A Case of Campomelic Dysplasia without Sex Reversal

Hyoung-Young Kim1, Chong Hyun Yoon2, Gu-Woo Kim3, Han-Wook Yoo3, Byong Sop Lee4, Ki Soo Kim1, and Ellen Ai-Rhan Kim1

Department of Pediatrics, Division of Neonatology, 2Department of Radiology, and 3Department of Medical Genetics Clinic and Laboratory, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Received: 19 July 2010
Accepted: 27 September 2010

Address for Correspondence:
Ellen Ai-Rhan Kim, MD
Department of Pediatrics, Division of Neonatology, University of Ulsan College of Medicine, Asan Medical Center, 86 Asanbyeongwon-gil, Songpa-gu, Seoul 138-736, Korea
Tel: +82-2-3010-3382, Fax: +82-2-3010-6978
E-mail: arkim@amc.seoul.kr

DOI: 10.3346/jkms.2011.26.1.143

A Case of Campomelic Dysplasia without Sex Reversal

INTRODUCTION

Campomelic dysplasia (CD; OMIM #114290), a rare form of congenital short-limbed dwarfism, is due to mutations in SOX9, a member of the SOX (SRY-related HMG box) gene family. Multiparous mother at 38 weeks' gestation delivered a 3,272 g baby boy with characteristic phenotypes including bowing of the lower limbs, a narrow thoracic cage, 11 pairs of ribs, hypoplastic scapulae, macrocephaly, flattened supraorbital ridges and nasal bridge, cleft palate, and micrognathia. He underwent a tracheostomy at the age of three months for severe laryngomalacia after a number of repeated hospitalizations due to respiratory problems and died at the age of four months from progressive respiratory failure. He was diagnosed as having CD based on a novel frameshift mutation (p.Gln458ArgfsX12) in the SOX9 gene, the mutation which has not yet been reported in Korea.

Key Words: Campomelic Dysplasia; SOX9 Gene

CASE DESCRIPTION

A baby boy was born to a gravida 2 mother with a vertex presen-
male external genitalia.

To screen for a mutation, we obtained informed consent from the parents for blood sampling. We isolated genomic DNA from peripheral blood using a QuickGene DNA kit (Fujifilm Life Science, Tokyo, Japan). To analyze the SOX9 gene’s mutation, we performed PCR using eight sets of primers designed in the intronic flanking region and containing three exons referred to by GenBank accession number NT_010641.15. We performed DNA sequencing using the same primers used in PCR and a BigDye Terminatore V3.1 Cycle Sequencing kit (Applied Biosystems, Foster City, CA, USA). Direct automated sequencing identified a novel frameshift mutation at nucleotide 1372 in exon 3 (Fig. 2). The patient carried both mutant and normal alleles, indicating that the mutation was heterozygous. Both parents declined genetic analysis.

After his discharge from NICU, the patient was hospitalized four times for treatments of pneumonia. He underwent a tracheostomy at the age of three months for severe laryngomalacia and died at the age of four months from progressive respiratory failure.

**DISCUSSION**

Characteristic features of CD are skeletal hypoplasias and anomalies affecting the face, head, scapulae, spine, pelvis, and upper and lower limbs. The head is macrocephalic with flattened face and nasal bridge, high forehead, low-set ears often with associated deafness, hypertelorism, long philtrum, small mouth, and micrognathia (6-9). The skeletal features are the most prominent characteristics of CD as presented in our case including anterior bowing of the tibia and characteristic pretibial skin dimples. The femurs are also mildly angulated, and talipes equinovarus and dislocation of the hips are usually present. Short fibulae, kyphoscoliosis, brachydactyly and clinodactyly are common. In addition, usually present are flat vertebrae (particularly at the cervical level), hypoplastic scapulae, and a small bell-shaped chest that’s often slender with 11 pairs of ribs and a poorly mineralized sternum (7-9). After the critical first year, quality of life tends to improve, although most survived patients are known to be mentally retarded. The oldest reported survivor was a 17-yr-old who had an IQ of 45 (7, 9).

Most cases of CD are caused by heterozygous de novo muta-
tions of the SOX9 gene at chromosome 17q 24.3-q25.1 (5, 10). A growing number of reports describes CD with the chromosome 17 rearrangement breakpoint located some distance from SOX9 (1, 10-12). SOX9 contains a 79-amino acid DNA-binding motif known as the high-mobility-group (HMG) domain, which recognizes typical SOX binding sequences and a second domain essential for its function, a proline/glutamine-serine-rich C-terminal transcription-activation domain (1, 13, 14). SOX9 is a transcription factor that plays a role in the expression of COL2A1, a major collagen gene, and anti-Müllerian hormone, which is secreted from the Sertoli cells for male sex differentiation (15, 16). The mutations cause a loss of either DNA binding or SOX9's transactivation function.

CD is a good model to illustrate how a single transcription factor can control the development of several organs. Both the skeletal dysplasia and the XY sex reversal in CD are caused by mutations in SOX9. All reported mutations in SOX9 can cause CD, and approximately 75% are associated with XY sex reversal; whereas no mutation in SOX9 has been associated with isolated sex reversal (17). The type and location of mutations in SOX9 have demonstrated no correlation with phenotype. Bernard et al. (18) demonstrated that cooperative dimerization of SOX9 was essential for activation of key chondrogenesis genes, but not for male gonadal development, which might explain why CD is not necessarily associated with XY sex reversal as shown in our case.

Four major classes of heterozygous SOX9 mutations cause CD: 1) amino acid substitutions in the HMG domain, 2) truncations or frameshifts that alter the C-terminus, 3) mutations at the splice junction, and 4) chromosomal translocations. All reported missense mutations lie in the HMG domain and affect DNA binding, frameshifts, and splice mutations that truncate SOX9's C-terminus, resulting in the loss of transactivation domains (17, 18). In the present case we identified, a novel frameshift mutation in codon 458 at nucleotide 1372. This mutation altered the transcription activation domain in the C-terminus, leading to a loss of SOX9's function.

To date, two cases of CD have been reported in Korea (19, 20). The first had multiple congenital anomalies (polydactyly, complex heart disease, bilaterally trilobed lungs, and a brain anomaly) and died immediately after delivery. The other was a case in which CD was identified in utero at 30 weeks of gestation whose pregnancy ended in abortion. Neither patient underwent a genetic analysis. Herein we report a novel de novo frameshift mutation (p.Gln458ArgfsX12) in the SOX9 gene of a Korean male with CD.

REFERENCES

1. Wagner T, Wirth J, Meyer J, Zabel B, Held M, Zimmer J, Pasantes J, Bricarelli FD, Keutel J, Hustert E, Wolf U, Tommerup N, Schep unp W, Scherer G. Autosomal sex reversal and campomelic dysplasia are caused by mutations in and around the SRY-related gene SOX9. Cell 1994; 79: 1111-20.
2. Kovic C, Weller PA, Guioli S, Foster JW, Mansour S, Zaffardi O, Punnett HH, Dominguez-Steglich MA, Brook JD, Young ID, Goodfellow PN, Schafer AI. Mutations in SOX9, the gene responsible for Campomelic dysplasia and autosomal sex reversal. Am J Hum Genet 1995; 57: 1028-36.
3. Stoll C, Dott B, Roth MP, Alembk Y. Birth prevalence rates of skeletal dysplasias. Clin Genet 1989; 35: 88-92.
4. Maroteaux P, Spranger J, Opitz JM, Kucera J, Lowry RB, Schimke RN, Kagan SM. The campomelic syndrome. Presse Med 1971; 79: 1157-62.
5. Mansour S, Hall CM, Pembrey ME, Young ID. A clinical and genetic study of campomelic dysplasia. J Med Genet 1995; 32: 415-20.
6. Horton WA, Hecht JT. The skeletal dysplasia. In: Behrman RE, Kliegman RM, Jenson HB, eds. Textbook of Pediatrics. 16th ed. Philadelphia: WB Saunders Co 2000; 2113-32.
7. Argaman Z, Hammerman CA, Kaplan M, Schimmel M, Rabinovich R, Tnnessen WW Jr. Picture of the month. Campomelic dysplasia. Am J Dis Child 1993; 147: 205-6.
8. Hall BD, Spranger JW. Campomelic dysplasia. Further elucidation of a distinct entity. Am J Dis Child 1980; 134: 285-9.
9. Jones KL. Smith's Recognizable Patterns of Human Malformation. 5th ed. Philadelphia: WB Saunders Co 1997; 344-5.
10. Foster JW, Dominguez-Steglich MA, Guioli S, Kovic C, Weller PA, Stevanovic M, Weissenbach J, Mansour S, Young ID, Goodfellow PN, Brook JD, Schafer AI. Campomelic dysplasia and autosomal sex reversal caused by mutations in an SRY-related gene. Nature 1994; 372: 525-30.
11. Offiah AC, Mansour S, McDowall S, Tolmie J, Sim P, Hall CM. Surviving campomelic dysplasia has the radiological features of the previously reported ischio-pubic-patella syndrome. J Med Genet 2002; 39: e50.
12. Hill-Harfe KL, Kaplan L, Stalker HJ, Zori RT, Pop R, Scherer G, Wallace MR. Fine mapping of chromosome 17 translocation breakpoints > or = 900 Kb upstream of SOX9 in acampomelic campomelic dysplasia and a mild, familial skeletal dysplasia. Am J Hum Genet 2005; 76: 663-71.
13. Bianchi ME, Beltramme M. Flexing DNA: HMG-box proteins and their partners. Am J Hum Genet 1998; 63: 1573-7.
14. McDowall S, Argentaro A, Ranganathan S, Weller P, Mertin S, Mansour S, Tolmie J, Harley V. Functional and structural studies of wild type SOX9 and mutations causing campomelic dysplasia. J Biol Chem 1999; 274: 24023-30.
15. Bell DM, Leung KK, Wheatley SC, Ng Lj, Zhou S, Ling KW, Sham MH, Koopman P, Tam PP, Cheah KS. SOX9 directly regulates the type-II collagen gene. Nat Genet 1997; 16: 174-8.
16. De Santa Barbara P, Bonneaud N, Desclouzeaux M, Monirot B, Sudbeck P, Scherer G, Poulat F, Berta P. Direct interaction of SRY-related protein SOX9 and steroidogenic factor 1 regulates transcription of the human anti-Müllerian hormone gene. Mol Cell Biol 1998; 18: 6653-65.
17. Cameron FJ, Sinclair AH. Mutations in SRY and SOX9: testis-determining genes. Hum Mutat 1997; 9: 388-95.
18. Bernard P, Tang P, Liu S, Dewing P, Harley VR, Vilain E. Dimerization of SOX9 is required for chondrogenesis, but not for sex determination. Hum Mol Genet 2003; 12: 1755-65.
19. Chung CQ, Bae HY, Kim DR, Park YH, Chung HS. A case of multiple congenital anomaly. Korean J Obstet Gynecol 1992; 35: 1407-13.
20. Kim SK, Kim HC, Shin SJ, Lee MW, Lee YM, Cho IH, Choi YJ, Kwon KW. A case of fetal skeletal anomaly of Campomelic syndrome. Korean J Obstet Gynecol 2000; 43: 311-4.