Ehlers-Danlos Syndrome Panel

Panel Gene List:

COL1A1, COL3A1, COL5A1, COL5A2

Clinical Features:

The Ehlers-Danlos syndromes (EDS) are a group of heritable disorders of connective tissue with at least 13 defined types.[1] This panel tests for classical EDS and vascular EDS. Classical EDS (cEDS) is typically characterized by joint hypermobility, skin hyperextensibility, and widened atrophic scarring.[2] Vascular EDS (vEDS) is typically characterized by arterial aneurysm/dissection/rupture, spontaneous bowel perforation, and/or uterine rupture in pregnancy.[3] Phenotypic variability occurs in both conditions and additional connective tissue features may also be present, such as easy bruising and thin/fragile skin. A family history of cEDS or vEDS is informative when present but does not exclude the diagnosis, as approximately 50% of cases are due to de novo occurrence of a pathogenic variant.[4,5] For more in-depth information about cEDS or vEDS, please refer to OMIM, GeneReviews, or to the references cited above.

Inheritance Pattern/Genetics:

Autosomal Dominant

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. 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, 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 Ehlers-Danlos Syndrome Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with a typical clinical presentation and 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)
COL1A1	COLLAGEN TYPE I, ALPHA I	AD	OI, OI-EDS spectrum disorder, COL1A1-related arthrochalasia EDS, classic non-deforming OI, COL1A1-related Caffey disease
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

Abbreviations: AD – autosomal dominant; EDS – Ehlers-Danlos syndrome; OI- Osteogenesis Imperfecta

References:

1. Malfait F, Francomano C, Byers P, et al. 2017. The 2017 International Classification of the Ehlers-Danlos syndromes. Am J Med Genet Part C Semin Med Genet 175 (1):8-26. (PMID: 28306229)
2. Bowen JM, Sobey GJ, Burrows NP, et al., Ehlers-Danlos Syndrome, Classical Type. Am J Med Genet Part C Semin Med Genet 175C (1):27-39. (PMID: 28192633)
3. Byers PH. Vascular Ehlers-Danlos Syndrome. GeneReviews. 2019 Vascular Ehlers-Danlos Syndrome.20301667
4. Byers PH et al. (2017) Am J Med Genet C Semin Med Genet. 175 (1):40-47 (PMID: 28306228)
5. Malfait F et al. (2018) GeneReviews. Classic Ehlers-Danlos Syndrome (PMID: 20301422)