A Case with Spondyloepiphyseal Dysplasia Tarda with TRAPPC2 Mutation

Hyun-Jin Kim1, Beom-Hee Lee1,2, Yoo-Mi Kim1, Gu-Hwan Kim2, Ok-Hwa Kim3 and Han-Wook Yoo1,2*

1Department of Pediatrics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
2Medical Genetics Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
3Department of Radiology, Ajou University Hospital, Suwon, Korea

Introduction

Spondyloepiphyseal dysplasia tarda (SEDT; OMIM 313400) is an X-linked skeletal dysplasia that primarily affects the vertebral bodies and epiphyses. Spondyloepiphyseal dysplasia has been divided into a congenital and a tarda form according to the age of onset and clinical severity.1 The different modes of inheritance within the group reflect the genetic heterogeneity. Autosomal dominant, autosomal recessive, and X-linked recessive patterns of inheritance have been described.2,3

X-linked SEDT is caused by mutations in the Trafficking protein particle complex, subunit 2 (TRAPPC2) gene. This gene contains six exons, spanning about 20kb of genomic DNA in Xp22.4 This disorder is usually identified in late childhood males with disproportionate short stature with short trunk and barrel-shaped chest. Heterozygous female carriers are usually clinically and radiographically normal.5 Radiologic evaluations can reveal narrow disc spaces and moderate epiphyseal dysplasia of long bones. Here we report a case of SEDT with a novel frameshift mutation in TRAPPC2, the disease-causing gene of SEDT. This is the first Korean report with SEDT confirmed by genetic testing.

Key Words: X-linked skeletal dysplasia, TRAPPC2 gene, Spondyloepiphyseal dysplasia tarda
Case Report

A 15-year-old boy visited our hospital due to disproportionate short stature. His birth weight and height was within normal range without perinatal problems. His developmental milestones were normal. His height was 147.6 cm (-2.66 SDS). His father’s height was 178 cm (0.81 SDS), whereas his mother was proportionately short at 146 cm (-3.12 SDS). His two sisters were 158 cm (-0.55 SDS) and 160 cm (-0.15 SDS) tall (Fig. 1A). His face was not dysmorphic and intelligence was normal. Normal ambulatory activities were possible without help. Trunk was relatively short and chest cage was barrel-shaped. Range of motion was not limited in all of the axial and peripheral joints. Pain, tenderness or swelling was not noticed. The shapes of his hands and feet were normal.

Skeletal survey revealed mild flattening of the epiphyses of long bones in knee and hip, but the metaphyses and diaphyses were normal. In addition, platyspondyly, reduced intervertebral spaces, bell shaped thorax, and scoliosis were observed. Femoral head was flattened and femoral neck was short and broad. The phalangeal bones of both hands and feet were normal (Fig. 2). With the impression of SED, genetic testing was done for \( \text{COL2A1} \), which was normal. Next, we searched \( \text{TRAPPC2} \) gene, in which a frameshift mutation was found, c.40del (p.Asp14Ilefs*24). This mutation was not previously reported. His mother was heterozygous carrier for the mutation, whereas his two sisters didn’t harbor the mutation.

**Fig. 1.** A) Pedigree of a SEDT family. Black box represents an affected male proband. B) Chromatograms of partial DNA sequence of \( \text{TRAPPC2} \). The patient harbors c.40del (p.Asp14Ilefs*24), and his mother was a heterozygote carrier for the frame shift mutation. The deletion site was indicated with arrows.

**Fig. 2.** A) Anteroposterior X-ray of the pelvis shows short and broad femoral neck and flattened femoral heads. Mild flattening of the epiphyses of long bones was also seen. B-D) There is no definite abnormality in the metaphyses of long bones and phalanges of hands and feet. E-F) Intervertebral disc spaces were decreased and scoliosis and platyspondyly were noted.
procedures may provide symptomatic relief. Some patients may suffer from the chronic joint pain and stiffness that can help make a diagnosis of SEDT. Investigations (normal acute phase reactants such as C-reactive protein, erythrocyte sedimentation rate and rheumatoid factor), family histories, typical radiologic finding, normal laboratory and structural deformities of the long bones, hands, and feet. Manifestations. Juvenile idiopathic arthritis (JIA) due to the similarity of clinical and structural deformities of the long bones, hands, and feet. Most SEDT patients are expected to have normal life, although the joint deformities are progressive and degenerative or restrictive changes can lead to severe joint impairments. Short stature is common in this condition and ongoing psychosocial support of the patient and the family is important with appropriate genetic counseling.

Acknowledgement

We thank our patient and his family members for their participation in this study. This study was supported by Grant A080588 from the Korean Ministry of Health, Welfare and Family Affairs.

References