Heritable Disorders of Connective Tissue Panel

Panel Gene List: *ACTA2, ADAMTS2, AEBP1, ALDH18A1, ATP6V0A2, ATP6V1E1, ATP7A, B3GALT6, B3GAT3, B4GALT7, BGN, CBS, CHST14, COL1A1, COL1A2, COL2A1, COL3A1, COL4A1, 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, TAB2, TGFB2, TGFB3, TGFBR1, TGFBR2, TNXB, ZNF469*

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 EDS[13] but may also occur in other HDCTs. Craniosynostosis may occur in LDS[10] or Sphrintzen-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 floculi 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

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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 disorders[20]), 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.

Genetics: Autosomal Dominant, Autosomal Recessive, 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) (only exons 1-31 for TNXB). 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. 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.

Clinical 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. Recombination of TNXB with its pseudogene (gene conversion or TNXB/XA fusion), is not evaluated.

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Gene	Protein	Inheritance	Disease Association(s)
ACTA2	ACTIN, ALPHA-2, SMOOTH MUSCLE, AORTA	AD	fTAAD
AEBP1	AORTIC CARBOXYPEPTIDASE-LIKE PROTEIN	AR	clEDS
ADAMTS2	ADAM METALLOPEPTIDASE WITH THROMBOSPONDIN TYPE 1 MOTIF 2	AR	dEDS
ALDH18A1	ALDEHYDE DEHYDROGENASE 18 FAMILY MEMBER A1	AD, AR	Cutis laxa
ATP6V0A2	ATPASE H+ TRANSPORTING V0 SUBUNIT A2	AR	Cutis laxa
ATP6V1E1	ATPASE H+ TRANSPORTING V1 SUBUNIT E	AR	Cutis laxa
ATP7A	ATPASE COPPER TRANSPORTING ALPHA	XL	Menkes, OHS
B3GALT6	BETA-1,3-GALACTOSYLTRANSFERASE 6	AR	spEDS
B4GALT7	BETA-1,4-GALACTOSYLTRANSFERASE 7	AR	spEDS
B3GAT3	BETA-1,3-GLUCURONYLTRANSFERASE 3	AR	Joint laxity/dislocations, short stature, dysmorphism, CHD
BGN	PROTEOGLYCAN I	XL	Meester-Loeys syndrome, SEMDX
CBS	CYSTATHIONINE BETA-SYNTHASE	AR	Homocystinuria
CHST14	CARBOHYDRATE (DERMATAN 4) SULFOTRANSFERASE 14	AR	mcEDS
COL1A1	COLLAGEN TYPE I ALPHA 1	AD	OI, aEDS, rarely cEDS or vEDS
COL1A2	COLLAGEN TYPE I ALPHA 2	AD, AR (rare)	OI, aEDS, cvEDS
COL2A1	COLLAGEN TYPE II ALPHA 1	AD, AR (rare)	Stickler syndrome, SED, achondrogenesis, Kniest syndrome
COL3A1	COLLAGEN TYPE III ALPHA 1	AD	vEDS
COL4A1	COLLAGEN TYPE IV ALPHA 1	AD	Hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC)
COL5A1	COLLAGEN TYPE V ALPHA 1	AD	cEDS
COL5A2	COLLAGEN TYPE V ALPHA 2	AD	cEDS
COL9A1	COLLAGEN TYPE IX ALPHA 1	AD, AR	MED, Stickler syndrome
COL9A2	COLLAGEN TYPE IX ALPHA 2	AD, AR	MED, Stickler syndrome
COL9A3	COLLAGEN TYPE IX ALPHA 3	AD, AR	MED, Stickler syndrome

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Gene	Protein	Inheritance	Disease Association(s)
COL11A1	COLLAGEN TYPE XI ALPHA 1	AD, AR	Stickler syndrome, Fibrochondrogenesis
COL11A2	COLLAGEN TYPE XI ALPHA 2	AD, AR	Stickler syndrome, Fibrochondrogenesis
COL12A1	COLLAGEN TYPE XIIALPHA 1	AD, AR	mEDS
DSE	DERMATAN SULFATE EPIMERASE	AR	mcEDS
EFEMP2	EGF CONTAINING FIBULIN-LIKE EXTRACELLULAR MATRIX PROTEIN 2	AR	Cutis laxa
ELN	ELASTIN	AD	Cutis laxa, Supravalvular Aortic Stenosis
FBLN5	FIBULIN 5	AD, AR	Cutis laxa
FBN1	FIBRILLIN 1	AD	Marfan syndrome, Acromicric dysplasia, Geleophysic dysplasia, Weill-Marschani syndrome, Stiff Skin syndrome
FBN2	FIBRILLIN 2	AD	Congenital contractural arachnodactyly
FKBP14	FK506 BINDING PROTEIN 14	AR	kEDS
FLNA	FILAMIN A	XL	EDS variant with PVH
LOX	LYSYL OXIDASE	AD	fTAAD
LTBP4	LATENT TRANSFORMING GROWTH FACTOR BETA BINDING PROTEIN 4	AR	Cutis laxa
MAT2A	METHIONINE ADENOSYLTRANSFERASE II, ALPHA	AD	fTAAD
MED12	MEDIATOR COMPLEX SUBUNIT 12	AD	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
PLOD1	PROCOLLAGEN-LYSINE, 2-OXOGLUTARATE 5-DIOXYGENASE	AR	kEDS
PRDM5	PR DOMAIN 5	AR	BCS
PRKG1	PROTEIN KINASE, cGMP-DEPENDENT, REGULATORY,	AD	fTAAD

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Gene	Protein	Inheritance	Disease Association(s)
	TYPE I		
PYCR1	PYRROLINE-5-CARBOXYLATE REDUCTASE 1	AR	Cutis laxa
RIN2	RAS AND RAB INTERACTOR 2	AR	MACS
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
SLC39A13	SOLUTE CARRIER FAMILY 39 MEMBER 13	AR	spEDS
SMAD2	MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILIA, HOMOLOG OF, 2	AD	fTAAD, LDS
SMAD3	MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILA, HOMOLOG OF, 3	AD	fTAAD, LDS
SMAD4	MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILA, HOMOLOG OF, 4	AD	JP/HHT
TAB2	TAK1-BINDING PROTEIN 2	AD	Congenital heart defects, nonsyndromic
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
TNXB	TENASCIN XB	AR	clEDS
ZNF469	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 – ostegenesis imperfecta; PVH – periventricular heterotopia; SEMDX – spondyloepimetaphyseal dysplasia, X-linked; spEDS-Spondyldysplasia type Ehlers-Danlos syndrome; vEDS- vascular Ehlers-Danlos syndrome; XL – X-linked

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