Case report

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A Leri-Weill dyschondrosteosis patient confirmed by mutation analysis of *SHOX* gene

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Leri-Weill dyschondrosteosis is characterized by *SHOX* deficiency, Madelung deformity, and mesomelic short stature. In addition, *SHOX* deficiency is associated with idiopathic short stature, Turner syndrome, and Langer mesomelic dysplasia. We report the first case of a Leri-Weill dyschondrosteosis patient confirmed by *SHOX* gene mutation analysis in Korea. The patient, who was a 7-year-old female, showed short stature. Her height and weight were 108.9 cm (<3rd percentile) and 19.7 kg (5th–10th percentile), respectively. Her arm span, height of trunk, leg length, and sitting length were 100.5 cm, 58 cm, 50.9 cm, and 62.5 cm, respectively. Her body proportion was 1.13:1. Extremities to trunk ratio was 2.61. Her hand radiograph showed Madelung deformity. And the growth hormone stimulation test showed a normal response. Furthermore, because of Madelung deformity with idiopathic short stature, she was suspected of *SHOX* deficiency. We performed *SHOX* gene mutation analysis and found a c.491G>A (p.W164X) mutation of the *SHOX* gene. Accordingly, this patient was diagnosed with Leri-Weill dyschondrosteosis. Recently, many mutations have been reported in the *SHOX* gene. However, to date, mutation analysis of the *SHOX* gene for Leri-Weill dyschondrosteosis has not been reported in Korea as yet. We report the first case of a Leri-Weill dyschondrosteosis patient confirmed by mutation analysis of the *SHOX* gene.

Keywords: Leri-Weill dyschondrosteosis, Madelung deformity, Idiopathic short stature

Introduction

Short stature is a common cause for referral to pediatric endocrinologists and other physicians related to children's health[1)]. The cause of short stature is thought to be multifactorial, with a strong genetic component. One of the common causes of short stature is a defect of the short stature homeobox containing (*SHOX*) gene, which is located in the pseudoautosomal region 1, on the distal end of the short arm of the Xp22.33 and Yp11.32 chromosomes[2,3)]. The *SHOX* gene encodes a transcription factor expressed in the developing limb and pharyngeal arch in the human embryo[4)] and plays an essential role in chondrocyte function in the growth plate as a regulator of cellular proliferation and differentiation[5,6)]. *SHOX* deficiency is associated with Leri-Weill dyschondrosteosis (LWD)[2,7)], idiopathic short stature[2,3,6)], Turner syndrome[4,8)], and Langer mesomelic dysplasia[9,10)]. More than 380 different *SHOX* gene mutations have been identified, distributed throughout the coding regions of the gene[3,11)]. To date, however, no case of *SHOX* gene mutation has been reported in Korea through genetic analysis. Therefore, we report the first case of a LWD patient confirmed by mutation analysis of the *SHOX* gene.

Case report

A 7-year-old female was visited for short stature on October 24th, 2014. She was born at

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term weighing 3,250 g by uncomplicated spontaneous vaginal delivery. Motor and language development showed normal development. In physical examination, her height was 106.1 cm (<3rd percentile) and weight was 17.5 kg (5th–10th percentile). Furthermore, body mass index (BMI) was 15.55 kg/m^2 (25th–50th percentile). She showed mesomelic disproportion of limbs. Her father's and mother's height was 165 cm and 154 cm respectively. Her father showed similar features but did not take a special examination for diagnosis. Laboratory findings were as follows: hemoglobin, 12.6 g/dL; white blood cell count, 9,350/μL; platelet, 301,000/μL; aspartate transaminase, 33 IU/L; alanine transaminase, 17 IU/L; T3, 175.9 ng/dL; free T4, 1.54 ng/dL; thyroid-stimulating hormone, 1.23 μIU/mL; insulin-like growth factor (IGF)-1, 95.36 ng/mL; and IGF-BP3, 1,902.41 ng/mL. Therefore, laboratory findings showed normal results. Her hand radiograph showed Madelung deformity. Bone age determined by the Greulich-Pyle method was 5 years 9 months at the chronological age of 7 years 2 months (Fig. 1). Except for mesomelic short stature and Madelung deformity, she did not show other physical abnormalities.

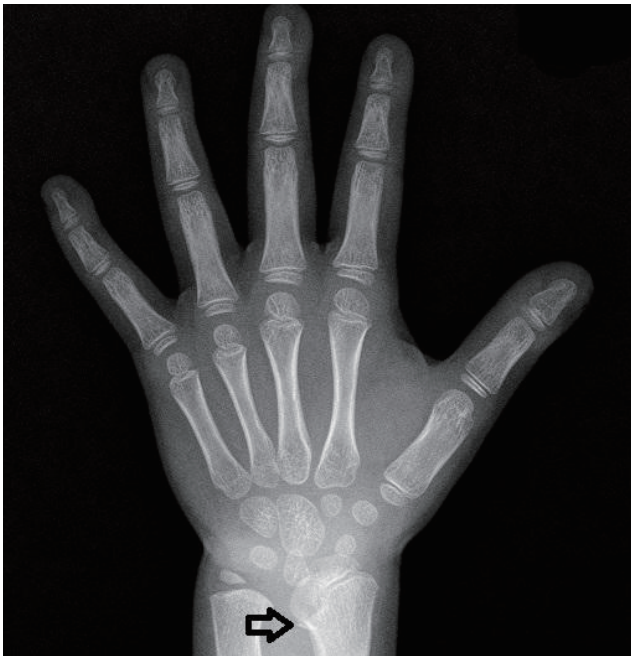

Fig. 1. Left hand radiograph. Bone age determined by the Greulich-Pyle method was 5 years 9 months (chonological age was 7 years 2 months). Madelung deformity is shown: triangularization of the distal radial epiphysis, and lucent ulnar side of distal radius (arrow).

Chromosome analysis revealed the normal female karyotype 46,XX. To determine the cause of short stature, the patient was admitted on April 28th, 2015. Her height and weight were 108.9 cm (<3rd percentile) and 19.7 kg (5th–10th percentile), respectively. Over the six-month monitoring period, her growth velocity was 5.6 cm/yr. BMI was 16.6 kg/m^2 (50th–75th percentile). Arm span, height of trunk, leg length, sitting height, and upper segment/lower segment ratio were 100.5 cm, 58 cm, 50.9 cm, 62.5 cm, and 1.13 (normal, 1.2), respectively.

Extremities to trunk ratio was 2.42 (normal, 2.49). For evaluation of growth hormone secretion function, a growth hormone stimulation test was done and showed a normal response.

Therefore, growth hormone secretion was normal. Because the patient showed mesomelic short stature, normal female karyotype, Madelung deformity, and low extremities to trunk ratio, she was suspected of having *SHOX* deficiency. Accordingly, we performed mutation analysis of the SHOX gene and found a c.491G>A (p.W164X) mutation (Fig. 2). Finally, the patient was diagnosed with LWD due to a *SHOX* gene mutation.

Discussion

SHOX deficiency leads to short stature with variable phenotype that is frequently nonspecific in preschool children because the main characteristics of mesomelic disproportion of the limbs and Madelung deformity of the forearm develop over time and appear during the second decade of life, if at all[5,11-13]. In addition, females are more severely affected than males, and this is explained by the presence of higher estrogen levels in females. The skeletal defects tend to worsen with puberty[3,14]. *SHOX* deficiency is associated with LWD[2,15,16], idiopathic

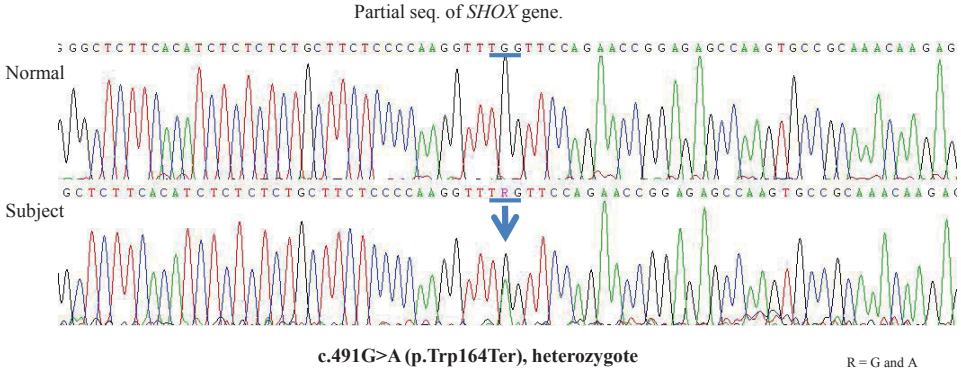

Fig. 2. Partial genomic DNA sequencing of the *SHOX* gene of the patient: heterogygous mutation of c.491G>A (p.W164X) in the *SHOX* gene.

short stature[2,3,6,11], Turner syndrome[4,8], and Langer mesomelic dysplasia[9,10]. Heterozygous mutations of *SHOX* cause LWD characterized by wrist deformity and mesomelic short stature, as well as idiopathic short stature without apparent skeletal malformations[2,10,15].

Prevalence of *SHOX* deficiency accounts for approximately 80% and 2%–16% of genetic causes of LWD and idiopathic short stature, respectively[3,5-7,11]. Also, Turner syndrome is associated with the loss of one *SHOX* gene because of the numerical or structural aberration of the X chromosome associated with this syndrome[3,8]. The loss of both SHOX alleles causes the complete lack of *SHOX* and an extreme phenotype of osteodysplasia called Langer mesomelic dysplasia[9,15,17]. Prevalence of this syndrome is relatively rare in comparison to what could be expected from the typical effects of *SHOX* haploinsufficiency in short children[3].

The characteristic skeletal deformity of *SHOX* deficiency is the Madelung deformity. This deformity is a cluster of anatomical changes in the forearm including bowing and shortening of the radius, prominence of the ulnar head, and palmar and ulnar deviation ("pyramidal configuration") of the carpal bones[7].

Also, *SHOX* deficiency is accompanied by short stature, mesomelic shortening of the limbs, decreased extremities to trunk ratio, increased sitting height, and radiological signs such as lucency in the ulnar border of the distal radius[3,7,11,12]. In addition, *SHOX* deficiency shows features of Turner syndrome. These include shortening of the fourth and fifth metacarpals, high arched palate, increased carrying angle of the elbow, scoliosis, and micrognathia[7,11]. Muscular hypertrophy of the calves is found in one third of *SHOX* deficiency cases[7,11].

Many mutations of *SHOX* deficiency have been reported, and most mutations are of the missense variety. Although more than 380 different *SHOX* gene mutations have been identified[3,11], mutations of the *SHOX* gene have not been reported in Korea, to date, through genetic analysis. To this point, only a single case of LWD by clinical description has been reported in Korea[3,11]. We report the first case of a LWD patient confirmed by mutation analysis of the *SHOX* gene. In idiopathic short stature, the same mutation like this patient was reported by Rappold et al.[11].

In *SHOX* deficiency, recombinant human growth hormone (rhGH) therapy has been approved by the U.S. Food and Drug Administration and supported by data from several randomized controlled trials. Treatment with rhGH is effective in growth promotion in children with *SHOX* deficiency, and the growth-promoting effect of rhGH therapy depends on age at treatment initiation[3,18,19]. However, rhGH therapy for *SHOX* deficiency is excluded from rhGH treatment indications criteria of the Korean National Health Insurance. Thus, *SHOX* deficiency patients do not receive medical insurance benefits in Korea.

Until now, cases of the *SHOX* gene mutation have not been reported in Korea through genetic analysis. Therefore, our case report should serve as a valuable finding of *SHOX* deficiency via genetic analysis. Additionally, our report should encourage researchers to analyze other genetic mutations related to *SHOX* deficiency, and can provide hope to advocate for rhGH treatment of *SHOX* deficiency patients.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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