

Stickler Syndrome Panel via Sequential *COL2A1*, *COL11A1*, and *COL11A2* Gene Sequencing (Test #830)

Brief Description of Clinical Features: Stickler syndrome (STL) is a multisystem and clinically variable disorder that can include ocular findings of myopia, cataract, and retinal detachment; hearing loss that is both conductive and sensorineural; midfacial underdevelopment and cleft palate (either alone or as part of the Robin sequence); and mild spondyloepiphyseal dysplasia and/or precocious arthritis (Robin et al. *GeneReview*, 2010). At present, at least three types of autosomal dominant and two types of autosomal recessive Stickler syndrome have been described. The majority (80-90%) of individuals with Stickler syndrome have Type I “membranous” congenital vitreous anomaly and milder hearing loss (STL1). About 10-20% of individuals with Stickler syndrome have Type II “beaded” congenital vitreous anomaly and significant hearing loss (STL2). Type III Stickler syndrome (STL3) is a rare form, which is characterized by craniofacial and joint abnormalities and hearing loss but without ocular findings. Autosomal recessive STL is very rare; only two families have been reported with this type to date (Van Camp et al. *Am J Hum Genet* 79:449-457, 2006; Baker et al. *Am J Med Genet* 155A: 1668-1672, 2011). For this reason, testing of the recessive STL is not included in the current panel, but is available through individual gene tests (See Tests #805 and 817)

Genetics: The dominant STL-associated genes are summarized in the following table.

Gene	Disorder	Inheritance	OMIM#	Protein
<i>COL2A1</i>	STL1	AD	108300	Collagen alpha-1(II) chain
<i>COL11A1</i>	STL2	AD	604841	Collagen alpha-1(XI) chain
<i>COL11A2</i>	STL3	AD	184840	Collagen alpha-2(XI) chain

Type XI procollagen is a heterotrimeric protein assembled from the products of three genes, *COL11A1*, *COL11A2*, and *COL2A1*. Mature type XI collagen accounts for 3%–10% of the collagenous protein content of cartilage (Tompson et al. *Am J Hum Genet* 87:708-712, 2010). *COL11A1* is presumed to play an important role in fibrillogenesis by controlling lateral growth of collagen II fibrils. The majority of reported cases with *COL2A1*-related STL had truncating mutations (nonsense, frameshift, or splicing) that result in functional haploinsufficiency of the *COL2A1* gene product. Mutations in *COL11A1* and *COL11A2* generally lead to a disruption of the Gly-X-Y collagen sequence and impaired synthesis or function of type XI collagen.

Description of This Particular Test: This test involves sequential sequencing of all three STL genes. When a likely causative mutation(s) is detected, testing stops at that point. The order of genes may be specified by the client. The default order is *COL2A1*, *COL11A1*, and *COL11A2*. *COL11A2* may be tested first for individuals with craniofacial and joint manifestations and hearing loss but without ocular findings. We will also sequence any single exon (Test #100, \$190) in any of these genes for family members of patients with known mutations, or to confirm research results. Tests for individual sequencing of these three genes are also available (see Tests #788, 831, and 829).

Reference Sequences:

Gene	Genomic	mRNA	Protein	CCDS
<i>COL2A1</i>	NC 000012.11	NM 001844.4	NP 001835.3	41778.1
<i>COL11A1</i>	NC 000001.10	NM 001854.3	NP 001845.3	778.1
<i>COL11A2</i>	NC 000006.11	NM 080681.2	NP 542412.2	43452.1

Indications for Test: Candidates for this test are patients with clinical findings suggestive of Stickler syndrome.

Sensitivity of Test: Sequencing of *COL2A1* and *COL11A1* is predicted to detect disease mutations in about 90% of cases with a clinical diagnosis of STL (Robin et al. *GeneReview*, 2010). Mutations in *COL11A2* are rare, and the detection rate is currently unknown.

Turnaround Time: Maximum of 40 calendar days for the first gene and 10 days each for subsequent gene, although most tests are completed much more rapidly.

Specimen Requirements: See page 4 of the Requisition Form.

Prices: \$1990 - \$5550

CPT Codes							
Test	83890	83891	83898	83904	83894	83912	Totals
<i>COL2A1</i> alone	\$30 (x1)	\$40 (x1)	\$660 (x47)	\$990 (x47)	\$140 (x1)	\$130 (x1)	\$1990
<i>COL11A1</i> alone	\$30 (x1)	\$40 (x1)	\$830 (x60)	\$1250 (x60)	\$170 (x1)	\$140 (x1)	\$2460
<i>COL11A2</i> alone	\$30 (x1)	\$40 (x1)	\$690(x49)	\$1040(x49)	\$150 (x1)	\$140 (x1)	\$2090
Complete Panel*	\$30 (x1)	\$40 (x1)	\$1900(x156)	\$2860(x156)	\$440 (x1)	\$280 (x1)	\$ 5550*

*When two or more genes in the Panel are tested, the price will be 85% of the sum of the individual gene prices.

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

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