CLINICAL REPORT

# Case report of the first molecular diagnosis of Stickler syndrome with a pathogenic *COL2A1* variant in a Mongolia family

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**Abstract**

**Background:** Stickler syndrome is a group of connective tissue disorders that can affect eye (myopia, cataract, and retinal detachment), skeleton (spondyloepiphyseal dysplasia and precocious arthritis), craniofacies (midfacial under development and cleft palate), and inner ear (conductive and sensorineural); with the degree of symptoms varying among patients. Mutations in the *COL2A1*, *COL11A1*, *COL11A2*, *COL9A1*, *COL9A2*, and *COL9A3* procollagen genes cause Stickler syndrome.

**Case presentation:** A 16-year-old Mongolian girl approached our clinics with retinal detachment. The proband had vitreous degeneration in both eyes, rhegmatogenous retinal detachment in her right eye, a large area of retina degeneration in her left eye, and coupled with severe myopia. No obvious hearing disorder was found, no abnormalities in bones and joints, and her communication and learning capability were also normal. Further clinical examination showed that the patient's other five family members across three generations had vitreous and retina degenerations. Exome sequencing showed a heterozygous splicing variant in *COL2A1* in all patients.

**Conclusions:** In this case report, a pathogenic splicing variant in the *COL2A1* gene was identified in a Mongolian family affected with Stickler syndrome type I by exome sequencing. This heterozygous splicing variant in *COL2A1* (NM_001844.4:C.2518-1G>A) that may impair splicing, which was suggested by in silico prediction. Next-generation sequencing is helpful for the differential diagnosis of this clinically variable and genetically heterogeneous disorder.

**KEYWORDS**

*COL2A1*, stickler syndrome, type I collagenopathy

# 1 | INTRODUCTION

Stickler syndrome is also referred to as hereditary progressive arthro-ophthalmo-dystrophy, which is a group of hereditary connective tissue disorders characterized by distinctive facial features, eye abnormalities, hearing loss, and joint problems (Stickler et al., 1965). Its incidence is around 1 in 7,500 to 1 in 9,000. The eye symptoms of Stickler syndrome may vary but include myopia, retinal detachment, cataracts, vitreous degeneration, glaucoma, and astigmatism. These eye abnormalities cause impaired vision or blindness in some cases (Snead et al., 2011). Oral or facial problems include flat cheeks, nasal bridge (most noticeable in infants), small jaw, and Pierre Robin sequence (small jaw, cleft palate, tongue placement abnormalities, and breathing problems; Stickler et al., 1965).

Stickler syndrome is caused by gene mutations in collagen genes during development, and can be divided into various subtypes based on the clinical manifestation and genetic mutations (Stickler et al., 1965). It has autosomal dominant and autosomal recessive forms, both resulting from mutations in genes encoding procollagens that are primarily expressed in cartilage (Khalifa et al., 2014). According to the characteristics of molecular genetics and vitreous phenotype, Stickler syndrome can be divided into five subtypes. *COL2A1* (OMIM # 120140), *COL11A1* (OMIM # 120280), and *COL11A2* (OMIM # 120290) gene mutations cause type I, II, and III, respectively, which belong to autosomal dominant inheritance; *COL9A1* (OMIM # 120210) and *COL9A2* (OMIM # 120260) gene mutations cause type IV and V, respectively, which belong to autosomal recessive inheritance (Hanson-Kahn, et al., 2018).

## 1.1 | Case presentation

A 16-year-old Mongolian girl with retinal detachment was recruited with a known familiar history of ocular disease (Table 1). The proband (III-5) had vitreous degeneration in both eyes. Fundus photography revealed rhegmatogenous retinal detachment in the inferior and temporal sides of her right eye, a large degeneration area in the retina, a retinal hole was located at 3 o'clock position, and proliferative cords were visible under the retina. In her left eye, a large area of retinal degeneration was observed, and small blood vessels were occluded (Figure S2). She developed severe myopia (−6D) at the age of 15. No obvious hearing disorder was found, and there were no abnormalities in bones and joints throughout the body. Her communication and learning capability were also normal. In the right eye, vitrectomy was performed. During the operation, it was found that the vitreous and retina were closely connected without posterior vitreous detachment. After the vitreous was removed, the retina was flattened. The hole was sealed with laser filled with silicone oil. Six months later, silicone oil was removed and the retina remains flat (Figure S3A1). There was no significant change in the size of retinal degeneration in the left eye (Figure S3A2), in which the macular morphology was improved compared with that of before operation (Figure S3B).

In further examination, it was found that all the patient's family members had vitreous and retina degenerations except the patient's mother. Glaucoma, cataracts, hypoplasia of the upper jaw, poor hearing, and joint disorders were also found in all family members. In this family, a total of six family members over three generations had clinical diagnosis of Stickler syndrome (Figure 1), and their clinical features are summarized in Table 1.

The patient's grandfather (I-1) had developed severe myopia (−6.25D), cataracts, and vitreous retinal degeneration in the right eye; his left eyes had atrophy and loss of function, and mild deafness in both ears (Figure S5).

The patient's father (II-2) had congenital cleft palate (Figure S4), cataracts, vitreous, and retinal degeneration in both eyes. He could not speak clearly.

**TABLE 1** Clinical features of the Stickler syndrome type I patient family

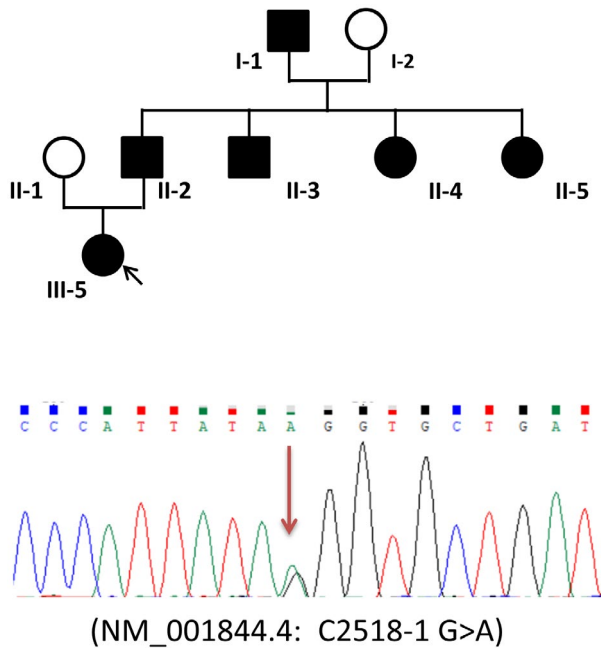| | I-1 | II-2 | II-3 | II-4 | II-5 | III-1 |
|---|---|---|---|---|---|---|
| Retinal degeneration | + | + | + | + | + | + |
| Vitreous anomalies | + | + | + | + | + | + |
| High myopia | + | | | | + | + |
| Glaucoma | | | | + | | |
| Cataract | + | + | | | + | |
| Midfacial hypoplasia/ micrognathia | | | | | | |
| Palatal defect | | + | | | | |
| Hearing loss | + | | | | + | |
| Skeletal features | | | | + | + | |
| Height SD score | −1.74 | −1.89 | −1.63 | −1.94 | −2.16 | −2.23 |

**FIGURE 1** Pedigrees in a Mongolian family with Stickler syndrome type I. Square symbols represent males, circle symbols represent females, empty symbols indicate unaffected individuals, filled symbols indicate affected patients, and arrows refer to the proband. A heterozygous splicing variant was detected in *COL2A1* (NM_001844.4: C.2518-1G>A)

The patient′s elderly auntie (II-4) underwent glaucoma surgery on right eye at the age of 45, and eyeballs were removed 1 year later. In the shallow anterior chamber of the left eye, the anterior lens capsule was pigmented and iris YAG laser was perforated. The vitreous body of the left eye was cloudy, and retinal degeneration was associated vitreous traction. Pigment-like lesions were observed at upper and lower temporal sides of retina (Figure S3). She also had hip dysplasia, lumbar dysplasia, and arthritis.

The patient′s younger auntie (II-5) was diagnosed with cataracts in both eyes. Her left eye was treated with phacoemulsification and intraocular lens implantation at the age of 40, and she also had vitreoretinal degeneration of both eyes. The retina of both eyes exhibited a leopard pattern, and a large area of retinal choroidal atrophy was noted. She also suffered from high frequency hearing loss in her two ears (Figure S5), lumbar spine hyperplasia, sacroiliac arthritis, hip arthritis, Knee arthritis, and femoral head necrosis (Figure S4).

## 1.2 | Exome sequencing

Exome sequence analysis was performed at the GiantMed Diagnostic (https://www.zhidezhenhe.com, Beijing, China) using genomic DNA extracted from patients′ blood. The exome sequencing library was prepared

with the NimbleGen SeqCap EZ Exome Library v2.0 kit and sequenced on the Illumina Genome Analyzer IIx platform. Reads were mapped to the human reference genome (GRch38) with the Burrows-Wheeler aligner version 0.7.10 (BWAMEM; Li, 2012). The gene variant in *COL2A1* identified in the family was confirmed by Sanger sequencing with genomic DNA extracted from the blood samples of the proband, her parents, and an unaffected sibling. Primer sequences used were: *COL2A1*-exon 13, Forward: 5′-CTACCAACATGGGGGGTGTTC-3′; Reverse: 5′-AGGGAAATGGATGCTCCTCT-3′.

In a Stickler syndrome type I family, exome sequencing was used to identify gene variant in exons of *COL2A1* (NM_001844.4) of the proband. A heterozygous splicing variant in *COL2A1* (NM_001844.4:C.2518-1G>A, p.Gly-840ValfsX41) was identified and confirmed with Sanger sequencing (Figure S1). Pathogenicity of this variant is assessed according to the American College of Medical Genetics and Genomics (ACMG) criteria. This heterozygous splicing variant (NM_001844.4:C.2518-1G>A) was reported previously (Hoornaert et al., 2010; Xiong et al., 2015), which predicted to induce a large splicing change of *COL2A1* gene (Xiong et al., 2015). Genotyping of the patients' family member showed that most of them were heterozygous for the sequence change (Figure S1). In silico analysis (https://web.expasy.org/translate/) shows that this variant would induce a premature stop codon into the open reading frame of *COL2A1*.

## 2 | DISCUSSION AND CONCLUSIONS

Stickler syndrome is a genetically heterogeneous disorder caused by abnormal synthesis of collagen type II, XI, or IX. Stickler syndrome type 1 (STL1) is the most common type, which is caused by mutations in the *COL2A1* gene on chromosome 12q13.11 (Faletra et al., 2014; Hoornaert et al., 2010). So far for STL1, the Human Gene Mutation Database (HGMD®) has recorded 261 variants of *COL2A1* associated with Stickler syndrome (http://www.hgmd.cf.ac.uk/ac/index.php). These variants include 40 missense mutations, 35 nonsense mutations, 70 splicing mutations, 109 small insertions/deletions/indels, 5 gross insertions/deletions, and 2 complex rearrangements. By either missplicing, frameshift or point mutations, a premature stop codon could enter into the open reading frame of *COL2A1* transcripts,causing haploinsufficiency of type II collagen (Hoornaert et al., 2010; Williams et al., 1996).

In this study, a heterozygous splicing variant (NM_001844.4:C.2518-1G>A) in *COL2A1* was identified in a Mongolian family across three generations.

This splicing variant is shown to induce a large splicing change, p.Gly840ValfsX41 that causes a frameshift with a premature stop codon in exon 41, which is consistent with previous report (Xiong et al., 2015). In a previous study, it was shown that *COL2A1* variants which led to premature termination codons and mediating nonsense-mediated decay, and that these kind of variants were quite common (68%) in Stickler syndrome (Barat-Houari et al., 2016).

Currently, the diagnosis of Stickler syndrome type I is mainly clinically based, and it is difficult to diagnose at the early stage. Previous study showed that 50% of Stickler syndrome type I patients were the first patient in their families (Zlotogora et al., 1992), which suggested that half of the patients could have no family history, further increasing the difficulty of diagnosis. Therefore, genetic analysis based on next-generation sequencing is essential and highly efficient as an auxiliary diagnostic approach. On the other hand, STL1 is the most common cause of hereditary rhegmatogenous retinal detachment (RRD) in children (Richards et al., 2002). Prophylactic cryotherapy, prophylactic retinal laser, and retinal detachment surgery could reduce the risk of retinal detachment and achieve functional visual results, if STL1 is diagnosed early (Abeysiri et al., 2007; Ang et al., 2008). Furthermore, clinical interventions can be made earlier so as to improve the prognosis and the quality of life.

There were a few numbers of studies performed on STL1 in the Caucasian population, but limited research in the Chinese population. Among them, 17 different variants of *COL2A1* have been reported in the Chinese population with STL1 (Wang et al., 2016; Yang et al., 2018). For the first time, our study reports a Mongolian family case of STL1 in Chinese population, which expand the spectrum of *COL2A1* mutations. In view of racial specificity and complicated genotype–phenotype relationship, further research is necessary to analyze *COL2A1* mutations in the Chinese population by genetic analysis.

To sum up, the phenotype of syndrome involves multiple systems and complex phenotypes, the clinical diagnosis is mostly atypical Stickler syndrome, more than 50% of Stickler syndrome type I patients have no family history, which make the early diagnosis difficult. As a high-throughput sequences approach and with the ability to sequence large gene pools with lower cost, next-generation sequencing (NGS) can be used as an important reference for early diagnosis and differentiation of Stickler syndrome.

## ETHICS APPRIVAL AND CONSENT TO PARTICIPATE

This study was approved by the ethics review board of the Eye Center of 2nd Hospital, Jilin University, and it was carried out in accordance with 1964 Helsinki declaration. Written informed consent was obtained from all the patients involved in this study.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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