Stickler Syndrome Panel, Sequencing

Stickler syndrome and related disorders are a group of inherited conditions characterized by ocular abnormalities, hearing loss, and skeletal or joint problems. Most individuals with Stickler syndrome have a distinct facial appearance with a flattened midface, sometimes with Pierre Robin sequence. The majority of cases of Stickler syndrome are caused by variants in the *COL2A1* gene, which codes for type II collagen. Variants in *COL2A1* are also associated with a number of related disorders with variable severity, including achondrogenesis type II, spondyloepiphyseal dysplasia congenita, and spondyloperipheral dysplasia. Pathogenic variants in *COL11A1* and other collagen genes cause a smaller percentage of Stickler syndrome cases, as well as other disorders with overlapping features such as fibrochondrogenesis and multiple epiphyseal dysplasia. Diagnosis of Stickler syndrome or a related disorder may be suspected based on clinical features, but confirmation of the condition requires genetic testing.

Tests to Consider

Stickler Syndrome Panel, Sequencing
3001613

Method: Massively Parallel Sequencing

- Use to confirm a diagnosis of Stickler syndrome or a related disorder
- Regions of low coverage and reported variants are confirmed by Sanger sequencing as necessary

See Related Tests

Disease Overview

Symptoms

- Ocular abnormalities (eg, high myopia, vitreous abnormalities, retinal detachment)
- Hearing impairment (both conductive and sensorineural)
- Skeletal abnormalities (eg, early-onset arthritis, short stature, spondyloepiphyseal dysplasia upon radiographic evaluation, scoliosis, or kyphosis)
- Craniofacial features (eg, flat facial profile/midface hypoplasia or cleft palate, sometimes with Pierre Robin sequence)

Genetics

Genes

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

Etiology

Stickler syndrome may be caused by pathogenic variants in the *COL2A1*, *COL11A1*, *COL11A2*, *COL9A1*, *COL9A2*, and *COL9A3* genes. In some rare families, other unknown genes may be involved. Pathogenic variants in *VCAN* cause Wagner syndrome, a condition with overlapping ocular symptoms.

Penetrance

100%

Prevalence

1/7,500 to 1/9,000 among newborns

Inheritance

See Genes Tested table below

Test Description

Clinical Sensitivity

Variable, dependent on phenotype/condition

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimatea (%)	Analytical Sensitivity (PPA) 95% Credibility Regiona (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	99.9	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	99.9	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Limitations

- A negative result does not exclude a diagnosis of Stickler syndrome or a related disorder.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted gene(s)
  - Regulatory region and deep intronic variants
  - Noncoding transcripts
  - Large deletions/duplications in any of the tested genes (large deletions/duplications account for <1% of causative variants for Stickler syndrome)
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants, due to technical limitations in the presence of pseudogenes or repetitive or homologous regions
  - Low-level somatic variants

Genes Tested

Gene	MIM Number	Associated Disorders	Inheritance
COL11A1	120280	Fibrochondrogenesis 1	AR
		Marshall syndrome	AD
		Stickler syndrome, type II	AD

AD, autosomal dominant; AR, autosomal recessive

Gene	MIM Number	Associated Disorders	Inheritance
COL11A2	120290	Fibrochondrogenesis 2	AD
		Otospondylomegaepiphyseal dysplasia	AD
		Otospondylomegaepiphyseal dysplasia	AR
COL2A1	120140	Legg-Calve-Perthes disease	AD
		Osteoarthritis with mild chondrodysplasia	AD
		Spondyloperipheral dysplasia	AD
		Epiphyseal dysplasia, multiple, with myopia and conductive deafness	AD
		Spondyloepimetaphyseal dysplasia, Strudwick type	AD
		Stickler syndrome, type I	AD
		Achondrogenesis, type II	AD
		Czech dysplasia	AD
		Stickler syndrome, type I, nonsyndromic ocular	AD
		Spondyloepiphyseal dysplasia, Stanescu type	AD
		Platyspondylic lethal skeletal dysplasia, Torrance type	AD
		Kniest dysplasia	AD
		Spondyloepiphyseal dysplasia congenita	AD
COL9A1	120210	Stickler syndrome, type IV	AR
COL9A2	120260	Epiphyseal dysplasia, multiple, type 2	AD
		Stickler syndrome, type V	AR
COL9A3	120270	Epiphyseal dysplasia, multiple, type 3	AD
VCAN	118661	Wagner vitreoretinopathy	AD

AD, autosomal dominant; AR, autosomal recessive

Additional Resources

Annunen S, Körkkö J, Czarny M, et al. Splicing mutations of 54-bp exons in the COL11A1 gene cause Marshall syndrome, but other mutations cause overlapping Marshall/Stickler phenotypes. Am J Hum Genet. 1999;65(4):974-983. PubMed

Guo L, Elcioglu NH, Wang Z, et al. Novel and recurrent *COL11A1* and *COL2A1* mutations in the Marshall-Stickler syndrome spectrum. Hum Genome Var. 2017;4:17040. PubMed

Robin NH, Moran RT, Ala-Kokko L. Stickler syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last update: Jun 2000; Accessed: Aug 2020]

Related Tests

Skeletal Dysplasia Panel, Sequencing and Deletion/Duplication 2012015

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

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