Stickler syndrome

Description

Stickler syndrome is a group of hereditary conditions characterized by a distinctive facial appearance, eye abnormalities, hearing loss, and joint problems. These signs and symptoms vary widely among affected individuals.

A characteristic feature of Stickler syndrome is a somewhat flattened facial appearance. This appearance results from underdeveloped bones in the middle of the face, including the cheekbones and the bridge of the nose. A particular group of physical features called Pierre Robin sequence is also common in people with Stickler syndrome. Pierre Robin sequence includes an opening in the roof of the mouth (a cleft palate), a tongue that is placed further back than normal (glossoptosis), and a small lower jaw (micrognathia). This combination of features can lead to feeding problems and difficulty breathing.

Many people with Stickler syndrome have severe nearsightedness (high myopia), which means they have trouble seeing things that are far away. In some cases, the clear gel that fills the eyeball (the vitreous) has an abnormal appearance, which is noticeable during an eye examination. Other eye problems are also common, including increased pressure within the eye (glaucoma), clouding of the lens of the eyes (cataracts), and tearing of the lining of the eye (retinal detachment). These eye abnormalities cause impaired vision or blindness in some cases.

In people with Stickler syndrome, hearing loss varies in degree and may become more severe over time. The hearing loss may be sensorineural, meaning that it results from changes in the inner ear, or conductive, meaning that it is caused by abnormalities of the middle ear.

Most people with Stickler syndrome have skeletal abnormalities that affect the joints. The joints of affected children and young adults may be loose and very flexible (hypermobile), though joints become less flexible with age. Arthritis often appears early in life and may cause joint pain or stiffness. Problems with the bones of the spine (vertebrae) can also occur, including abnormal curvature of the spine (scoliosis or kyphosis) and flattened vertebrae (platyspondyly). These spinal abnormalities may cause back pain.

Researchers have described several types of Stickler syndrome, which are distinguished by their genetic causes and their patterns of signs and symptoms. In

particular, the eye abnormalities and severity of hearing loss differ among the types. Type I has the highest risk of retinal detachment. Type II also includes eye abnormalities, but type III does not (and is often called non-ocular Stickler syndrome). Types II and III are more likely than type I to have significant hearing loss. Types IV, V, and VI are very rare and have each been diagnosed in only a few individuals.

A condition similar to Stickler syndrome, called Marshall syndrome, is characterized by a distinctive facial appearance, eye abnormalities, hearing loss, and early-onset arthritis. Marshall syndrome can also include short stature. Some researchers have classified Marshall syndrome as a variant of Stickler syndrome, while others consider it to be a separate disorder.

Frequency

Stickler syndrome affects an estimated 1 in 7,500 to 9,000 newborns. Type I is the most common form of the condition.

Causes

Variants (also known as mutations) in several genes cause the different types of Stickler syndrome. Between 80 and 90 percent of all cases are classified as type I and are caused by variants in the *COL2A1* gene. Another 10 to 20 percent of cases are classified as type II and result from variants in the *COL11A1* gene. Marshall syndrome, which may be a variant of Stickler syndrome, is also caused by *COL11A1* gene variants. Stickler syndrome types III through VI result from variants in other, related genes.

All of the genes associated with Stickler syndrome provide instructions for making components of collagens, which are complex molecules that give structure and strength to the connective tissues that support the body's joints and organs. Variants in any of these genes impair the production, processing, or assembly of collagen molecules. Defective collagen molecules or reduced amounts of collagen impair the development of connective tissues in many different parts of the body, leading to the varied features of Stickler syndrome.

Not all individuals with Stickler syndrome have variants in one of the known genes. Researchers believe that variants in other genes may also cause this condition, but those genes have not been identified.

Learn more about the genes associated with Stickler syndrome

- COL11A1
- COL11A2
- COL2A1
- COL9A1
- COL9A2
- COL9A3

Inheritance

Stickler syndrome types I, II, and III are inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. In some cases, an affected person inherits a gene variant from one affected parent. Other cases result from new variants. These cases occur in people with no history of Stickler syndrome in their family.

Marshall syndrome also typically has an autosomal dominant pattern of inheritance.

Stickler syndrome types IV, V, and VI are inherited in an autosomal recessive pattern. Autosomal recessive inheritance means both copies of the gene in each cell have variants. The parents of an individual with an autosomal recessive condition each carry one copy of the altered gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- Hereditary arthro-ophthalmo-dystrophy
- Hereditary arthro-ophthalmopathy
- Stickler dysplasia

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Otospondylomegaepiphyseal dysplasia, autosomal dominant (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1848488/)
- Genetic Testing Registry: Marshall syndrome (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0265235/)
- Genetic Testing Registry: Stickler syndrome (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0265253/)
- Genetic Testing Registry: Stickler syndrome type 1 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C2020284/)
- Genetic Testing Registry: Stickler syndrome type 2 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1858084/)
- Genetic Testing Registry: Stickler syndrome, type 4 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C3279941/)
- Genetic Testing Registry: Stickler syndrome, type 5 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C3280342/)

Genetic and Rare Diseases Information Center

- Marshall syndrome (https://rarediseases.info.nih.gov/diseases/6984/index)

- Stickler syndrome (https://rarediseases.info.nih.gov/diseases/10782/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Clinical Trials

- ClinicalTrials.gov (https://clinicaltrials.gov/search?cond=%22Stickler syndrome%22)

Catalog of Genes and Diseases from OMIM

- STICKLER SYNDROME, TYPE I; STL1 (https://omim.org/entry/108300)
- MARSHALL SYNDROME; MRSHS (https://omim.org/entry/154780)
- OTOSPONDYLOMEGAEPIPHYSEAL DYSPLASIA, AUTOSOMAL DOMINANT; OSMEDA (https://omim.org/entry/184840)
- STICKLER SYNDROME, TYPE II; STL2 (https://omim.org/entry/604841)
- STICKLER SYNDROME, TYPE I, NONSYNDROMIC OCULAR (https://omim.org/entry/609508)
- STICKLER SYNDROME, TYPE V; STL5 (https://omim.org/entry/614284)
- STICKLER SYNDROME, TYPE IV; STL4 (https://omim.org/entry/614134)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28Stickler+syndrome%5BTIAB%5D%29+OR+%28arthro-ophthalmopathy%5BTIAB%5D%29+OR+%28Marshall+syndrome%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

References

- Acke FR, Dhooge IJ, Malfait F, De Leenheer EM. Hearing impairment in Sticklersyndrome: a systematic review. Orphanet J Rare Dis. 2012 Oct 30;7:84. doi: 10.1186/1750-1172-7-84. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/23110709) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3551705/)
- Annunen S, Korkko J, Czarny M, Warman ML, Brunner HG, Kaariainen H, MullikenJB, Tranebjaerg L, Brooks DG, Cox GF, Cruysberg JR, Curtis MA, Davenport SL,Friedrich CA, Kaitila I, Krawczynski MR, Latos-Bielenska A, Mukai S, Olsen BR,Shinno N, Somer M, Vikkula M, Zlotogora J, Prockop DJ, Ala-Kokko L. Splicingmutations of 54-bp exons in the COL11A1 gene cause Marshall syndrome,

but othermutations cause overlapping Marshall/Stickler phenotypes. Am J Hum Genet. 1999Oct;65(4):974-83. doi: 10.1086/302585. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/10486316) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1288268/)

- Baker S, Booth C, Fillman C, Shapiro M, Blair MP, Hyland JC, Ala-Kokko L. Aloss of function mutation in the COL9A2 gene causes autosomal recessive Sticklersyndrome. Am J Med Genet A. 2011 Jul;155A(7):1668-72. doi: 10.1002/ajmg.a.34071.Epub 2011 Jun 10. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/21671392)
- Faletra F, D'Adamo AP, Bruno I, Athanasakis E, Biskup S, Esposito L, GaspariniP. Autosomal recessive Stickler syndrome due to a loss of function mutation inthe COL9A3 gene. Am J Med Genet A. 2014 Jan;164A(1):42-7. doi:10.1002/ajmg.a.36165. Epub 2013 Nov 22. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/24273071)
- Khalifa O, Imtiaz F, Ramzan K, Allam R, Hemidan AA, Faqeih E, Abuharb G, Balobaid A, Sakati N, Owain MA. Marshall syndrome: further evidence of a distinctphenotypic entity and report of new findings. Am J Med Genet A. 2014Oct;164A(10):2601-6. doi: 10.1002/ajmg.a.36681. Epub 2014 Jul 29. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/25073711)
- Liberfarb RM, Levy HP, Rose PS, Wilkin DJ, Davis J, Balog JZ, Griffith AJ,Szymko-Bennett YM, Johnston JJ, Francomano CA, Tsilou E, Rubin BI. The Sticklersyndrome: genotype/phenotype correlation in 10 families with Stickler syndromeresulting from seven mutations in the type II collagen gene locus COL2A1. GenetMed. 2003 Jan-Feb;5(1):21-7. doi: 10.1097/00125817-200301000-00004. Erratum In:Genet Med. 2003 Nov-Dec;5(6):478. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/12544472)
- Mortier G. Stickler Syndrome. 2000 Jun 9 [updated 2023 Sep 7]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews(R) [Internet]. Seattle (WA): University ofWashington, Seattle; 1993-2024. Available fromhttp://www.ncbi.nlm.nih.gov/books/NBK1302/ Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20301479)
- Van Camp G, Snoeckx RL, Hilgert N, van den Ende J, Fukuoka H, Wagatsuma M, Suzuki H, Smets RM, Vanhoenacker F, Declau F, Van de Heyning P, Usami S. A newautosomal recessive form of Stickler syndrome is caused by a mutation in theCOL9A1 gene. Am J Hum Genet. 2006 Sep;79(3):449-57. doi: 10.1086/506478. Epub2006 Jun 26. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16909383) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1559536/)

Last updated September 14, 2022