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# Early Onset High Myopia in a Child with Stickler Syndrome Type II: A Case Report

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Stickler syndrome is a rare genetic disorder that affects the connective tissue of different body systems. It is characterised by moderate to severe myopia, cataract, retinal detachment, hearing loss, facial dysmorphic features, cleft palate, and joint problems. Mutations in collagen genes including *COL2A1, COL11A1, COL11A2, COL9A1, COL9A2, COL9A3, BMP4*, and *LOXL3* are associated with Stickler syndrome. Herein, we report the case of a 9-year-old girl with Stickler syndrome, who presents early onset of high-myopia and a mildly depressed nasal bridge. No hearing disorder was found, no abnormalities in bones and joints, and her communication and learning capability were also normal. To identify the underlying genetic cause, Whole Exome Sequencing (WES) was carried out using genomic DNA extracted from patient's blood. A likely pathogenic heterozygous missense variant of the *COL11A1* gene (NM_001854.4: c.1927G>C), which had not been previously reported, was identified in the patient. The patient was subsequently diagnosed with Stickler syndrome Type II.

**Keywords:** Stickler syndrome; myopia; genetic variant; *COL11A1* gene

## I. INTRODUCTION

Stickler syndrome (STL) is a rare genetic disorder that affects the connective tissue in the body, with an estimated prevalence of 1 in 7,500 to 9,000 newborns (McArthur *et al.*, 2018). It is a type of collagenopathy, which means it affects the structure and function of collagen, the protein that gives strength and support to tissues and organs in the body (Rose *et al.,* 2005; Stickler *et al.*, 1965). Most forms of Stickler syndrome are characterised by high myopia, retinal detachment, vitreoretinal degeneration, and cataracts which can cause impaired vision or blindness in some cases (Snead *et al.,* 2011). Additional findings may include flat cheeks, nasal bridge (most noticeable in infants), Pierre Robin syndrome (small jaw, cleft palate, tongue placement abnormalities, and breathing problems), mild spondyloepiphyseal dysplasia, early-onset osteoarthritis, and hearing loss (Stickler *et al.,* 1965). However, people affected by Stickler syndrome usually have normal intellect and normal stature (Vijzelaar *et al.*, 2013).

Stickler syndrome is caused by mutations in one of several genes that encode for different components of the collagen network (Khalifa *et al.,* 2014). Most of the cases (80%–90%) are inherited in an autosomal dominant pattern caused by

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mutations in *COL2A1* gene (STL Type I), *COL11A1* gene (STL Type II), and *COL11A2* gene (STL Type III) (Carvalho *et al.,* 2022; Wu *et al.,* 2021; Hanson-Kahn *et al.,* 2018). In contrast, the less frequent autosomal recessive inherence pattern is caused by mutations in *COL9A1* gene (STL Type IV) and *COL9A2* gene (STL Type V). The severity of the disorder can vary depending on the type of Stickler syndrome and the specific gene affected.

## II. CASE PRESENTATION

A 9-year-old girl was referred to the Genetics Department, Hospital Kuala Lumpur, because of high myopia. She is the younger child of a non-consanguineous couple who had four children with no history of STL in their family. Further examination revealed that both the patient's mother and oldest sister also had high myopia.

At six years old, she was diagnosed with high myopia and astigmatism by an ophthalmologist after experiencing blurred vision in both eyes for nine months. The ophthalmologic assessment confirmed severe myopia in both eyes: the right eye (RE): -16.00 -3.00X10 and the left eye (LE): -13.00 -2.50X170. In addition, her visual acuity was 6/24 in both eyes. The ocular examination also showed tigroid fundus in both eyes. The patient was given a low dose of atropine and was taught patching exercises to slow the progression of myopia.

She had no history of trauma or surgery and showed no hearing problems. There were no abnormalities in her bones and joints, and her communication and learning capabilities were normal. At the age of seven, she was already wearing glasses. During observation, she showed a slightly flattened nasal bridge, which raised the possibility of Stickler syndrome. The patient was then referred to the Genetics Department for further genetic evaluation.

## III. WHOLE EXOME SEQUENCING

The patient's parent was subsequently counseled and written assent was obtained for whole exome sequencing (WES) analysis to be conducted for patient's sample to identify sequence variations that are pathogenic for patient's clinical phenotype.

Peripheral blood sample was collected from the patient, and genomic DNA was extracted using QIAamp DNA Mini kit (Qiagen, Germany). The extracted DNA was fragmented, adapted, barcoded, and subjected to a solution phase hybridisation with the Agilent SureSelect Human All Exon V5 Plus probe kit (Agilent, Santa Clara, CA, USA) and sequenced on the NovaSeq 6,000 (Illumina, San Diego, CA, USA). Sequence reads were mapped to the human genome hg38/GRCh38 using the Burrows-Wheeler Aligner (BWA) software. Duplicates were removed by Picard v1.57 (http://picard.sourceforge.net/). The average sequencing depth was targeted for 125X, and data with Q30 was used for analysis. GATK (https://software.broadinstitute.org/gatk/) was employed to identify SNVs and Indels. Variant annotation and interpretation were conducted by ANNOVAR (Wang *et al.,* 2010) and variants were searched in the dbSNP (http://www.ncbi.nlm.nih.gov/SNP/) and 1000 Genomes Project (http://www.1000genomes.org/) databases. Functional annotation and pathogenicity of mutations were predicted by SNPeffect (De Baets *et al.,* 2012). Disease and phenotype databases such as OMIM (http://www.omim.org), ClinVar (http://www.ncbi.nlm.nih.gov/clinvar), HGMD (http://www.hgmd.org), PubMed (http://www.ncbi.nlm.nih.gov/pubmed), ClinGen (http://www.clinicalgenenome.org) and Orphanet (https://www.orpha.net) were also searched. The variants with a minor allele frequency of less than 0.05 were selected for interpretation based on pathogenicity, clinical synopsis, and inheritance mode of associated disease.

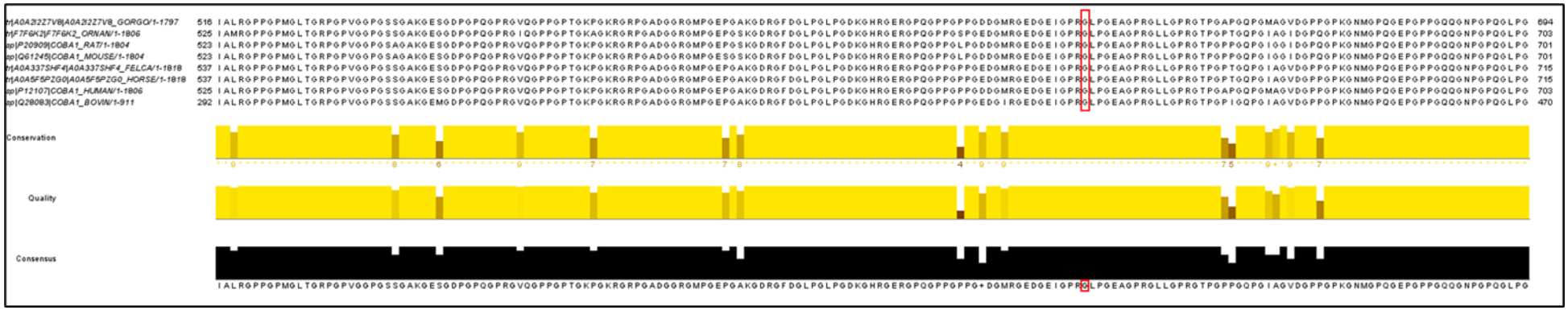
Mutations in seven genes associated with Stickler syndrome were identified in the patient. These genes include *COL2A1, COL11A1, COL11A2, COL9A2, COL9A3, BMP4,* and *LOXL3* (Table 1). Among these mutations, a heterozygous missense variant in *COL11A1* (NM_001854.4: c.1927G>C, p.Gly643Arg) identified to be likely pathogenic according to the American College of Medical Genetics and Genomics (ACMG) criteria. The variant was predicted to cause deleterious effects, suggested by *in silico* prediction in Franklin Genoox (https://franklin.genoox.com/clinical-db/home). The variant was absent in control populations, including dbSNP, 1000 Genomes Project, and GnomAD, and no clinical evidence was found for this variant. Comparing the encoded protein sequence across species, the mutation site, p.Gly643Arg , was found to be a highly conserved region across all species (Figure 1).

Table 1. List of variants associated with Stickler syndrome identified in the study.

| Gene | Variant | Zygosity | Inheritance[a] | Nucleotide | Amino-acid change | Molecular consequences | SNP effect[b] | ACMG classification[c] |
|---|---|---|---|---|---|---|---|---|
| *COL2A1* | rs3803183 | Homozygous | AD | NM_001844.5: c.25A>T | p.Thr9Ser | Missense variant | Moderate | Benign |
| | rs1635553 | Homozygous | AD | NM_001844.5: c.2400T>C | p.Asn800= | Synonymous variant | Low | Benign |
| | rs2276454 | Homozygous | AD | NM_001844.5: c.2295C>T | p.Gly765= | Synonymous variant | Low | Benign |
| | rs3737548 | Heterozygous | AD | NM_001844.5: c.504C>A | p.Gly168= | Synonymous variant | Low | Benign |
| *COL11A1* | - | Heterozygous | AD | NM_001854.4: c.1927G>C | p.Gly643Arg | Missense variant | Moderate | Likely pathogenic |
| | rs2229783 | Homozygous | AD | NM_001854.4: c.4770T>C | p.Ile1590= | Synonymous variant | Low | Benign |
| | rs1763347 | Homozygous | AD | NM_001854.4: c.4512T>C | p.Gly1504= | Synonymous variant | Low | Benign |
| | rs1676486 | Homozygous | AD | NM_001854.4: c.4603T>C | p.Ser1535Pro | Missense variant | Moderate | VUS |
| | rs3753841 | Homozygous | AD | NM_001854.4: c.3968C>T | p.Pro1323Leu | Missense variant | Moderate | Benign |
| *COL11A2* | rs9277934 | Heterozygous | AD | NM_080680.3: c.826G>A | p.Glu276Lys | Missense variant | Moderate | Benign |
| *COL9A2* | rs2228564 | Homozygous | AD | NM_001852.4: c.977A>G | p.Gln326Arg | Missense variant | Moderate | Benign |
| *COL9A3* | rs2294995 | Heterozygous | AR | NM_001853.4: c.1740T>C | p.Ala2Asp | Synonymous variant | Low | VUS |
| | rs2273079 | Heterozygous | AR | NM_001853.4: c.129C>T | p.Pro43= | Synonymous variant | Low | Benign |
| *BMP4* | rs17563 | Homozygous | AD | NM_001202.6: c.455T>C | p.Val152Ala | Missense variant | Moderate | Benign |
| *LOXL3* | rs17010022 | Homozygous | AR | NM_032603.5: c.1113G>C | p.Leu371= | Synonymous variant | Low | Benign |

[a]AD = Autosomal dominant; AR = Autosomal recessive
[b]SNPeffect: Moderate = The genetic variant is predicted to have non-disruptive effect, which might change protein effectiveness; Low = The genetic variant is predicted to be mostly harmless or unlikely to affect protein function.
[c]Franklin ACMG Classification. VUS = Variant of Uncertain Significance.

Figure 1. Protein alignment analysis of human COL11A1 protein sequence against 7 species of mammals.




Protein alignment showed that the mutation on COL11A1:p.G643R occurred at a highly conserved region (marked in red box) across the multiple species of mammals: rat (*R. norvegicus*; RAT), mouse (*M. musculus*; MOUSE), cow (*B. taurus*; BOVIN), gorilla (*G. gorilla*; GORGO), horse (*E. caballus*; HORSE), cat (*F. catus*; FELCA) and platypus (*O. anatinus*; ORNAN).

## IV. PROTEIN SEQUENCE ANALYSIS USING ROBETTA

Robetta was used to predict the effect of the missense variant in *COL11A1* (NM_001854.4: c.1927G>C, p.Gly643Arg) on the protein structure (Kim *et al.,* 2004). Robetta is a freely accessible server-based software that relies on deep learning methods to predict the three-dimensional structure of a protein. The full-length, three-dimensional structure of wild-type COL11A1 protein was predicted. A structure containing the mutation (G643R) was then computed with *ab initio* modeling using the Robetta server. The change of DNA has resulted in a missense non-conservative point mutation that replaces glycine with arginine. However, this substitution occurred at the mobile loop region of COL11A1 protein, which may slightly alter the protein function and cause misfolding (Figure 2). Further study is needed to confirm the effect of this mutation.

## V. DISCUSSION

Stickler syndrome is a disorder characterized by a clinically variable and genetically heterogeneous presentation resulting from the abnormal synthesis of collagen types II, XI, or IX. Diagnosis of Stickler syndrome is typically made based on a combination of clinical symptoms, family history, and genetic testing (Shively *et al.,* 2020). In this report, a 9-year-old child was diagnosed with Stickler syndrome due to the early onset of high myopia. At the time of medical genetic evaluation, no clinically significant hearing loss was reported. The clinical diagnosis of Stickler syndrome was confirmed through genetic analysis, which identified the c.1927G>C heterozygous variant in the exon 20 of the *COL11A1* gene, a missense mutation still not described in mutational databases, but it is highly probable to be pathogenic.

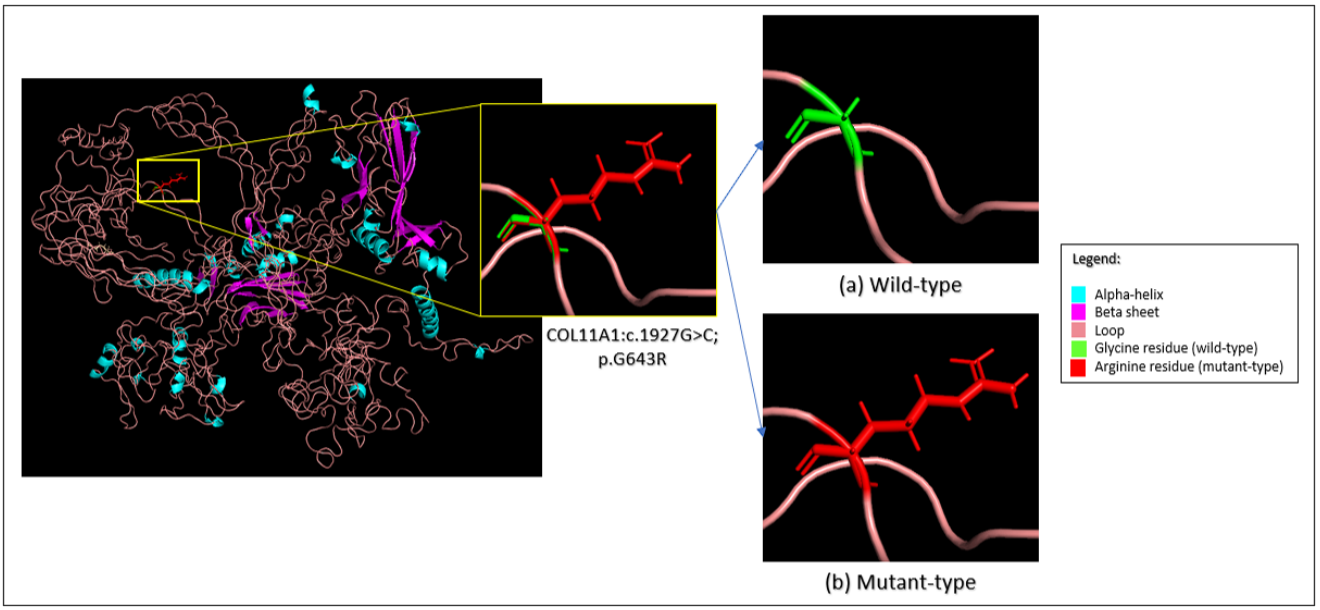
*COL11A1* is located on chromosome 1p21, encoded alpha 1 chain of type IV collagen, and seems to play an essential role in fibrillogenesis (Richards *et al.,* 1996). Mutations in *COL11A1* gene have been associated with autosomal dominant disorders, STL type II (OMIM 604841), and Marshall syndrome (OMIM 154780). Clinical overlap between Marshall syndrome and STL cases is commonly observed, although a more severe phenotype is typically seen in patients affected by Marshall syndrome. However, in contrast to STL type II, Marshall syndrome has less severe eye findings but striking ocular hypertelorism, more pronounced maxillary hypoplasia, and ectodermal abnormalities ( Ala-Kokko and Shanske, 2009). Phenotypic expression of Stickler syndrome with mutations in different causative genes is also difficult, but some differences may be present. For example, patients with STL type I due to mutations in *COL2A1*, exhibit a characteristic 'membranous' or type 1 vitreous phenotype, while those patients with STL type II due to mutations in *COL11A1* show a 'beaded' or type 2 vitreous phenotype (Martin *et al.,* 1999).

Most patients with Stickler syndrome develop eye manifestations, including myopia, vitreous degeneration, retinal detachment, and cataracts (Guo *et al.,* 2017). Our case showed a significant early onset of ocular involvement that is most frequently described in STL type I and STL type II. In addition, the patients with *COL11A1* mutations seldom had vitreoretinal degeneration and retinal detachment compared with a higher incidence in those with *COL2A1* mutations (Annunen *et al.,* 1999). In contrast to Marshall syndrome, patients with STL type II normally had more severe eye findings (Ala-Kokko and Shanske, 2009).

The other important aspect of the differential diagnosis is that patients with *COL11A1* mutations are more common to have severe hearing impairment than those with *COL2A1* mutations. Additionally, Stickler syndrome-associated *COL11A1* mutations are also suggested to have more pronounced facial dysmorphic characteristics than that caused by *COL2A1* (Brizola *et al.,* 2020; Poulson *et al.,* 2004). By contrast, our patient, who carries a novel mutation in *COL11A1* shows no significant hearing disorder and a very mild flattened facial appearance. The overlapping phenotypes of STL type 1 and STL type II are reasonable because of the structural nature of the molecules. *COL2A1, COL11A1*, and *COL11A2* encode each of the three alpha chains. These alpha chains are finally assembled into one protein type, type IV collagen, characterized by a triple helix (Guo *et al.*, 2017).

The severity of the ocular condition in the Stickler syndrome cases associated with COL11A1 mutations reported before shows that an early diagnosis of STL is crucial for the management of a patient with STL to help them get the best

Figure 2. Protein structural model of COL11A1.




*The domains of the protein containing the substitution were predicted and modeled using ab initio modeling method in Robetta. The substitution of G to C (c.1927G>C) has resulted in a missense variant that replaces glycine to arginine (G643R) in the mobile loop region of COL11A1 of the mutant-type protein.*

possible outcome and quality of life. Early diagnosis of STL cases has improved the prevention of blindness in STL patients over the last few decades (Shapiro *et al.,* 2018). The diagnosis of Stickler syndrome is mainly clinically based, and it is difficult to diagnose at the early stage. Therefore, genetic analysis based on next-generation sequencing should be widely used in the identification of such rare genetic variants for early clinical diagnosis and differentiation of STL. We believe that screening of other family members and initiation of genetic counseling should be performed.From the genetic analysis, the variant, c.1927G>C, which was detected in this study, causes an amino acid change, p.Gly643Arg, in the protein structure. The amino acid substitution occurred at the mobile loop region of COL11A1 protein which may slightly altered the protein function and causes misfolding. This is potentially the cause of Stickler Syndrome Type II in this patient who was presented with mild severity of myopia. However, further study is needed to confirm the effect of this mutation.

## VI. ACKNOWLEDGEMENT

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## VII. CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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