

Ehlers-Danlos Syndrome, Type IV via *COL3A1* Gene Sequencing (Test #844)

Brief Description of Clinical Features: Ehlers-Danlos syndrome type IV (EDS IV or Vascular EDS, OMIM# 130050) is characterized by thin, translucent skin; easy bruising; characteristic facial appearance, and arterial, intestinal, and/or uterine fragility (Pepin & Byers *GeneReviews* 2011). Vascular dissection or rupture, gastrointestinal perforation, or organ rupture are the presenting signs in the majority of adults identified to have EDS IV. In childhood, inguinal hernia, pneumothorax, and recurrent joint subluxation or dislocation can occur. Pregnancy for women with EDS type IV has as much as a 12% risk for death from peripartum arterial rupture or uterine rupture.

Genetics: EDS IV is inherited in an autosomal dominant manner and is caused by mutations in the *COL3A1* gene. About half of affected individuals have inherited the mutation from an affected parent, and the other half have a *de novo COL3A1* mutation. *COL3A1* encodes the pro α 1(III) chain of type III procollagen, a major structural component of skin, blood vessels, and hollow organs. The type III procollagen molecule is a homotrimer; *COL3A1* mutations typically result in a structural alteration of type III collagen that leads to intracellular storage and impaired secretion of collagen chains. The majority of identified mutations result in substitution of other amino acids for glycine residues in the Gly-X-Y triplets of the triple helical domain. Most of the remaining mutations affect splice sites and usually result in exon skipping. Less common mutations are those that create premature stop codons and result in *COL3A1* haploinsufficiency (Schwarze et al. *Am J Hum Genet* 69:989–1001, 2001).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of all coding exons of the *COL3A1* gene plus ~50 bp of flanking non-coding DNA on each side. As indicated, we will sequence any single exon (Test #100, \$190) in family members of patients with known mutations, or to confirm research results.

Reference Sequences: Genomic: NC_000002.11 mRNA: NM_000090.3
Protein: NP_000081.1 mRNA and Protein: CCDS 2297.1

Indications for Test: Candidates for this test are patients with clinical and/or biochemical features consistent with EDS IV, and family members of patients who have known *COL3A1* mutations.

Sensitivity of Test: This test is predicted to detect disease mutations in at least 95% of individuals with EDS IV (Pepin & Byers *GeneReviews* 2011). About 2% of individuals with EDS IV have large deletion involving single or multiple exons, which would not be detected by this sequencing assay. A gene-centric array comparative genomic hybridization (aCGH) test is available to evaluate copy number changes in *COL3A1* (see Test #600).

Turnaround Time: Maximum of 40 calendar days.

Specimen Requirements: See page four of the Requisition Form.

Prices:	Sequencing of <i>COL3A1</i> gene	\$ 2230
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x53	83898 \$ 740	Sequencing x53 83904 \$1095
Separation x1	83894 \$ 180	Interpretation/Report x1 83912 \$ 145

Accreditation: CLIA ID:52D1027685 (expires 1/18/13) CAP ID:7185561, AU ID:1407125 (expires 12/20/12)

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