Autosomal Recessive Multiple Epiphyseal Dysplasia in a Korean Girl Caused by Novel Compound Heterozygous Mutations in the DTDST (SLC26A2) Gene

Tae-Joon Cho1, Ok-Hwa Kim2, Hye-Ran Lee1, Sung Jin Shin1, Won Joon Yoo1, Woong Yang Park3, Sung Sup Park4, Sung Im Cho4, and In Ho Choi1

Department of Orthopaedic Surgery1, Seoul National University Children’s Hospital, Seoul; Department of Radiology2, Ajou University Hospital, Suwon; Department of Biochemistry and Molecular Medicine3, Seoul National University College of Medicine, Seoul; Department of Laboratory Medicine4, Seoul National University Children’s Hospital, Seoul, Korea

Received: 10 February 2009
Accepted: 24 April 2009

Address for Correspondence:
Tae-Joon Cho, M.D.
Department of Orthopaedic Surgery, Seoul National University Children’s Hospital, 101 Daehang-ro Jongno-gu, Seoul 110-744, Korea
Tel: +82.2-2072-2878, Fax: +82.2-745-3367
E-mail: tjcho@snu.ac.kr

This study was supported by a grant of the Korea Healthcare technology R&D Project, Ministry for Health, Welfare and Family Affairs, Republic of Korea (A080588).

CASE REPORT

INTRODUCTION

Multiple epiphyseal dysplasia is a heterogenous group of diseases, clinically characterized by a mild-to-moderate short stature, angular deformities of the extremities, short hands and feet, and precocious osteoarthritis. The severity of the disease varies case to case even in those with the same genotype, and the most severe cases are sometimes difficult to differentiate from pseudoachondroplasia (PSACH). Mutations in genes coding cartilage oligomeric matrix protein (COMP), type IX collagen alpha 1, 2, and 3 chains (COL9A1, COL9A2, COL9A3), and matrilin 3 (MATN3) cause the dominantly inherited forms of MED, while homozygous or compound heterozygous mutations in diastrophic dysplasia sulfate transporter (DTDST or SLC26A2) gene cause recessively inherited MED (rMED, EDM4 OMIM 226900) (1, 2). However, additional MED loci have been suggested, as many MED patients do not show any mutations in the above genes (1, 2). Superti-Furga et al. (3) first reported that a homozygous p.R279W mutation in the DTDST gene developed a phenotype resembling MED, rather than diastrophic dysplasia (DTD). Subsequently, more homozygous or compound heterozygous mutations in the DTDST gene were reported in rMED patients (4, 5). However, no rMED case caused by DTDST gene mutations has been reported in the Asian population (2). Only an intermediate phenotype of Desbuquois dysplasia, diastrophic dysplasia and rMED with compound heterozygotic mutation in DTDST gene was reported in a Japanese patient (6). In the present study, we identified novel compound heterozygous mutations in a Korean girl with the rMED phenotype.

CASE REPORT

A girl was born to non-consanguineous, healthy Korean parents after a normal pregnancy with a birth weight of 3.06 kg. Any family history of musculoskeletal system was denied. Her motor development was within normal limit. At age 9 yr, she visited our clinic due to an apparent foot deformity, which was first noticed at age 3 yr. She did not have any limitation in daily activity or joint

Key Words: Osteochondrodysplasias; Diastrophic Dysplasia Sulfate Transporter
pain, but was poor at sports. Her height was 131 cm (42th percentile) and her weight 37.9 kg (80th percentile). Her face, palate, and external ears were normal. Fingers and thumbs were short but in normal alignment. Both knees and ankles were in valgus alignment. Her forefeet were adducted, which was more severe on the right side (Fig. 1A-C). A radiographic examination showed small, dysplastic epiphyses at hips, knees, ankles, and wrists. Metacarpals and phalanges were short and had flat epiphyses, and premature physeal closure at the proximal and middle phalanges of both hands had resulted in brachydactyly. A lateral view of the knees revealed double layered patellae. Forefoot adduction deformity had been caused by deformed medial cuneiform bones and twisted metatarsals (Fig.1D-G). The spine was normal in appearance and alignment. Detailed clinical and radiographic surveys were performed to the parents of proband. Her father’s height was 174 cm and her mother’s 160 cm. They did not show any deformity on physical examination.

Genetic and biochemical study for this family was approved by the Institutional Review Board of Seoul National University Hospital. Direct sequencing analysis of PCR amplified DNA from the proband genomic DNA demonstrated no mutation in COMP, COL9A1, COL9A2, COL9A3, and MATN3. However, she had a compound heterozygous mutations in the DTDST gene, i.e., a c.485_486delTG, p.Val162GlyfsX12 mutation and a c.1153G>A, p.D385N mutation in exon 3, neither of which has been previously reported to be associated with any disease. Her mother’s genomic DNA had a heterozygous c.485_486delTG mutation while her father’s contained a heterozygous c.1153G>A (Fig. 2). None of 171 normal subjects (342 normal chromosomes) were shown to contain c.1153G>A variation. Interspecies amino acid

Fig. 1. The proband aged 9 yr. Mild genu valgum, forefoot adduction, and hindfoot valgus were noted (A-C). Radiographs showed genu valgum with flattening of epiphyses at the hips, knees, and ankles (D); double layered patella (E); shortening of the metacarpals and phalanges, premature physeal closure at the middle phalanges, cone-shaped epiphyses of the proximal phalanges (F); twisted, oblique arrays of the metatarsals, triangular medial cuneiforms (G).

Fig. 2. Sequencing results of the DTDST gene showed compound heterozygous mutations of c.485_486delTG and c.1153G>A in the proband. The c.485_486delTG mutation was inherited maternally, and the c.1153G>A point mutation paternally.

Fig. 3. Conservation of p.D385 in DTDST protein among different species.
with rMED, i.e., double layered patellae, flattened proximal femoral epiphyses, brachydactyly, feet deformity, and genu valgum. Full sequencing of the DTDST gene in the proband and both parents revealed two previously unreported mutations that had been inherited by the proband from both parents.

Hastbacka et al. (8) identified a gene for diastrophic dysplasia by linkage disequilibrium mapping. As encoded a novel sulfate transporter, it was named as DTDST, and later as SLC26A2. Undersulfation of proteoglycan, which was an important component of cartilage matrix, was found in DTD patient (9). Fortiino et al. (10) showed impaired sulfate uptake in chondrocytes, osteoblasts and fibroblasts, significant proteoglycan undersulfation in cartilage, and reduced proliferation and/or lack of terminal chondrocyte differentiation in homozygous SLC26A2-mutant knock-in mice.

Recessive mutations in the DTDST gene cause a spectrum of osteochondrodysplasias, including achondrogenesis type IB, atelosteogenesis type II, and DTD. rMED has been reported to be caused by homozygous or compound heterozygous mutations of the DTDST gene, containing either R–279W or C635S (3-5). Mikaye et al. (6) reported a case with an intermediate phenotype between rMED and DTD caused by a compound heterozygote of novel p.T266I and a recurrent p.∆V340 mutation. As pointed by these authors the expression “clubfoot”, as generally used to describe foot deformity in DTD, is a misnomer. A more specific description of foot deformity is required in patients with DTDST-associated diseases.

**REFERENCES**

1. Jakkula E, Makitie O, Czarny-Ratajczak M, Jackson GC, Damignani R, Susic M, Briggs MD, Cole WG, Ala-Kokko L. Mutations in the known genes are not the major cause of MED; distinctive phenotypic entities among patients with no identified mutations. Eur J Hum Genet 2005; 13: 292-301.
2. Itoh T, Shirahama S, Nakashima E, Maeda K, Haga N, Kitoh H, Kosaki R, Ohashi H, Nishimura G, Ikegawa S. Comprehensive screening of multiple epiphyseal dysplasias mutations in Japanese population. Am J Med Genet A 2006; 140: 1280-4.
3. Superti-Furga A, Neumann L, Riebel T, Eich G, Steinmann B, Spranger J, Kunze J. Recessively inherited multiple epiphyseal dysplasia with normal stature, clubfoot, and double layered patella caused by a DTDST mutation. J Med Genet 1999; 36: 621-4.
4. Makitie O, Savarirayan R, Bonafe L, Robertson S, Susic M, Superti-Furga A, Cole WG. Autosomal recessive multiple epiphyseal dysplasia with homozygosity for C635S in the DTDST gene; double-layered patella as a reliable sign. Am J Med Genet A 2003; 122: 187-92.
5. Ballhausen D, Bonafe L, Terhal P, Unger SL, Bellus G, Classen M, Hamel BC, Spranger J, Zabel B, Cohn DH, Cole WG, Hecht JT, Superti-Furga A. Recessive multiple epiphyseal dysplasia (rMED); phenotype delineation in eighteen homozygotes for DTDST mutation R279W. J Med Genet 2003; 40: 65-71.
6. Miyake A, Nishimura G, Futami T, Ohashi H, Chiba K, Toyama Y, Furuchi T, Ikegawa S. A compound heterozygote of novel and recurrent DTDST mutations results in a novel intermediate phenotype of Desbuquois dysplasia, diastrophic dysplasia, and recessive form of multiple epiphyseal dysplasia. J Hum Genet. 2008; 53: 764-8.
7. Imauchi Y, Lombes M, Laine P, Sterkers O, Ferrery E, Grayeli AB. Glucocorticoids inhibit diastrophic dysplasia sulfate transporter activity in otosclerosis by interleukin-6. Laryngoscope 2006; 116: 1647-50.
8. Hastbacka J, de la Chapelle A, Mahtani MM, Clines G, Reeve-Daly MP,

---

**Fig. 4.** Proband dermal fibroblast sulfate uptake was about 65-75% that of the normal control.
Daly M, Hamilton BA, Kusumi K, Trivedi B, Weaver A, Coloma A, Lovett M, Buckler A, Kaitila I, Lander ES. The diastrophic dysplasia gene encodes a novel sulfate transporter: positional cloning by fine-structure linkage disequilibrium mapping. Cell 1994; 78: 1073-87.

9. Rossi A, Bonaventure J, Delezoide AL, Cetta G, Superti-Furga A. Undersulfation of proteoglycans synthesized by chondrocytes from a patient with achondrogenesis type II homozygous for an L483P substitution in the diastrophic dysplasia sulfate transporter. J Biol Chem 1996; 271: 18456-64.

10. Forlino A, Piazza R, Tiveron C, Della Torre S, Tatangelo L, Bonafe L, Guallen B, Romano A, Pecora F, Superti-Furga A, Cetta G, Rossi A. A diastrophic dysplasia sulfate transporter (SLC26A2) mutant mouse: morphological and biochemical characterization of the resulting chondrodysplasia phenotype. Hum Molec Genet 2005; 14: 859-71.

11. Hastbacka J, Superti-Furga A, Wilcox WR, Rimoin DL, Cohn DH, Lander ES. Atelosteogenesis type II is caused by mutations in the diastrophic dysplasia sulfate transporter gene (DTDST): evidence for a phenotypic series involving three chondrodysplasias. Am J Hum Genet 1996; 58: 255-62.

12. Peterson HA. Skewfoot (forefoot adduction with heel valgus). J Pediatr Orthop 1986; 6: 24-30.

13. Ryoppy S, Poussa M, Merikanto J, Marttinen E, Kaitila I. Foot deformities in diastrophic dysplasia. An analysis of 102 patients. J Bone Joint Surg Br 1992; 74: 441-4.