HUMAN GENETIC EXPERT OPINION

Sample Case | Pediatric Report

COL2A1-associated Stickler syndrome type 1 | Growth disorder, ocular and craniofacial involvement

Case Number	Ref.: [Court / Insurance Carrier] - [Sample Case]
Client	Court / Health Insurance / Social Services
Expert	Prof. Dr. med. Christian T. Thiel, MBA
Qualifications	Board-certified specialist in human genetics; University Hospital Erlangen; 30 years of clinical and scientific experience; expert witness for courts and insurance carriers
Date	March 28, 2026
Data Subject	School-age child [Name, Date of Birth] (fictitious example case)
Key question	Assessment of the combination of characteristic clinical findings and a heterozygous canonical splice donor variant NM_001844.4(COL2A1):c.1833+1G>A in terms of diagnosis, causality, and socio-medical consequences

Declaration pursuant to § 407a ZPO

The undersigned declares that he has prepared this expert opinion impartially and to the best of his knowledge and belief. He affirms that he has no personal or financial relationship with the parties to the proceedings that could compromise his impartiality. This expert opinion is based exclusively on the documents submitted, his own examination, and the current state of medical science. The assessment is conducted in accordance with the principles of evidence-based medicine as well as the guidelines of the German Society of Human Genetics (GfHG) and the American College of Medical Genetics and Genomics (ACMG).

1. Assignment and Research Question

In the present case, a human genetic assessment is requested regarding how a clinical presentation featuring disproportionate short stature, early ocular manifestation, craniofacial involvement, and mild skeletal dysplasia should be classified from a medical-scientific perspective in light of molecular genetic evidence of the heterozygous variant NM_001844.4(COL2A1): c.1833+1G>A. In particular, the following must be assessed:

1. Whether the findings support with sufficient certainty a diagnosis of COL2A1-associated Stickler syndrome type 1
2. The relationship between the molecular findings and the clinical presentation (genotype-phenotype correlation)
3. Which differential diagnostic alternatives should be seriously considered
4. Whether a genetic causal relationship between the predisposition and health impairments
5. What preventive, socio-medical, and care-related consequences result from the diagnosis

2. Study materials and methodology

2.1 Submitted documents

- Molecular genetic report (NGS panel, COL2A1 c.1833+1G>A, pathogenic, ACMG Class 5)
- Previous ophthalmological findings: high myopia, vitreoretinal involvement
- Pediatric orthopedics Findings reports: Short stature, mild spondyloepiphyseal involvement, ligamentous hypermobility
- ENT documentation (cleft palate/palatal involvement, Pierre Robin sequence in medical history)
- Radiological findings (skeletal X-rays, MRI if available)
- Family history questionnaire

2.2 Methodological principles

Variant assessment is performed according to the ACMG/AMP classification standards (Richards et al., 2015 [7]) using the ClinGen-SVI recommendations for splicing variants (Walker et al., 2023 [9]) as well as the PVS1 specifications (Abou Tayoun et al., 2018 [8]). The clinical gene-phenotype mapping follows the information in GeneReviews [2] as well as the cited original publications. Causal attributions are made according to the criteria of scientific causality assessment (Bradford-Hill criteria).

3. Medical History

The affected school-aged child has had documented short stature since early childhood, with a physique suggestive of disproportion, as well as mild radiological spondyloepiphyseal involvement and accompanying ligamentous hypermobility. Ocular symptoms manifested early: there is pronounced high myopia. Ophthalmologically, a vitreoretinal abnormality was documented. In the craniofacial region, midface hypoplasia is evident; anamnesis and clinical findings indicate a Pierre Robin-associated palatal problem.

4. Family history

Stickler syndrome type 1 is inherited in an autosomal dominant manner. In approximately 70–80% of cases, one parent is also a carrier of the pathogenic variant; de novo mutations occur but are less common in canonical loss-of-function variants. A 50% recurrence risk for siblings and offspring of the affected individual should be assumed in cases of confirmed autosomal dominant inheritance.

Parents who are clinically unaffected or mildly affected may have been overlooked due to variable expressivity. A targeted ophthalmological and clinical examination of the parents and siblings is recommended.

5. Clinical findings and overall phenotypic assessment

5.1 Constellation of findings

- Growth: Short stature since early childhood, physique suggestive of disproportion, radiologically mild spondyloepiphyseal involvement
- Musculoskeletal system: ligamentous hypermobility
- Eyes: severe myopia (early onset), vitreoretinal abnormalities
- Craniofacial: Midface hypoplasia, Pierre Robin-associated palatal abnormalities

5.2 Diagnostic evaluation of the clinical presentation

This combination of features is highly indicative for genetic evaluation. Such a complex of findings can no longer be equated with nonspecific or idiopathic short stature, but rather necessitates classification as a syndromic connective tissue or collagen disorder. For COL2A1-associated Stickler syndrome type 1, GeneReviews [2] describes precisely these key features: ocular manifestations with high myopia and an increased risk of vitreoretinal complications, craniofacial abnormalities including Pierre Robin sequence or isolated cleft palate, as well as variable, mostly mild to moderate skeletal manifestations.

Relevant prevalence data for COL2A1-Stickler Type 1 [2-6]: *myopia 80–90%; retinal detachment 40–70%; cleft palate 30–60%; hearing impairment 20–50%; skeletal manifestations 35–40%.* The combined ocular, orofacial, and skeletal symptoms in the index case do not represent a coincidental convergence of individual features, but rather a classic COL2A1-associated organ pattern. [1–6]

The ocular axis carries particular weight in the diagnostic reasoning. In Stickler syndrome type 1, vitreoretinal involvement is pathophysiologically closely linked to the function of type II collagen in the vitreous body. In their series of 100 molecularly confirmed COL2A1 cases, Hoornärt et al. [1] demonstrated that vitreous anomalies and retinal detachments were significantly more common in COL2A1-positive cases. Cleft palate, vitreoretinal abnormalities, and a positive family history were strong predictors of a COL2A1-associated disorder.

6. Molecular genetic findings

6.1 Identified variant

Molecular genetic findings
Gene: COL2A1 (chromosome 12q13.11)
Transcript: NM_001844.4
Variant: c.1833+1G>A | Exon-intron boundary (canonical +1 splice site) Zygosity: heterozygous
Classification: Pathogenic (ACMG Class 5)

6.2 Molecular basis and functional classification

The variant c.1833+1G>A is a canonical splice donor variant at the invariant +1 position of the intron. The +1/+2 positions are essential for correct splicing. [7-9] The ClinGen-SVI recommendations for the application of the ACMG PVS1 criterion explicitly identify canonical +-1/+2 splicing variants as prototypical loss-of-function variants, provided that a loss-of-function mechanism has been established as disease-causing for the gene in question. [8,9]

This is precisely the case for COL2A1 in the context of Stickler syndrome type 1: GeneReviews states that COL2A1-associated Stickler syndrome is typically caused by loss-of-function variants with haploinsufficiency of type II collagen; these explicitly include nonsense, frameshift, and splicing variants that lead to premature stop codons or nonsense-mediated decay. [2,4,5]

Hoornärt et al. [1] were able to show in their series of 100 patients that over 90% of the COL2A1 mutations causing Stickler type 1 lead to nonsense-mediated decay; among the 77 different variants, 22 were splice-site alterations, and RNA analyses revealed unusual isoforms with premature stop codons. The present variant c.1833+1G>A has been repeatedly observed in this series and was confirmed as a recurrent Stickler variant in subsequent East Asian cohorts [10,11].

6.3 ACMG classification in the context of medical evaluation

The COL2A1 variant c.1833+1G>A should be classified as pathogenic (ACMG Class 5) in the expert assessment context. The rationale is not limited to merely stating the ACMG final result but is made transparent:

- PVS1 (very strong): Canonical +1 splicing variant in a gene where loss of function is a confirmed disease mechanism [7-9]
- PM2 (moderate): Variant not present or extremely rare in large population-based control cohorts (gnomAD); consistent with a highly penetrant autosomal dominant disorder [7,8]
- PP4 (supportive): Phenotype with high myopia, vitreoretinal involvement, Pierre Robin/palatal component, and mild skeletal manifestations classically corresponds to the COL2A1 Stickler spectrum [1-5]
- PS1/PS3 (supportive): Identical variant repeatedly described in large, molecularly confirmed Stickler cohorts [1,10,11]

The combination of a canonical splice site alteration, an established haploinsufficiency mechanism, and a highly specific phenotype supports classification as pathogenic without any relevant residual doubt.

7. Assessment and human genetic classification

7.1 Genotype-phenotype correlation

For COL2A1, it is not sufficient to say that the gene fits the phenotype. It must be demonstrated why this specific variant type is expected to result in the observed phenotype. GeneReviews emphasizes that COL2A1-associated Stickler syndrome is typically caused by loss-of-function variants with haploinsufficiency, whereas more severe type II collagenopathies (e.g., spondyloepiphyseal dysplasia congenita) are more frequently caused by dominant-negative missense

variants, particularly glycine substitutions in the triple helix. [2,4,5,11,17]

This distinction is central to the expert assessment: it explains why, in the case of a canonical splice site variant such as c.1833+1G>A, one would not expect the presentation of severe neonatal skeletal dysplasia, but rather a milder, ocular-craniofacial-dominant Stickler syndrome with variable skeletal involvement. This expectation corresponds exactly with the clinical presentation of the present case. [4,5,11,17]

7.2 Diagnostic certainty

In the present case, the diagnosis of Stickler syndrome should not be formulated as a suspicion but as a confirmed molecular genetic diagnosis. This is based on the convergence of:
(1) a pathogenic canonical COL2A1 splicing variant, (2) a highly typical multi-component phenotype, and (3) the published observation of the identical mutation in large Stickler cohorts. This triple convergence meets the requirements for an evidence-based, legally sound attribution of causality.

8. Causality Assessment

8.1 Causality: Genetic Cause and Clinical Manifestation

The causal relationship between the identified COL2A1 variant c.1833+1G>A and the clinical presentation can be established with a probability bordering on certainty. The rationale follows the Bradford Hill criteria:

- Strength of association: canonical loss-of-function variant in a region defined for Stickler syndrome type 1
- Consistency: Variant observed to be disease-causing in several independent cohorts (Hoornärt et al. [1], Kondo et al. [10], Wang et al. [11])
- Specificity: Phenotype corresponds highly specifically to the COL2A1 Stickler spectrum; no equivalent alternative hypothesis
- Biological plausibility: Haploinsufficiency of type II collagen explains ocular, craniofacial, and skeletal manifestations pathomechanistically
- Timing: the genetic cause is congenital and necessarily precedes the manifestation

8.2 Differential diagnosis

Differential diagnosis must specifically distinguish this condition from other type II collagenopathies as well as other Stickler genes:

- COL11A1-associated Stickler syndrome: clinically similar, but with a different genetic mechanism; true haploinsufficiency in COL11A1 is rare and tends to result in a milder phenotype [2,4,5]
- COL11A2-associated forms: ocular involvement is NOT of the same nature, as COL11A2 is not expressed in the vitreous; pronounced myopia and vitreoretinal risk strongly suggest COL2A1 [5,6,18]
- Severe COL2A1 dysplasias (congenital spondyloepiphyseal dysplasia): different molecular mechanism (dominant-negative), more pronounced skeletal severity; not consistent with the present findings [4,5,11,17]

In the present case, there is no diagnostic gray area. COL2A1-Stickler Type 1 offers the most consistent and literature-supported explanation for all components of the findings. No competing differential diagnosis can better explain the overall findings from molecular genetics, ocular profile, craniofacial involvement, and mild skeletal manifestations. [1-6,18]

9. Conclusion / Expert Assessment

Summary of the expert findings

6. **Confirmed diagnosis:** The patient has COL2A1-associated Stickler syndrome type 1 (OMIM #108300), caused by the pathogenic heterozygous variant c.1833+1G>A in the COL2A1 gene. The diagnosis is confirmed by molecular genetics (ACMG Class 5). The formulation as a suspicion is not medically or scientifically appropriate.
7. **Genotype-phenotype concordance:** The observed phenotype is consistent not only with COL2A1 in general, but specifically with a haploinsufficiency-mediated COL2A1 Stickler mechanism. The canonical splicing variant explains the mild-to-moderate presentation (not the severe skeletal dysplasia). The genotype-phenotype correlation is highly consistent.
8. **Causal relationship:** The causal relationship between the genetic variant and the clinical presentation is virtually certain. The disease has a monocausal genetic origin. External, environmental, or traumatic contributing factors are not to be assumed.
9. **Prognosis and Duration:** The disease is chronic and irreversible. There is a permanent risk of progressive ocular complications (retinal detachment 40–70%) and functional limitations of the musculoskeletal system. A structured prevention and monitoring program is medically indicated.
10. **Social and medical relevance:** The diagnosis serves as the basis for specific medical interventions, preventive strategies, and genetic risk counseling for family members. In a legal context, it should be regarded as a sound foundation for issues related to healthcare provision and insurance law.

The foregoing expert findings are rendered to the best of my knowledge and belief, impartially and conscientiously, in accordance with § 407a of the German Code of Civil Procedure (ZPO). The undersigned certifies that he is not in a relationship of dependency with the parties and has no financial interest in the outcome of the proceedings.

9a. Care, Prevention, and Management

The diagnosis has immediate implications for management. The following measures are indicated from a human genetic and clinical perspective:

Ophthalmology (highest priority)

- Regular ophthalmological examinations with vitreoretinal expertise are mandatory
- In the presence of relevant prior findings or risk factors: consider a prophylactic or interventional strategy to prevent retinal detachment (Cambridge Protocol [19,20])
- Prescription of magnifying glasses or contact lenses for high myopia

Audiology

- Follow-up audiological examinations (hearing impairment is not uncommon in COL2A1-Stickler syndrome, approx. 20–50%) [6,13]

Orthopedics

- Structured follow-up monitoring of the skeleton; even in cases of initially mild dysplasia, degenerative joint changes may occur later [2–5,11,17]

Genetic counseling

- Explanation of the autosomal dominant inheritance pattern and the 50% risk of recurrence in offspring
- Presymptomatic testing of parents and siblings recommended

Interdisciplinary

- Depending on the severity: involvement of ophthalmology, ENT, maxillofacial surgery, orthopedics, and human genetics

9b. Medical-Social-Legal Classification

The present constellation meets the criteria for a confirmed genetic systemic disorder with structural connective tissue involvement and multisystemic manifestation. From a medical perspective, this is not a functional variant within the normal range, but a clearly defined, pathogenically based disorder with objectifiable organ involvement. [2-5,7-9]

Diagnostic certainty stems not only from the molecular genetic classification as a pathogenic variant (ACMG Class 5), but particularly from the high degree of concordance between genotype, established pathomechanism, and specific clinical presentation. This convergence meets the requirements for an evidence-based, legally sound attribution of causality. [1-5,7-11]

From a socio-medical perspective, it is important to note that the disease is associated with a significant risk of progressive ocular complications, functional limitations of the musculoskeletal system, and potential manifestations in other organs. This results in a long-term need for medical monitoring and treatment. The diagnosis warrants specific medical interventions and preventive strategies, as well as genetic risk assessment for family members. In a legal context, it should be regarded as a solid basis for addressing issues related to healthcare provision and insurance law. [2-5,12-16,19,20]

10. References

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