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The Role of Genetic Mutations in Genes COL2A1, COL11A1, COL11A2, COL9A1, COL9A2, COL9A3 in Stickler Syndrome

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Abstract

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. Stickler syndrome is caused by genetic changes (mutations or pathogenic variants) in one of six genes: COL2A1, COL11A1, COL11A2, COL9A1, COL9A2, or COL9A3. These genes are all responsible for providing instructions to the body to produce collagen.

Keywords: *Stickler syndrome, Genetics Mutations, COL2A1, COL11A, COL11A2, COL9A1, COL9A2, COL9A3 genes.*

Overview of Stickler Syndrome

Stickler Syndrome is a genetic disorder that refers to connective tissue and is characterized by distinct facial features, eye problems, hearing loss and articular problems. Signs and symptoms of Stickler Syndrome are significantly different among people with the disease[1].

Clinical Signs and Symptoms of Stickler Syndrome

One of the distinctive features of Stickler Syndrome is the somewhat smooth face appearance. This flat facial appearance is due to the low bones developed in the middle of the face including the cheeks and nasal bridge. Signs and symptoms associated with Pierre Robin syndrome are common in Stickler syndrome patients. Symptoms of Pierre-Robin syndrome include: cleft palate (mouth roof), enlargement of the tongue more than normal (glossoptosis), and lower jaw than normal (microgonadia). Combining these features together can lead to nutritional and respiratory problems in Stickler syndrome sufferers[1,2].

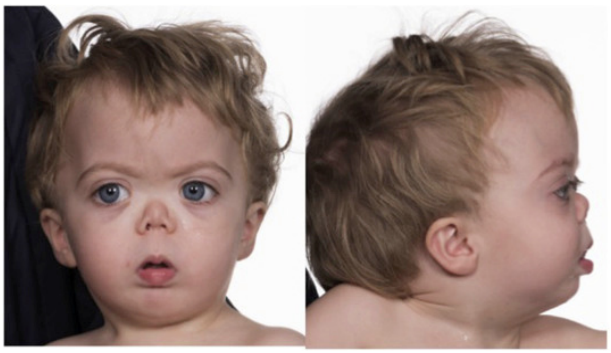
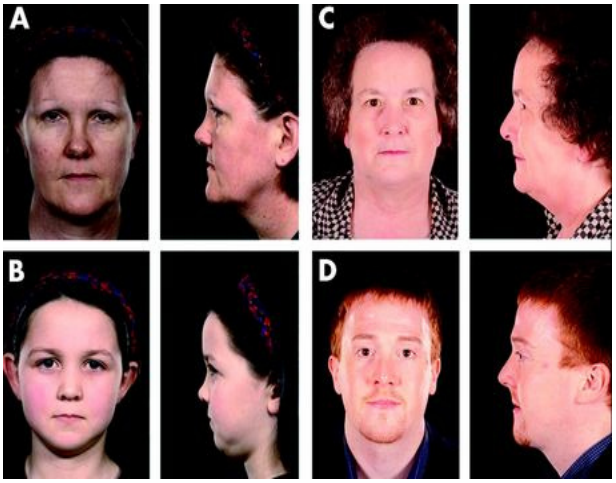


Fig1. *Picture of a child with Stickler syndrome with facial disorders*

Many people with Stickler Syndrome have severe myopia. In some cases, the clear gel that fills the eye has an abnormal appearance that is very noticeable in an eye examination. Other eye problems are also common in Stickler Syndrome, including increased intraocular pressure (glaucoma), cloudy lens (cataract), lacunae (strabismus), and rupture of the eyelid (retinal detachment). It should be noted that these abnormalities of the eyes may in some cases cause visual or blindness[1,3].

Fig 2. *Pictures of children and adults with Stickler syndrome*

In people with Stickler Syndrome, hearing loss varies with age, and over time, the hearing loss may worsen. Chronic recurrent otitis media (otitis media) occurs in Stickler Syndrome and can help guide hearing loss. Some sufferers of Stickler syndrome may experience thick, sticky fluid accumulation on the back of the ear. People with Stickler Syndrome often have a variety of features, including mid-facial hypoplasia with abnormal bones and nasal bridge, small nose, long upper lip (filtrum), prominent eyes, and small chin. Dental malformations, such as upper and lower teeth fractures during development, can occur in children with Stickler Syndrome. Most people with Stickler Syndrome have skeletal disorders that affect the joints. The affected joints of children and adults can be loose and very flexible (hypermobiles). Arthritis often occurs early in the life of patients with Stickler Syndrome and may cause joint pain or stiffness[1,4].



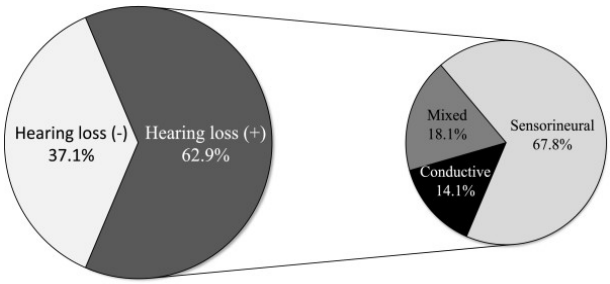


Fig 3. *Another view of Stickler Syndrome sufferers and Circular diagram of the frequency of hearing loss in Stickler syndrome patients*

In addition, bone problems (spine) can also occur, including abnormal spine curvature (scoliosis or kyphosis) and flat vertebrae, which can cause back pain or back pain. Muscle tone (muscular hypotonia), abnormal long fingers, flat feet and degenerative mental disorder that begins in childhood also occur in Stickler syndrome[1,5].

Researchers have divided Stickler Syndrome into 6 different types, each with its own clinical signs and symptoms. Patients with Stickler syndrome type 1 have the highest risk of retinal detachment (retinal rupture). Stickler syndrome type 2 also has eye anomalies, but stickler syndrome type 3 has non-eye disorders. It is noteworthy that type 2 and type 3 Stickler Syndrome are more likely to have hearing loss than type 1 Stickler Syndrome. Stickler Syndrome type 4,5,6 is very rare and has been observed in several people so far. Stickler Syndrome is closely related to Marshall Syndrome, because features of Marshall Syndrome include: eye disorders, short stature, hearing loss, and premature arthritis. Some researchers have classified Marshall Syndrome as a type of Stickler Syndrome, while others see it as a separate disorder[1,6].

Etiology of Stickler Syndrome

Each of the different types of Stickler Syndrome is caused by mutations in different genes. About 80 to 90 percent of all cases of Stickler Syndrome are classified as Stickler Syndrome type 1, which is caused by the COL2A1 gene mutation. The COL2A1 gene is located on the long arm of chromosome 12 as 12q13.11. About 10% to 20% of other Stickler Syndrome cases are classified as Stickler Syndrome type 2 due to the COL11A1 gene mutation. The COL11A1 gene is located on the short arm of chromosome 1 as 1p21.1. Stickler syndrome type 3 is caused by a mutation in the COL11A2 gene located on the short arm of

chromosome 6 as 6p21.32. Stickler syndrome type 4 is caused by the mutation of the COL9A1 gene, which is located on the long arm of chromosome 6 as 6q13. Stickler syndrome type 5 is caused by the mutation of the COL9A2 gene, located on the short arm of chromosome 1 as 1p34.2. Stickler syndrome type 6 is caused by the mutation of the COL9A3 gene located on the long arm of chromosome 20 at 20q13.33[1,7].

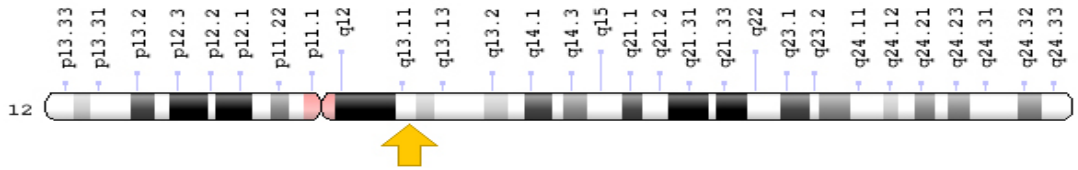


Fig 4. *Schematic overview of chromosome 12 where the COL2A1 gene is located in the long arm of chromosome 12q13.11*

All genes associated with Stickler Syndrome provide guidelines for the synthesis of proteins that are essential for the proper development and function of collagen, one of the most abundant proteins in the body, accounting for about 25% of all connective tissue proteins. , It is necessary. There are different types of collagen protein that are indicated by Roman marks. For example, the COL2A1 gene encodes type II collagen protein. The COL11A1 and COL11A2 genes encode collagen type XI proteins. The genes COL9A1, COL9A2 and COL9A3 encode type IX collagen protein. It is worth noting that collagen protein is very important in the tissues of the human body and acts as a cushion for bone in cartilage and gel-like fluid in the center of the eye. Therefore, any mutation in the genes associated with collagen encoding will result in a lack of collagen synthesis or inappropriate collagen synthesis, which is one of the main causes of Stickler syndrome[1,8].

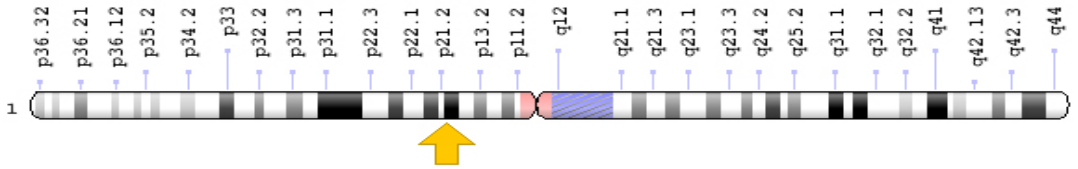


Fig 5. *Schematic overview of chromosome 1, the COL11A1 gene located on the short arm of chromosome 1p21.1*

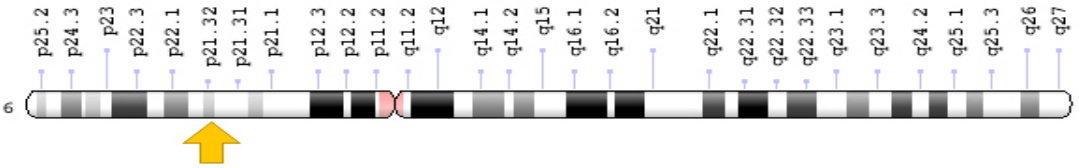


Fig 6. *Schematic overview of chromosome 6 where the COL11A2 gene is located in the short arm of chromosome 6p21.32*

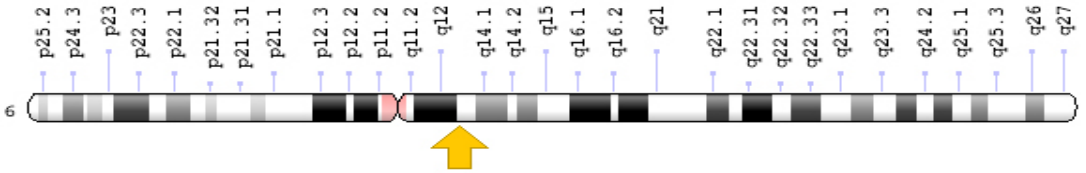


Fig 7. *Schematic overview of chromosome 6 where the COL9A1 gene is located on the long arm of chromosome 6q13*

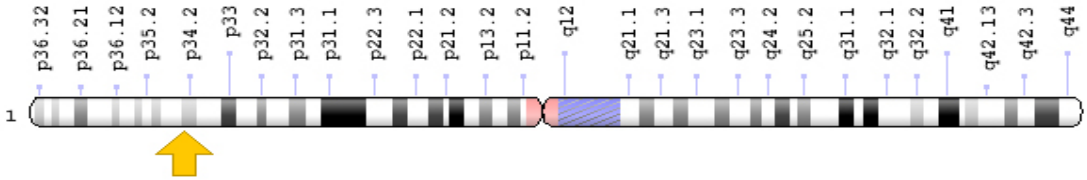


Fig 8. *Schematic overview of chromosome 1 where the COL9A2 gene is located in the short arm of chromosome 1p34.2*

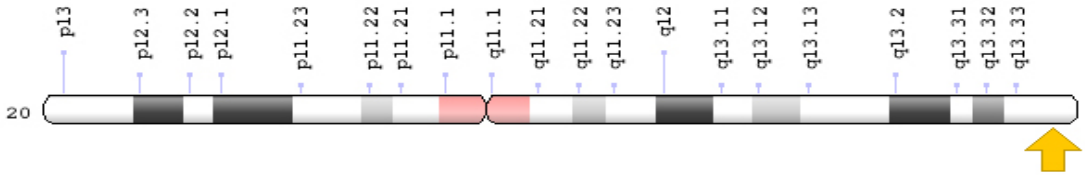


Fig 9. *Schematic overview of chromosome 20 where the COL9A3 gene is located on the long arm of chromosome 20q13.33*

Stickler Syndrome type 1,2,3 follows the dominant autosomal inherited pattern. Therefore, a copy of the mutated genes COL2A1, COL11A1, COL11A2 (including parents) is required for this syndrome, and the chance of having a child with Stickler Syndrome Type 1,2,3 in this case for any possible pregnancy The rate is 50%. It is worth noting that Marshall Syndrome follows the dominant autosomal inherited pattern[1,9].

Stickler Syndrome type 4,5,6 follows an autosomal recessive inheritance pattern. Therefore, two copies of the mutated genes COL9A1, COL9A2, COL9A3 (one from the father and the other from the mother) are required to develop the syndrome, and the chance of having a child with type 4,5,6 Stichler's syndrome in this case for each pregnancy The probability is 25%.[1,10]

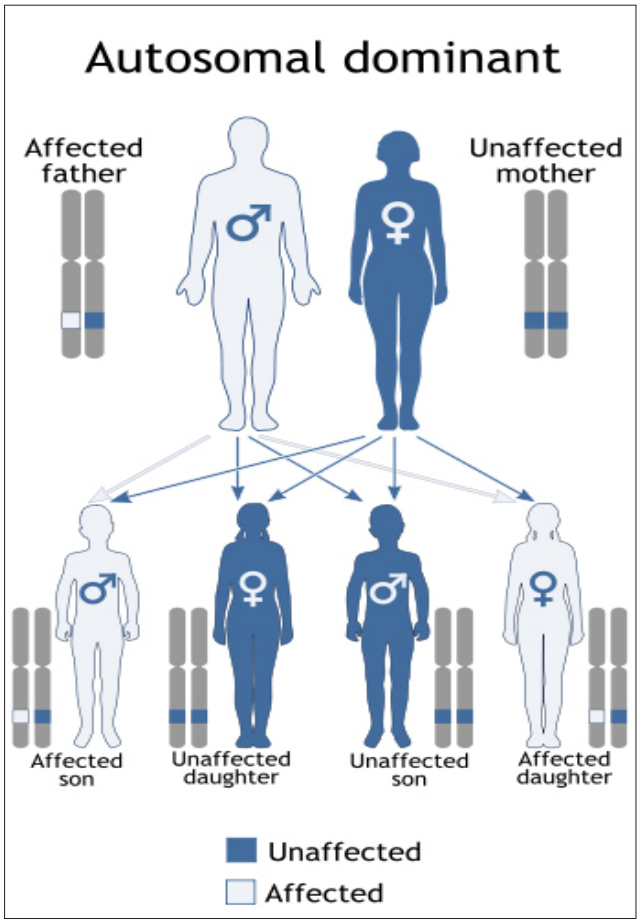


Fig 10. *Schematic overview of the dominant autosomal inherited pattern, which also follows the Stickler Syndrome type 1,2,3*

Frequency of Stickler Syndrome

Stickler Syndrome is a genetic disorder that affects men and women. The average prevalence rate of this syndrome is about 1 in 7500 to 1 in 9000 or 1 in 10,000 live births worldwide. Stickler syndrome type 1 is the most common type of syndrome. Most researchers believe the disorder is diagnosed very low, so it is

difficult to determine the prevalence of Stickler Syndrome in the general population. It is worth noting that Stickler Syndrome is one of the most common connective tissue disorders in the United States[1,11].

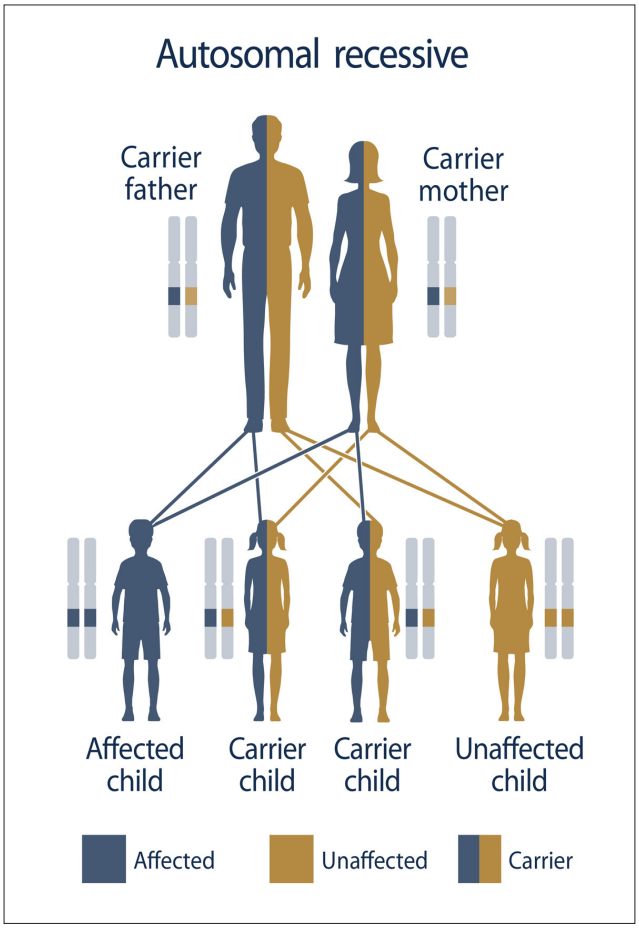


Fig 11. *Schematic overview of the recessive autosomal recessive pattern that also follows the Stickler type 4,5,6 syndrome*

Diagnosis of Stickler Syndrome

Stickler Syndrome is diagnosed on the basis of thorough clinical evaluation, patient history, and identification of clinical findings. There are currently no general criteria for the clinical diagnosis of Stickler Syndrome. Various tests, such as X-ray studies and eye disorders assessment tests, may also be helpful to diagnose Stickler Syndrome. Prenatal diagnosis is also possible using amniocentesis fluid or chorionic villus biopsy. However, the most definitive method of diagnosing Stickler Syndrome is molecular genetic testing for the genes mentioned to investigate the presence of possible mutations[1,12].

Treatment Pathways of Stickler Syndrome

The treatment strategy and management of Stickler Syndrome is based on the signs and symptoms that each person is exposed to. In other words, the treatment of Stickler Syndrome is symptomatic and supportive. Treatment may be performed with the coordination of a team of specialists including oral and maxillofacial surgeon, nose surgeon, otolaryngologist, ophthalmologist, optometrist, audiologist, speech pathologist, orthopedic surgeon, physiotherapist and rheumatologist. There is no cure for Stickler syndrome. Early diagnosis and prompt treatment can alleviate the suffering of Stickler syndrome. Genetic counseling is also important for all parents who want a healthy baby[1,12].

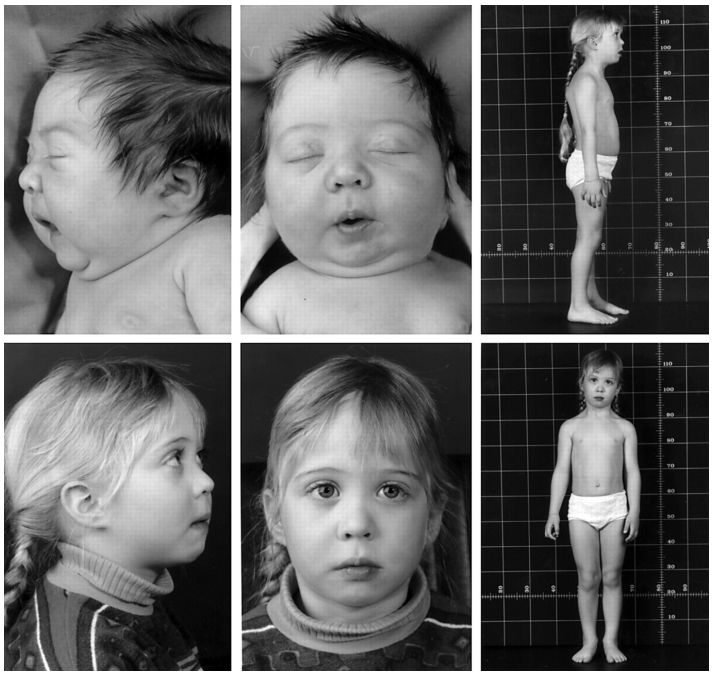


Fig 12. *Pictures of the types of disorders associated with stickler syndrome*

Discussion and Conclusion

Because the symptoms of Stickler syndrome are variable, it can be difficult to predict what the long-term outlook is for people who have the syndrome. There is an increased risk for eye problems associated with Stickler syndrome including retinal detachment and cataracts. These symptoms can lead to vision loss. People with Stickler syndrome may also experience arthritis before 40-years-old. In general, people with Stickler syndrome have typical intelligence and can function well in society. Some people do not know they have Stickler syndrome until another family member is diagnosed because the symptoms can be relatively mild[1-12].

History of Stickler Syndrome

Stickler syndrome was first reported in 1965 by B.David, Gunnar B.Stickler, G.Weissenbacher, Ernest Zweymuller[1,12].

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