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CLINICAL REPORT

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A Syrian patient with Steel syndrome due to compound heterozygous *COL27A1* mutations with colobomata of the eye

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Abstract

The joint occurrence of short stature, congenital dislocation of the hip, carpal coalition, dislocation of the radial head, cavus deformity, scoliosis, and vertebral anomalies was first described in 1993 by Steel et al. (OMIM #615155) in 23 children from Puerto Rico. The condition is caused by a deficient matrix protein, collagen type XXVII alpha 1 chain, due to bi-allelic loss of function mutations in the gene *COL27A1*. Outside of Puerto Rico, only four families have been described, in three of which the patients also had hearing loss. However, structural eye defects have not yet been reported in conjunction with this rare autosomal recessive syndrome. Here, we describe a 9-year-old girl born to nonconsanguineous Syrian parents with the characteristic features of Steel syndrome, including short stature, massive malalignment of large joints, kyphoscoliosis, hearing loss, and typical facial dysmorphism. However, she was also born with bilateral colobomata of the irides and choroido-retinae with unilateral affection of the macula. Whole exome sequencing identified two pathogenic compound heterozygous variants in *COL27A1*: c.93del, p.(Phe32Leufs*71) and c.3075del, p.(Lys1026Argfs*33). There was no discernible alternative cause for the colobomata. Our findings might indicate an association of this exceptionally rare disorder caused by *COL27A1* mutations with developmental defects of the eye from the anophthalmia/microphthalmia/coloboma spectrum.

KEYWORDS

Steel syndrome, *COL27A1*, phenotype, coloboma

1 | INTRODUCTION

The joint occurrence of scoliosis, abnormal fusion of carpal bones, dislocation of major joints such as hip, radial head and tali, short stature, and facial dysmorphisms, was first described in 1993 (Steel, Piston, Clancy, & Betz, 1993) and later referred to as Steel syndrome (Flynn et al., 2010). It is caused by bi-allelic loss of function mutations in *COL27A1* and inherited as an autosomal recessive trait (Gonzaga-Jauregui et al., 2015). The homozygous missense mutation identified in the original family was also found in other affected individuals of Puerto Rican ancestry and constitutes a founder effect in that population (Belbin et al., 2017; Gonzaga-Jauregui et al., 2015). Four additional reports of patients from outside Puerto Rico with other *COL27A1* mutations have extended the phenotypic spectrum of Steel syndrome by including hearing loss and—possibly—developmental delay (Gariballa et al., 2017; Kotabagi, Shah, Shukla, & Girisha, 2017;

Maddirevula et al., 2019; Thuresson et al., 2019). Here, we describe a patient with Steel syndrome and bilateral colobomata of the eyes who is compound heterozygous for two novel *COL27A1* putative null mutations c.93del and c.3075del.

2 | CASE REPORT

Our patient, a 9-year-old girl, was born to nonconsanguineous Syrian parents following a normal pregnancy. Delivery was prolonged due to shoulder dystocia. Postnatal findings encompassed joint contractures and scoliosis, without other reported anomalies. Between 1 and 2 years of age, a sensorineural hearing impairment was discovered. She was provided with hearing aids from the age of 7. Measurement of the auditory brainstem response at the age of 8 returned signals down to 90 dB (dB; right ear) and 80 dB (left ear). Her motor development was markedly delayed (e.g. walking at the age of 5), most probably due to her skeletal dysfunctions. At the age of 9 (Figure 1), she spoke only individual words but no sentences, potentially due to her hearing impairment, while her capacity of language reception was much better. Her intellectual ability was reported to be normal by her parents, however, there had been no formal neuropsychological testing. An MRI of the brain yielded normal results. An ophthalmological examination revealed bilateral inferior nasal iris colobomata and bilateral choroido-retinal colobomata next to the lower nasal border of the optic disc and extending to the inferior vasculature. In the right eye, the coloboma also covered the lower part of the macula. In addition, the patient had bilateral hyperopia and strabism as well as amblyopia of the right eye. There was no discernible clouding of the lens.

Our patient is the second of four children. At the time of the consultation, her parents as well as her siblings (an 11- and an 8-year-old brother and a 6-year-old sister) were noted to be healthy. They did not have hearing problems or colobomata of the eyes. The remaining family history was also normal.

Blood samples from our patient and both her parents were taken and whole exome sequencing was performed on our patient's DNA (Kremer et al., 2017). Two novel heterozygous variants in *COL27A1* (NM_032888.4; hg38 chr9:114155537–114312511), c.93del [p.(Phe32Leufs*71)] in exon 2 and c.3075del [p.(Lys1026Argfs*33)] in exon 26 were detected, which were then confirmed through Sanger sequencing. Compound-heterozygosity in the patient was proven by the heterozygous detection of c.93del and c.3075del, respectively, in the parents' DNA. The first of these variants has not yet been listed in the databases dbSNP, ESP, gnomAD, ClinVar, and HGMD, while the second of these variants was listed only in dbSNP, and without further information. These variants have also not been recorded within the local whole exome dataset of about 12,500 individuals (Munich Exome Server; Kremer et al., 2017). Both variants are single nucleotide deletions predicted to cause a frameshift of the reading frame and the introduction of a premature stop codon. Both variants are expected to either lead to truncated proteins or to the nonsense mediated decay of the mRNA with the associated complete loss of protein function (null mutations). Both mutations can be classified as pathogenic (Class 5) when applying the American College of Medical Genetics classification criteria (PVS1, PM2, PM3; Richards et al., 2015).

Finally, we filtered the patients' exome data for variants in OMIM listed genes that are associated with coloboma of the eye. No currently known alternative genetic cause for her eye malformations was identified.

3 | DISCUSSION

We report on the fifth case of Steel syndrome outside of the Puerto Rican population, here caused by compound heterozygosity of two

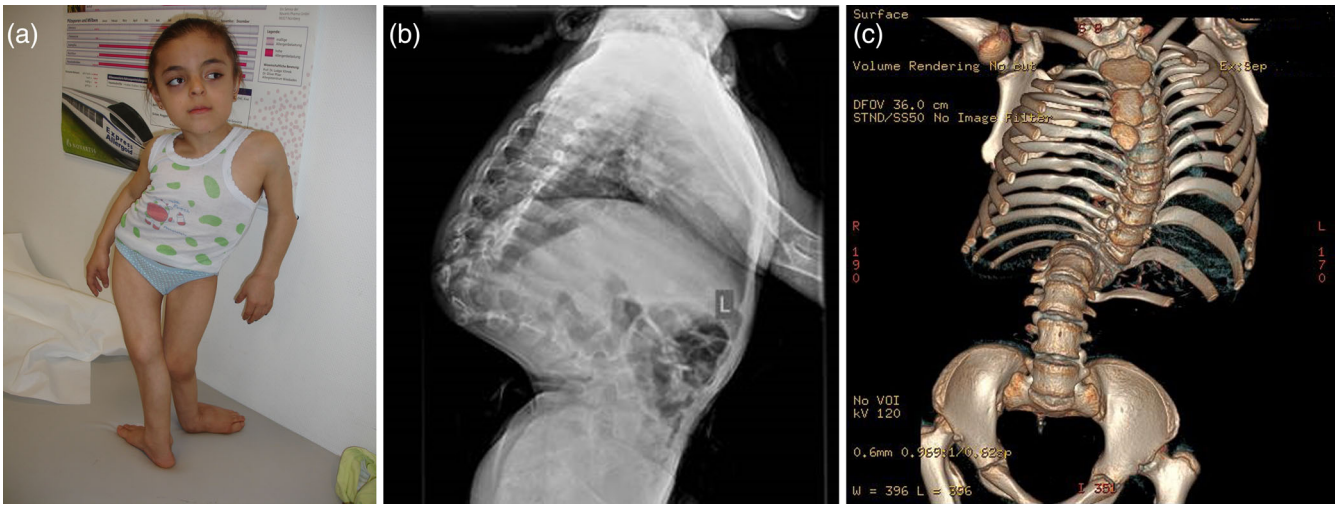

FIGURE 1 Clinical features of the patient at the age of 9 years. (a) Note facial dysmorphism (flat midface, arched eyebrows, large and laterally extended palpebral fissures, short nose with low hanging Columella nasi, long philtrum), severe thoracic hyperkyphosis with lumbar hyperlordosis and scoliosis, and massive malalignment of the lower extremities. (b) Skeletal radiograph confirming thoracolumbar kyphosis and scoliosis without structural bone abnormalities. (c) 3D modeling of the skeletal survey [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Clinical details of Steel syndrome patients

Item	Our patient	Patient 1 (Gariballa et al., 2017)	Patient 2 (Kotabagi et al., 2017)	Patient 3 (Maddirevula et al., 2019)	Patient 4 (Thuresson et al., 2019)	Puerto Ricans (Flynn et al., 2010; Gonzaga-Jauregui et al., 2015)
Age at consultation (years)	9	3	3	5		3–50
Sex	F	F	F	M	F	M/F
Origin	Syria	UAE	India	n.a.	n.a.	Puerto Rico
Consanguinity of parents	N	Y	N	Y	n.a.	Founder effect
Length	85.5 cm (−7.9 *SD*)	n.a.	84 cm (−3 *SD*)	n.a.	Growth retardation	100% short stature
OFC	n.a.	45.5 cm (−2 *SD*)	44 cm (−3 *SD*)	n.a.	n.a.	n.a.
Congenital hip dislocation	Y	Y	Y	Y	Y	100%
Scoliosis	Y	n.a.	n.a.	Y	Y	53%
Carpal coalition	n.a.	n.a.	Y	n.a.	n.a.	73%
Radial head dislocation	Y	Y	Y	n.a.	n.a.	91%
Genu valgum	n.a.	Y	Y	n.a.	n.a.	n.a.
Coxa vara	Y	Y	Y	n.a.	Y	n.a.
Vertical talus/luxation of talus	Y	n.a.	Y	n.a.	n.a.	n.a.
Pes cavus	N	n.a.	N	n.a.	Y	34%
Cervical spine abnormalities	n.a.	Y	n.a.	n.a.	Y	10%
Hearing impairment	Y	Y	Y	n.a.	Y	n.a.
Speech delay	Y	Y	Y	Y	Mild ID	n.a.
Motor developmental delay	Y	N	Y	Y	Mild ID	n.a.
Additional findings	Colobomata of irides, choroideae, macula			Inguinal hernia, cryptorchidism	SGA, delayed myelination	
COL27A1 mutations	c.93del, p.(Phe32Leufs*71), c.3075del, p.(Lys1026Argfs*33) Compound heterozygous	c.3556-2A>G Homozygous	c.521_528del, p.(Cys174Serfs*34), c.2119C>T, p.(Arg707Ter) Compound heterozygous	c.4261-1G>A Homozygous	c.2710G>A, p.(Gly904Arg) Homozygous	c.2089G>C, p.(Gly697Arg) Homozygous

Abbreviations: F, female; ID, intellectual disability; M, male; N, no; n.a., not available; OFC, occipitofrontal circumference; *SD*, standard deviation; SGA, small for gestational age; UAE, United Arab Emirates; Y, yes.

novel predicted null mutations in *COL27A1*. Our patient's clinical presentation matches the clinical features of Steel syndrome described in previous patients, including typical facial dysmorphy, short stature, kyphoscoliosis, malalignment of multiple large joints including congenital bilateral hip dislocation, and hearing impairment (Figure 1 and Table 1; Flynn et al., 2010; Gariballa et al., 2017; Kotabagi et al., 2017; Maddirevula et al., 2019; Thuresson et al., 2019).

In addition, clinical and ophthalmological examinations revealed bilateral colobomata of the irides, retinae, and choroideae with unilateral affection of the macula. To our knowledge, this is the first description of an ophthalmological phenotype in a patient with Steel syndrome, whereas eye involvement has been discussed as a potential phenotype from a functional viewpoint (Gariballa et al., 2017).

Collagens are crucial components of the extracellular matrix of connective tissues and comprise a family of proteins with a high degree of diversity among its members (Exposito, Valcourt, Cluzel, & Lethias, 2010). *COL27A1* codes for the pro-alpha chain 1 of the collagen XXVII, which belongs to the subgroup of fibrillary collagens, where its closest relatives are *COL5A1*, *COL5A3*, *COL11A1*, *COL11A2*, *and COL24A1* (Boot-Handford, Tuckwell, Plumb, Rock, & Poulsom, 2003; Pace, Corrado, Missero, & Byers, 2003). While colobomata in general are not part of collagenopathies and have not been described in Steel syndrome, expression analyses of the *COL27A1* equivalent in mice have suggested functions in the embryonic structures of the eyes (Pace et al., 2003), next to its main expression in cartilage (Hjorten et al., 2007; Pace et al., 2003). Another link between *COL27A1* and colobomata may include Lc-Maf, a splice variant of the transcription factor c-Maf with similar expression patterns, which is an active positive regulator of *COL27A1* expression in mouse cartilage (Mayo, Holden, Barrow, & Bridgewater, 2009). Loss of function mutations in the gene *MAF*, which is also expressed in early eye development (Kawauchi et al., 1999), and encodes for the human equivalent of Lc-Maf, have been described in multiple families with autosomal dominant cataracts and iris colobomata (Dudakova et al., 2017; Jamieson et al., 2003; Narumi et al., 2014). Therefore, it seems possible that disturbances in the Maf/collagen XXVII pathway give rise to colobomata as part of a variable eye phenotype. Finally, in a *TGFβ*-mutated coloboma mouse model—TGFβ is assumed to hinder the closure of the optic fissure during embryonic development—*COL27A1*, among other collagens, was significantly downregulated (Knickmeyer et al., 2018), giving another possible indication for involvement of *COL27A1* in early structural eye development. In Farrell, Siegel-Bartelt, and Teshima (1991), the joint occurrence of moderate sensorineural hearing loss and colobomata of the left choroid and both optic discs extending into the pigmentary epithelium has, as part of a complex phenotype, been associated with a heterozygous de novo deletion of the region 9q31q32, potentially harboring *COL27A1* among others at chromosome band 9q32.

In conclusion, the bilateral colobomata in our patient might well be a part of the clinical spectrum of Steel syndrome, even if our molecular evidence is only indirect and hypothetical, and does not rule out random coincidence, which is noteworthy given that genetic analyses of patients with colobomata prove the molecular basis in up to 75% of severe cases but only in 20–30% of milder cases of eye malformations from the anophthalmia/microphthalmia/coloboma spectrum (Harding, Brooks, FitzPatrick, & Moosajee, 2019; Plaisancié et al., 2019). We suggest detailed ophthalmological investigations in all individuals with this condition in order to investigate a possible association between structural eye defects and Steel syndrome.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy or ethical restrictions.

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