

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.

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. 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 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)
<i>COL1A1</i>	COLLAGEN TYPE I ALPHA 1	AD	Osteogenesis, Impertecta, Arthrochalasia EDS, Vascular EDS, Caffey disease
<i>COL3A1</i>	COLLAGEN TYPE III ALPHA 1	AD	Vascular EDS
<i>COL5A1</i>	COLLAGEN TYPE V ALPHA 1	AD	Classical EDS
<i>COL5A2</i>	COLLAGEN TYPE V ALPHA 2	AD	Classical EDS

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

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, Belmont J, Black J, et al. 2017. Diagnosis, natural history, and management in vascular Ehlers–Danlos syndrome. *Am J Med Genet Part C Semin Med Genet* 175C:40–47. (PMID: 28306228)
4. Pepin MG, Murray ML, Byers PH. Vascular Ehlers-Danlos Syndrome. 1999 Sep 2 [Updated 2015 Nov 19]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1494/> Gomez-Ospina & Bernstein (2016) *Am. J. Med. Genet. A* 170A(4):870-80 (PMID: 26756138)
5. Malfait F, Wenstrup R, De Paepe A. Classic Ehlers-Danlos Syndrome. 2007 May 29 [Updated 2018 Jul 26]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1244/> Snead et al. (2011) *Eye (Lond)*. 25(11):1389-1400 (PMID: 21921955)