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Mutation-in-Brief

A familial case of spondyloepiphyseal dysplasia tarda caused by a novel splice site mutation in *TRAPPC2*

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Introduction

Spondyloepiphyseal dysplasia tarda (SEDT: MIM # 313400) is a rare, X-linked recessive skeletal disease, characterized by disproportionately short stature with vertebral malformation. Clinical expression of SEDT begins with flattening of the growth curve before puberty (1). Defects in trafficking protein particle complex subunit 2 (*TRAPPC2*; MIM # 300202) are the only known causes of SEDT (2). TRAPPC2 plays an important role in transporting protein from the endoplasmic reticulum (ER) to cytoplasm. Most newly synthesized proteins leave the ER via coat protein complex II (COPII) vesicles. However, procollagen (PC) that is too large to fit into typical COPII vesicles requires larger transport carriers. It is known that TRAPPC2, acting in concert with transport and Golgi organization 1 (TANGO1), is pivotal for biogenesis of a megacarrier for large PC. This collaborative action of TANGO1 and TRAPPC2 sustains ER export of large PC, and its derangement may explain the defective chondrogenesis underlying SEDT (3).

To date, approximately 50 *TRAPPC2* mutations have been reported in families with SEDT (Human Gene Mutation Database; http://www.hgmd.cf.ac.uk/ac); however, only 9 mutations in the splice site are known. Here, we report a familial case of SEDT that harbors a novel splice site mutation, c.94-2A>G, in *TRAPPC2*.

Patient Report

The propositus (III-1) was a 13-yr-old Japanese male individual. He was the first child of nonconsanguineous healthy parents; the father was 175.0 cm (0.7 SD) tall and the mother 160.0 cm (0.4 SD). He was born at 39 wk of gestation after an uncomplicated pregnancy and delivery

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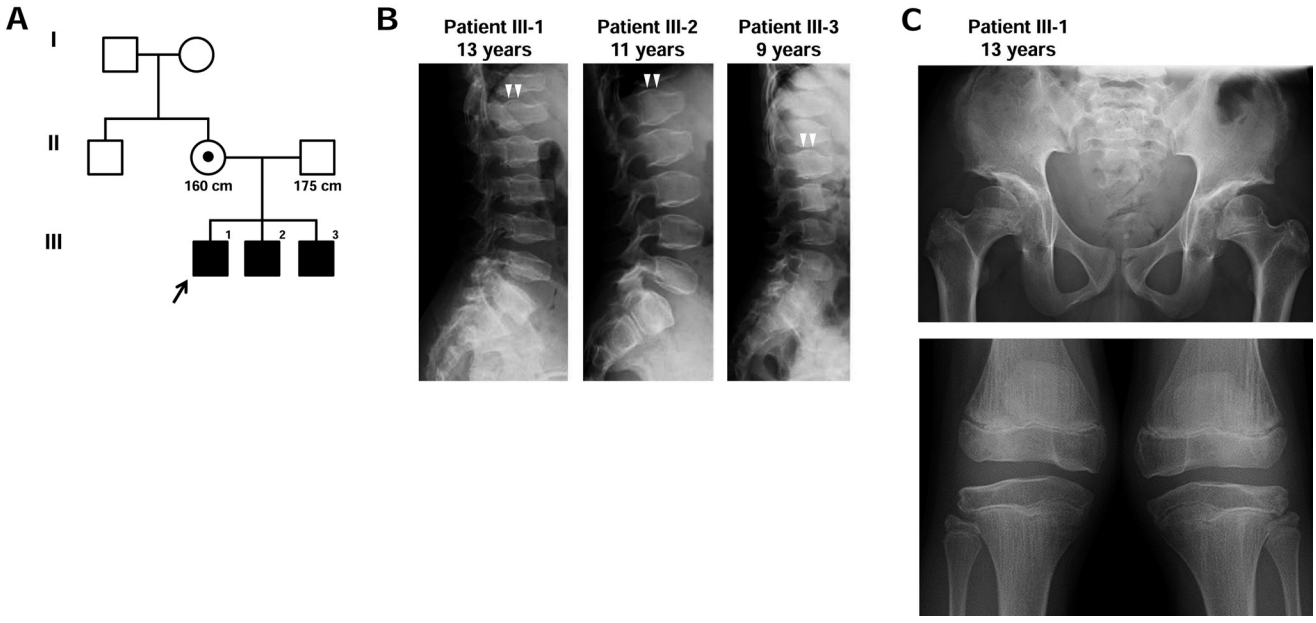

Fig. 1. Characterization of the patients. (A) Pedigree of the patients with SEDT. (B) Radiographs of the patients. Radiographs of the lateral lumbosacral spine showed platyspondyly with posterior hump of the vertebral bodies (arrowheads). (C) Radiographs of patient III-1. Radiographs of the hip and knee joints showed epiphyseal dysplasia.

(Fig. 1A). Birth length was 48 cm (−0.5 SD), and birth weight 2,448 g (−1.5 SD). He was referred to us at 8 yr of age because of stunted growth. Height was 109.8 cm (−3.1 SD), and weight 18.8 kg (−1.8 SD) (Supplementary Fig. 1: online only). The trunk was disproportionately short. Radiological examination showed platyspondyly with posterior hump of the vertebral bodies (Fig. 1B). On radiological grounds, he was diagnosed with SEDT. At his last examination at 13 yr of age, his height was 128.0 cm (−3.9 SD), weight was 26.9 kg (−2.2 SD), and arm span was 134.0 cm (Supplementary Fig. 1). He complained of moderate pain in the hip and knee joints. Radiological examination revealed mild epiphyseal dysplasia, and iliac hypoplasia with lacy iliac crests as well as typical spondylar dysplasia (Fig. 1C).

Patient III-2 was an 11-yr-old Japanese male, and was the younger brother of Patient III-1. He also showed disproportionately short stature and mild thoracolumbar scoliosis. His height was 121.7 cm (−3.4 SD) and arm span was 122 cm (Supplementary Fig. 1). On radiographs, he showed platyspondyly with posterior hump of the vertebral bodies, which is consistent with SEDT (Fig. 1B).

Patient III-3 was a 10-yr-old Japanese male, and was the youngest brother of Patient III-1. He also showed disproportionately short stature and mild thoracolumbar scoliosis. His height was 112.0 cm (−4.1 SD) and arm span was 114.5 cm (Supplementary Fig. 1). On radiographs, he showed platyspondyly with posterior hump of the vertebral bodies (Fig. 1B). He was also diagnosed with SEDT.

Mutational Analysis

We assessed all 4 coding exons (exons 3–6) and flanking introns of *TRAPPC2* with polymerase chain reaction (PCR)-direct sequencing, and identified a novel hemizygous splice site mutation, c.94-2A>G, in all 3 patients (Fig. 2). Their mother had the same mutation in a heterozygous state. This mutation was not

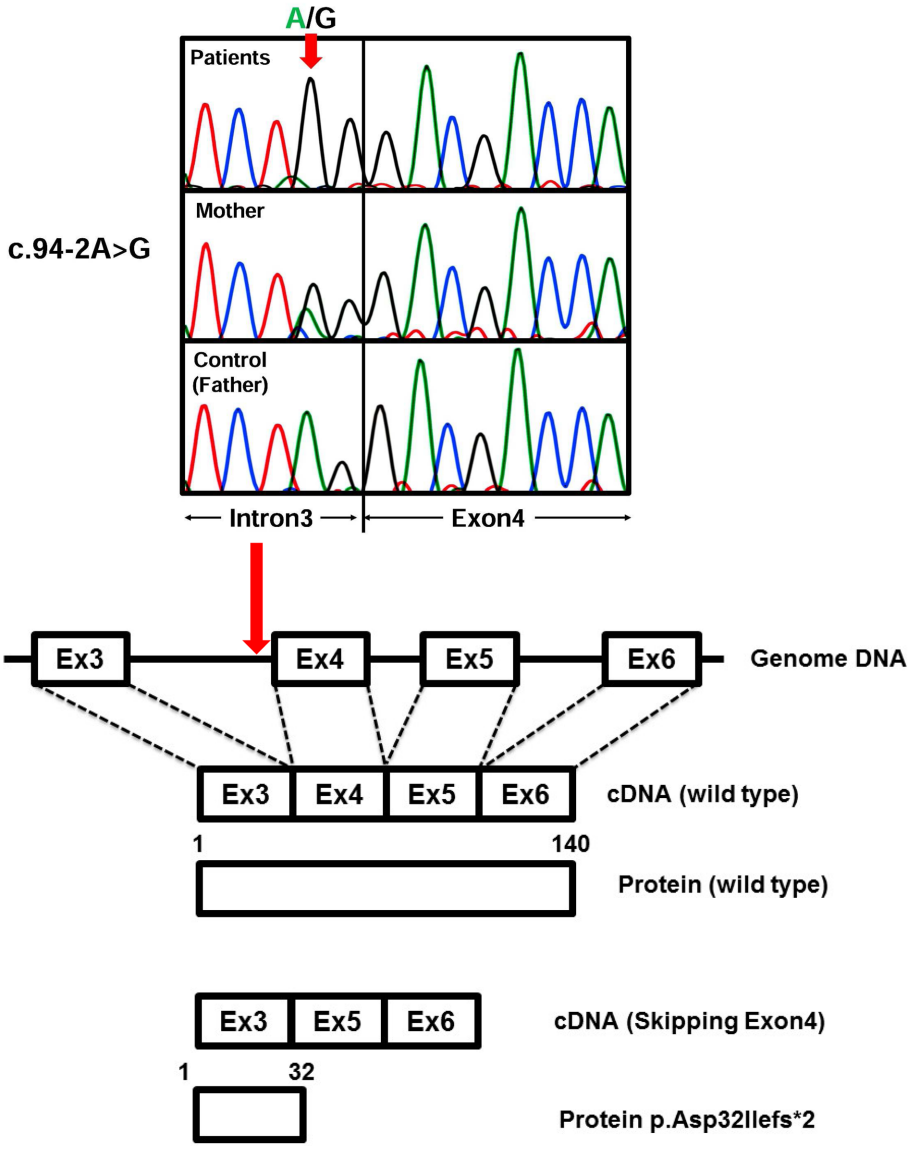

Fig. 2. Identification of a splice site mutation, c.94-2A>G, in *TRAPPC2*. Partial sequences of PCR products of the patients, the mother, and father are shown. The chromatogram represents a single nucleotide substitution, A to G, in the splice acceptor site of exon 4. The c.94-2A>G mutation is supposed to cause exon 4 skipping, which results in premature stop codon in exon 5. If translated, this abnormal transcript would generate a protein lacking about three-quarters of TRAPPC2 (p.Asp32Ilefs*2).

described in various databases, including dbSNP, the 1,000 Genomes Project, Exome Variant Server, NHLBI Exome Sequencing Project, and Human Genetic Variation Database in Japan.

Discussion

We report a family that manifested with the typical clinical and radiological features of SEDT due to a novel splice site mutation in *TRAPPC2*. Premature degenerative joint disease is the rule in affected males, who commonly require hip

joint replacement in the fourth or fifth decade of life (4). Genetic analysis can assist definitive diagnosis, which is helpful in follow-up and decision-making for surgical intervention, which may improve the physical outcome of affected individuals.

Although we have not performed RNA analysis in these patients, the c.94-2A>G splice site mutation is supposed to cause exon 4 skipping, which results in premature termination codon in exon 5 (Fig. 2). If translated, this abnormal transcript would generate a protein lacking about three-quarters of TRAPPC2 (p.Asp32Ilefs*2). Our finding will improve the understanding of the pathogenesis of *TRAPPC2* mutations in SEDT.

Conflict of Interest: The authors have nothing to declare.

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