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CLINICAL REPORT

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Variable clinical expression of Stickler Syndrome: A case report of a novel *COL11A1* mutation

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Abstract

Background: Stickler Syndrome is a rare connective tissue disorder, characterized by clinical, and genetic heterogeneity. The clinical expression is highly variable, including moderate to severe myopia in childhood, hearing loss, facial dysmorphic features, cleft palate, and early osteoarthritis. *COL2A1*, *COL11A1*, and *COL11A2* mutations account of the majority of autosomal dominant Stickler Syndrome and, in particular, a heterozygous mutation in *COL11A1* gene is identified in about 10 to 20% of Stickler Syndrome patients.

Methods: Herein, we report a case of an 8-year- old child with Stickler Syndrome, presenting with early-onset of myopia with vitreal abnormalities, facial dysmorphic characteristics, and mild hearing loss later in childhood. To identify the underlying genetic cause, Whole Exome Sequencing was carried out for *COL11A1* gene.

Results: A novel de novo heterozygous splice site variant (NM_001854: c.1845 + 5G> C) of the *COL11A1* gene, which had not been previously reported, was identified by Whole Exome Sequencing.

Conclusion: We reported a novel *COL11A1* mutation in a child with Stickler Syndrome presenting a phenotype of early-onset of ocular anomalies and mild hearing loss later in childhood. Our findings confirm the variability of the expression of the disease, even in the contest of the same gene-related disorder, thus, contributing to improve the knowledge on clinical and molecular basis of this rare disease.

KEYWORDS

COL11A1, early myopia, hearing loss, novel mutation, stickler syndrome

1 | INTRODUCTION

Stickler Syndrome (STL) (OMIM 108300, 604841, 184840) is a clinically variable and genetically heterogeneous collagenopathy that affect types II, IX, and XI collagen expressed in cartilage, vitreous, and connective tissues. It is estimated an incidence of ~ 1:7,500–9,000 newborns (McArthur et al., 2018; Printzlau & Andersen, 2004) being classified as a rare disease (5–7 individuals in 10,000) (Auvin, Irwin, Abi-Aad, & Battersby, 2018). The diagnosis of STL is clinically based, but there is still no consensus on minimal clinical diagnostic criteria and, molecular genetic analysis can be used for diagnosis confirmation (Kohmoto et al., 2015; Robin, Moran, & Ala-Kokko, 2017).

STL phenotype may include craniofacial abnormalities such as malar and midfacial underdevelopment, micro and retrognathia and cleft palate; also congenital vitreous anomalies, early onset myopia, cataract, retinal detachment, hearing loss, spinal abnormalities, precocious osteoarthritis, joint hypermobility, and mitral prolapse (Couchouron & Masson, 2011; Huang, Kuo, Hsieh, Lai, & Chain, 2007; Lauritsen et al., 2017; McArthur et al., 2018; Richards et al., 2010; Robin et al., 2017; Shapiro, Blair, Solinski, Zhang, & Jabbehdari, 2018; Vijzelaar et al., 2013). However, usually people affected by STL have normal intellect and normal stature (Vijzelaar et al., 2013).

The majority of the cases (80%–90%) are inherited in an autosomal dominant pattern caused by *COL2A1* (OMIM 120140), *COL11A1* (OMIM 120280), and *COL11A2* (OMIM 120290) mutations. Less frequent, autosomal recessive inherence pattern has been correlated to pathogenic variants in *COL9A1, COL9A2, COL9A3, BMP4,* and *LOXL3* genes (Chan, Alkaabi, ElBarky, & El-Hattab, 2019; Lauritsen et al., 2017; McArthur et al., 2018; Nixon et al., 2018; Robin et al., 2017).Only ~10% of STL cases are attributed to mutations in *COL11A1* gene. *COL11A1* is located on chromosome 1p21, encodes alpha 1 chain of type XI collagen and seems to play an important role in fibrillogenesis (Robin et al., 2017).

Mutations in *COL11A1* gene have been associated with autosomal dominant disorders such as STL type II (OMIM 604841) and Marshall Syndrome (OMIM 154780) and with Fibrochondrogenesis 1 (OMIM 228520) a recessive skeletal dysplasia (Lauritsen et al., 2017; Majava et al., 2007; Tompson et al., 2010; Vijzelaar et al., 2013). STL phenotype of *COL11A1* mutations is associated to vitreoretinal anomalies and sensorineural hearing loss (McArthur et al., 2018), whereas *COL11A2* has a non-ocular phenotype. A clinical overlap is commonly observed between Marshall Syndrome and STL cases, even expecting a more severe phenotype in a patient affected by Marshall syndrome, when facial characteristics are not very specific the diagnosis can be difficult to define.

Hereby, we report a novel *COL11A1* splicing mutation in a child with early-onset of ocular anomalies, facial dysmorphic characteristics, and mild hearing loss. The clinical findings were compared to the only other two cases with a similar splicing mutation previously described in the medical literature.

2 | CASE REPORT

A study for collecting data and samples for clinical and molecular characterization of Skeletal Rare Diseases was approved by the local Ethical Committee (Prot. no 0041207 December 4, 2015) and a specific written informed consent was obtained from the patient's parents for publication of this case report and any accompanying images.

2.1 | Clinical description

The male child is the second son of non-consanguineous parents with no history of STL in their family. The mother of the proband had a normal pregnancy, eutocic delivery without signs of perinatal suffering. His birth parameters included weight of 3,200 g (25th percentile), length of 50 cm (50th percentile), cephalic perimeter of 34.5 cm (25th percentile), and Apgar score of 9–10/10. During the neonatal period the child was treated for gastroesophageal reflux and laryngomalacia.

The boy carried out several audiometric medical controls due to a suspect of hearing loss following an alterated result of the transient-evoked otoacoustic emission (TEOE) testing bilaterally at the neonatal screening. An auditory brainstem response audiometry test at 3-month-old showed auditory function at the lower limit of normality for bilateral mid-acute frequencies (reduction of 2–4 kHz). Tympanogram exams at ages 2, 4, and 6 years old showed auditory function at the lower limits of normality bilaterally for mid-acute frequencies. At age 4 years old, he underwent an adenoidectomy and myringotomy due to chronic adenoiditis and recurrent otitis episodes. However, a tone audiometry examination at 8-year-old showed mild bilateral sensorineural hearing impairment, zonal on middle tones at 8 khz.

A routine ophthalmological evaluation disclosed a significant myopia at 2 years old. At the age of 4-year-old, the boy was already wearing glasses, and was referred for a second opinion to a University Ophthalmology Department: the ophthalmologic assessment confirmed the severe myopia with right eye (RE): −5.75 –2.00/20 and left eye (LE): −5.00 –2.00/170. In addition, visual acuity was 20/60 in both eyes, light reflexes symmetrical, orthotropic at cover test with normal ocular motility, and stereoacuity was 400 s of arc. Cycloplegic refraction disclosed a light hypocorrection of RE: −6.00 –2.00/20 and LE: −5.75 –2.00/170.

Slit lamp examination was unremarkable except for the evidence of “mobile optical empty vitreous” and fundus examination showed vitreous thickening, myopic staphyloma and myopic fundus (Figure 1a,b). In the same setting, an ocular ultrasound confirmed the presence of vitreous floaters, uncommon finding in a 4 years old child, for this reason the suspect of a Stickler Syndrome was raised (Figure 1c,d). A follow-up at 8-year-old showed a progression of the myopia to −7.25 RE and −8 LE.

In the first medical genetic evaluation at 5-year-old, the child height was 109 cm (<50th percentile), weight 18 kg (25th percentile), and cephalic perimeter 52.5 cm (75th percentile). He displayed epicanthus, midface hypoplasia, low slanting palpebral fissures, small nose with mild depressed

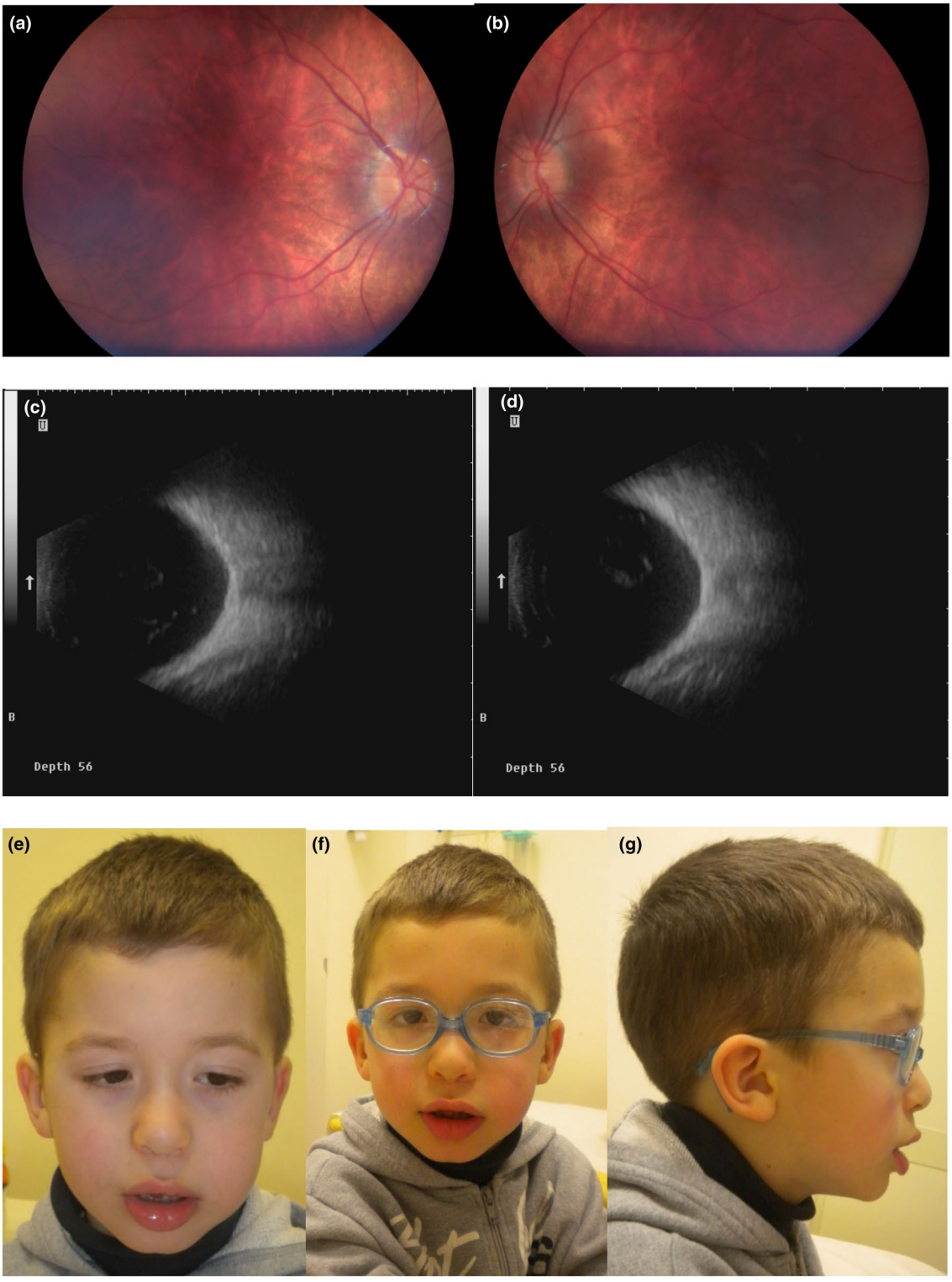

FIGURE 1 Patient and ocular images. (a) ocular fundus exam showing vitreous thickening, myopic and myopic fundus at right eye. (b) and at left eye. (c) ocular echography showing vitreous floaters at right eye. (d) and at left eye. (e) patient's face overall presentation. (f) and in profile

nasal bridge, micrognathia, high and narrow palate, mild joint hyperlaxity, pectus carinatum, abducted shoulders, winged scapulae, and bilateral flat feet (Figure 1e-g).

Considering that STL might be associated to mitral valve prolapse, pediatric echocardiography follow-up was performed at ages 5, 6, and 7 years old with no functional or structural cardiac abnormalities was observed.

There is no familial history of STL. The child has a healthy older brother and the parents have no clinical signs of the syndrome. However, his mother (41 years old) presented

astigmatism, fibromyalgia, asthma, and celiac disease and his father (46 years old) has amblyopia and hypermetropia.

2.2 | Molecular findings

Whole Exome Sequencing was carried out at the Medical Genetics Laboratory of the Meyer University Hospital (Florence, Italy) identifying a de novo heterozygous splice site variant NM_001854.4: c.1845 + 5G> C in *COL11A1* gene (Richards et al., 2015). The variant was absent from the control populations (dbSNP, ESP, ExAC), and from GnomAD).

This variant was still not described in the medical literature and could cause an alteration of the splicing process, suggesting a pathological significance. In order to obtain a further element to confirm pathological effect of the variant both child's parents, who did not show any clinical signs of STL, provided informed consent and blood samples for molecular testing and the presence of the variant c.1845 + 5G> C of the C*OL11A1* gene was excluded in both parents.

3 | DISCUSSION

In this report the clinical diagnosis of STL was defined in a child at 4-year-old due to early-onset of myopia, vitreous abnormality, and facial dysmorphisms. At the moment of the medical genetic evaluation, no clinically significant hearing loss was reported. The clinical suspicion of STL has been confirmed by molecular analysis, which identified the c.1845 + 5G> C heterozygous variant in the intron 18 of the *COL11A1* gene, a splicing mutation still not described in mutational databases, but highly probable to be pathogenic.

Pathogenetic collagen type XI variants involve for the most splice sites, particularly intron 50 is a mutational hot spot, however, others sites have been reported (Majava et al., 2007). Interestingly, mutations in the same splice site found in this case have been previously reported in two studies (Guo et al., 2017; Richards et al., 2010). Comparing all three cases, the one reported here and the two others from the literature, the variability of expression of the disease is noticed (Table 1 shows a summary of the 3 cases).

Richards and collaborators identified a splice site alteration in intron 18 (c.1845 + 5G>A) in the *COL11A1* gene in a patient with systemic characteristics of STL with beaded vitreous appearance. The authors focused on the ocular phenotype, observing different vitreal aspects in *COL2A1* versus *COL11A1* mutations (Richards et al., 2010). The study from Guo e colleagues described a baby boy with severe hypotonia, muscle contractures of the hands, mild hypermobility, degenerative myopia, tigroid retinae, and mild hearing loss caused by a nucleotide substitution (c.1845 + 1G>A) in *COL11A1* gene (Guo et al., 2017).

Guo et al. (2017) also highlighted the fact that the clinical signs found in the patient were more commonly observed in the STL related to *COL2A1* mutations. The patient had very mild hearing loss and the facial phenotype observed was nearly normal contrasting with data from the literature that suggests more pronounced facial dysmorphic characteristics

TABLE 1 Comparison of the reported case with similar cases from the literature

	This case report	Guo et al., 2017	Richards et al., 2010
Genotype			
Gene	*COL11A1*	*COL11A1*	*COL11A1*
Mutation	c.1845 + 5G> C	c.1845 + 1G>A	c.1845 + 5G>A
Phenotype			
Ocular abnormalities	++	++	++
Midfacial hypoplasia	+	+	NA
Micrognathia	+	+	NA
Hearing loss	+	+	NA
Joint hypermobility	+	++	NA
Congenital heart defect	−	−	NA
Other abnormalities	Pectus carinatum, abducted shoulders, winged scapulae, bilateral flat feet	Severe hypotonia and contractures of the hands at birth, phimosis	NA

The number of the plus signs indicates the severity of the abnormality.

Abbreviation: NA, not assessed.

associated to *COL11A1* mutations. As the case from Guo and colleagues, which had retinal detachment and vitreoretinal degeneration, our case showed a significant early-onset of ocular involvement what is more frequently described in *COL2A1* mutations. In addition, our patient had a facial phenotype suggestive of STL, even if the midface hypoplasia observed was not as severe as expected in *COL11A1* related syndrome, however, it was not also nearly normal as the Guo's case (Guo et al., 2017).

The severity of the ocular condition described in our case and in the other two cited before shows that an early diagnosis of STL is important for correct clinical management. The literature available highlights that only vitreous appearance is not always able to predict the causative gene in STL and Marshall syndrome cases (Majava et al., 2007; Shapiro et al., 2018). According to Shapiro et al. (2018) the prevention of blindness in STL cases has improved in the last decades through the management of four aspects: early diagnosis of STL, early detection of retinal detachment, prevent of giant retinal tear, and treatment of giant retinal tear detachment (Shapiro et al., 2018).

In general, a severe hearing impairment can be expected in individuals carrying a *COL11A1* mutation. A systematic review performed by Acke, Dhooge, Malfait, and De Leenheer (2012) reported a frequency of hearing loss in 82.5% of the cases related to *COL11A1* mutations, most of them have sensorineural loss. Therefore, our patient manifested initially an abnormal hearing screening test and currently mild hearing loss what leads to the need of an otorhinological follow-up.

A cardiac periodic screening was considered because cardiac abnormalities, mostly mitral valve prolapse, have been previously reported in individuals with STL but not linked to specific gene mutations (Liberfarb & Goldblatt, 1986). Nonetheless, a study including a large cohort of UK patients with STL confirmed by molecular analysis including *COL1A2* and *COL11A1* mutations found no individuals with significant mitral valve or other valve abnormalities suggesting a prevalence of mitral valve prolapse similar to the normal population (Ahmad et al., 2003).

In conclusion, we reported a novel *COL11A1* mutation in a child with Stickler Syndrome presenting a phenotype of early-onset of ocular anomalies and mild hearing loss later in childhood. Our findings confirm the variability of the expression of the disease, even in the contest of the same gene-related disorder, reinforcing the complexity to predict the causative gene based on the clinical phenotype.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR'S CONTRIBUTION

EB, MG, MT, and LS contributed to the conception and design of this research. SB, ALB, and SG performed genetic analysis and contributed to the molecular description. EB, MG, and PN contributed to the clinical characterization of the patient. EB wrote the draft of the manuscript. All authors contributed to manuscript revision and approved the final version.

DATA AVAILABILITY STATEMENT

Not applicable. No data sets were generated or analyzed during the current study and all related information is included in this published article.

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