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Clinical report

SOX9 dimerization domain mutation mimicking type 2 collagen disorder phenotype

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ABSTRACT

The classification of bone dysplasia has relied on a clinical/radiographic interpretation and the identification of specific genetic alterations. The clinical presentation of the *SOX9* mutation and type 2 collagen disorders overlap with the Pierre-Robin sequence and talipes equinovarus, but the former is often accompanied by the bent long bones. In its milder form, the *SOX9* mutation is not necessarily associated with the bent long bones. Here, we report a patient with the Pierre-Robin sequence and talipes equinovarus who did not exhibit either bent long bones or scapular hypoplasia; thus, this patient was instead classified as having a type 2 collagen disorder. Despite this phenotypic presentation, the proposita was found to have a *de novo SOX9* mutation. The peculiar location of the mutation within the dimerization domain might account for the relatively mild phenotypic effect of the *SOX9* mutation to a degree that is compatible with a clinical diagnosis of type 2 collagen disorder, except for a developmental delay. We concluded that mutations in *SOX9* can mimic a type 2 collagen disorder-like phenotype.

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1. Introduction

The "Nosology and Classification of Genetic Skeletal Disorders" defines each skeletal disorder based on the rather arbitrary combination of morphological assessments and the confirmation of specific genetic alterations [Spranger et al., 2012]. In general, alterations in different molecules involved in the same signaling pathway result in similar phenotypes, defining a specific disease spectrum. Within such spectra, the functional degree of molecular disturbance, rather than the name of the molecule *per se*, can be the major determinant of the patient's phenotype. Accordingly, clinicians often have difficulty identifying the causative gene based on a patient's clinical features alone.

According to the most recent "Nosology and Classification of Genetic Skeletal Disorders," revised in 2010, type 2 collagen disorders include nine disorders [Warman et al., 2011]. Traditionally, clinical features that point to an underlying type 2 collagen disorders include micrognathia, cleft palate, flat midface, visual or hearing impairment, and variable radiographic changes. Achondrogenesis type 2 (OMIM 200610) represents the severe end that is characterized by lethal degree of skeletal undermineralization. Spondyloepiphyseal dysplasia congenita (OMIM 183900) and Kniest dysplasia (OMIM 156550) are characterized by retarded enchondral ossification of the appendicular skeleton and odontoid hypoplasia. Stickler syndrome represents the mild end [Kannu et al., 2010].

The causative gene of these disorders, type 2 collagen gene, *COL2A1*, is directly regulated by *SOX9* [Bell et al., 1997]. The classic presentations of a *SOX9* mutation, campomelic dysplasia, resembles those of type 2 collagen disorders and are often accompanied by severe morphological changes, such as the bending of the long bones. Furthermore, SOX9 plays an essential role in the gonads and in the central nervous system, leading to sex differentiation disorders in male patients and developmental delays when *SOX9* is mutated [Foster et al., 1994; Wagner et al., 1994]. When the molecular defect is less severe, the *SOX9* mutant can manifest as a mild phenotype without the bending of the long bones and is called acampomelic campomelic dysplasia (ACD). In patients with ACD, who lack the characteristic finding of

Abbreviations: ACD, acampomelic campomelic dysplasia; NGS, next generation sequencing.

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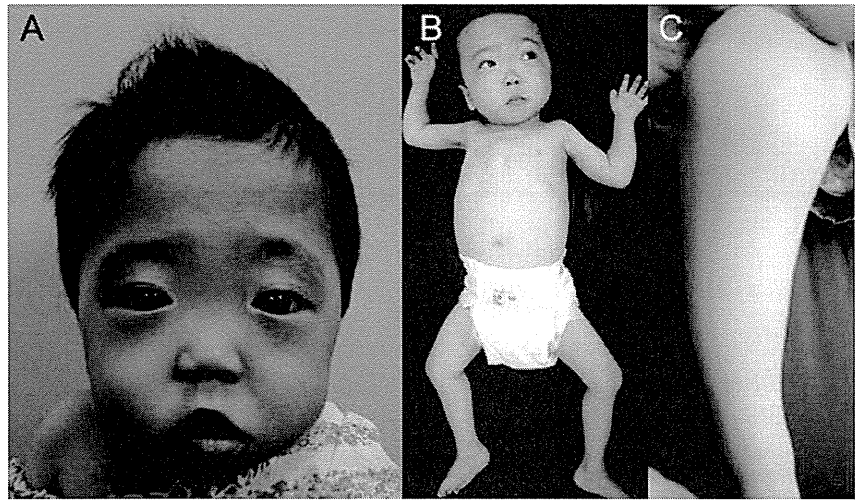

Fig. 1. Morphological characteristics of the proposita. (A) A facial photograph of the proposita at the age of 2 years showing hypertelorism, downslanting palpebral fissures, hypoplasia of the mid-facial structures and micrognathia. Photographs of the propisita's full-length figure (B) and right lower extremity (C) show the absence of bowed tibiae or pretibial dimples.

bent long bones, the presence of scapular hypoplasia is a key diagnostic finding [Glass and Rosenbaum, 1997; Lecointre et al., 2009; Macpherson et al., 1989; Moog et al., 2001; Thong et al., 2000; Wada et al., 2009].

2. Clinical report

The proposita was a product of natural conception by parents with no family history of known genetic conditions. The mother was a 37-year-old primipara woman who had a history of depression and asthma. Her pregnancy was complicated by polyhydramnios, which was first noted at 37 weeks of gestation. The proposita was born at 41 5/7 weeks of gestation via cesarean section because of a non-reassuring fetal status. Her birth weight was 2716 g (−1.5 SD), her length was 44.8 cm (−3.0 SD), and her head circumference was 35 cm (+0.9 SD). The Apgar scores were 8 and 8 at 1 and 5 min, respectively. At birth, her physical examination revealed multiple congenital anomalies including a cleft palate, micrognathia, right talipes equinovarus, thin ribs, absent toenails, and short ulnae. An echocardiogram revealed a patent ductus arteriosus and atrial septal defect, which closed spontaneously.

Soon after birth, she was noted as having severe stridor with retraction and obstructive apnea secondary to glossoptosis and tracheomalacia. She was treated using positive airway pressure support. She was discharged home on a bilevel positive airway pressure and a feeding tube at 4 months of age with a weight of 4881 g (−2.1 SD). After hospital discharge, she experienced multiple episodes of upper airway infections requiring hospitalization. These findings led to a provisional diagnosis of type 2 collagen disorder without molecular confirmation.

During outpatient follow-up examinations, it became apparent that she had a developmental delay. She gained head control at 10 months, rolled over at 12 months, and smiled at 18 months of age. The developmental delay was incompatible with a diagnosis of type 2 collagen disorder. Hence, we performed a mutation analysis for *COL2A1* but did not find a pathologic mutation. An expanded analysis using a custom-designed mutation analysis panel that included *COL2A1, COL11A1, COL11A2, COL9A1, COL9A2*, and *SOX9* revealed a *de novo* missense mutation in the dimerization domain of *SOX9*.

At the age of 2 years and 2 months, she continued to exhibit a severe developmental delay. She sat without support but did not have any meaningful words. Her weight was 7.035 kg (−3.6 SD), her length was 68.8 cm (−5.5 SD), and her head circumference was 48.2 cm (+0.66 SD). A physical examination showed hypertelorism with an inner canthal distance of 3.2 cm, downslanting palpebral fissures, hypoplasia of the mid-facial structures and micrognathia, cleft palate, limitations in the range of joint motions, and normal female external genitalia. A pretibial dimple was not present (Fig. 1). An ophthalmologic examination showed severe myopia, while an audiological evaluation showed severe deafness. Plain radiographs showed a narrow thorax, slender long bones and hip dislocation. Scapular hypoplasia, and bending of the long bones were absent (Fig. 2).

3. Molecular analysis

The present research protocol was approved by an institutional review board. Written consent was obtained from the parents. DNA was extracted from whole blood samples that were obtained from the proposita and her biological parents. Target resequencing using a custom-designed mutation analysis panel (SureSelect XT-Auto;

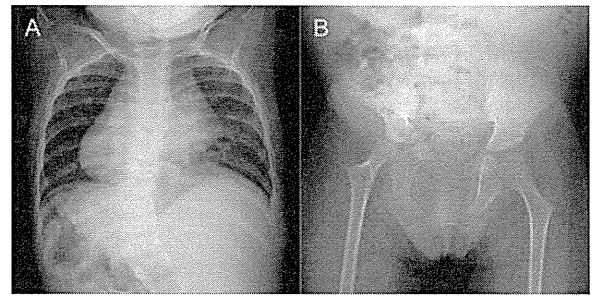

Fig. 2. Skeletal characteristics of the proposita. Anteroposterior radiographs of the chest (A), pelvis and the lower extremities (B) at 2 years and 6 months of age show vertical iliac wings and a right dislocated hip. Neither bent long bones nor scapular hypoplasia was present.

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Agilent Technologies, Santa Clara, CA, USA) was performed. The list of genes (manuscript in preparation) included 100 common genes described in a classic textbook of dysmorphology: Smith's Recognizable Patterns of Human Malformation [Jones, 2006].

This panel was run on a next-generation sequencer (NGS: MiSeq; Illumina, Inc., San Diego, CA, USA). After the sequencing reads were aligned to the reference human genome sequence (hs37d5) using BWA [Li and Durbin, 2009], local realignment around the indels and base quality score recalibration were performed using Genome Analysis Toolkit software [McKenna et al., 2010]. Duplicate reads were removed using Picard (http://picard.sourceforge.net). This trio analysis revealed that the proposita had a *de novo* heterozygous missense mutation, i.e., c.239T>G p.Val80Gly, in exon 1 of *SOX9*. This mutation was located in the dimerization domain of *SOX9* and is a novel variant that is not present in the dbSNP137, 1000 genomes, ESP6500, or our in-house Japanese SNP dataset. We confirmed the mutation detected in the proposita using Sanger sequencing with the following primers: GCGCCTTCCTAAGTGCTC (forward) and AGCGTCCAGTCGTAG CCTTT (reverse). Sex differentiation disorder has been reported in patients with campomelic dysplasia arising from a *SOX9* mutation, but PCR-amplification of the *SRY* region using SRY primers revealed no amplification of these products [Berta et al., 1990].

4. Discussion

Here we report a patient with *de novo SOX9* mutation who exhibited many features of the type 2 collagen disorder including micrognathia, cleft palate, flat midface, and visual and hearing impairment, and a retarded enchondral ossification of the appendicular skeleton during the infantile period. However, the severe developmental delay, which became apparent over time, was rather atypical for a type 2 collagen disorder. A target analysis of the most frequent causative gene for type 2 collagen disorder, i.e., *COL2A1*, failed to detect pathologic mutations, but an expanded mutation analysis using NGS revealed a mutation in *SOX9*, which is an upstream regulator of *COL2A1*.

Lines of existing evidence suggest a causal relationship between the detected mutation in *SOX9* and the patient's phenotype. In general, only single amino acid substitutions occur in the coding region of the genome per generation [Lynch, 2010]. A similar *de novo* amino acid substitution in the dimerization domain was reported in a patient with ACD [Sock et al., 2003]. Although a functional assay would provide more insight into the mechanism, we concluded that the *de novo* amino acid substitution change in the dimerization domain of *SOX9* was responsible for the constellation of short limb dwarfism, Pierre-Robin sequence, and severe developmental delay in the proposita.

SOX9 is expressed in many organs including the brain, testis, pancreas, gut, and inner ear [Gordon et al., 2009]. In the downstream signal transduction, a tissue-specific requirement for the dimerization of SOX9 exists. In vitro studies have shown that the dimerization of SOX9 is required in cartilage but that SOX9 binds as a monomer to the downstream regulatory region of the sex-determining gene in the gonads [Bernard et al., 2003]. In the central nervous system, the structural requirement, i.e., the monomerization or dimerization, of SOX9 remains unclear. The severe developmental delay in the proposita could be considered as in vivo evidence that the dimerization of SOX9 is necessary in the developing brain. The presence of a developmental delay in an ACD patient arising from an amino acid substitution in the dimerization domain of *SOX9* further supports this possibility [Sock et al., 2003].

The identification of the causative mutation was rather challenging in the proposita. After the Sanger sequencing of *COL2A1* failed to detect a causative genetic alteration, we resorted to an NGS-based molecular diagnostic approach [Takenouchi et al., 2013]. By using the customly-designed mutation analysis panel covering congenital skeletal disorders, we successfully identified a causative mutation in *SOX9* in the proposita, who did not exhibit campomelia or scapular hypoplasia.

From a radiographic standpoint, she could be classified as having mild end of ACD in that she did not have overt scapular hypoplasia with the molecular diagnosis in mind. According to the most updated 'Nosology and Classification of Genetic Skeletal Disorders', ACD is classified under "bent bone dysplasia" [Warman et al., 2011]. However, the morphological features of the proposita, namely the absence of bent long bones or scapular hypoplasia (which is pathognomonic for ACD), make it unclear whether the proposita should be placed within the group characterized by "bent bone dysplasia". The mere combination of the Pierre-Robin sequence and talipes equinovarus points to a type 2 collagen disorder. Further refinement of the classification of bent bone dysplasia and type 2 collagen disorders may be warranted.

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