

Ehlers-Danlos Syndrome, Classic Type via *COL5A1* (Test #841), *COL5A2* (Test #842), or *COL5A1* & *COL5A2* (Test #840) Gene Sequencing

Brief Description of Clinical Features: Classic Ehlers-Danlos syndrome (EDS) is a heritable connective tissue disorder characterized by skin hyperextensibility, fragile and soft skin, delayed wound healing with formation of atrophic scars, easy bruising, and generalized joint hypermobility (Malfait et al. *Genet Med* 12:597-605, 2010). It includes two previously designated subtypes, EDS type I (OMIM#130000) and EDS type II (OMIM#130010), which are now recognized to form a continuum of clinical findings and differ only in phenotypic severity.

Genetics: EDS, classic type is inherited in an autosomal dominant manner. It is estimated that approximately 50% of affected individuals have a *de novo* mutation. Mutations in the *COL5A1* and the *COL5A2* genes, encoding the $\alpha 1$ and the $\alpha 2$ -chain of type V collagen respectively, are responsible for the majority of patients with classic EDS (Malfait et al. *Am J Med Genet C Semin Med Genet.* 139C:17-23, 2005). Type V collagen is a quantitatively minor fibrillar collagen that is widely distributed in a variety of tissues, and present mainly as $[\alpha 1(V)]_2 \alpha 2(V)$ heterotrimers in skin, bone, and tendon. It forms heterotypic fibrils with type I collagen and controls collagen fibril assembly in several tissues (Wenstrup et al. *J Biol Chem* 279:53331–53337, 2004). In approximately 40% of individuals with classic EDS, nonsense or frameshift mutations are found in *COL5A1*, which lead to haploinsufficiency of the $\alpha 1$ -chain of type V collagen (Malfait et al. *Hum Mutat* 25:28–37, 2005). A small proportion of cases have *COL5A1* or *COL5A2* mutations that produce a functionally defective type V collagen protein exerting a dominant-negative effect; these mutations are most commonly splice-site mutations that result in exon skipping or point mutations that result in a glycine substitution in the triple-helical region of the collagen molecule (Giunta & Steinmann. *Am J Med Genet* 90:72–79, 2000; Malfait et al. *Hum Mutat* 25:28–37, 2005).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of all coding exons of the *COL5A1* and *COL5A2* genes plus ~50 bp of flanking non-coding DNA on each side. Unless specially requested, we will sequence *COL5A1* first. If a pathogenic mutation is found, testing will stop; if no mutation (or a variant of unknown significance) is found in *COL5A1*, we will proceed with sequencing *COL5A2*. Sequencing of either gene may also be ordered separately (Tests #841 and 842). As indicated, we will sequence any single exon (Test #100, \$190) in family members of patients with known mutation, or to confirm research results.

Reference Sequences:

Gene	Genomic	mRNA	Protein	CCDS
<i>COL5A1</i>	NC 000009.11	NM 000093.3	NP 000084.3	6982.1
<i>COL5A2</i>	NC 000002.11	NM 000393.3	NP 000384.2	33350.1

Indications for Test: Candidates for this test are patients with clinical features consistent with EDS, classic type, and family members of patients who have known *COL5A1* or *COL5A2* mutations.

Sensitivity of Test: Combining *COL5A1* and *COL5A2*, this test is predicted to detect disease mutations in at least 50% of affected individuals with classic EDS (Malfait et al. *GeneReviews* 2011). No large deletions/duplications involving *COL5A1* or *COL5A2* as causative of EDS have been reported.

Turnaround Time: Maximum of 50 calendar days, although many tests are completed in 2 - 3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Prices: Sequencing of both *COL5A1* and *COL5A2* Genes \$ 4290

Test	CPT Codes						Totals
	83890	83891	83898	83904	83894	83912	
<i>COL5A1</i> Only (Test# 841)	\$30 (x1)	\$40 (x1)	\$835 (x60)	\$1250 (x60)	\$175 (x1)	\$140 (x1)	\$2470
<i>COL5A2</i> Only (Test # 842)	\$30 (x1)	\$40 (x1)	\$740 (x55)	\$1110 (x54)	\$200 (x1)	\$140 (x1)	\$2260
Both genes (Test # 840)	\$30 (x1)	\$40 (x1)	\$1480 (x114)	\$2215 (x114)	\$375 (x1)	\$150 (x1)	\$4290

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

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