

## Mutation-in-Brief

# A Japanese familial case of Schmid metaphyseal chondrodysplasia with a novel mutation in *COL10A1*

Shinji Higuchi<sup>1</sup>, Masaki Takagi<sup>1,2</sup>, Satoshi Shimomura<sup>3</sup>, Gen Nishimura<sup>4</sup>, and Yukihiro Hasegawa<sup>1,2</sup>

<sup>1</sup>Department of Endocrinology and Metabolism, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan

<sup>2</sup>Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan

<sup>3</sup>Department of Orthopedics, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan

<sup>4</sup>Department of Radiology, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan

**Key words:** Schmid metaphyseal chondrodysplasia, coxa vara, *COL10A1*, bowlegs

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### Introduction

Schmid metaphyseal chondrodysplasia (SMCD; OMIM #156500) is an autosomal dominant skeletal dysplasia, characterized by short stature with short legs, bowing of the long bones, and waddling gait. Radiographic features include metaphyseal irregularities with fraying and splaying, and coxa vara, which is defined as a deformity of the hip, wherein the angle between the head and the shaft of the femur is reduced to less than 120 degrees (1).

SMCD is caused by heterozygous mutations in *COL10A1* (MIM#120110), encoding the  $\alpha 1(X)$  chains of type X collagen, which is a homotrimeric molecule that consists of three identical  $\alpha 1(X)$  chains. Each  $\alpha 1(X)$  chain contains a core triple helical domain, composed of uninterrupted

repeats of the Gly-Xaa-Yaa tripeptide, flanked by two globular domains (NC2 and NC1) at both the amino and carboxyl-terminal ends (2). To date, 48 *COL10A1* mutations have been reported in families with SMCD of different ethnic origin (Human Gene Mutation Database; <http://www.hgmd.cf.ac.uk/ac>). Most *COL10A1* mutations identified to date were located in the NC1 domain, which contains motifs that promote trimerization of  $\alpha 1(X)$  chains and subsequent formation of the triple helix to yield stable collagen X molecules. Here, we report a Japanese familial case of SMCD with a novel mutation in *COL10A1*.

### Patient Report

The proband was a three-year-old Japanese male, who was born at 40 wk of gestation after an uncomplicated pregnancy and delivery. He was the third child of nonconsanguineous parents (Fig. 1). At birth, his height was 46.4 cm (−1.2 SD), and his weight was 2.8 kg (−0.5 SD). At 11 mo of age, he started to walk. At 1 yr and 5 mo of age, he was referred to our hospital because of bowlegs. His height was 73.0 cm (−2.7 SD), body weight was 9.1 kg (−1.2 SD), arm span was 72.0 cm, and intercondylar distance, measured in standing position, was 8.0 cm. Clinical findings

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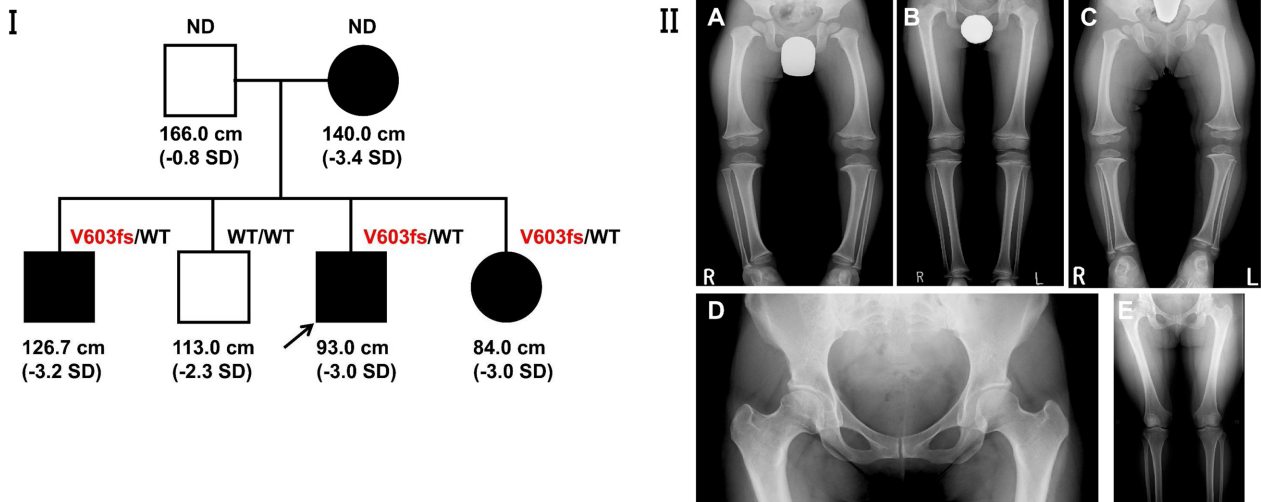
Received: December 15, 2015

Accepted: April 6, 2016

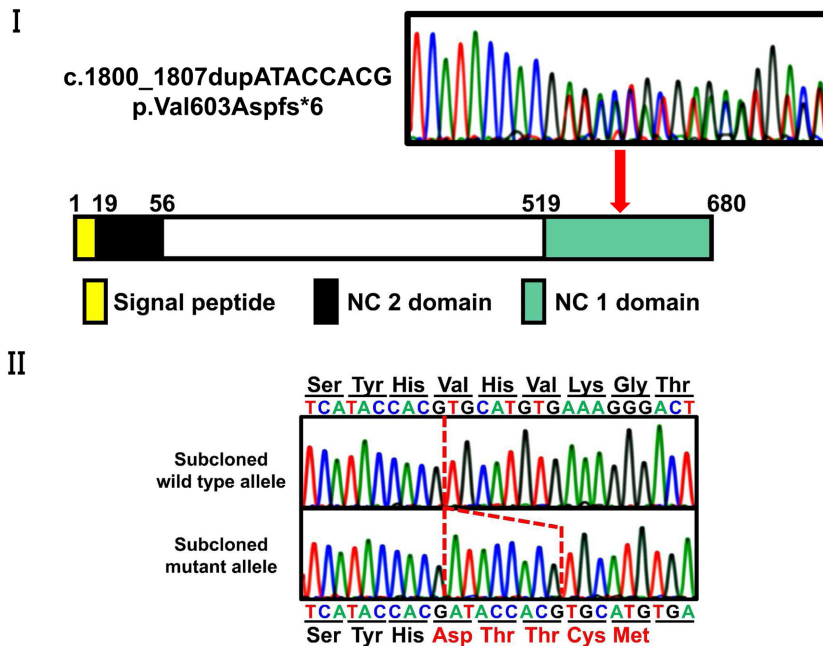
Corresponding author: Dr. Yukihiro Hasegawa, Department of Endocrinology and Metabolism, Tokyo Metropolitan Children's Medical Center, 2-8-29 Musashidai, Fuchu-shi, Tokyo 183-8561, Japan

E-mail: yhaseta@gmail.com

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**Fig. 1.** Characterization of the patient and his family. I: Pedigree of the family. II: Radiographs of the patient and his family. Radiographs of the proband at 3 yr of age (A), of the eldest brother at 11 yr of age (B), and of the younger sister at 2 yr of age (C). The three siblings showed metaphyseal irregularities in the hip and knee, coxa vara, and coxa magna. Both the proband and his younger siblings had bowlegs. Metaphyseal dysplasia was the most conspicuous in the youngest sibling. Radiograph of the mother at 30 yr of age (D, E). The mother showed coxa vara and short femoral necks. The long bones were somewhat stubby.



**Fig. 2.** Identification of a frame-shift mutation in *COL10A1*. I: Partial sequence of PCR product and schematic diagrams of the type X collagen  $\alpha 1$  chain are shown. Heterozygous 8 base pair duplication (c.1800\_1808 dupATACCACG) in the patient is indicated by arrow. II: The mutation was subsequently confirmed by sequencing of the subcloned normal and mutant alleles.

included short stature due to limb truncation and varus deformity of the knee. Coxa vara, fraying, and splaying were evident in radiographs of the lower limbs (Fig. 1). Laboratory examinations revealed no abnormality. Based on these clinical findings, we diagnosed him as having SMCD. At his last examination at the age of 4 yr and 10 mo, his height was 93.0 cm (−3.0 SD), his weight was 14.3 kg (−1.3 SD), and his arm span was 92.0cm.

The eldest brother, younger sister, and mother of the propositus also exhibited short stature that was due to limb truncation. The three siblings showed metaphyseal irregularities in the hip and knee, and coxa vara. The two younger siblings also showed bowlegs. Metaphyseal dysplasia was most conspicuous in the youngest sibling. The mother showed coxa vara and short femoral necks (Fig. 1). They did not need osteotomy.

### Mutational Analysis

After obtaining informed consent, and with the approval of the Institutional Review Board of Keio University School of Medicine, genomic DNA was extracted from the patient's peripheral blood leukocytes. We checked all four coding exons and flanking introns of *COL10A1* by PCR-direct sequencing. We identified a novel c.1800\_1807dupATACCACG frame-shift mutation located in the NC1 domain (Fig. 2), which, subsequently, was confirmed by sequencing of the subcloned normal and mutant alleles (Fig. 2). This mutation was not found in any databases, including dbSNP, the 1,000 Genomes Project, Exome Variant Server, NHLBI Exome Sequencing Project, and the Human Genetic Variation Database in Japanese. Familial analysis indicated that the elder brother and younger sister of the propositus had the same mutation. Analysis of the parental genomes was refused.

### Discussion

We described a Japanese familial case of SMCD with a novel frame-shift mutation, which resulted in a stop codon in the NC1 domain of *COL10A1*. The mRNA containing c.1800\_1807dupATACCACG appears to escape nonsense-mediated decay, possibly because this frameshift occurred in the last exon of *COL10A1*. Although the functional consequence of this mutation remains to be determined *in vitro*, we believe that this mutation is pathological because (1) the NC1 domain is the most common site of *COL10A1* mutations and (2) the transcript of the c.1800\_1807 dupATACCACG, if translated, would generate a protein lacking half of the NC1 domain (p.Val603Aspfs\*6).

From a clinical viewpoint, the radiographic changes of SMCD are similar to those caused by rickets; therefore, careful differential diagnosis of metaphyseal dysplasia in infants and small children is required. Gene analysis may be useful for differential diagnosis between SMCD and rickets in the cases with no biological abnormality.

Radiological manifestations of SMCD have been reported to resolve over time via bone remodeling (3). However, coxa vara can occasionally be detected in the radiograph of SMCD patients, even after metaphyseal closure. In the present study, we were able to diagnose the mother as having SMCD because she had limb-truncated short stature and coxa vara was evident in her radiograph.

In summary, the present study provides information about radiological findings associated with *COL10A1* mutations. Further studies are warranted to better understand the phenotypic spectrum of patients with SMCD.

### Acknowledgments

We thank the patient and his family for participating in this study. We also thank Kazue Kinoshita for technical assistance.

**Conflict of Interest:** The authors have no competing interests to declare.

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