenic variant in one of several genes, including *TGFBR1*⁴, *TGFBR2*⁴, *SMAD2*⁵, *SMAD3*⁶, *TGFB2*^{7,8} or *TGFB3*^{9,10}. Shprintzen-Goldberg syndrome¹¹, Meester-Loeys syndrome¹², vascular Ehlers-Danlos syndrome¹³, arterial tortuosity syndrome¹⁴, congenital contractural arachnodactyly¹⁵, and Lujan syndrome¹⁶ may also present with some features overlapping those of Marfan syndrome and Loeys-Dietz syndrome.

Familial non-syndromic TAAD may be due to a pathogenic variant in one of the same genes that cause Marfan syndrome and LDS, or in one of a number of other genes, including *ACTA2*¹⁷, *LOX*^{18,19}, *MAT2A*²⁰, *MFAP5*²¹, *MYH11*²², *MYLK*²³, *PRKG1*²⁴. Pathogenic variants in other genes included on this panel, such as *NOTCH1*²⁵ and *SMAD4*²⁶, may have a distinct clinical presentation but are also associated with increased risk of aortopathy.

Inheritance Pattern/Genetics: Autosomal Dominant, Autosomal Recessive or X-linked

Test Methods:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely

pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request. Sequencing and deletion/duplication analysis of the remaining genes on the Heritable Disorders of Connective Tissue Panel is available as a separate test if the Marfan/TAAD Panel is negative.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in the Marfan/TAAD Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with clearly defined Marfan/TAAD-related disorder and a family history of disease. The technical sensitivity of the sequencing test is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. This test may not reliably detect copy number variants of less than 500 base pairs or low level mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

Gene	Protein	Inheritance	Disease Association(s)
<i>ACTA2</i>	ACTIN, ALPHA-2, SMOOTH MUSCLE, AORTA	AD	fTAAD
<i>BGN</i>	PROTEOGLYCAN I	XL	Meester-Loeys syndrome, SEMDX
<i>CBS</i>	CYSTATHIONINE BETA-SYNTHASE	AR	Homocystinuria
<i>COL3A1</i>	COLLAGEN TYPE III ALPHA 1	AD	Vascular EDS
<i>COL5A1</i>	COLLAGEN TYPE V ALPHA 1	AD	Classical EDS
<i>COL5A2</i>	COLLAGEN TYPE V ALPHA 2	AD	Classical EDS
<i>FBN1</i>	FIBRILLIN 1	AD	Marfan syndrome, Acromicric dysplasia, Geleophysic dysplasia, Weill-Marschani syndrome, Stiff Skin syndrome
<i>FBN2</i>	FIBRILLIN 2	AD	Congenital contractural arachnodactyly
<i>FLNA</i>	FILAMIN A	XL	EDS variant with PVH
<i>LOX</i>	LYSYL OXIDASE	AD	fTAAD
<i>MAT2A</i>	METHIONINE ADENOSYLTRANSFERASE II, ALPHA	AD	fTAAD
<i>MED12</i>	MEDIATOR COMPLEX SUBUNIT 12	XL	Lujan syndrome, Ohdo syndrome, FG syndrome
<i>MFAP5</i>	MICROFIBRILLAR-ASSOCIATED PROTEIN 5	AD	fTAAD
<i>MYH11</i>	MYOSIN, HEAVY CHAIN 11, SMOOTH MUSCLE	AD	fTAAD
<i>MYLK</i>	MYOSIN LIGHT CHAIN KINASE	AD	fTAAD
<i>NOTCH1</i>	NOTCH, DROSOPHILA, HOMOLOG OF, 1	AD	Aortic valve disease
<i>PRKG1</i>	PROTEIN KINASE, cGMP-DEPENDENT, REGULATORY, TYPE I	AD	fTAAD
<i>SKI</i>	V-SKI AVIAN SARCOMA VIRAL ONCOGENE HOMOLOG	AD	Shprintzen-Goldberg syndrome
<i>SLC2A10</i>	SOLUTE CARRIER FAMILY 2 (FACILITATED GLUCOSE TRANSPORTER), MEMBER 10	AR	Arterial tortuosity syndrome
<i>SMAD2</i>	MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILA, HOMOLOG OF, 2	AD	fTAAD, LDS
<i>SMAD3</i>	MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILA, HOMOLOG OF, 3	AD	fTAAD, LDS
<i>SMAD4</i>	MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILA, HOMOLOG OF, 4	AD	JP/HHT
<i>TGFB2</i>	TRANSFORMING GROWTH FACTOR, BETA-2	AD	fTAAD, LDS
<i>TGFB3</i>	TRANSFORMING GROWTH FACTOR, BETA-3	AD	fTAAD, LDS

Gene (Cont.)	Protein	Inheritance	Disease Association(s)
<i>TGFBR1</i>	TRANSFORMING GROWTH FACTOR-BETA RECEPTOR, TYPE I	AD	fTAAD, LDS
<i>TGFBR2</i>	TRANSFORMING GROWTH FACTOR-BETA RECEPTOR, TYPE II	AD	fTAAD, LDS

Abbreviations: AD – autosomal dominant; AR – autosomal recessive; EDS Ehlers-Danlos syndrome; fTAAD – familial thoracic aortic aneurysm and dissection; JP/HHT – juvenile polyposis/hereditary hemorrhagic telangiectasia; LDS – Loeys-Dietz syndrome; PVH – periventricular heterotopia; XL – X-linked; SEMDX- spondyloepimetaphyseal dysplasia

References:

- Milewicz DM, Regalado E. Thoracic Aortic Aneurysms and Aortic Dissections. 2003 Feb 13 [Updated 2012 Jan 12]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015.
- Pomianowski et al. (2013) Ann Cardiothorac Surg 2 (3): 271-9 (PMID: 23977594).
- Loeys et al. (2010) Journal Of Medical Genetics 47 (7): 476-85 (PMID: 20591885).
- Loeys et al. (2005) Nature Genetics 37 (3): 275-81 (PMID: 15731757).
- Micha et al. (2015) Hum. Mutat. 36 (12):1145-9 (PMID: 26247899).
- van de Laar et al. (2011) Nature Genetics 43 (2): 121-6 (PMID: 2121753).
- Lindsay et al. (2012) Nature Genetics 44 (8): 922-7 (PMID: 22772368).
- Boileau et al. (2012) Nature Genetics 44 (8): 916-21 (PMID: 22772371).
- Rienhoff et al. (2013) American Journal Of Medical Genetics. Part A 161A (8): 2040-6 (PMID: 23824657).
- Bertoli-Avella et al. (2015) Journal Of The American College of Cardiology 65 (13): 1324-36 (PMID: 25835445).
- Doyle et al. (2012) Nature Genetics 44 (11): 1249-54 (PMID: 23023332).
- Meester et al. (2017) Genet. Med. 19 (4): 386-395 (PMID: 27632686).
- Pepin MG et al. Vascular Ehlers-Danlos Syndrome. 1999 Sep 2 [Updated 2015 Nov 19]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015.
- Callewaert B et al. Arterial Tortuosity Syndrome. 2014 Nov 13. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015.
- Godfrey M. Congenital Contractural Arachnodactyly. 2001 Jan 23 [Updated 2012 Feb 23]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015.
- Lyons MJ. MED12-Related Disorders. 2008 Jun 23 [Updated 2013 Jun 6]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015.
- Guo et al. (2007) Nature Genetics 39 (12): 1488-93 (PMID: 17994018).
- Guo et al. (2016) Circ. Res. 118 (6):928-34 (PMID: 26838787).
- Lee et al. (2016) Proc. Natl. Acad. Sci. U.S.A. 113 (31):8759-64 (PMID: 27432961).
- Guo et al. (2015) American Journal Of Human Genetics 96 (1): 170-7 (PMID: 25557781).
- Barbier et al. (2014) American Journal Of Human Genetics 95 (6): 736-43 (PMID: 25434006).
- Zhu et al. (2006) Nature Genetics 38 (3): 343-9 (PMID: 16444274).
- Wang et al. (2010) American Journal Of Human Genetics 87 (5): 701-7 (PMID: 21055718).
- Guo et al. (2013) American Journal Of Human Genetics 93 (2): 398-404 (PMID: 23910461).
- McKellar et al. (2007) The Journal Of Thoracic And Cardiovascular Surgery 143 (2): 290-6 (PMID: 17662764).
- Heald et al. (2015) American Journal Of Medical Genetics A 167 (8): 1758-62 (PMID: 25931195).