GENEReviews

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Stickler Syndrome

[*Arthro-Ophthalmopathy; Arthroophthalmopathy, Hereditary; Arthroophthalmopathy, Hereditary Progressive*]

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Summary

Disease 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 Robin sequence); and mild spondyloepiphyseal dysplasia and/or precocious arthritis. Variable phenotypic expression of Stickler syndrome occurs both within families and among families; interfamilial variability is in part explained by locus and allelic heterogeneity.

Diagnosis/testing. The diagnosis of Stickler syndrome is clinically based. At present, no consensus minimal clinical diagnostic criteria exist. Mutations affecting one of three genes (*COL2A1*, *COL11A1*, and *COL11A2*) have been associated with Stickler syndrome; because a few families with features of Stickler syndrome are not linked to any of these three loci, mutations in other genes may also cause the disorder. In many affected individuals and families, the diagnosis can be confirmed by clinically available molecular genetic testing; however, these results are primarily used to obtain information for genetic counseling.

Management. Infants with Robin sequence may need tracheostomy to ensure a competent airway. The tracheostomy may be removed when micrognathia becomes less prominent; if micrognathia persists, a mandibular advancement procedure is done to correct malocclusion. Individuals with Stickler syndrome who have mild spondyloepiphyseal dysplasia need antibiotic prophylaxis for surgery. Treatment for arthropathy is symptomatic and includes anti-inflammatory medications before and after physical activity. Often, myringotomy tubes are required to treat otitis media.

Genetic counseling. Stickler syndrome is inherited in an autosomal dominant manner. Affected individuals have a 50% chance of passing on the mutant gene to each offspring. Because of the possibility of wide clinical variability within families, it is appropriate to evaluate at-risk relatives for management reasons and genetic counseling. If the disease-

causing mutation has been identified in an individual or a family, molecular genetic testing can be used for clarification of each family member's genetic status and for prenatal testing.

Diagnosis

Clinical Diagnosis

Clinical diagnostic criteria have not been established for Stickler syndrome. The disorder should be considered in individuals with clinical findings in two or more of the following categories:

- **Ophthalmologic**
  - Congenital or early-onset cataract
  - Congenital vitreous anomaly, rhegmatogenous retinal detachment
  - Myopia greater than -3 diopters

Note: Newborns are typically hyperopic (+1 diopter or greater); thus the finding of any degree of myopia in an at-risk newborn (e.g., a newborn who has Pierre-Robin sequence or an affected parent) is suggestive of the diagnosis of Stickler syndrome.

- **Craniofacial**
  - Midface hypoplasia, depressed nasal bridge, anteverted nares (Characteristic facies are typically more pronounced in childhood.)
  - Bifid uvula, cleft hard palate
  - Micrognathia
  - Robin sequence (micrognathia, cleft palate, glossoptosis)
- **Audiologic**
  - Sensorineural or conductive hearing loss
  - Hypermobile middle ear systems, representing an additional diagnostic feature (reported in 46% of affected individuals in one cohort [Szymko-Bennet et al 2001])
- **Joint**
  - Hypermobility
  - Mild spondyloepiphyseal dysplasia
  - Precocious osteoarthritis

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. Mutations in three genes, *COL2A1*, *COL11A1*, and *COL11A2*, have been associated with the Stickler syndrome, termed Stickler syndrome type I, II, and III respectively.

Other loci. In rare families with clinical findings consistent with Stickler syndrome, linkage to any of the three known loci cannot be established; hence, mutations in other as-yet-unidentified genes presumably account for Stickler syndrome as well.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

- **Sequence analysis/mutation scanning.** Mutation scanning of exons 1-52 of *COL2A1* and exons 13-67 of *COL11A1* identified stop mutations in *COL2A1* and missense and splicing mutations in both *COL2A1* and *COL11A1* in 45 of 62 (73%) individuals who had clinical diagnoses consistent with both Stickler syndrome and Marshall syndrome (all had ophthalmic findings) [communication, D Prockop, Matrix DNA Diagnostics, July 2005].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Stickler Syndrome

Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
Sequence analysis/mutation scanning	*COL2A1* sequence variants	8/30 [1]	Clinical Testing
		70-80% [2]	
	COL11A1 sequence variants	15/30 [1]	Clinical Testing
		70-80% [2]	
Sequence analysis of select exons	*COL11A2* sequence variants	Unknown	Clinical Testing

1. Annunen et al 1999
2. Individuals with diagnosis of either Stickler syndrome or Marshall syndrome [communication, D Prockop, Matrix DNA Diagnostics, July 2005]

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy for a Proband

The order in which the two genes are tested may be influenced by the clinical findings:

- *COL2A1* may be tested first in individuals with ocular findings including type 1 congenital vitreous anomaly and milder hearing loss.
- *COL11A1* may be tested first in individuals with typical ocular findings including type 2 congenital vitreous anomaly and significant hearing loss.
- *COL11A2* may be tested for in individuals with craniofacial and joint manifestations and hearing loss, but lacking ocular findings.

Genetically Related Disorders

Other phenotypes associated with mutations in *COL2A1*

- **Achondrogenesis type II** (OMIM: 200610). This disorder is characterized by virtual absence of ossification in the vertebral column, sacrum, and pubic bones [Saldino 1971, Spranger et al 1974]. There is marked shortening of the limbs and trunk, with a prominent abdomen and hydropic appearance. Death occurs in utero or in the early neonatal period. Vissing et al (1989) identified a *COL2A1* mutation in affected

individuals. Achondrogenesis Type II is inherited in an autosomal dominant manner. All cases represent *de novo* mutations.

- **Hypochondrogenesis.** This term has been used to describe a more mild variant of achondrogenesis (as, for example, hypochondroplasia is to achondroplasia) [Hendrickx et al 1983]. Mutations in *COL2A1* are causative [Feshchenko et al 1989].
- **Spondyloepiphyseal dysplasia congenita (SED congenita)** (OMIM: 183900). Although the skeletal changes in SED congenita are similar to those seen in Stickler syndrome, they are more severe and result in significant short stature. In addition, individuals manifest flat facial profile, myopia, and vitreoretinal degeneration. SED congenita is inherited in an autosomal dominant manner.
- **Spondyloepimetaphyseal dysplasia (SEMD) Strudwick type** (OMIM: 184250). The common clinical manifestations of this *COL2A1*-related skeletal disorder include severe short stature with severe pectus carinatum and scoliosis, cleft palate, and retinal detachment. A distinctive radiographic finding is irregular sclerotic changes (described as "dappled") in the metaphyses of the long bones. This mottled appearance is created by alternating zones of osteosclerosis and osteopenia. Radiologically, the disorder is indistinguishable from SED congenita (OMIM: 183900) during infancy. Tiller et al (1995) identified a heterozygous *COL2A1* mutation, confirming that this is an autosomal dominant disorder.
- **Kneist dysplasia** (OMIM: 156550). Affected individuals manifest disproportionate short stature, flat facial profile, myopia and vitreoretinal degeneration, cleft palate, kyphoscoliosis, and a variety of radiographic changes. It is inherited in an autosomal dominant manner.
- **Spondyloperipheral dysplasia.** This is a rare autosomal dominant condition. Zabel et al (1996) reported on an individual with short stature, radiographic changes consistent with a spondyloepiphyseal dysplasia, and brachydactyly E. A heterozygous *COL2A1* mutation was identified in the C-terminus, resulting in a truncated C-propeptide region.
- **Early-onset arthropathy.** This condition can be transmitted in an autosomal dominant manner [Knowlton et al 1990]. Ala-Kokko et al (1990) were the first to identify a *COL2A1* mutation in a kindred, an arginine-to-cysteine substitution at position 519 of the alpha-1(II) chain.
- **Autosomal dominant rhegmatogenous retinal detachment (ARDD)** is associated with pathologic myopia and vitreoretinal degeneration. Go et al (2003) described two large families with ARDD with linkage to *COL2A1*. Most had mild or absent systemic features of Stickler syndrome. In one family, an Arg453Ter mutation was found in the helical domain of the *COL2A1* gene resulting in protein truncation [Donoso et al 2003].

Other phenotypes associated with mutations in *COL11A1*

- **Marshall syndrome** (OMIM: 154780). Individuals with Marshall syndrome manifest ocular hypertelorism, hypoplasia of the maxilla and nasal bones, flat nasal bridge, and small upturned nasal tip [Marshall 1958]. In contrast to Stickler syndrome, the flat facial profile of Marshall syndrome is usually evident into adulthood. Radiographs demonstrate hypoplasia of the nasal sinuses and a thickened calvarium. Ocular manifestations include high myopia, fluid vitreous humor, and early-onset cataracts (subcapsular, cortical, nuclear, zonular, or anterior axial embryonic sites). Sensorineural hearing loss is common and can be progressive. Cleft palate, both as

part of the Pierre Robin sequence and as an isolated anomaly, is seen. Other manifestations include short stature and early-onset arthritis. Skin manifestations include mild hypotrichosis and hypohidrosis [Cohen 1974, Winter et al 1983, Griffith et al 1998, Shanske et al 1998]. Splice site mutations in the *COL11A1* gene have been identified by Griffith et al (1998) and Annunen et al (1999).

Other phenotypes associated with mutations in *COL11A2*

- **Autosomal recessive otospondylometaepiphyseal dysplasia (OSMED)** (OMIM: 215150). This disorder is characterized by flat facial profile, cleft palate, and severe hearing loss [van Steensel et al 1997]. Vikkula et al (1995) and Melkoniemi et al (2000) identified homozygous loss-of-function mutations of *COL11A2* in individuals with OSMED. It has been suggested that anocular Stickler syndrome (caused by heterozygous *COL11A2* mutations) is more appropriately considered a type of OSMED because of its closer similarity to OSMED than Stickler syndrome.
- **Weissenbach-Zweymuller syndrome (WZS)** (OMIM: 277610). WZS has been described as "neonatal Stickler syndrome," but is actually a distinct entity [Kelly et al 1982]. It is characterized by midface hypoplasia with a flat nasal bridge, small upturned nasal tip, micrognathia, sensorineural hearing loss, and rhizomelic limb shortening. Radiographic findings include dumbbell-shaped femora and humeri and vertebral coronal clefts. The skeletal findings become less apparent in later years, and catch-up growth after age two to three years is common [Weissenbacher & Zweymuller 1964, Hall & Herrod 1975, Winter et al 1983]. Although myopia has been reported in some individuals, it is not a manifestation of WZS [Chemke et al 1992]. WZS is inherited in an autosomal recessive manner. Pihlajamaa et al (1998) identified mutations in the *COL11A2* gene in Weissenbacher and Zweymuller's (1964) original family.
- **Nonsyndromic sensorineural hearing loss.** McGuirt et al (1999) reported heterozygous mutations in *COL11A2* in two unrelated families with autosomal dominant non-progressive predominantly middle-frequency nonsyndromic deafness. The deafness in these families had previously been mapped to 6p21.3 and designated DFNA13 (Hereditary Hearing Loss and Deafness Overview).

Clinical Description

Natural History

Stickler syndrome is a multisystem connective tissue disorder that can affect the eye, craniofacies, inner ear, skeleton, and joints.

Eye findings include high myopia (greater than -3 diopters) that is non-progressive and detectable in the newborn period [Snead & Yates 1999] and vitreous abnormalities. Two types of vitreous abnormalities are observed.

- Type 1, which is much more common, is characterized by a persistence of a vestigial vitreous gel in the retrolental space, and is bordered by a folded membrane.
- Type 2 is much less common and is characterized by sparse and irregularly thickened bundles throughout the vitreous cavity. These ocular phenotypes run true within families [Snead & Yates 1999].

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

Note: Previously, families with posterior chorioretinal atrophy were thought to have Wagner disease.

Craniofacial findings include a flat facial profile often referred to as a "scooped out" face [Temple 1989]. This profile is caused by underdevelopment of the maxilla and nasal bridge, which can cause telecanthus and epicanthal folds. The midfacial hypoplasia is most pronounced in infants and young children; older individuals may have a normal facial profile. Often the nasal tip is small and upturned, making the philtrum appear long.

Micrognathia is common and may be associated with cleft palate as part of the Pierre Robin sequence (micrognathia, cleft palate, glossoptosis). The degree of micrognathia may compromise the upper airway, necessitating tracheostomy [Shprintzen et al 1988].

Cleft palate may be seen in the absence of micrognathia.

Hearing impairment is common. The degree of hearing impairment is variable and may be progressive [Keith et al 1972].

Some degree of sensorineural hearing impairment is found in 40% of individuals — typically high-tone, often subtle hearing loss [Snead & Yates 1999]. The exact mechanism is unclear, although it is related to the expression of type II and IX collagen in the inner ear [Admiraal et al 2000]. Overall sensorineural hearing loss in type I Stickler syndrome is typically mild and not significantly progressive; it is less severe than that reported for types II and III Stickler syndrome.

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 are early-onset arthritis, short stature relative to unaffected siblings, and radiographic findings consistent with mild spondyloepiphyseal dysplasia [Temple 1989]. Some individuals have a marfanoid body habitus, but without tall stature [Beals 1977].

Joint laxity, sometimes seen in young individuals, becomes less prominent (or resolves completely) with age [Snead & Yates 1999].

Early-onset arthritis is common and may be severe, leading to the need for surgical joint replacement even as early as the third or fourth decade [Rai et al 1994]. More commonly, the arthropathy is mild, and affected individuals often do not complain of joint pain unless specifically asked. However, nonspecific complaints of joint stiffness can be elicited even from young children.

Spinal abnormalities commonly observed in Stickler syndrome that result in chronic back pain are scoliosis, endplate abnormalities, kyphosis, and platyspondylia [Rose et al 2001].

Mitral valve prolapse (MVP) has been reported in almost 50% of individuals with Stickler syndrome in one series [Liberfarb & Goldblatt 1986] and no individuals in another [Snead 1996].

Genotype-Phenotype Correlations

Although inter- and intrafamilial variation was observed among 25 individuals from six families with the same molecular diagnosis [Liberfarb et al 2003], some generalities can be made regarding genotype-phenotype correlation.

- ***COL2A1* mutations.** The majority of individuals who have Stickler syndrome as a result of *COL2A1* mutations, including the kindred originally reported by Stickler et al (1965), have premature stop (i.e., nonsense or frameshift) mutations that result in functional haploinsufficiency of the *COL2A1* gene product. Most affected individuals have type 1 congenital vitreous abnormalities and are at high risk for retinal detachment, normal hearing or mild sensorineural hearing loss, and precocious osteoarthritis. The craniofacial features are variable, ranging from mild nasal anteversion to Robin sequence [Faber et al 2000]. A large family with linkage to *COL2A1* revealed a unique L467 mutation producing a novel "afibrillar" vitreous gel devoid of all normal lamella structure [Richards et al 2000].

  A *COL2A1* missense mutation has been described in one family with characteristic ophthalmologic and craniofacial findings, as well as a mild multiple epiphyseal dysplasia with brachydactyly, suggesting that mild heterozygous mutations may also cause Stickler syndrome. Mutations involving exon 2 of *COL2A1* are characterized by a predominantly ocular variant, in which individuals are at high risk of retinal detachment.

  In the nine families with exon 2 mutations of the *COL2A1* gene reported by Donoso et al (2003), all mutations resulted in stop codons. The phenotype was characterized by optically empty vitreous, typical perivascular pigmentary changes, and/or early-onset retinal detachment with minimal or absent system findings of Stickler syndrome.
- ***COL11A1* mutations.** Missense mutations within *COL11A1* have been observed in individuals with the typical Stickler syndrome phenotype. Typically these individuals have more severe hearing loss and type 2 congenital vitreous anomaly or "beaded" vitreous phenotype; however, one family with a "membranous" vitreous (type 1) phenotype has been reported [Parentin et al 2001].
- ***COL11A2* mutations.** Mutations in the *COL11A2* gene have been shown to cause autosomal dominant non-ocular Stickler syndrome.

Penetrance

Penetrance is complete.

Anticipation

Anticipation is not observed.

Prevalence

No studies to determine the prevalence of Stickler syndrome have been undertaken. However, an approximate incidence of Stickler syndrome among newborns can be estimated from data regarding the incidence of Robin sequence in newborns (one in 10,000-14,000) and the percent of these newborns who subsequently develop signs or symptoms of Stickler syndrome (35%). These data suggest that the incidence of Stickler syndrome among neonates is approximately one in 7,500-9,000 [Printzlau & Anderson 2004].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

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

- For allelic disorders see Genetically Related Disorders.
- **Wagner syndrome** (OMIM: 143200). Described by Wagner in 1938, this condition is characterized by the presence of ocular findings similar to those seen in Stickler syndrome and Marshall syndrome but without the other clinical manifestations. The ocular findings, which progress in severity with age, include high myopia, an empty vitreous cavity with avascular strands, chorioretinal atrophy, and cataract. Retinal detachment and glaucoma are also observed. Abnormalities with dark adaptation are evident on electroretinography. The gene responsible for Wagner syndrome maps to 5q13-q14, the same locus for another primary ocular disorder, erosive vitreoretinopathy [Brown et al 1995].
- **High-grade myopia** is a refractive error greater than or equal to six diopters. Several loci for myopia have been mapped: MYP1 (OMIM: 310460) on Xq28, MYP2 on chromosome 18p, MYP3 (OMIM: 603221) on chromosome 12q, MYP4 (OMIM: 608367) on chromosome 7q, MYP5 (OMIM: 608474) on chromosome 17q, MYP6 (OMIM: 608908) on chromosome 22q12, MYP7 (OMIM: 609256) on chromosome 11p13, MYP8 (OMIM: 609257) on chromosome 3q26, MYP9 (OMIM: 609258) on chromosome 4q12, and MYP10 (OMIM: 609259) on chromosome 8p23.
- **Nonsyndromic congenital retinal nonattachment** (NCRNA) (OMIM: 221900) comprises congenital insensitivity to light, massive retrolental mass, shallow anterior chamber, microphthalmia, and nystagmus in otherwise normal individuals. The gene maps to 10q21 [Ghiasvand et al 2000].
- **Snowflake vitreoretinal degeneration** (OMIM: 193230) is characterized by cataract, fibrillar degeneration of the vitreous, and peripheral retinal abnormalities including minute, shiny crystalline-like deposits resembling snowflakes. Individuals show a low rate of retinal detachment [Lee et al 2003].
- **Binder syndrome (maxillonasal dysplasia)** (OMIM: 155050). This condition is characterized by midfacial hypoplasia and absence of the anterior nasal spine on radiographs [Munro et al 1979, Quarrell et al 1990]. While some families with vertical transmission have been reported [Roy-Doray et al 1997], Binder syndrome is not considered a genetic syndrome, but rather a nonspecific abnormality of the nasomaxillary complex [Quarrell et al 1990].
- **Robin sequence.** Approximately half of all individuals with Robin sequence have an underlying syndrome, of which Stickler syndrome is the most common. In one study, 34 of 100 individuals with Robin sequence had Stickler syndrome [Shprintzen et al 1988]. A retrospective study of 74 individuals with Pierre Robin sequence also found that more than 30% of these individuals had Stickler syndrome [van den Elzen et al 2001].

Management

Evaluations at Initial Diagnosis

- A baseline ophthalomologic examination
- A baseline audiogram
- A directed history to elicit complaints suggestive of MVP, such as episodic tachycardia and chest pain. If symptoms are present, referral to a cardiologist should be made.

Treatment of Manifestations

Ophthalomologic. Refractive errors should be corrected with spectacles.

Individuals with Stickler syndrome should be advised of the symptoms associated with retinal detachment and the need for immediate evaluation and treatment when such symptoms occur.

Craniofacial. Infants with Robin sequence need immediate attention from specialists in otolaryngology and pediatric critical care, as they may require tracheostomy to ensure a competent airway. It is recommended that evaluation and management occur in a comprehensive craniofacial clinic that provides all the necessary services, including otolaryngology, plastic surgery, oral and maxillofacial surgery, pediatric dentistry, orthodontics, and medical genetics.

In most individuals, micrognathia tends to become less prominent over time, allowing for removal of the tracheostomy. However, in some individuals, significant micrognathia persists, causing orthodontic problems. In these individuals, a mandibular advancement procedure is often required to correct the malocclusion.

Audiologic. See Hereditary Hearing Loss and Deafness Overview.

Joints. Treatment of arthropathy is symptomatic and includes using over-the-counter anti-inflammatory medications before and after physical activity.

Prevention of Secondary Complications

Otitis media may be a recurrent problem secondary to palatal abnormalities. Myringotomy tubes are often required.

At present, no prophylactic therapies to minimize joint damage in affected individuals exist. Some physicians recommend avoiding physical activities that involve high impact to the joints in an effort to delay the onset of the arthropathy. While this recommendation seems logical, there are no data to support it.

Individuals with MVP need antibiotic prophylaxis for certain surgical procedures.

Surveillance

Annual examination by a vitreoretinal specialist is indicated.

Hearing loss can be progressive, so follow-up audiologic evaluations are recommended every six months through age five years, and annually thereafter.

While the prevalence of MVP among affected individuals is unclear, all individuals with Stickler syndrome should be screened for MVP through routine physical examination. More advanced testing such as echocardiogram should be reserved for those with suggestive symptoms.

Testing of Relatives at Risk

Because of the variable expression of Stickler syndrome [Faber et al 2000], it is appropriate to evaluate family members at risk by documenting medical history and performing 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.

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

Agents/Circumstances to Avoid

Affected individuals should be advised to avoid activities such as contact sports that may lead to traumatic retinal detachment.

Therapies Under Investigation

Search Clinical Trials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Stickler syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- The majority of individuals with Stickler syndrome have inherited the mutant allele from a parent.
- A proband with Stickler syndrome may have the disorder as the result of a *de novo* gene mutation. The prevalence of *de novo* gene mutations is not known.
- When the diagnosis of Stickler syndrome is considered in an individual, it is appropriate to evaluate both parents for manifestations of Stickler syndrome (see Management).

Sibs of a proband

- The risk to sibs depends upon the genetic status of the parents.
- If a parent has Stickler syndrome, the risk to each sib of a proband is 50%.
- When the parents are clinically unaffected and/or the disease-causing mutation identified in the proband has not been identified in either parent, the risk to the sibs of a proband appears to be low.
- If the disease-causing mutation cannot be detected in the DNA of either parent of the proband, it is presumed that the proband has a *de novo* gene mutation. No instances of germline mosaicism have been reported, although it remains a possibility.

Offspring of a proband. Each child of an individual with Stickler syndrome has a 50% chance of inheriting the disease-causing mutation.

Other family members. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

High-risk pregnancies

- **Molecular genetic testing.** Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. The disease-causing allele in an affected family member must be identified before prenatal testing can be performed.

  Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

- **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 disease-causing mutation in a parent.

Requests for prenatal testing for conditions such as Stickler syndrome that do not affect intellect and have some treatment available are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD). Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Stickler Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
COL11A1	1p21	Collagen alpha 1(XI) chain
COL11A2	6p21.3	Collagen alpha 2(XI) chain
COL2A1	12q13.11-q13.2	Collagen alpha 1(II) chain

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Stickler Syndrome

108300	STICKLER SYNDROME, TYPE I; STL1
120140	COLLAGEN, TYPE II, ALPHA-1; COL2A1
120280	COLLAGEN, TYPE XI, ALPHA-1; COL11A1
120290	COLLAGEN, TYPE XI, ALPHA-2; COL11A2
184840	STICKLER SYNDROME, TYPE III; STL3
604841	STICKLER SYNDROME, TYPE II; STL2

Table C. Genomic Databases for Stickler Syndrome

Gene Symbol	Locus Specific	Entrez Gene	HGMD
COL11A1	COL11A1	1301 (MIM No. 120280)	COL11A1
COL11A2	COL11A2	1302 (MIM No. 120290)	COL11A2
COL2A1	COL2A1	1280 (MIM No. 120140)	COL2A1

For a description of the genomic databases listed, click here.

COL2A1

Normal allelic variants: *COL2A1* comprises 54 exons.

Pathologic allelic variants: Over 17 different mutations resulting in premature termination of translation, either by single base substitution or by insertion or deletion of a small number of nucleotides, have been reported to cause Stickler syndrome.

Normal gene product: The *COL2A1* gene encodes the chains of type II collagen, a major structural component of cartilaginous tissues.

Abnormal gene product: Mutations of the *COL2A1* gene typically result in premature termination of translation and decreased synthesis of type II.

COL11A1

Normal allelic variants: *COL11A1* comprises 68 exons.

Pathologic allelic variants: Several mutations resulting in aberrant splicing, missense mutations, and in-frame deletions have been described.

Normal gene product: The *COL11A1* gene encodes for the alpha 1 chain of type XI collagen. It is presumed to play an important role in fibrillogenesis by controlling lateral growth of collagen II fibrils.

Abnormal gene product: Mutations in the *COL11A1* gene generally lead to a disruption of the Gly-X-Y collagen sequence and impaired synthesis or function of type XI collagen.

COL11A2

Normal allelic variants: *COL11A2* comprises 62 exons.

Pathologic allelic variants: Mutations resulting in aberrant splicing, exon skipping, and in-frame deletions have been described in individuals with non-ocular Stickler syndrome.

Normal gene product: The *COL11A2* gene encodes for the alpha 2 chain of type XI collagen expressed in cartilage but not in adult liver, skin, tendon, or vitreous.

Abnormal gene product: Mutations of the *COL11A2* gene are speculated to result in abnormal synthesis or function of type XI collagen.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
Stickler syndrome

Stickler Involved People
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References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

- 2 August 2005 (me) Comprehensive update posted to live Web site
- 18 January 2005 (bp/cd) Revision: sequence analysis for Stickler I, II, III
- 16 June 2003 (ca) Comprehensive update posted to live Web site
- 9 June 2000 (me) Review posted to live Web site
- 31 August 1999 (nr) Original submission