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Autosomal recessive Stickler syndrome resulting from a *COL9A3* mutation

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Abstract

Stickler syndrome is a connective tissue disorder characterized by hearing loss, ocular anomalies, palatal defects, and skeletal abnormalities. The autosomal dominant form is the most common, but autosomal recessive forms have also been described. We report the second case of autosomal recessive Stickler syndrome due to homozygosity for a loss of function mutation in *COL9A3*, which encodes the α3 chain of type IX procollagen. The clinical features were similar to the previously described *COL9A3* Stickler syndrome family, including moderate to severe sensorineural hearing loss, high myopia, and both tibial and femoral bowing at birth. Radiographs demonstrated abnormal capital femoral epiphyses and mild irregularities of the vertebral endplates. This case further establishes the phenotype associated with mutations in this gene. We suggest that loss of the α3 chain of type IX collagen results in a Stickler syndrome phenotype similar to that of the other autosomal recessive forms caused by mutations in genes encoding the α1 and α2 chains of type IX collagen.

Keywords

autosomal recessive; *COL9A3*; Stickler syndrome; type IX procollagen

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1 | INTRODUCTION

Stickler syndrome is a genetically heterogeneous connective tissue disorder first described in 1965 (Stickler et al., 1965). There is substantial inter and intrafamilial variability, with the features most commonly associated including sensorineural hearing loss, high myopia, retinal detachment, vitreous anomalies, cataracts, midface hypoplasia, palatal defects, joint hypermobility, and early onset osteoarthritis.

Both autosomal dominant and autosomal recessive forms have been described, all resulting from mutations in genes encoding procollagens that are primarily expressed in cartilage. The autosomal dominant form is most common, with 80–90% of the cases caused by heterozygosity for mutations in *COL2A1* (Ahmad et al., 1991; Lieberfarb et al., 2003), which encodes type II procollagen. Mutations in the type XI procollagen gene, *COL11A1*, account for additional autosomal dominant cases (Majava et al., 2007; Richards et al., 1996) and mutations in *COL11A2* cause autosomal dominant OSMED[A] syndrome, formerly known as nonocular Stickler syndrome (Pihlajamaa et al., 1998; Spranger, 1998).

Four families have been described with autosomal recessive Stickler syndrome due to mutations in the *COL11A1* type XI procollagen gene (Alzahrani, Alshammari, & Alkuraya, 2012; Richards et al., 2013). Five families have been described with autosomal recessive Stickler syndrome due to homozygosity for loss-of-function mutations in the *COL9A1* and *COL9A2* type IX procollagen genes (Baker et al., 2011; Nikopoulos et al., 2011; Van Camp et al., 2006) and, more recently, *COL9A3* (Faletra et al., 2014).

Autosomal recessive mutations in *COL11A2* have also been associated with OSMED[B] syndrome (Temtamy et al., 2006; Vikkula et al., 1995), an osteochondrodysplasia with features that overlap with both the autosomal dominant and autosomal recessive forms of Stickler syndrome. Variants in *COL9A3* have previously been associated with autosomal dominant multiple epiphyseal dysplasia (Jeong et al., 2014; Nakashima et al., 2005; Paassilta et al., 1999), adult onset autosomal dominant sensorineural hearing loss (Asamura, Abe, Fukuoka, Nakamura, & Usami, 2005), and increased risk for lumbar disc disease (Paassilta et al., 2001). We report the second family with autosomal recessive Stickler syndrome resulting from a mutation in *COL9A3* and compare the phenotype to the other autosomal recessive forms caused by mutations in *COL9A1*, *COL9A2*, and *COL11A1*.

2 | MATERIALS AND METHODS

2.1 | Case report

The patient, International Skeletal Dysplasia Registry reference number R08–308A, was born to a 31-year-old G2 P1–2 mother and 33-year-old father via Caesarean section due to failure to progress. The pregnancy was uncomplicated and prenatal ultrasounds were normal. Birth weight was 7 lbs 5 oz (75–90th %ile) and birth length was 19 in. (50–75th %ile).

The patient failed his newborn hearing screen. Audiology evaluation at 5 months identified moderate to severe sensorineural hearing loss on the right from 250 through 4,000 Hz and severe sensorineural hearing loss on the left from 250 through 4,000 Hz. Hearing loss has

been stable. A head CT of the temporal bones at 7 months was negative apart from mild enlargement of the vestibular aqueducts.

Ophthalmological evaluation at 5 months showed no evidence of myopia. However, by 2 years, he had developed myopia of −6.75 OD and −8 OS. By 12 years, this had progressed to −10.75 OD and −11.25 OS. No vitreous abnormalities have been noted.

Femoral and tibial bowing were noted at birth. Radiographs at 6 years demonstrated slightly flattened proximal femoral epiphyses, normal knee epiphyses, and mild platyspondyly (Figure 1). Growth parameters have been in the normal range.

The patient also had autoimmune hypothyroidism that was identified at 10 years. Gross motor development has been normal. Speech was initially delayed but was thought to be related to hearing loss. Intelligence was normal. Clinical features are summarized in Table 1.

Connexin 26 sequencing identified heterozygosity for a 380G>A (R127H) variant. A second variant in the gene was not identified. Testing for the common deletion in connexin 30 was negative. The patient was heterozygous for a variant in the *SLC6A4* gene (IVS13 1,544 + 9 C>C/T). Sequence and deletion/duplication analysis of *COL2A1*, *COL11A1*, and *COL11A2* were negative. Sequence and deletion/duplication analysis of specific exons in *COL9A1, COL9A2*, and *COL9A3* were also negative.

The parents of the patient are third cousins from India. The patient has one older sister. There is no report of hearing loss, myopia, other ocular anomalies, or skeletal anomalies in either parent or in the sister. Neither the parents nor the sister have been examined for features suggestive of an osteochondrodysplasia, nor have they had audiology or ophthalmology evaluations or had radiographs taken. A paternal cousin had moderate hearing loss with onset in adolescence of unknown etiology. Family history was otherwise noncontributory.

2.2 | Exome sequencing

Exome sequence analysis was performed at the University of Washington Center for Mendelian Genomics using DNA derived from blood from the R08–308 family members. 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 (NCBI build 37) with BWA (Li & Durbin, 2009) and variants were called with the Genome Analysis Toolkit following their Best Practices recommendations (McKenna et al., 2010). The variants were filtered as described previously (Taylor et al., 2015) and annotated with the SeattleSeq138 Annotation Server. The variant in *COL9A3* identified in the family was confirmed by Sanger sequencing with DNA from the proband, parents and an unaffected sibling. Primer sequences used were: COL9A3-exon 13, F: 5′- CTTGGGCTTGAGTAGGGTGACT −3′; R: 5′- GGTAGATATGTGCAGGGCTTGAT −3′.

3 | RESULTS

In consanguineous Stickler syndrome family R08–308, exome sequencing was used to identify homozygosity for single base duplication c.650dupC in exon 13 of *COL9A3* (RefSeq accession number NM_001853.3) of the proband. The frameshift mutation predicts premature termination of translation and absence of the *COL9A3* gene product. The nucleotide change was not found in public SNP databases, suggesting that it was unique to the family. Genotyping of the parents and an unaffected sibling showed that all of them were heterozygous for the sequence change (Figure 2).

4 | DISCUSSION

As in the case described here, the three siblings with autosomal recessive Stickler syndrome described by Faletra et al. (2014) were homozygous for a loss-of-function mutation in *COL9A3*. The phenotype consisted of moderate to severe sensorineural hearing loss, high myopia, normal vitreous, midface hypoplasia, tibial rotation, mild irregularities of the capital femoral and metacarpal epiphyses, and pes planus. The patients also had moderate to severe intellectual disability, which the authors suggested was unrelated to the *COL9A3* mutations.

The features of the patient described here were similar, including moderate to severe sensorineural hearing loss, high myopia, normal vitreous, tibial, and femoral bowing at birth and mild capital femoral epiphyseal flattening. In addition, he had mild platyspondyly with irregularities of the vertebral endplates. Hand radiographs were not available, so we do not know whether there was involvement of the metacarpal epiphyses.

Six families, comprising 12 known cases, have been reported with autosomal recessive Stickler syndrome resulting from homozygosity for loss-of-function mutations in the *COL9A1, COL9A2*, or *COL9A3* genes. Based on studies in the knockout mouse, loss of *Col9a1* leads to absence of type IX collagen in cartilage (Hagg et al., 1997) and a similar consequence has been assumed for loss of the α2(IX) or α3 (IX) chains. This inference is supported by the Stickler syndrome phenotype resulting from the loss-of-function mutations in the corresponding human orthologues. Consequently, it is perhaps not surprising that the clinical phenotypes among these autosomal recessive forms of the disorder are similar.

All of the Stickler syndrome patients with type IX collagen defects have exhibited high myopia, midface hypoplasia, and mild–severe hearing loss. Vitreous and retinal degeneration have been reported in patients with mutations in *COL9A1* and *COL9A2*, but have not been reported in patients with mutations in *COL9A3*.

The phenotype of these patients also appears to be distinct from that of the autosomal recessive form of Stickler syndrome caused by mutations in *COL11A1*. The patients described by Richards et al. (2013) and Alzahrani et al. (2012) have sensorineural hearing loss, myopia, vitreous abnormalities, and cleft palate. In contrast to patients with type IX collagen defects, the hearing loss is severe-profound. Midfacial hypoplasia and orthopedic issues have not been described.

In conclusion, we report the second family with autosomal recessive Stickler syndrome due to homozygosity for a loss-of-function mutation in *COL9A3* and further establish the phenotype associated with mutations in this gene. We suggest that loss of the α3 chain of type IX collagen results in a Stickler syndrome phenotype similar to that of the other autosomal recessive forms caused by mutations in the genes encoding the α1 and α2 chains of type IX collagen.

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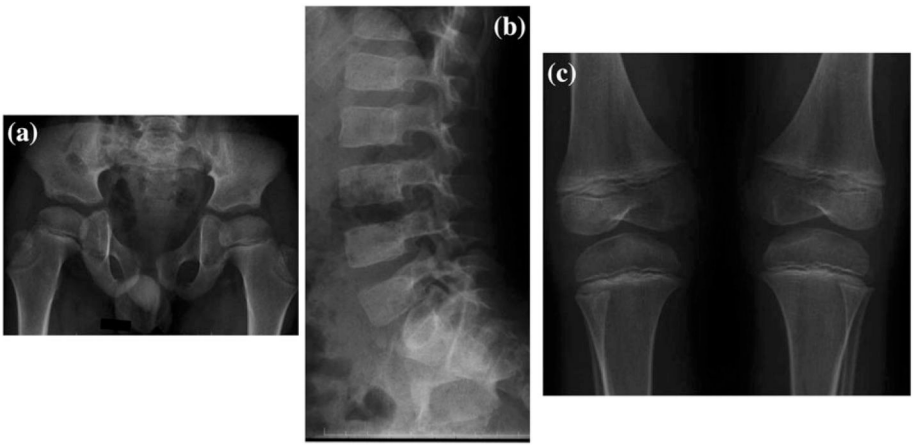

FIGURE 1.

Radiographs at age 6. (a) Flattening of the acetabula and slightly flattened proximal femoral epiphyses. (b) Mild platyspondyly. (c) Irregularity of the medial distal femoral epiphyses

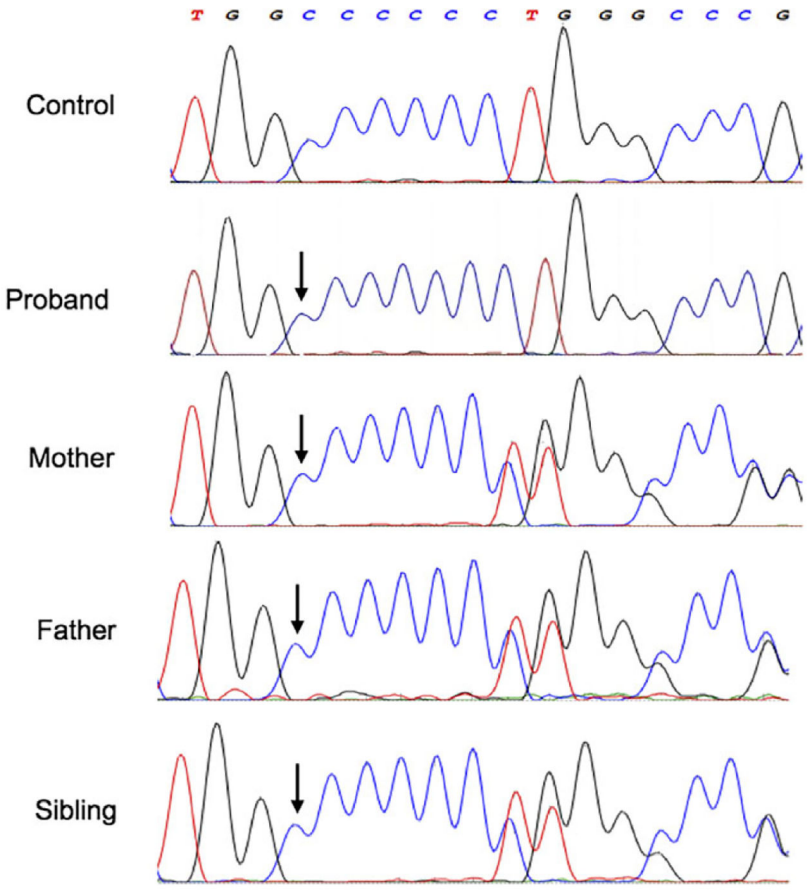

FIGURE 2.

COL9A3 mutation in family R08–308. Electropherogram representation of genomic DNA fragments from the patient family members and an unaffected person (control). From top to bottom, an unaffected person, proband, mother, father, and an unaffected sibling. The human reference sequence is shown on top. The location of the single base insertion is indicated by arrows

TABLE 1

Clinical features associated with autosomal recessive Stickler syndrome

	COL9A1	COL9A1	COL9A2	COL9A3	COL11A1	COL9A3
	Van Camp et al. (2006)	**Nikopoulos et al. (2011)**	**Baker et al. (2011)**	**Faletra et al. (2014)**	**Alzahrani et al. (2012); Richards et al. (2013)**	**Our patient**
Craniofacial						
Midfacial hypoplasia	+	+	+	+	−	+
Cleft palate	−	−	−	−	+	−
Ophthalmologic						
Myopia	+	+	+	+	+	+
Retinal degeneration	+	+	+	−	−	−
Vitreous anomalies	+	+	+	−	+	−
Other	Amblyopia, astigmatism	Amblyopia, cataracts		Amblyopia, astigmatism		
Hearing						
Sensorineural hearing loss	+ (mod-severe)	+ (mild-mod)	+ (mild-mod)	+ (mod-severe)	+ (severe-profound)	+
Orthopedic						
Pes planus	+	+	+	+	−	−
Epiphyseal changes	+	+	−	+	−	+
Other	Genu valga, platyspondyly	Scoliosis, degenerative disc changes, coxa vara		Tibial rotation		Tibial bowing

+ = present; − = absent.