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Stickler Syndrome

Synonym: Arthroophthalmopathy

Geert Mortier, MD, PhD[1]

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Summary

Clinical characteristics

Stickler syndrome is a connective tissue 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 Pierre Robin sequence); and early-onset degenerative joint disease. Variable phenotypic expression of Stickler syndrome occurs both within and among families; interfamilial variability is in part explained by locus and allelic heterogeneity.

Diagnosis/testing

The diagnosis of Stickler syndrome can be established in a proband with characteristic clinical features and/or a heterozygous pathogenic variant in *COL2A1*, *COL11A1*, or *COL11A2* or biallelic pathogenic variants in *COL9A1*, *COL9A2*, or *COL9A3* identified by molecular genetic testing.

Management

Treatment of manifestations: Management in a comprehensive craniofacial clinic when possible; tracheostomy as needed in infants with Pierre Robin sequence; mandibular advancement procedure to correct malocclusion for those with persistent micrognathia; feeding and nutritional management as needed per craniofacial specialists; laser therapy for prevention of retinal detachment; education on risks and symptoms of retinal detachment; correction of refractive errors with spectacles; standard treatment of sensorineural and conductive hearing loss; prompt treatment of otitis media; consider myringotomy tubes for recurrent otitis media; symptomatic treatment for arthropathy; treatment of osteoarticular manifestations per orthopedist.

Surveillance: Annual examination by a vitreoretinal specialist; audiologic evaluations annually; clinical, radiographic, and/or orthopedic assessment as needed.

Agents/circumstances to avoid: Activities such as contact sports that may lead to traumatic retinal detachment.

Author Affiliation: 1 Center for Human Genetics, University Hospitals Leuven, Leuven, Belgium; Email: geert.mortier@uzleuven.be.

Evaluation of relatives at risk: It is appropriate to determine which family members at risk have Stickler syndrome and thus warrant ongoing surveillance and possible treatment to prevent retinal detachment.

Genetic counseling

Stickler syndrome caused by pathogenic variants in *COL2A1*, *COL11A1*, or *COL11A2* is inherited in an autosomal dominant manner; Stickler syndrome caused by pathogenic variants in *COL9A1*, *COL9A2*, or *COL9A3* is inherited in an autosomal recessive manner.

Autosomal dominant inheritance: Each child of an individual with autosomal dominant Stickler syndrome has a 50% chance of inheriting the pathogenic variant.

Autosomal recessive inheritance: If both parents are known to be heterozygous for an autosomal recessive Stickler syndrome-related pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives requires prior identification of the pathogenic variants in the family.

Once the Stickler syndrome-related pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for Stickler syndrome have been published.

Suggestive Findings

Stickler syndrome **should be suspected** in individuals with a combination of the following clinical and radiographic findings.

Clinical findings

- Cleft palate (open cleft, submucous cleft, or bifid uvula)
- Characteristic facial features including malar hypoplasia, broad or flat nasal bridge, and micro- or retrognathia
- Ocular manifestations including high myopia, vitreous abnormalities, cataracts, and/or retinal abnormalities
- Sensorineural hearing loss with or without conductive hearing loss
- Osteoarticular manifestations with joint pain in childhood and early-onset degenerative joint disease in adulthood

Imaging findings

- Signs of mild spondyloepiphyseal involvement can be present on radiographs: mild flattening of the vertebrae with or without end plate irregularities; small or dysplastic epiphyses, especially at the hips or knees; Legg-Calvé-Perthes-like changes in the hips [Wang et al 2023]
- Early-onset degenerative joint disease

Establishing the Diagnosis

The diagnosis of Stickler syndrome can be **established** in a proband with characteristic clinical features and a heterozygous pathogenic (or likely pathogenic) variant in *COL2A1*, *COL11A1*, or *COL11A2* or biallelic pathogenic (or likely pathogenic) variants in *COL9A1*, *COL9A2*, or *COL9A3* (see Table 1) identified by molecular genetic testing.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of variant(s) of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

A multigene panel that includes *COL2A1*, *COL11A1*, *COL11A2*, *COL9A1*, *COL9A2*, *COL9A3*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Stickler Syndrome

Gene [1]	Proportion of Stickler Syndrome Attributed to Pathogenic Variants in Gene	MOI	Proportion of Pathogenic Variants [2] Identified by Method	
			Sequence analysis [3]	Gene-targeted deletion/duplication analysis [4]
COL2A1	~80% [5]	AD	~99%	<1% [6]
COL11A1	~20% [5]	AD [7]	~99%	<1% [6]
COL11A2	<1% [6]	AD	~100%	None reported [6, 8]
COL9A1	<1% [6]	AR	~100%	None reported [6, 8]
COL9A2	<1% [6]	AR	~100%	None reported [6, 8]
COL9A3	<1% [6]	AR	~100%	None reported [6, 8]

Table 1. continued from previous page.

Gene [1]	Proportion of Stickler Syndrome Attributed to Pathogenic Variants in Gene	MOI	Proportion of Pathogenic Variants [2] Identified by Method	
			Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
Unknown [9]	1%	NA	NA	NA

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; NA = not applicable
1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in these genes.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. Choi et al [2021], Soh et al [2022]
6. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
7. Rarely, biallelic *COL11A1* pathogenic variants have been reported in individuals with Stickler syndrome [Snead et al 2022]; in these instances, at least one pathogenic variant affects the alternatively spliced exon 9, and individuals have presented with more severe hearing loss [Richards et al 2013, Nixon et al 2020, Nixon et al 2022].
8. To date, large exon or multiexon deletions or duplications in *COL11A2*, *COL9A1*, *COL9A2*, and *COL9A3* have not been reported in individuals with Stickler syndrome.
9. Pathogenic variants in *BMP4*, *GZF1*, *LOXL3*, and *LRP2* have been reported in individuals with features overlapping those of Stickler syndrome (see Differential Diagnosis).

Clinical Characteristics

Clinical Description

Stickler syndrome is characterized by typical craniofacial features, ocular manifestations, hearing impairment, and osteoarticular problems. To date, more than 1,000 individuals have been identified with Stickler syndrome due to a pathogenic variant(s) in one of the genes listed in Table 1 [Wang et al 2020]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Stickler Syndrome: Frequency of Select Features by Related Gene

Feature	% of Persons w/Feature [1]			
	COL2A1-SS	*COL11A1*-SS	*COL11A2*-SS	*COL9A1*-, *COL9A2*-, & *COL9A3*-SS
Cleft palate	30%-60%	60%	35%	--
Myopia	80%-90%	80%-85%	--	90%-95%
Retinal detachment	40%-70%	<40%	--	13%-18%
Hearing impairment	20%-50% (SNHL ± conductive HL)	75%-80%	60%	90%-95% (SNHL)
Skeletal manifestations [2]	35%-40%	25%	50%	25%

-- = not reported; HL = hearing loss; SNHL = sensorineural hearing loss; SS = Stickler syndrome
1. Hoornaert et al [2010], Boothe et al [2020], Wang et al [2020]
2. Includes mainly early-onset degenerative joint disease

Craniofacial findings include a flat face or midface retrusion with underdevelopment of the maxilla and nasal bridge. Midface retrusion is most pronounced in infants and young children; older individuals may have a normal facial profile.

Micrognathia is common and may be associated with cleft palate as part of the Pierre Robin sequence (micrognathia, glossoptosis, cleft palate). The degree of micrognathia may compromise the upper airway, necessitating tracheostomy in the neonatal period.

Cleft palate may be seen in the absence of micrognathia. Cleft palate may range from open cleft to submucous cleft or just bifid uvula.

Ocular manifestations include myopia, vitreous abnormalities, spontaneous retinal detachments, cataracts, and glaucoma. The ocular phenotype is often consistent between affected family members.

High myopia (greater than −3 diopters) is common; myopia may be progressive and is detectable in the newborn period.

Two types of vitreous abnormalities are observed:

- Type 1 ("membranous"), which is much more common, is characterized by a persistence of vestigial vitreous gel in the retrolental space that is bordered by a folded membrane.
- Type 2 ("beaded"), much less common, is characterized by sparse and irregularly thickened bundles throughout the vitreous cavity.

The development of a retinal tear and subsequent retinal detachment is increased in individuals with Stickler syndrome. Prophylactic retinopexy is recommended, as surgical repair of retinal detachment in individuals with Stickler syndrome is often not successful [Alexander & Snead 2022], and recurrent detachment is reported to be common [Lee et al 2020]. Comparison of prophylactic treatment options to prevent retinal detachment have been reported in some recent retrospective studies [Khanna et al 2022, Ripandelli et al 2022].

Posterior chorioretinal atrophy was described in a family with vitreoretinal dystrophy, systemic features of Stickler syndrome, and a novel pathogenic variant in *COL2A1* [Vu et al 2003], suggesting that individuals with Stickler syndrome may have posterior pole chorioretinal changes in addition to the vitreous abnormalities.

Cataracts were reported to be more common in individuals with *COL11A1*-related Stickler syndrome (59%) compared to individuals with *COL2A1*-related Stickler syndrome (36%) [Boysen et al 2020]. Glaucoma has been reported in 10% of individuals with Stickler syndrome [Wubben et al 2018, Boysen et al 2020, Walters et al 2020].

Hearing impairment is common. The degree of hearing impairment is variable and may be progressive. Sensorineural hearing loss in individuals with *COL2A1*-related Stickler syndrome is typically mild, usually involves the higher frequencies, and is not significantly progressive; it is less severe than that reported for *COL11A1*-related Stickler syndrome [Acke & De Leenheer 2022].

Conductive hearing loss can also be seen. This may be secondary to recurrent ear infections that are often associated with cleft palate and/or may be secondary to a defect of the ossicles of the middle ear.

Skeletal manifestations include mainly early-onset degenerative joint disease with radiographic findings consistent with mild spondyloepiphyseal dysplasia. Stature is within normal limits, but affected individuals may be relatively short in comparison to their unaffected first-degree relatives.

Early-onset osteoarthrosis is common and may be severe, leading to the need for surgical joint replacement even as early as the third or fourth decade. More commonly, the arthropathy is mild with mild joint pain and nonspecific joint stiffness.

Spinal abnormalities sometimes observed in Stickler syndrome that result in chronic back pain are scoliosis and kyphosis [Rose et al 2001]. There is no good documentation in the literature of the presence/occurrence of odontoid hypoplasia, resulting in clinically significant atlantoaxial instability, in individuals with Stickler syndrome. This is in contrast to other, more severe type II collagen disorders such as *COL2A1*-related spondyloepiphyseal dysplasia congenita (see Genetically Related Disorders).

Phenotype Correlations by Gene

COL11A1. Individuals with *COL11A1*-related Stickler syndrome typically have more pronounced midface hypoplasia (flat face), more severe hearing loss, and type 2 congenital vitreous anomaly or "beaded" vitreous phenotype; however, individuals or families with a "membranous" vitreous (type 1) phenotype have been reported [Parentin et al 2001, Majava et al 2007]. The risk for retinal detachments may be lower (<40%) than in *COL2A1*-related Stickler syndrome [Boothe et al 2020].

COL11A2. Pathogenic variants in *COL11A2* cause autosomal dominant non-ocular Stickler syndrome [Vikkula et al 1995, Sirko-Osadsa et al 1998, Vuoristo et al 2004, Acke et al 2014].

COL9A1, COL9A2, COL9A3. Biallelic pathogenic variants in the type IX collagen genes cause autosomal recessive Stickler syndrome. Almost all affected individuals have sensorineural hearing loss (usually moderate to severe) and moderate-to-high myopia with vitreoretinopathy. Retinal detachments are not as frequent, with a rate of 13%-18%. Interestingly, cleft palate has not yet been reported in this group of individuals [Nixon et al 2022].

Genotype-Phenotype Correlations

Although inter- and intrafamilial variation is common, some generalities can be made regarding genotype-phenotype correlations.

***COL2A1*-related Stickler syndrome.** Pathogenic variants in *COL2A1* that cause Stickler syndrome are typically loss-of-functions variants associated with haploinsufficiency of type II collagen (e.g., nonsense variants, small deletions/duplications, splicing variants that cause a frameshift). *COL2A1* pathogenic variants that do not result in a premature stop codon and/or nonsense-mediated RNA decay but have a dominant-negative effect are causative for the more severe type II collagenopathies such as spondyloepiphyseal dysplasia congenita (see Table 3). These are usually missense variants causing a glycine substitution in the triple helical domain. However, glycine substitutions have been reported in individuals with Stickler syndrome, and these tend to cluster at the N-terminal end of the protein.

COL2A1 pathogenic variants involving exon 2 are characterized by a predominantly ocular variant phenotype in which individuals are at high risk for retinal detachment. Affected individuals from nine families with an exon 2 variant resulting in a premature stop codon had optically empty vitreous, typical perivascular pigmentary changes, and/or early-onset retinal detachment with minimal or absent systemic findings of Stickler syndrome [Donoso et al 2003].

***COLL11A1*-related Stickler syndrome.** Heterozygous pathogenic *COL11A1* variants are predominantly splice site alterations and missense variants including glycine substitutions. The splice site alterations usually result in in-frame deletions (exon skipping) and therefore most likely have a dominant-negative effect. Intron 50 (donor splice site) is a mutational hot spot. Rarely, biallelic *COL11A1* pathogenic variants have been reported in individuals with Stickler syndrome; in these instances, at least one pathogenic variant affects the alternatively spliced exon 9. Pathogenic variants of *COL11A1* resulting in haploinsufficiency (e.g., nonsense variants) are rare and cause a milder and less obvious phenotype such as nonsyndromic hearing loss.

***COLL11A2*-related Stickler syndrome.** Heterozygous pathogenic *COL11A2* variants are rare and usually have a dominant-negative effect. They include missense variants in the helical domain, in-frame deletions, or splice site alterations.

***COL9A1*-, *COL9A2*-, and *COL9A3*-related Stickler syndrome.** Pathogenic variants in *COL9A1*, *COL9A2*, and *COL9A3* associated with Stickler syndrome are biallelic and have a loss-of-function effect, resulting in complete absence of the protein.

Penetrance

Penetrance is complete.

Nomenclature

COL11A2-related Stickler syndrome (Stickler syndrome type 3) is also referred to as otospondylomegaepiphyseal dysplasia (OSMED), dominant type, *COL11A2*-related [Unger et al 2023].

Prevalence

The prevalence of Stickler syndrome is unknown.

Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in Stickler syndrome-related genes are summarized in Table 3.

Table 3. Stickler Syndrome: Selected Allelic Disorders

Gene	Phenotype [1]	
COL2A1 [2] (See Type II Collagen Disorders Overview,)	Most severe (often lethal perinatally)	Achondrogenesis, *COL2A1*-related (formerly type 2, type Langer-Saldino)
		Hypochondrogenesis, *COL2A1*-related
		Platyspondylic dysplasia, type Torrance, *COL2A1*-related
	Severe / moderately severe (neonatal presentation)	Kniest dysplasia, *COL2A1*-related
		Spondyloepiphyseal dysplasia congenita (SEDC), *COL2A1*-related
		SEMD, *COL2A1*-related (incl SEMD type Strudwick)
		Spondylometaphyseal dysplasia Sutcliffe (or "corner fractures" type), *COL2A1*-related (See SMD, Corner Fracture Type.)
	Intermediate (neonatal/childhood/ adolescent presentation)	Spondyloperipheral dysplasia, *COL2A1*-related
		Spondyloepiphyseal dysplasia w/metatarsal shortening, *COL2A1*-related
	Mild (adolescent/adult presentation)	Mild spondyloepiphyseal dysplasia w/premature-onset arthrosis, *COL2A1*-related
COL9A1	Multiple epiphyseal dysplasia, *COL9A1*-related (See MED, Autosomal Dominant.)	
COL9A2	Multiple epiphyseal dysplasia, *COL9A2*-related (See MED, Autosomal Dominant.)	
COL9A3	Multiple epiphyseal dysplasia, *COL9A3*-related (See MED, Autosomal Dominant.)	

Table 3. continued from previous page.

Gene	Phenotype [1]
COL11A1	Autosomal dominant nonsyndromic hearing loss, *COL11A1*-related (OMIM 618533)
	Fibrochondrogenesis, *COL11A1*-related (OMIM 228520)
	Marshall syndrome, *COL11A1*-related (OMIM 154780)
COL11A2	Otospondylomegaepiphyseal dysplasia (OSMED), recessive type, *COL11A1*-related (OMIM 215150)
	Otospondylomegaepiphyseal dysplasia (OSMED), dominant type, *COL11A1*-related (OMIM 184840)
	Fibrochondrogenesis, *COL11A1*-related (OMIM 614524)
	Autosomal dominant nonsyndromic hearing loss, *COL11A2*-related (OMIM 601868)

MED = multiple epiphyseal dysplasia; SEMD = spondyloepimetaphyseal dysplasia; SMD = spondylometaphyseal dysplasia
1. Phenotype names are based on the 2023 revision of the Nosology of Genetic Skeletal Disorders [Unger et al 2023].
2. See OMIM 120140 for additional *COL2A1* allelic disorders.

Differential Diagnosis

A number of disorders have features that overlap with those of Stickler syndrome.

Pierre Robin sequence. Approximately one third of individuals with Pierre Robin sequence have an underlying syndrome, of which Stickler syndrome is the most common [Karempelis et al 2020, Davies et al 2023].

Binder syndrome (maxillonasal dysplasia) (OMIM 155050). Affected individuals typically have an unusually flat, underdeveloped midface (midfacial hypoplasia), with an abnormally short nose and flat nasal bridge and underdeveloped upper jaw. Binder syndrome may not represent a distinct disease entity or syndrome but rather a developmental anomaly that can be seen in several syndromes such as Stickler syndrome, campomelic dysplasia, and chondrodysplasia punctata.

Table 4. Genes of Interest in the Differential Diagnosis of Stickler Syndrome

Gene(s)	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder
ARR3 *CPSF1* *LRPAP1* *P4HA2* *PRIMPOL* *SCO2* *SLC39A5* *ZNF644*	High-grade myopia (OMIM PS160700)	AD AR XL [1]	Refractive error ≥ −6 diopters
ATOH7	Nonsyndromic congenital retinal nonattachment (NCRNA) (OMIM 221900)	AR	Congenital insensitivity to light, massive retrolental mass, shallow anterior chamber, microphthalmia, & nystagmus in otherwise normal individuals
BMP4	*BMP4*-related disorder [2]	AD	High myopia, congenital hypoplasia of the vitreous, retinal detachment, high-arched palate, retrognathia, sensorineural hearing loss
GZF1	*GZF1*-related disorder [2]	AR	High myopia, retinal detachment, chorioretinal coloboma, hearing loss, joint laxity & dislocations, kyphoscoliosis, talipes
KCNJ13	Snowflake vitreoretinal degeneration (OMIM 193230)	AD	Cataract, fibrillar degeneration of the vitreous, & peripheral retinal abnormalities incl minute, shiny, crystalline-like deposits resembling snowflakes. Individuals show a low rate of retinal detachment.

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder
LOXL3	*LOXL3*-related disorder [2]	AR	Myopia, vitreous detachment, flat midface, cleft palate, micrognathia, mild conductive hearing loss, joint laxity
LRP2	*LRP2*-related disorder [2] (See also Donnai-Barrow Syndrome.)	AR	Myopia, retinal detachment, abnormal vitreous, flat midface, retrognathia, joint pain
VCAN	*VCAN*-related vitreoretinopathy (incl Wagner syndrome & erosive vitreoretinopathy) (OMIM 143200)	AD	"Optically empty vitreous" on slit lamp exam & avascular vitreous strands & veils, myopia, presenile cataract, night blindness of variable degree assoc w/progressive chorioretinal atrophy, retinal traction & retinal detachment at advanced stages of the disease & ↓ visual acuity. 1st signs usually become apparent during early adolescence, but onset can be as early as age 2 yrs.

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked
1. *ARR3*-related high-grade myopia is inherited in an X-linked manner. *CPSF1*-, *P4HA2*-, *PRIMPOL*-, *SCO2*-, *SLC39A5*-, and *ZNF644*-related high-grade myopia are inherited in an autosomal dominant manner. *LRPAP1*-related high-grade myopia is inherited in an autosomal recessive manner.
2. Pathogenic variants in *BMP4*, *GZF1*, *LOXL3*, and *LRP2* have been reported in individuals with features overlapping those of Stickler syndrome [Nixon et al 2019, Nixon et al 2022].

Management

No clinical practice guidelines for Stickler syndrome have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Stickler syndrome, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Stickler Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
ENT	• Eval of palate by craniofacial specialist • Feeding assessment	Persons w/PRS need immediate assessment by ENT & pediatric critical care to assess airway.
	Audiology eval	
Eyes	Ophthalmologic exam	Preferably by expert ophthalmologist familiar w/the ophthalmic complications (e.g., high myopia, vitreous changes, retinal detachment)
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of Stickler syndrome to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

MOI = mode of inheritance; PRS = Pierre Robin sequence
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by a comprehensive craniofacial clinic that provides all the necessary services, including otolaryngology, plastic surgery, oral and maxillofacial surgery, pediatric dentistry, orthodontics, and medical genetics (see Table 6).

Table 6. Stickler Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Respiratory	Infants w/PRS may require tracheostomy to ensure a competent airway.	In most persons, micrognathia tends to become less prominent over time, allowing for removal of tracheostomy.
Micrognathia	Mandibular advancement procedure may be needed for persistent micrognathia to correct malocclusion.	
Cleft palate	Mgmt per craniofacial specialists incl feeding/nutrition mgmt	
Ocular manifestations	• Laser therapy for prevention of retinal detachment [1] • Education on risk & symptoms of retinal detachment & need for immediate eval & treatment • Refractive errors should be corrected w/spectacles.	
Hearing impairment	• See Genetic Hearing Loss Overview. • Prompt treatment of otitis media • Consider myringotomy tubes for recurrent otitis media.	
Early-onset arthropathy	Symptomatic treatment incl over-the-counter anti-inflammatory medications before & after physical activity	At present, no prophylactic therapies to minimize joint damage in affected persons exist.
Spinal & other osteoarticular abnormalities	Treatment per orthopedist	

PRS = Pierre Robin sequence
1. Morris et al [2021]

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 7 are recommended.

Table 7. Stickler Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Eyes	Exam by vitreoretinal specialist	Annually
Hearing	Audiologic eval	
Orthopedic	Clinical & radiographic assessment for joint & spine manifestations	As needed

Agents/Circumstances to Avoid

Affected individuals should be advised to avoid activities that may lead to traumatic retinal detachment (e.g., contact sports).

Some physicians recommend avoiding physical activities that involve high impact to the joints to delay the onset of the arthropathy. While this recommendation seems logical, there are no data to support it.

Evaluation of Relatives at Risk

Because of the variable expression of Stickler syndrome, it is appropriate to evaluate the older and younger sibs of a proband as well as other at-risk relatives in order to identify those who warrant ongoing evaluation (see Surveillance). Evaluation can be done in one of two ways:

- Documentation of medical history, physical examination, and ophthalmologic, audiologic, and radiographic assessments. The examination of childhood photographs may be helpful in the assessment of craniofacial findings of adults, since the craniofacial findings characteristic of Stickler syndrome may become less distinctive with age.
- Molecular genetic testing if the pathogenic variant(s) in the family are known

It is recommended that relatives at risk in whom the diagnosis of Stickler syndrome cannot be excluded with certainty be followed for potential complications.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Stickler syndrome caused by a heterozygous pathogenic variant in *COL2A1*, *COL11A1*, or *COL11A2* is inherited in an autosomal dominant manner.

Stickler syndrome caused by biallelic pathogenic variants in *COL9A1*, *COL9A2, or COL9A3* is inherited in an autosomal recessive manner.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- The majority of individuals with autosomal dominant Stickler syndrome have an affected parent.
- A proband with Stickler syndrome may have the disorder as the result of a *COL2A1*, *COL11A1*, or *COL11A2* pathogenic variant that occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic, apparently unaffected parent. The proportion of individuals with Stickler syndrome caused by a *de novo* pathogenic variant is unknown.
- If the proband appears to be the only affected family member (i.e., a simplex case), recommendations for the parents of the proband include:
  - Evaluation of both parents for manifestations of Stickler syndrome (see Management);

- If a molecular diagnosis has been established in the proband, molecular genetic testing to confirm the genetic status of the parents and to allow reliable recurrence risk counseling.

- If the proband has a known pathogenic variant that is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism * [Nagendran et al 2012, Stevenson et al 2012]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

    * A parent with somatic and germline mosaicism for a Stickler syndrome-related pathogenic variant may be mildly/minimally affected [Nagendran et al 2012, Lauritsen et al 2017].

Sibs of a proband. The risk to sibs depends on the genetic status of the parents:

- If a parent has autosomal dominant Stickler syndrome, the risk to each sib of a proband is 50%. Clinical variability is common among affected family members; however, some generalities can be made regarding genotype-phenotype correlation (see Genotype-Phenotype Correlations).
- If the proband has a known *COL2A1*, *COL11A1*, or *COL11A2* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be slightly greater than that of the general population because of the possibility of parental mosaicism [Nagendran et al 2012, Stevenson et al 2012, Lauritsen et al 2017].
- If the parents are clinically unaffected but their genetic status is unknown, the risk to the sibs of a proband appears to be low but increased over that of the general population because of the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant Stickler syndrome has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, the parent's family members may be at risk.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of a child with Stickler syndrome caused by biallelic pathogenic variants in *COL9A1*, *COL9A2*, or *COL9A3* are presumed to be heterozygous for a pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *COL9A1*, *COL9A2*, or *COL9A3* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *COL9A1*, *COL9A2*, or *COL9A3* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with autosomal recessive Stickler syndrome are obligate heterozygotes (carriers) for a pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the *COL9A1*, *COL9A2*, or *COL9A3* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected with Stickler syndrome or are carriers (or are at risk of being carriers) of autosomal recessive Stickler syndrome.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

High-risk pregnancies

- **Molecular genetic testing.** Once the Stickler syndrome-related pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.
- **Ultrasound evaluation.** Alternatively, or in conjunction with molecular genetic testing, ultrasound examination can be performed at 19-20 weeks' gestation to detect cleft palate. Absence of a cleft palate, however, does not exclude the diagnosis of Stickler syndrome.

Low-risk pregnancies. For fetuses with no known family history of Stickler syndrome, but in which cleft palate is detected prenatally, it is appropriate to obtain a three-generation pedigree and to evaluate relatives who have findings suggestive of Stickler syndrome. Molecular genetic testing of the fetus is usually not offered in the absence of a known pathogenic variant in a parent.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Stickler syndrome
- **Stickler Involved People**
  Phone: 316-259-5194
  Email: sip@sticklers.org
  www.sticklers.org
- **Stickler Syndrome UK**
  United Kingdom
  Phone: 01903 785771
  Email: info@stickler.org.uk
  www.stickler.org.uk

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Stickler Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
COL2A1	12q13.11	Collagen alpha-1(II) chain	COL2A1 database	COL2A1	COL2A1
COL9A1	6q13	Collagen alpha-1(IX) chain	COL9A1 database	COL9A1	COL9A1
COL9A2	1p34.2	Collagen alpha-2(IX) chain	COL9A2 database	COL9A2	COL9A2
COL9A3	20q13.33	Collagen alpha-3(IX) chain	COL9A3 database	COL9A3	COL9A3
COL11A1	1p21.1	Collagen alpha-1(XI) chain	COL11A1 database	COL11A1	COL11A1
COL11A2	6p21.32	Collagen alpha-2(XI) chain	Hereditary Hearing Loss Homepage (COL11A2) COL11A2 database	COL11A2	COL11A2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Stickler Syndrome (View All in OMIM)

108300	STICKLER SYNDROME, TYPE I; STL1
120140	COLLAGEN, TYPE II, ALPHA-1; COL2A1
120210	COLLAGEN, TYPE IX, ALPHA-1; COL9A1
120260	COLLAGEN, TYPE IX, ALPHA-2; COL9A2

Table B. continued from previous page.

120270	COLLAGEN, TYPE IX, ALPHA-3; COL9A3
120280	COLLAGEN, TYPE XI, ALPHA-1; COL11A1
120290	COLLAGEN, TYPE XI, ALPHA-2; COL11A2
184840	OTOSPONDYLOMEGAEPIPHYSEAL DYSPLASIA, AUTOSOMAL DOMINANT; OSMEDA
604841	STICKLER SYNDROME, TYPE II; STL2
614134	STICKLER SYNDROME, TYPE IV; STL4
614284	STICKLER SYNDROME, TYPE V; STL5

Molecular Pathogenesis

COL2A1 encodes the alpha 1 chain of type II collagen, the major structural fibrillar component of hyaline cartilage. *COL2A1* pathogenic variants typically result in premature termination of translation and decreased synthesis of type II collagen.

COL11A1 encodes the alpha 1 chain of type XI collagen. Type XI collagen is presumed to play an important role in fibrillogenesis of type II collagen by controlling lateral growth of collagen fibrils. Pathogenic variants in *COL11A1* generally have a dominant-negative effect on formation of the type XI collagen heterotrimer.

COL11A2 codes for the alpha 2 chain of type XI collagen. It is expressed in cartilage but not in adult liver, skin, tendon, or vitreous. The latter explains the absence of ocular features in *COL11A2*-related Stickler syndrome. Pathogenic variants of *COL11A2* generally have a dominant-negative effect on formation of the type XI collagen heterotrimer.

COL9A1 encodes the alpha 1 chain, *COL9A2* encodes the alpha 2 chain, and *COL9A3* encodes the alpha 3 chain of type IX collagen. Type IX collagen is a structural component of hyaline cartilage, vitreous of the eye, and intervertebral disc. The type IX collagen heterotrimer is located on the outside of the collagen type II/XI fibril. It forms a bridge between the collagen fibril and other structural components of the cartilaginous matrix.

Table 8. Stickler Syndrome: Gene-Specific Mechanism of Disease Causation

Gene [1]	Mechanism of Disease Causation
COL2A1	Loss of function
COL9A1 *COL9A2* *COL9A3*	Loss of function
COL11A1 *COL11A2*	Dominant-negative effect

1. Genes are in alphabetic order.

Table 9. Stickler Syndrome: Gene-Specific Laboratory Considerations

Gene [1]	Special Consideration(s)
COL2A1	Intragenic & whole-gene deletions have been identified. Mosaicism has been reported.
COL11A1	Mosaicism has been reported.

1. Genes are in alphabetic order.

Chapter Notes

Author History

Leena Ala-Kokko, MD, PhD; Connective Tissue Gene Tests (2000-2023)
Rocio T Moran, MD, The MetroHealth System (2000-2023)
Geert Mortier, MD, PhD (2023-present)
Nathaniel H Robin, MD; University of Alabama (2000-2023)
Matthew Warman, MD; Children's Hospital Boston (2000-2011)

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