Heritable Disorders of Connective Tissue Panel

Panel Gene List: *ACTA2, ADAMTS2, ALDH18A1, ATP6V0A2, ATP7A, B3GALT6, B4GALT7, CBS, CHST14, COL11A1,COL11A2, COL1A1, COL1A2, COL2A1, COL3A1, COL5A1, COL5A2, COL9A1, COL9A2, DSE, EFEMP2, ELN, FBLN5, FBN1, FBN2, FKBP14, FLNA, LTBP4, MAT2A, MED12, MFAP5, MYH11, MYLK, NOTCH1, PLOD1, PRDM5, PRKG1, PYCR1, RIN2, SKI, SLC2A10, SLC39A13, SMAD3, SMAD4, TGFB2, TGFB3, TGFBR1, TGFBR2, ZNF469*

Additional genes from our cardiology test menu may be added to this panel by selecting test code J555C.

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, 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, other valvular disease and patent ductus arteriosus may also occur. 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 (EDS).[5] Aortopathy also occurs more frequently in individuals with pathogenic variants in a number of other genes, including ACTA2, MAT2A, MFAP5, MYH11, MYLK, NOTCH1, PRKG1 and SMAD4.[3,6,7,8] Aneurysms, tortuosity, dissections and/or rupture of other arteries can occur in vascular EDS, LDS, arterial tortuosity syndrome (ATS), other rare forms of Ehlers-Danlos syndrome and several other HDCTs.[9,10,11] Supravalvular aortic and other arterial stenosis may be due to pathogenic variants in ELN12; arterial stenosis may occur in ATS.[9]

Musculoskeletal features in HDCTs include joint hypermobility with or without dislocations, scoliosis and/or kyphosis, pectus excavatum/carinatum and precocious osteoarthritis. Congenital hip dislocation is a hallmark feature of arthrochalasia type EDS[13] but may also occur in other HDCTs. Craniosynostosis may occur in LDS10 or Sphrintzen-Goldberg syndrome.[14] Contractures may be seen in individuals with congenital contractural arachnodactyly, musculocontractural type EDS, or ATS. Stature may be tall in individuals with Marfan syndrome or homocystinuria and short in individuals with Stickler syndrome or rare types of EDS.

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 (dislocated lenses) occurs in Marfan syndrome and homocystinuria.[15] Keratoconus can occur in individuals with vascular EDS, BCS or ATS.[9] Iris floculi or iris hypoplasia may be present in individuals 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 vascular EDS, LDS or other rare forms of EDS. Livedo reticularis may be present in some individuals 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 vascular EDS. Spontaneous bowel and hollow organ rupture can occur in persons with vascular EDS, as well.[11] Hearing loss is associated with Stickler syndrome, 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 Gene Reviews for the condition of interest or to the references cited above.

Inheritance Pattern/Genetics: Autosomal Dominant or Autosomal Recessive

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. 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

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.

Gene	Protein	Inheritance	Disease Association(s)
ACTA2	ACTIN, ALPHA-2, SMOOTH MUSCLE, AORTA	AD	fTAAD
ADAMTS2	ADAM METALLOPEPTIDASE WITH THROMBOSPONDIN TYPE 1 MOTIF 2	AR	dEDS
ALDH18A1	ALDEHYDE DEHYDROGENASE 18 FAMILY MEMBER A1	AD AR	Cutis laxa Cutis laxa
ATP6V0A2	ATPASE H+ TRANSPORTING V0 SUBUNIT A2	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
CBS	CYSTATHIONINE BETA-SYNTHASE	AR	Homocystinuria
CHST14	CARBOHYDRATE (DERMATAN 4) SULFOTRANSFERASE 14	AR	mcEDS
COL11A1	COLLAGEN TYPE XI ALPHA 1	AD	Fibrochondrogenesis Stickler syndrome
COL11A2	COLLAGEN TYPE XI ALPHA 2	AD	Fibrochondrogenesis Stickler syndrome, non-ocular
COL1A1	COLLAGEN TYPE I ALPHA 1	AD	aEDS cEDS Osteogenesis Imperfecta
COL1A2	COLLAGEN TYPE I ALPHA 2	AD AR	EDS, type VIIB Osteogenesis Imperfecta cvEDS
COL2A1	COLLAGEN TYPE II ALPHA 1	AD AR	OSMED Stickler syndrome
COL3A1	COLLAGEN TYPE III ALPHA 1	AD	vEDS
COL5A1	COLLAGEN TYPE V ALPHA 1	AD	cEDS
COL5A2	COLLAGEN TYPE V ALPHA 2	AD	cEDS
COL9A1	COLLAGEN TYPE IX ALPHA 1	AD AR	Stickler syndrome
COL9A2	COLLAGEN TYPE IX ALPHA 2	AD AR	Stickler syndrome
DSE	DERMATAN SULFATE EPIMERASE	AR	mcEDS
EFEMP2	EGF CONTAINING FIBULIN-LIKE EXTRACELLULAR MATRIX PROTEIN 2	AR	Cutis laxa
ELN	ELASTIN	AD	Cutis laxa
FBLN5	FIBULIN 5	AD AR	Cutis laxa Cutis laxa
FBN1	FIBRILLIN 1	AD	Marfan syndrome
FBN2	FIBRILLIN 2	AD	Congenital contractural arachnodactyly
FKBP14	FK506 BINDING PROTEIN 14	AR	EDS with progressive kyphoscoliosis, myopathy, and hearing loss
FLNA	FILAMIN A	XL	EDS with periventricular heterotopia
LTBP4	LATENT TRANSFORMING GROWTH FACTOR BETA BINDING PROTEIN 4	AR	Cutis laxa, autosomal recessive
MAT2A	METHIONINE ADENOSYLTRANSFERASE II, ALPHA	AD	fTAAD
MED12	MEDIATOR COMPLEX SUBUNIT 12	AD	fTAAD, Lujan syndrome
MFAP5	MICROFIBRILLAR-ASSOCIATED PROTEIN 5	AD	fTAAD
MYH11	MYOSIN, HEAVY CHAIN 11, SMOOTH MUSCLE	AD	fTAAD
MYLK	MYOSIN LIGHT CHAIN KINASE	AD	fTAAD

Gene (cont.)	Protein	Inheritance	Disease Association(s)
NOTCH1	NOTCH, DROSOPHILA, HOMOLOG OF, 1	AD	fTAAD
PLOD1	PROCOLLAGEN-LYSINE, 2-OXOGLUTARATE 5-DIOXYGENASE	AR	kEDS
PRDM5	PR DOMAIN 5	AR	BCS
PRKG1	PROTEIN KINASE, cGMP-DEPENDENT, REGULATORY, TYPE I	AD	fTAAD
PYCR1	PYRROLINE-5-CARBOXYLATE REDUCTASE 1	AR	Cutis laxa, autosomal recessive
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	EDS, Spondylocheirodysplasia type
SMAD3	MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILA, HOMOLOG OF, 3	AD	LDS
SMAD4	MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILA, HOMOLOG OF, 4	AD	JP/HHT
TGFB2	TRANSFORMING GROWTH FACTOR, BETA-2	AD	LDS
TGFB3	TRANSFORMING GROWTH FACTOR, BETA-3	AD	LDS
TGFBR1	TRANSFORMING GROWTH FACTOR-BETA RECEPTOR, TYPE I	AD	LDS
TGFBR2	TRANSFORMING GROWTH FACTOR-BETA RECEPTOR, TYPE II	AD	LDS
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; 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; spEDS- Spondylocheirodysplasia type Ehlers-Danlos syndrome; vEDS- vascular Ehlers-Danlos syndrome; XL – X-linked

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