

Heritable Disorders of Connective Tissue Panel

Panel Gene List: *ACTA2, ADAMTS2, ALDH18A1, ATP6V0A2, ATP6V1E1, ATP7A, B3GALT6, B3GAT3, B4GALT7, BGN, CBS, CHST14, COL1A1, COL1A2, COL2A1, COL3A1, COL5A1, COL5A2, COL9A1, COL9A2, COL9A3, COL11A1, COL11A2, COL12A1, DSE, EFEMP2, ELN, FBLN5, FBN1, FBN2, FKBP14, FLNA, LOX, LTBP4, MAT2A, MED12, MFAP5, MYH11, MYLK, NOTCH1, PLOD1, PRDM5, PRKG1, PYCR1, RIN2, SKI, SLC2A10, SLC39A13, SMAD2, SMAD3, SMAD4, TGFB2, TGFB3, TGFB1, TGFB2, TNXB, ZNF469*

Additional genes from our cardiology test menu may be added to this panel by selecting test code J556C.

Clinical Features:

The heritable disorders of connective tissue (HDCT) are a group of clinically and genetically heterogeneous conditions that variably involve the cardiovascular, musculoskeletal, cutaneous, ocular, craniofacial, pulmonary, gastrointestinal and/or neurologic systems.¹ Overlapping features and variable expressivity may challenge clinical diagnosis.^{2,3,4}

Cardiovascular complications that occur in some HDCTs include aortic and arterial aneurysm, dissection or rupture, as well as arterial tortuosity and stenosis, mitral valve prolapse, and patent ductus arteriosus. An increased risk for thoracic aortic aneurysm and dissection (TAAD) may be associated with other syndromic features in Marfan syndrome, Loeys-Dietz syndrome (LDS), Shprintzen-Goldberg syndrome and vascular Ehlers-Danlos syndrome (vEDS).⁵ Aortopathy also occurs more frequently in individuals with pathogenic variants in a number of other genes, including *ACTA2, BGN, LOX, MAT2A, MFAP5, MYH11, MYLK, NOTCH1, PRKG1* and *SMAD4*.^{3,6,7,8} Aneurysms, tortuosity, dissections and/or rupture of other arteries can occur in vEDS, LDS, arterial tortuosity syndrome (ATS), and other rare forms of Ehlers-Danlos syndrome.^{9,10,11} Supravalvular aortic stenosis may be due to pathogenic variants in *ELN*.¹²

Musculoskeletal features in HDCTs include joint hypermobility, scoliosis and/or kyphosis, pectus excavatum/carinatum, precocious osteoarthritis and/or various forms of skeletal dysplasias. Congenital hip dislocation is a hallmark feature of arthrochalasia type EDS¹³ but may also occur in other HDCTs. Craniosynostosis may occur in LDS¹⁰ or Shprintzen-Goldberg syndrome.¹⁴ Contractures may be seen in individuals with congenital contractural arachnodactyly, musculocontractural EDS, or ATS. Stature may be tall in individuals with Marfan syndrome or homocystinuria and short in individuals with Stickler syndrome, or osteogenesis imperfecta (OI).

Ocular complications are associated with some HDCTs. High myopia with or without retinal detachment is a feature of Stickler syndrome or Marfan syndrome. Ectopia lentis occurs in Marfan syndrome and homocystinuria.¹⁵ Keratoconus can occur in individuals with vEDS, brittle cornea syndrome (BCS), or ATS.⁹ Iris flocculi may be associated with pathogenic variants in *ACTA2*.¹⁶ Individuals with BCS or kyphoscoliotic EDS are at risk of spontaneous perforation of the eye.^{13,17}

The cutaneous features of HDCTs include relatively common findings, such as striae and easy bruising, or less frequently seen characteristics, such as hyperextensible or doughy skin, skin fragility and atrophic scars. Loose inelastic skin is a key finding in cutis laxa but also occurs in other conditions, such as ATS or occipital horn syndrome (OHS).⁹ Increased skin transparency may occur in vEDS, LDS, or other rare forms of EDS. Livedo reticularis may be associated with pathogenic

variants in *ACTA2*.¹⁶

Complications of HDCTs may also occur in other systems. Pneumothorax with or without pulmonary blebs are seen in Marfan syndrome and vEDS. Spontaneous bowel and hollow organ rupture can occur in persons with vEDS, as well.¹¹ Hearing loss is associated with Stickler syndrome, OI, BCS, and FKBP14-related EDS.^{17,18,19} Other neurological complications of some HDCTs include hypotonia, myopathy, periventricular heterotopia with or without seizures (*FLNA*-related disorders²⁰), developmental delays or intellectual disability (Sprintzen-Goldberg syndrome, homocystinuria) or psychiatric illness (homocystinuria).^{21,22}

For more in-depth information on a specific HDCT, please refer to OMIM or GeneReviews for the condition of interest or to the references cited above.

Inheritance Pattern/Genetics: Autosomal Dominant, Autosomal Recessive, 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 were 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 were 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.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in the HDCT Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with clearly defined connective tissue disease and a family history of disease. 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 the *B3GALT6* gene, sequencing but no deletion/duplication analysis, is performed.

Gene	Protein	Inheritance	Disease Association(s)
<i>ACTA2</i>	ACTIN, ALPHA-2, SMOOTH MUSCLE, AORTA	AD	fTAAD
<i>ADAMTS2</i>	ADAM METALLOPEPTIDASE WITH THROMBOSPONDIN TYPE 1 MOTIF 2	AR	dEDS
<i>ALDH18A1</i>	ALDEHYDE DEHYDROGENASE 18 FAMILY MEMBER A1	AD, AR	Cutis laxa
<i>ATP6V0A2</i>	ATPASE H+ TRANSPORTING V0 SUBUNIT A2	AR	Cutis laxa
<i>ATP6V1E1</i>	ATPASE H+ TRANSPORTING V1 SUBUNIT E	AR	Cutis laxa
<i>ATP7A</i>	ATPASE COPPER TRANSPORTING ALPHA	XL	Menkes, OHS
<i>B3GALT6</i>	BETA-1,3-GALACTOSYLTRANSFERASE 6	AR	spEDS
<i>B4GALT7</i>	BETA-1,4-GALACTOSYLTRANSFERASE 7	AR	spEDS
<i>B3GAT3</i>	BETA-1,3-GLUCURONYLTRANSFERASE 3	AR	Joint laxity/dislocations, short stature, dysmorphism, CHD
<i>BGN</i>	PROTEOGLYCAN I	XL	Meester-Loeys syndrome, SEMDX
<i>CBS</i>	CYSTATHIONINE BETA-SYNTHASE	AR	Homocystinuria
<i>CHST14</i>	CARBOHYDRATE (DERMATAN 4) SULFOTRANSFERASE 14	AR	mcEDS
<i>COL1A1</i>	COLLAGEN TYPE I ALPHA 1	AD	OI, aEDS, rarely cEDS or vEDS
<i>COL1A2</i>	COLLAGEN TYPE I ALPHA 2	AD, AR (rare)	OI, aEDS, cvEDS
<i>COL2A1</i>	COLLAGEN TYPE II ALPHA 1	AD, AR (rare)	Stickler syndrome, SED, achondrogenesis, Kniest syndrome
<i>COL3A1</i>	COLLAGEN TYPE III ALPHA 1	AD	vEDS
<i>COL5A1</i>	COLLAGEN TYPE V ALPHA 1	AD	cEDS
<i>COL5A2</i>	COLLAGEN TYPE V ALPHA 2	AD	cEDS
<i>COL9A1</i>	COLLAGEN TYPE IX ALPHA 1	AD, AR	MED, Stickler syndrome
<i>COL9A2</i>	COLLAGEN TYPE IX ALPHA 2	AD, AR	MED, Stickler syndrome
<i>COL9A3</i>	COLLAGEN TYPE IX ALPHA 3	AD, AR	MED, Stickler syndrome
<i>COL11A1</i>	COLLAGEN TYPE XI ALPHA 1	AD, AR	Stickler syndrome, Fibrochondrogenesis
<i>COL11A2</i>	COLLAGEN TYPE XI ALPHA 2	AD, AR	Stickler syndrome, Fibrochondrogenesis
<i>COL12A1</i>	COLLAGEN TYPE XII ALPHA 1	AD, AR	mEDS
<i>DSE</i>	DERMATAN SULFATE EPIMERASE	AR	mcEDS
<i>EFEMP2</i>	EGF CONTAINING FIBULIN-LIKE EXTRACELLULAR MATRIX PROTEIN 2	AR	Cutis laxa
<i>ELN</i>	ELASTIN	AD	Cutis laxa, Supravalvular Aortic Stenosis
<i>FBLN5</i>	FIBULIN 5	AD, AR	Cutis laxa
<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>FKBP14</i>	FK506 BINDING PROTEIN 14	AR	kEDS
<i>FLNA</i>	FILAMIN A	XL	EDS variant with PVH
<i>LOX</i>	LYSYL OXIDASE	AD	fTAAD
<i>LTBP4</i>	LATENT TRANSFORMING GROWTH FACTOR BETA BINDING PROTEIN 4	AR	Cutis laxa
<i>MAT2A</i>	METHIONINE ADENOSYLTRANSFERASE II, ALPHA	AD	fTAAD
<i>MED12</i>	MEDIATOR COMPLEX SUBUNIT 12	AD	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>PLOD1</i>	PROCOLLAGEN-LYSINE, 2-OXOGLUTARATE 5-DIOXYGENASE	AR	kEDS
<i>PRDM5</i>	PR DOMAIN 5	AR	BCS
<i>PRKG1</i>	PROTEIN KINASE, cGMP-DEPENDENT, REGULATORY, TYPE I	AD	fTAAD
<i>PYCR1</i>	PYRROLINE-5-CARBOXYLATE REDUCTASE 1	AR	Cutis laxa
<i>RIN2</i>	RAS AND RAB INTERACTOR 2	AR	MACS
<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>SLC39A13</i>	SOLUTE CARRIER FAMILY 39 MEMBER 13	AR	spEDS
<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
<i>TNXB</i>	TENASCIN XB	AR	cEDS
<i>ZNF469</i>	ZINC FINGER PROTEIN 469	AR	BCS

Abbreviations: AD – autosomal dominant; aEDS- arthrochalasia Ehlers-Danlos syndrome; AR – autosomal recessive; BCS – Brittle Cornea Syndrome; cEDS-classical Ehlers-Danlos syndrome; CHD – congenital heart defect; clEDS – classical-like EDS; cvEDS - Cardiac-valvular Ehlers-Danlos syndrome; dEDS- dermatosparaxis Ehlers-Danlos syndrome; fTAAD – familial thoracic aortic aneurysm and dissection; JP/HHT – juvenile polyposis/hereditary hemorrhagic telangiectasia; kEDS- kyphoscoliotic Ehlers-Danlos syndrome; LDS – Loeys-Dietz syndrome; MACS - Macrocephaly, alopecia, cutis laxa, and scoliosis; mcEDS- musculocontractural Ehlers-Danlos syndrome; OHS – Occipital horn syndrome; OI – osteogenesis imperfecta; PVH – periventricular heterotopia; SEMDX – spondyloepimetaphyseal dysplasia, X-linked; spEDS- Spondylodysplasia type Ehlers-Danlos syndrome; vEDS- vascular Ehlers-Danlos syndrome; XL – X-linked

References:

- Murphy-Ryan M et al. (2010) *Genet Med* 12(6):344-54 (PMID: 20467323).
- Alazami AM et al. (2016) *Hum Genet* 135(5):525-40 (PMID: 27023906).
- Bradley TJ et al. (2016) *Can J Cardiol* 32(1):86-99 (PMID: 26724513).
- Weerakkody et al. (2016) *Genet Med* [Epub ahead of print] (PMID: 27011056).
- Ziganshin et al. (2015) *Ann Thorac Surg* 100(5):1604-11 (PMID: 26188975).
- 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.
- Guo et al. (2015) *Am J Hum Genet* 96 (1):170-7 (PMID: 25557781).
- Barbier et al. (2014) *Am J Hum Genet* 95(6):736-43 (PMID: 25434006).
- 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.
- Loeys BL, Dietz HC. Loeys-Dietz Syndrome. 2008 Feb 28 [updated 2013 Jul 11]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015.
- 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.
- Merla et al. (2012) *Circ Cardiovasc Genet* 5(6):692-6 (PMID: 23250899).
- Beighton P et al. (1998) *Am J Med Genet* 77(1):31-7 (PMID: 9557891).
- Doyle AJ et al. (2012) *Nat Genet* 44(11):1249-54 (PMID: 23023332).
- Sadiq MA, Vanderveen D. (2013) *Semin Ophthalmol* 28(5-6):313-20 (PMID: 24138040).
- Guo et al. (2007) *Nat Genet* 39(12):1488-93 (PMID: 17994018).
- Al-Hussain H et al. (2004) *Am J Med Genet* 124A(1):28-34 (PMID: 14679583).
- Acke FR et al. (2012) *Orphanet J Rare Dis* 7:84 (PMID: 23110709).
- Baumann et al. (2012) *Am J Hum Genet* 90(2):201-16 (PMID: 22265013).
- Chen MH, Walsh CA. FLNA-Related Periventricular Nodular Heterotopia. 2002 Oct 8 [updated 2015 Sep 17]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015.
- Greally MT. Shprintzen-Goldberg Syndrome. 2006 Jan 13 [updated 2013 Jun 13]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015.
- Picker JD, Levy HL. Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency. 2004 Jan 15 [updated 2014 Nov 13]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015.