

Case Report

An Unusual Retinal Presentation of a Novel *COL11A1* Mutation: A Case Report

Tobias Peschaut^a Monja Michelitsch^a Martina Brandner^a
Sandra Kamper^b Lisa Ofner-Ziegenfuss^b Jasmin Blatterer^b
Heidelis Anna Tichy^b Laura Posch-Pertl^a

^aDepartment of Ophthalmology, Medical University of Graz, Graz, Austria; ^bDepartment of Medical Genetics, Medical University of Graz, Graz, Austria

Keywords

Stickler syndrome · Collagenopathy · COL11A1 · Mutation · Genetics · Case report

Abstract

Introduction: Stickler syndrome is a rare collagenopathy, caused by mutations in various genes coding for fibrillar collagens II, IX, and XI. The disorder can be subdivided into different groups, depending on the genes affected and clinical features found in patients. Ocular symptoms, such as high myopia, retinal detachments, or anomalies in the vitreous, are present in most forms of Stickler syndrome. In this case report, we present a patient with an unusual retinal phenotype.

Case Presentation: Subject of this case report is a 33-year-old woman, who was examined at the Department of Ophthalmology at Medical University of Graz. A thorough ophthalmological examination was conducted, detailed medical and family history acquired, and genetic testing performed. Best corrected visual acuity was 20/20 on both eyes; however, impaired binocular vision associated with intermittent exotropia was found. Furthermore, dilated funduscopy showed an unusual, hypopigmented spotted retinal phenotype. Fundus autofluorescence showed multiple hyperfluorescent spots corresponding with the spotted retinal appearance. Genetic testing revealed a novel variant in the gene *COL11A1*. No other ocular abnormalities which are associated with *COL11A1* were found. **Conclusion:** Several subtypes of Stickler syndrome have been reported in medical literature, greatly varying in clinical manifestations. Many different mutations in the gene *COL11A1* have been discovered and are typically associated with Stickler syndrome type 2. To our best knowledge, this is the first report of a patient with a mutation in the *COL11A1* gene presenting with a hypopigmented spotted retina.

© 2025 The Author(s).
Published by S. Karger AG, Basel

Correspondence to:
Laura Posch-Pertl, laura.pertl@medunigraz.at

Introduction

Stickler syndrome, also known as hereditary arthro-ophthalmopathy, is a rare, genetic disorder of the connective tissue, typically caused by mutations in the genes coding for fibrillar collagens II, IX, and XI. These types of collagens are mainly found in the vitreous, as well as in elastic and hyaline cartilage, the corresponding genes are found on chromosome number 1, 6, and 12 [1]. The typical pattern of inheritance is dominant with variable expressivity, although in rare cases, it can manifest as recessive [2, 3]. Depending on the affected gene, multiple types of Stickler syndrome have been described and can be subdivided based on their clinical manifestations.

Type 1 is caused by a mutation in the gene *COL2A1*, and this type of Stickler syndrome is characterized by a wide array of ocular manifestations such as membranous and vitreous anomalies, congenital myopia, perivascular lattice degeneration, and retinal detachment. Furthermore, systemic complications such as arthropathy, deafness, facial anomalies (Pierre Robin sequence) and cleft palate are possible [1, 2]. Type 1 is the most common form of Stickler syndrome, associated with a very high risk of retinal detachment at an early age (>50%) and giant retinal tears [4].

Type 2 is caused by a mutation in *COL11A1*. This form, otherwise similar to Stickler type 1, is mainly characterized by beaded congenital vitreous anomalies and high myopia [1, 2]. Retinal detachment is still a dominating feature, however, less commonly caused by giant retinal tears [5]. Hearing impairment is more common, with a prevalence of up to 83% [6].

Type 3, also known as non-ocular Stickler syndrome, is caused by a mutation in the gene *COL11A2* and is characterized by a normal vitreous and ocular phenotype. However, deafness, arthropathy, facial anomalies, and cleft palate are possible [1]. Notably, this form has also been reclassified as “oto-spondylo-mega-epiphyseal dysplasia” [2].

Type 4, also described in literature as ocular-only variant, is inherited in an autosomal recessive manner. Autosomal recessive forms of Stickler syndrome, mainly affecting the three genes for collagen type IX, *COL9A1*, *COL9A2*, and *COL9A3*, have been reported less commonly than dominant forms. Aside from the three genes mentioned above, variants of *COL11A1*, as well as variants of non-collagen genes *LRP2*, *LOXL3*, and *GZF1* have been reported. The most dominant symptom of autosomal recessive Stickler syndrome is high myopia, followed by sensorineural hearing loss. Retinal detachments and joint pain are less common in these cases, with a prevalence of 18% and 15%, respectively [2].

The first ophthalmologic presentation of patients with Stickler syndrome typically occurs in early childhood, with high, nonprogressive myopia. During slit-lamp examination, clinical findings may vary depending on the present type of the syndrome, with type 1 typically presenting with retrolenticular and circular membranes around the vitreous equator. In type 2, changes in the structure of the vitreous described as fibrillar and beaded can be found. Despite of carrying mutations in the same gene, clinical findings may also vary strongly among affected members of the same family [3].

Over the course of their lives, about 60–70% of patients suffering from Stickler syndrome type 1 will develop a retinal detachment, with an average age between 10 and 30 years [7]. In type 2, the rate of retinal detachments has been less widely studied but has been reported to be approximately 40% [5]. Therefore, regular checkups are obligatory for successful, early treatment of retinal tears and prophylactic laser treatment may be beneficial [8]. Complications, such as presenile or cortical cataract, ectopia lentis, and infantile-onset glaucoma have been described [9]. Due to the substantial risk of retinal detachments leading to blindness and a high rate of recurrence, the overall ophthalmologic prognosis of Stickler syndrome is poor [7].

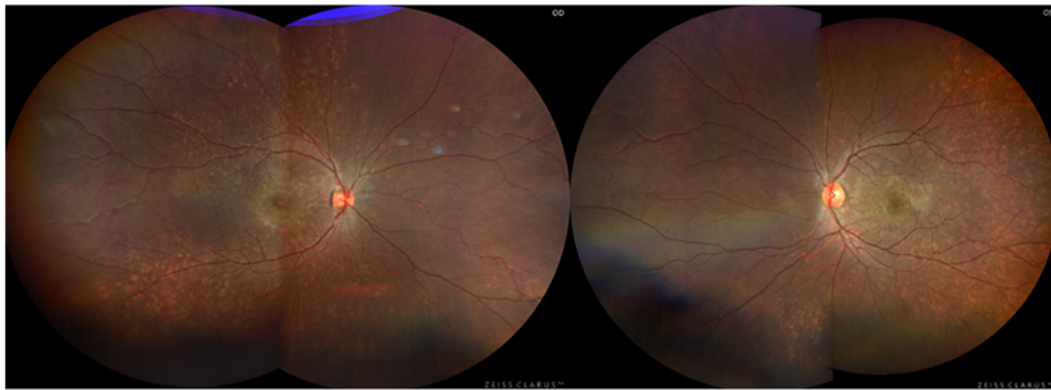


Fig. 1. Retinal imaging shows an unusual, hypopigmented spotted retinal phenotype in both eyes.

Case Presentation

Subject of this case report is a 33-year-old woman who was examined at the Department of Ophthalmology at Medical University of Graz. Complete ophthalmological examination was conducted, including measurement of best corrected visual acuity (BCVA), slit-lamp examination, visual field testing, fundoscopy, optical coherence tomography, and fundus autofluorescence. Further evaluation consisted of a detailed medical history and genetic testing.

Signed informed consent for genetic testing was obtained from the patient and included permission to publish anonymized findings. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000542708>).

The 33-year-old female patient initially complained about problems in her binocular vision. She was sent to the Department of Ophthalmology at Medical University of Graz, where she presented with strabismus on the right eye (intermittent exotropia) and physiological anisocoria. The patient's BCVA was 20/20 on both eyes with a spherical refractive error of -1.5 D. Goldmann visual field examination showed no abnormalities. During slit-lamp examination and dilated fundoscopy, an unusual, hypopigmented spotted retinal phenotype was observed (Fig. 1). These spots were predominantly found in the macular region, around the arcades and mid periphery with no signs of lattice degeneration, retinal tears, and vitreous anomalies. Subsequently, the examination was expanded by optical coherence tomography (Fig. 2) and fundus autofluorescence (Fig. 3). Corresponding to the hypopigmented spots, near-infrared imaging showed subtle hyporeflective lesions which were more prominent on fundus autofluorescence as hyperautofluorescent spots, merging in the macular region. The retinal layers on the optical coherence tomography B-scan were normal.

Medical history revealed a resolved hepatitis B infection during childhood which, according to the patient, subsequently caused a hearing impairment requiring hearing aids. However, the underlying cause is more likely to be due to the *COL11A1* mutation, which is widely linked to sensorineural hearing loss [6]. Serology results showed no signs of acute or other past infections besides the resolved hepatitis B infection mentioned above. No permanent medication had been prescribed. The patient showed no facial anomalies or arthropathies. Family history revealed the diagnosis of Stickler syndrome type 2 in the patient's daughter, which was genetically verified. Apart from high myopia (-21 D/ -20.5 D), additional ocular changes including peripheral retinal degenerations and vitreous opacifications were found in the patient's daughter, consistent with Stickler syndrome type 2.

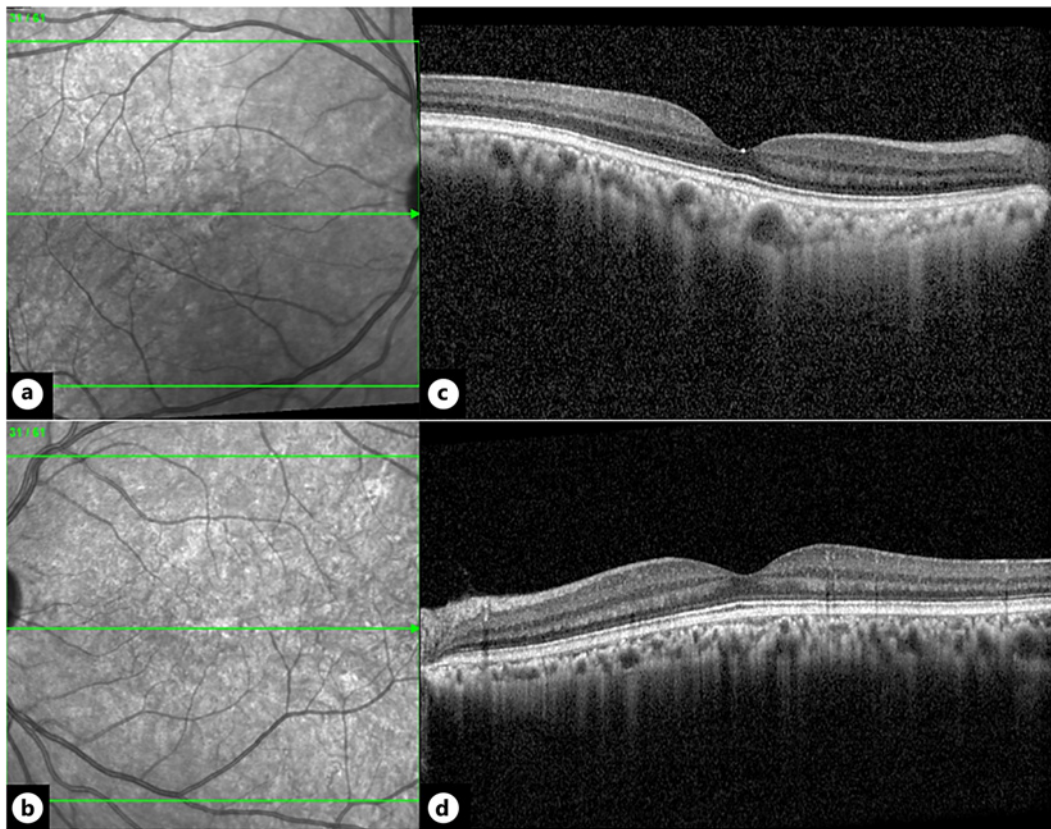


Fig. 2. Near-infrared reflectance (NIR) and B-scan spectral domain optical coherence tomography (SDOCT). Multiple, subtle hyporeflective lesions in NIR (**a**, **b**; right/left eye). Normal B-scan SDOCT (**c**, **d**; right/left eye).

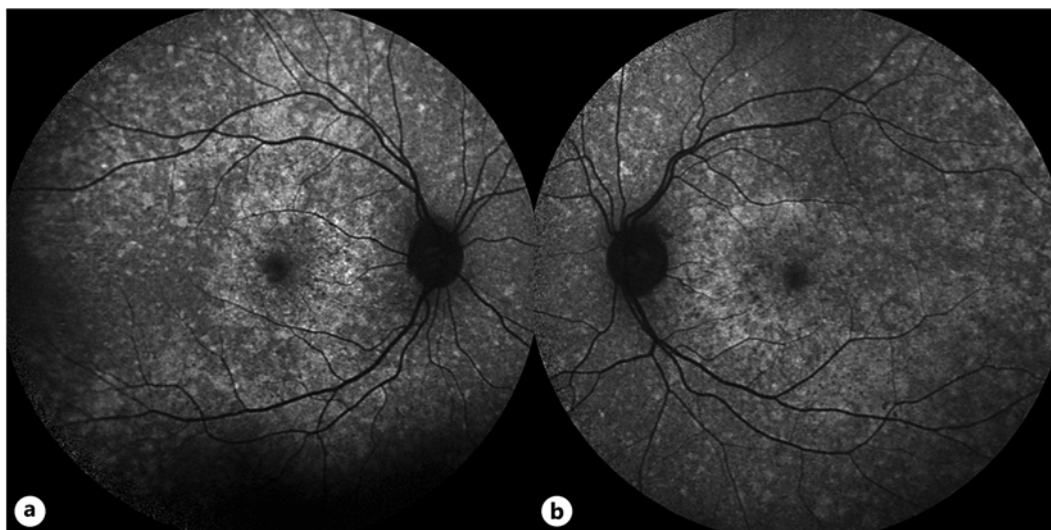


Fig. 3. Hyperfluorescent, spotted appearance in fundus autofluorescence, right eye (**a**), left eye (**b**).

Genetic testing was conducted primarily for the mutation found in the daughter and confirmed that our patient had the same heterozygous variant in the gene *COL11A1* (*c.1351-1G>A*; NM_001854) as her daughter. According to ACMG (American College of Medical Genetics and Genomics) guidelines, the variant was classified as pathogenic. The nucleotide exchange affects an intronic splice-acceptor site of the gene, most probably leading to aberrant splicing and skipping of exon 11. The proven variant has not yet been described in the literature or international databases, but splice or loss-of-function mutations in this gene are considered pathogenic. An RNA analysis was performed, but no transcript of the *COL11A1* gene could be detected in blood. To detect other possible variants, causing this retinal phenotype, we performed a retinal dystrophy panel (Blueprint Genetics, Finland). In total, 314 genes and 4,998 exons in the retinal dystrophy panel and 37 genes in the mitochondrial genome have been evaluated, and no further mutations were detected in the patient.

Discussion

To our best knowledge, this is the first report of a patient with a mutation in the *COL11A1* gene presenting with a hypopigmented spotted retina. The patient did not show any problems in BCVA and visual fields. However, due to an associated intermittent exotropia, she had difficulties with her binocular vision. Her daughter with the same mutation, on the other hand, presented with high myopia (axial length 29.64 mm on the right and 29.8 mm on the left eye), showing again how one mutation can lead to very different phenotypes.

The *COL11A1* gene, located on chromosome 1p21.1 and consisting of 67 exons, encodes one of the two alpha chains of type XI collagen [10]. Pathogenic variants primarily cause autosomal dominant Stickler syndrome type 2 and Marshall syndrome, as well as autosomal recessive fibrochondrogenesis [10]. While Marshall syndrome closely resembles Stickler syndrome and is even considered a subform of the disease by some authors, fibrochondrogenesis is a severe, rare skeletal dysplasia, clinically characterized by a flat midface and significant shortening of the limbs [11]. Additionally, heterozygous pathogenic variants in the *COL11A1* gene have been associated with non-syndromic sensorineural hearing loss [10].

According to the genetic report, the novel variant found in our patient, *c.1351-1G>A*, substitutes a nucleotide within a canonical splice site, making it likely to lead to abnormal splicing. This specific mutation is suspected to cause the in-frame skipping of an exon, resulting in the loss of 21 amino acids from the collagen-like 1 functional domain of the protein. However, since this specific variant has never been mentioned in medical literature, the exact impact on the encoded protein is difficult to predict without further transcriptional studies.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Funding Sources

The authors report that there is no funding associated with the work featured in this article.

Author Contributions

Tobias Peschaut: writing – original draft and visualization. Laura Posch-Pertl: conceptualization, investigation, resources, supervision, project administration, and writing – review and editing. Monja Michelitsch and Martina Brandner: resources, supervision, and writing – review and editing. Sandra Kamper, Lisa Ofner-Ziegenfuss, Jasmin Blatterer, and Heidelis Anna Tichy: formal analysis, investigation, and writing – review and editing.

Data Availability Statement

The data and material that support the findings of this case report are not publicly available due to privacy and confidentiality concerns. Access to the data is restricted to protect the privacy of participating individuals. Requests for data access can be directed to the corresponding author, but any such access will be subject to review and approval by the relevant Ethics Committee to ensure compliance with data protection regulations.

References

- 1 Soh Z, Richards AJ, McNinch A, Alexander P, Martin H, Snead MP. Dominant stickler syndrome. *Genes*. 2022; 13(6):1089. <https://doi.org/10.3390/genes13061089>
- 2 Nixon TRW, Richards AJ, Martin H, Alexander P, Snead MP. Autosomal recessive stickler syndrome. *Genes*. 2022;13(7):1135. <https://doi.org/10.3390/genes13071135>
- 3 Boothe M, Morris R, Robin N. Stickler syndrome: a review of clinical manifestations and the genetics evaluation. *J Pers Med*. 2020;10(3):105. <https://doi.org/10.3390/jpm10030105>
- 4 Fincham GS, Pasea L, Carroll C, McNinch AM, Poulson AV, Richards AJ, et al. Prevention of retinal detachment in Stickler syndrome: the Cambridge prophylactic cryotherapy protocol. *Ophthalmology*. 2014;121(8):1588–97. <https://doi.org/10.1016/j.ophtha.2014.02.022>
- 5 Poulson AV, Hooymans JM, Richards AJ, Bearcroft P, Murthy R, Baguley DM, et al. Clinical features of type 2 Stickler syndrome. *J Med Genet*. 2004;41(8):e107. <https://doi.org/10.1136/jmg.2004.018382>
- 6 Acke FRE, Dhooge IJM, Malfait F, De Leenheer EMR. Hearing impairment in Stickler syndrome: a systematic review. *Orphanet J Rare Dis*. 2012;7(1):84–10. <https://doi.org/10.1186/1750-1172-7-84>
- 7 Ang A, Poulson AV, Goodburn SF, Richards AJ, Scott JD, Snead MP. Retinal detachment and prophylaxis in type 1 Stickler syndrome. *Ophthalmology*. 2008;115:164–8. <https://doi.org/10.1016/j.ophtha.2007.03.059>
- 8 Coussa RG, Sears J, Traboulsi EI. Stickler syndrome: exploring prophylaxis for retinal detachment. *Curr Opin Ophthalmol*. 2019;30(5):306–13. <https://doi.org/10.1097/ICU.0000000000000599>
- 9 Wubben TJ, Branham KH, Besirli CG, Bohnsack BL. Retinal detachment and infantile-onset glaucoma in Stickler syndrome associated with known and novel COL2A1 mutations. *Ophthalmic Genet*. 2018;39(5):615–8. <https://doi.org/10.1080/13816810.2018.1509355>
- 10 Ciorba A, Corazzi V, Melegatti M, Morgan A, Pelliccione G, Girotto G, et al. Non-syndromic sensorineural prelingual and postlingual hearing loss due to COL11A1 gene mutation. *J Int Adv Otol*. 2021;17(1):81–3. <https://doi.org/10.5152/iao.2020.8179>
- 11 Thompson SW, Bacino CA, Safina NP, Bober MB, Proud VK, Funari T, et al. Fibrochondrogenesis results from mutations in the COL11A1 type XI collagen gene. *Am J Hum Genet*. 2010;87(5):708–12. <https://doi.org/10.1016/j.ajhg.2010.10.009>