A Venezuelan Case of Schmid-Type Metaphyseal Chondrodysplasia with a Novel Mutation in *COL10A1*

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Established Facts

- Schmid-type metaphyseal chondrodysplasia is an uncommon autosomal dominant skeletal dysplasia, with 50% risk of recurrence in descendants of affected individuals.
- It is caused by heterozygous mutations in the *COL10A1* gene, encoding the $\alpha 1(X)$ chains of type X collagen.
- Mutations in *COL10A1* disrupt growth plate function and endochondral ossification.

Novel Insights

- The p.Leu633Thrfs*45 mutation detected in the *COL10A1* gene is novel as well as the predicted effect of this mutation on protein function.
- This unreported frameshift mutation presents a similar phenotype found in other cases with the same type of mutation, including short stature, waddling gait, metaphyseal irregularities and coxa vara.

Keywords

COL10A1 mutation · Schmid-type metaphyseal chondrodysplasia

Abstract

Schmid-type metaphyseal chondrodysplasia (MIM 156500) is an uncommon autosomal dominant skeletal dysplasia

caused by heterozygous mutations in the *COL10A1* gene (MIM 120110) encoding the $\alpha 1(X)$ chains of type X collagen. We report an 8-year-old girl with waddling gait, short stature, mild dorsal scoliosis, coxa vara, short lower limbs, bowing of the femurs, genu varum, and metaphyseal fraying and splaying, who is a carrier of a novel heterozygous 2-bp (c.1894_1895dupTA; p.Leu633Thrfs*45) duplication in exon 3 of the *COL10A1* gene.

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Fig. 1. Pedigree of the family. Arrow indicates the proband (III:3) affected with Schmid-type metaphyseal chondrodysplasia.

Schmid-type metaphyseal chondrodysplasia (SMCD; MIM 156500) is an uncommon autosomal dominant skeletal dysplasia, characterized clinically by mild to moderate disproportionate short stature, short legs, bowing of the long bones, and a waddling gait [Woelfle et al., 2011; Zhu et al., 2011; Park et al., 2015; Higuchi et al., 2016; Wang et al., 2017]. Radiographic findings include metaphyseal abnormalities, widening and irregularity of the growth plates, scoliosis [Park et al., 2015], shortening of tubular bones, coxa vara, and genu varum [Woelfle et al., 2011; Zhu et al., 2011; Wang et al., 2017]. The distal femoral and proximal tibial metaphyses are the most severely affected sites [Park et al., 2015], and the lumbar spine, anterior ribcage, forearms, and hands can also be affected [Woelfle et al., 2011].

SMCD is caused by heterozygous mutations in the *COL10A1* gene (MIM 120110), located at 6q22, encoding the $\alpha 1(X)$ chains of type X collagen [Mäkitie et al., 2005; Woelfle et al., 2011; Higuchi et al., 2016; Wang et al., 2017]. Type X collagen is a short chain, non-fibrillar collagen [Park et al., 2015] which is a homotrimeric molecule consisting of 3 identical $\alpha 1(X)$ chains [Park et al., 2015; Higuchi et al., 2016]. Each $\alpha 1(X)$ chain contains a core triple-helical domain, composed of uninterrupted repeats of the Gly-Xaa-Yaa tripeptide, flanked by 2 globular domains (noncollagenous domains [NC1] and [NC2]) at both the amino and carboxyl-terminal ends [Zhu et al., 2011; Higuchi et al., 2016]. Type X collagen is an extracellular matrix protein which is normally expressed in the hypertrophic zone of the growth plate adjacent to the calcifying cartilage [Mäkitie et al., 2005; Zhu et al., 2011]. Mutations in *COL10A1* disrupt the growth plate function and endochondral ossification [Woelfle et al., 2011; Park et al., 2015; Wang et al., 2017]. Histological studies showed a decreased tendency of growth plate chondrocytes to form normal cell columns [Woelfle et al., 2011]. Herein, we report the clinical and radiological findings of a patient with SMCD carrying a novel mutation in the *COL10A1* gene.

Table 1. Measurements of different body segments in percentiles or standard deviation

Segments	Measurements	Percentile or SD
Height	111.5 cm	–3 SD to –4 SD
Weight	19 kg	3–10
Head circumference	50.1 cm	3–10
Upper arm length	20.9 cm	<3
Forearm length	16.8 cm	<3
Hand length	14.4 cm	25–50
Upper leg (thigh) length	29.1 cm	–2 SD
Lower leg (calf) length	28.5 cm	10
Foot length	19.5 cm	3–25
Upper segment	57.6 cm	<3
Lower segment	53.9 cm	–

Age of the patient is 8 years and 3 months.

Case Report

The proband was an 8-year-old Venezuelan girl, born prematurely at 33 weeks of gestation following a complicated pregnancy with oligohydramnios, preeclampsia, and severe anemia. At birth, her length was 44 cm (–1.2 SD), and weight was 1.1 kg (–4.1 SD). She was the only daughter of nonconsanguineous parents with no pre-existing family history of SMCD (Fig. 1).

She demonstrated normal psychomotor development and was referred due to short stature and skeletal dysplasia. Clinical findings included short lower limbs, genu varum, bowing of the femur and waddling gait. Measurements of the different body segments are presented in Table 1. Bone age corresponded to chronological age, and mild dorsal scoliosis, coxa vara, metaphyseal fraying and splaying were evident in radiographs of the lower limbs (Fig. 2). The cytogenetic analysis confirmed 46,XX in 40 analyzed metaphases.

Methods and Results

Genomic DNA was extracted from the patient's peripheral blood leukocytes by standard methods [Sambrook et al., 1989]. Sequencing of the *COL10A1* gene detected a novel heterozygous 2-bp duplication (c.1894_1895dupTA; p.Leu633Thrfs*45) in exon

Fig. 2. Radiographs of the patient showing mild dorsal scoliosis, coxa vara, metaphyseal widening, and irregularity of the distal femoral and proximal tibia.

Fig. 3. DNA sequence electropherogram of the *COL10A1* gene, exon 3 of the patient showing the c.1894_1895dupTA mutation.

3 (Fig. 3), resulting in a frameshift mutation. This mutation was novel and had not been previously reported in online databases, including dbSNP, the 1000 Genomes Project, Exome Aggregation Consortium (ExAC), and the NHLBI Exome Sequencing Project. The duplication creates a frameshift starting at codon Leu633 located in the nonhelical region (NC1) of the protein resulting in 41 amino acid substitutions in C-terminal of the protein and a STOP codon 44 positions downstream of the duplication (p.Leu633Thrfs*45); this is expected to produce a truncated protein of 677 amino acids instead of 680 amino acids.

Discussion

The diagnosis of metaphyseal chondrodysplasia is clinically challenging as all long bones of the growing human skeleton can be potentially affected [Woelfle et al., 2011]. The clinical and radiological findings of SMCD are similar to those caused by rickets. Genetic analysis may be required to assist in the differential diagnosis between SMCD and rickets, especially in the cases with no biological abnormality [Higuchi et al., 2016].

Following the initial report of the *COL10A1* gene mutation in SMCD [Mäkitie et al., 2005], at least 48 different heterozygous *COL10A1* mutations have been reported in families with SMCD of different ethnic origin [Higuchi et al., 2016]. To date, the majority of mutations occur within the C-terminal NC1 domain [Mäkitie et al., 2005; Park et al., 2015; Higuchi et al., 2016; Goyal et al., 2018], which contains motifs that promote trimerization of the $\alpha 1(X)$ chains and subsequent formation of the triple helix to yield stable collagen X molecules [Higuchi et al., 2016; Goyal et al., 2018]. Missense, nonsense, and frameshift mutations have been reported in the NC1 domain, and in 53% of the cases, premature termination codons resulting from nonsense and frameshift mutations have been reported. In a murine model of SMCD, nonsense mutations lead to mRNA nonsense-mediated decay and haploinsufficiency. In SMCD, expressed mutant $\alpha 1(X)$ chains are unable to trimerize to form a stable collagen and accumulate intracellularly leading to endoplasmic reticulum stress in hypertrophic chondrocytes [Zhu et al., 2011].

The p.Leu633Thrfs*45 mutation detected in this study is novel and the predicted effect of this mutation on protein function was assessed using MutationTaster software [Schwarz et al., 2014], a free software that uses several algorithms and databases to estimate the impact of mutations on proteins. The amino acid substitutions in $\alpha 1(X)$ chains of type X collagen are in a highly conserved region and are predicted to result in nonsense-mediated decay. Several frameshift mutations have been reported in the *COL10A1* gene and affected patients present with a similar phenotype as seen in our case, including short stature, waddling gait, metaphyseal irregularities, and coxa vara. However, the phenotype severity and others findings

such as hyperlordosis showed both inter- and intrafamilial variability [Mäkitie et al., 2005; Woelfle et al., 2011; Park et al., 2015; Higuchi et al., 2016; Goyal et al., 2018].

Conclusion

This study reports the clinical and radiological findings of a case of SMCD associated with a novel, previously unreported frameshift mutation in the *COL10A1* gene. The mutation is located at the carboxyl-terminal ends in the NC1 domain and is predicted to produce a premature stop codon resulting in a truncated protein. Further studies are required to understand genotype-phenotype correlations resulting from mutations of the *COL10A1* gene in SMCD.

Acknowledgment

We would like to thank Rosalia Gumina for her support with the literature review.

Statement of Ethics

Informed consent for manuscript publication and accompanying photographs was obtained from the patient and her mother. Procedures performed were in accordance with ethical standards (the Helsinki Declaration).

Disclosure Statement

The authors have no conflicts of interest to disclose.

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