

## Stickler Syndrome Panel

### PANEL GENE LIST

*COL2A1, COL9A1, COL9A2, COL9A3, COL11A1, COL11A2*

### CLINICAL FEATURES

Stickler syndrome is a heritable disorder of connective tissue characterized by ocular, auditory, craniofacial, and musculoskeletal manifestations. Ocular features include high myopia, congenital vitreous anomalies, cataracts, and retinal detachment.<sup>1,2</sup> Hearing impairment of variable severity is present in 40% of individuals with Stickler syndrome.<sup>3</sup> Mid-facial hypoplasia, micrognathia, and cleft palate may be present, and a diagnosis of Stickler syndrome is established in approximately 10-20% of individuals with Robin sequence.<sup>4,5</sup> Skeletal involvement may manifest as early-onset osteoarthritis, relative short stature, joint hypermobility, and scoliosis/kyphosis; radiographic features include mild spondyloepiphyseal dysplasia and platyspondyly.<sup>6</sup> Variable expressivity is observed both within and between families, though the ocular phenotype tends to be consistent within families.<sup>3,7</sup> In addition, both ocular-only and non-ocular forms of Stickler syndrome are described.<sup>2,6,8</sup>

For more in-depth information about Stickler syndrome, please refer to OMIM or GeneReviews, or to the references cited above.

### INHERITANCE PATTERN/GENETICS

Autosomal Dominant, Autosomal Recessive

### 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.

### TEST SENSITIVITY

The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in the Stickler Syndrome Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with clearly defined Stickler syndrome and a family history of disease. The technical sensitivity of sequencing 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
<i>COL2A1</i>	COLLAGEN TYPE II ALPHA 1	AD, AR (rare)	Stickler syndrome, SED, achondrogenesis, Kniest dysplasia
<i>COL9A1</i>	COLLAGEN TYPE IX ALPHA 1	AD, AR	MED, Stickler syndrome
<i>COL9A2</i>	COLLAGEN TYPE IX ALPHA 2	AD, AR	MED, Stickler syndrome
<i>COL9A3</i>	COLLAGEN TYPE IX ALPHA 3	AD, AR	MED, Stickler syndrome
<i>COL11A1</i>	COLLAGEN TYPE XI ALPHA 1	AD, AR	Stickler syndrome, Fibrochondrogenesis
<i>COL11A2</i>	COLLAGEN TYPE XI ALPHA 2	AD, AR	Stickler syndrome, Fibrochondrogenesis

Abbreviations: AD – autosomal dominant; AR – autosomal recessive; MED - Multiple epiphyseal dysplasia; SED – Spondyloepiphyseal dysplasia

## REFERENCES:

- Rose et al. (2005) *Am. J. Med. Genet. A* 138A (3):199-207 (PMID: 16152640)
- Snead et al. (2011) *Eye (Lond)*. 25(11):1389-1400 (PMID 21921955)
- Snead & Yates. (1999) *J. Med. Genet.* 36:353-359. (PMID 10353778)
- Evans et al. (2006) *Int. J. Pediatr. Otorhinolaryngol.* 70(6):973-80 (PMID 16443284)
- Gomez-Ospina & Bernstein (2016) *Am. J. Med. Genet. A* 170A(4):870-80 (PMID 26756138)
- Robin et al. Stickler Syndrome. 2000 Jun 9 [Updated 2017 Mar 16]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015.
- Richards et al. (2010) *Hum. Mutat.* 31(6):E1461-71. (PMID 20513134)
- Acke et al. (2014) *Mol. Genet. Metab.* 113 (3):230-5 (PMID: 25240749)