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

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 syndrome[11], Meester-Loeys syndrome[12], vascular Ehlers-Danlos syndrome[13], arterial tortuosity syndrome[14], congenital contractural arachnodactyly[15], and Lujan syndrome[16] 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 extracted from the submitted specimen, the complete coding regions and splice site junctions of the genes tested 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; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Sequence variants are reported according to the Human Genome Variation Society (HGVS) guidelines. Copy number variants are reported based on the probe coordinates, the coordinates of the exons involved, or precise breakpoints when known. Reportable variants include pathogenic variants,

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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 technical sensitivity of sequencing 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. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or 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. For *FBN1*, sequencing of exons 2-66 only. For *MYLK* and *SKI* genes, only whole gene deletions or duplications may be detected.

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

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SMAD4	MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILA, HOMOLOG OF, 4	AD	JP/HHT
TGFB2	TRANSFORMING GROWTH FACTOR, BETA-2	AD	fTAAD, LDS
TGFB3	TRANSFORMING GROWTH FACTOR, BETA-3	AD	fTAAD, LDS
TGFBR1	TRANSFORMING GROWTH FACTOR-BETA RECEPTOR, TYPE I	AD	fTAAD, LDS
TGFBR2	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:

1. 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.
2. Pomianowski et al. (2013) Ann Cardiothorac Surg 2 (3): 271-9 (PMID: 23977594).
3. Loeys et al. (2010) Journal Of Medical Genetics 47 (7): 476-85 (PMID: 20591885).
4. Loeys et al. (2005) Nature Genetics 37 (3): 275-81 (PMID: 15731757).
5. Micha et al. (2015) Hum. Mutat. 36 (12):1145-9 (PMID: 26247899).
6. van de Laar et al. (2011) Nature Genetics 43 (2): 121-6 (PMID: 2121753).
7. Lindsay et al. (2012) Nature Genetics 44 (8): 922-7 (PMID: 22772368).
8. Boileau et al. (2012) Nature Genetics 44 (8): 916-21 (PMID: 22772371).
9. Rienhoff et al. (2013) American Journal Of Medical Genetics. Part A 161A (8): 2040-6 (PMID: 23824657).
10. Bertoli-Avella et al. (2015) Journal Of The American College of Cardiology 65 (13): 1324-36 (PMID: 25835445).
11. Doyle et al. (2012) Nature Genetics 44 (11): 1249-54 (PMID: 23023332).
12. Meester et al. (2017) Genet. Med. 19 (4): 386-395 (PMID: 27632686).
13. 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.
14. Callewaert B et al. Arterial Tortuosity Syndrome. 2014
15. 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.
16. 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.
17. Guo et al. (2007) Nature Genetics 39 (12): 1488-93 (PMID: 17994018).
18. Guo et al. (2016) Circ. Res. 118 (6):928-34 (PMID: 26838787).
19. Lee et al. (2016) Proc. Natl. Acad. Sci. U.S.A. 113 (31):8759-64 (PMID: 27432961).
20. Guo et al. (2015) American Journal Of Human Genetics 96 (1): 170-7 (PMID: 25557781).
21. Barbier et al. (2014) American Journal Of Human Genetics 95 (6): 736-43 (PMID: 25434006).
22. Zhu et al. (2006) Nature Genetics 38 (3): 343-9 (PMID: 16444274).
23. Wang et al. (2010) American Journal Of Human Genetics 87 (5): 701-7 (PMID: 21055718).
24. Guo et al. (2013) American Journal Of Human Genetics 93 (2): 398-404 (PMID: 23910461).
25. McKellar et al. (2007) The Journal Of Thoracic And Cardiovascular Surgery 143 (2): 290-6 (PMID: 17662764).
26. Heald et al. (2015) American Journal Of Medical Genetics A 167 (8): 1758-62 (PMID: 25931195)

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