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Original Article

Different Skeletal Phenotypes in a Mother and Two Daughters with Short Stature Homeobox-Containing Haploinsufficiency

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Abstract. Haploinsufficiency of the short stature homeobox-containing (SHOX) gene causes Turner skeletal features such as short metacarpals, cubitus valgus, and Madelung deformity. We report the clinical findings of a Japanese family consisting of two daughters with SHOX haploinsufficiency (46, X, del(X) (p.22.3)) and their mother with 45,X [9]/ 46, X, del(X) (p22.3) [11] karyotype. Physical and auxological examinations revealed a mesomelic appearance, cubitus valgus, a short neck and short stature in the daughters, but on the other hand, only a short neck and short stature in the mother. Radiological studies indicated markedly curved radii in the daughters, but only mild curvature of the radii in the mother. Regular menstruation had taken place since the age of 12 yr in the elder daughter, but the mother had irregular menstruation and she had received fertility treatment for pregnancy. The different skeletal phenotypes of the mother and her daughters with SHOX haploinsufficiency might be due to the mild gonadal estrogen deficiency found in the mother, which was caused by mosaic Turner syndrome, and the phenotypic variability of SHOX haploinsufficiency.

Key words: SHOX, Madelung deformity, haploinsufficiency, Turner syndrome, mother and daughter

Introduction

Short stature homeobox-containing gene (SHOX) was cloned from the short arm pseudoautosomal region of the X and Y chromosome, and has been implicated in the short stature of Turner syndrome (1). Haploinsufficiency of SHOX has been reported in some individuals with idiopathic short stature (1) and in many patients with Leri-Weill dyschondrosteosis (LWD) (2, 3). LWD is characterized by mesomelic short stature and Madelung deformity of the wrists. While inter- and intra-familial phenotypic heterogeneity is a frequent finding, phenotypic manifestations are generally more severe in females (4). We report the clinical findings of a Japanese family consisting of two daughters with SHOX haploinsufficiency (46, X, del(X) (p22.3)) and their mother with mosaic 45 X and 46, X, del(X) (p22.3), and different skeletal phenotypes in the mother and the daughters.

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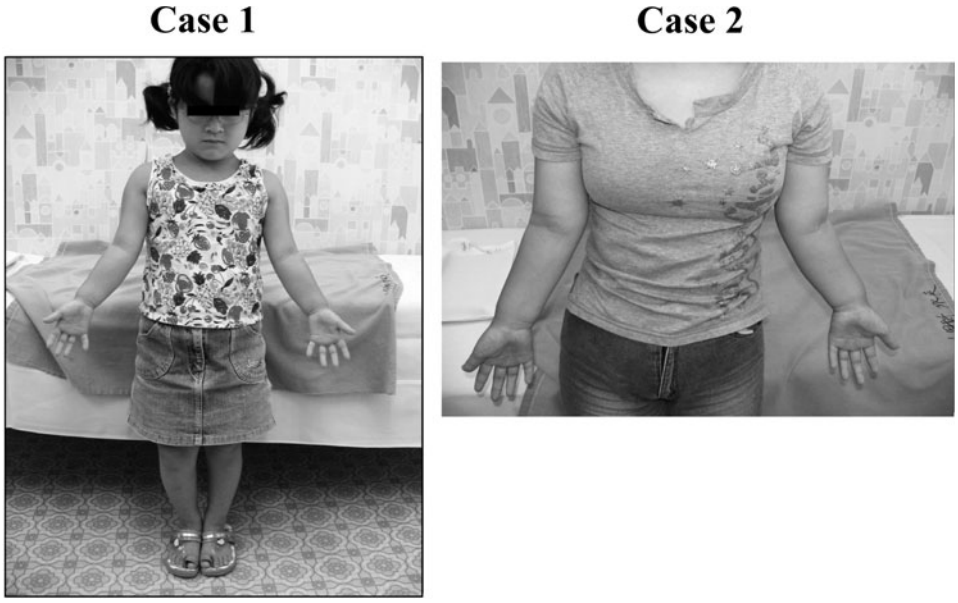


Fig. 1 Case 1 (proband, left) at the age of 7 yr and Case 2 (elder sister, right) at the age of 14 yr show mesomelic short stature and cubitus valgus.

Case report

Case 1

The proband was referred to us because of short stature at the age of 7 yr. She was born at 39 wk of gestation in a cephalic delivery with a birth weight of 2,282 g (–2.4 SD) and birth length 45 cm (–1.6 SD). Her psychomotor development was normal. She had been the shortest in her grade since kindergarten.

Her height was 109.3 cm (–2.5 SD) and she weighed 22.0 kg (–0.4 SD). The percent of relative body weight was +27.5%. Her arm span was 99 cm, indicating relatively short arms. The upper-to-lower segment ratio was 1.53 (+6.0 SD). She had no sexual development, and had a strabismus, short neck, cubitus valgus, broad thorax and limitaion of elbow extension. Her mesomelic short stature and Turner skeletal phenotypes are shown in Fig. 1; the growth chart of the patients is shown in Fig. 2. Her endocrinological findings were within normal range (Table 1) and chromosomal analysis of peripheral lymphocytes using G-banding revealed 46,X,del(X)(p22.3). SHOX is detected in a single copy by fluorescence in situ hybridization (FISH) analysis (Fig. 3). Haploinsufficiency of SHOX is postulated to have caused her mesomelic short stature.

Case 2 (elder sister of proband)

Case 2 was referred to our department because of familial investigations at 13 yr of age. She was born at 39 wk of gestation in a cephalic delivery with a birth weight of 2500 g (–1.3 SD) and birth length 45 cm (–1.6 SD). Her psychomotor development was normal. At the age of 8 yr she underwent an operation for strabismus. Puberty progressed normally and menarche occurred at the age of 12 yr. Thereafter, menstruation was regular. Her short stature has never been pointed out to her.

Her height was 144.3 cm (–1.8 SD) and she weighed 51 kg (+0.6 SD) at her first visit. The percent of relative body weight was +26.6%. Her arm span was 124 cm, indicating extremely short

Table 1 Endocrinological findings

	Case 1 (7 yr)	Case 2 (13 yr)	Case 3 (43 yr)	
IGF-1 (ng/ml)	150	467	n.d.	
TSH (μU/ml)	2.09	1.79	10.59	(0.6–4.1)
FT_4 (ng/dl)	1.1	1.1	1.1	(0.9–1.6)
TPOAb (U/ml)	n.d.	n.d.	3.2	(<0.3)
TgAb (U/ml)	n.d.	n.d.	22.6	(<0.3)
LH (mIU/ml)	<0.6	2.7	13.8	
FSH (mIU/ml)	2.2	2.7	51.9	
E_2 (pg/ml)	13	98	11	

TPOAb, thyroid peroxidase antibody. n.d., no data.

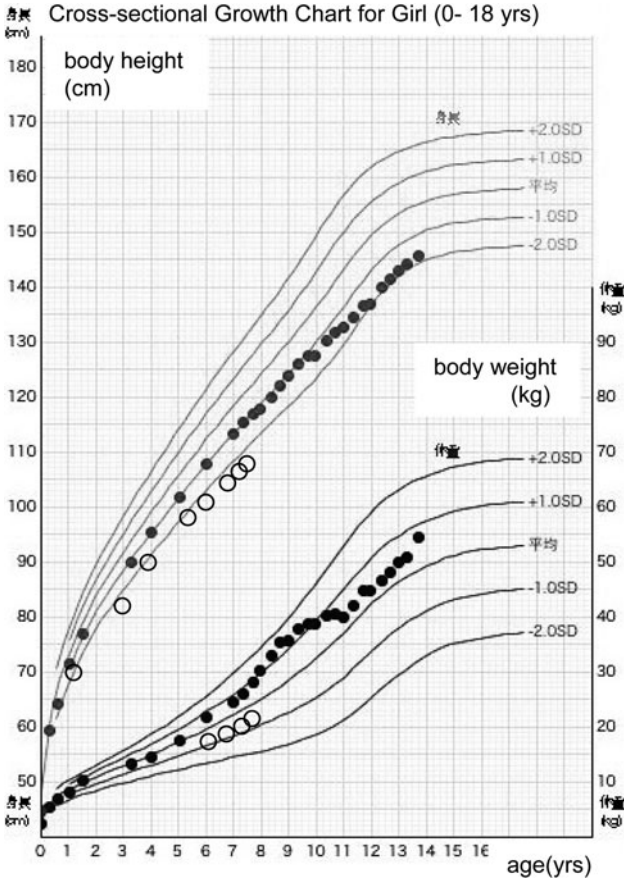


Fig. 2 Growth chart. The open and closed circles indicate the height and weight of Case 1 and 2, respectively.

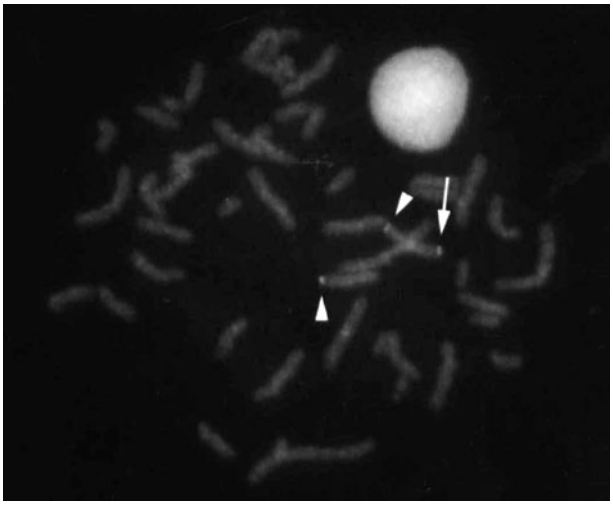
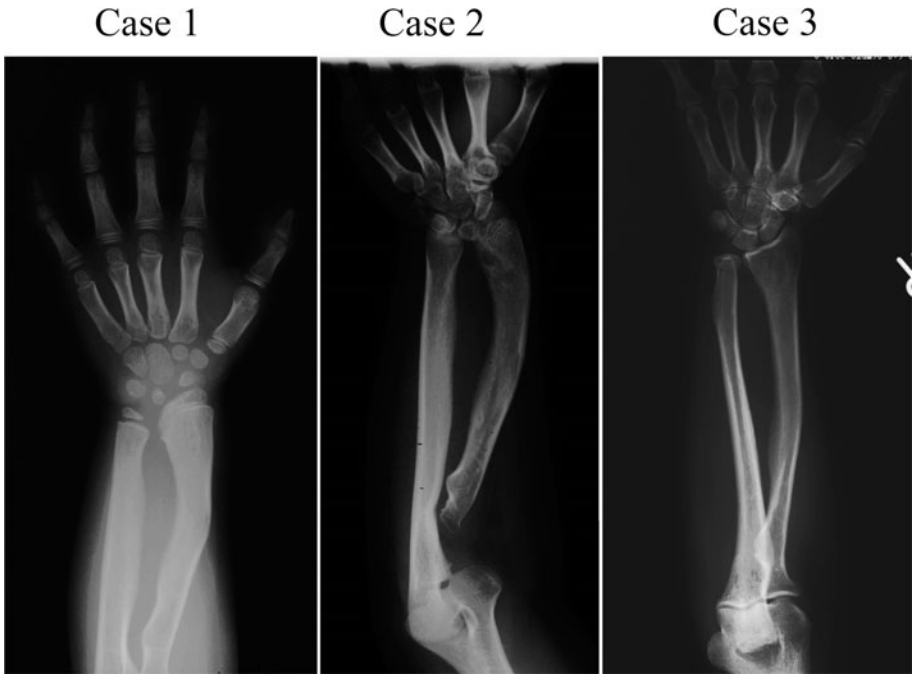


Fig. 3 SHOX deletion detected by fluorescence *in situ* hybridization analysis SHOX is detected in a single copy (arrow), wheres the Xq/Yq telomeric region is presented in two copies (arrowhead).

arms. The upper-to-lower segment ratio was 1.38 (+3.5 SD). Her breasts were Tanner stage 5 and pubic hair was Tanner stage 4. She had a short neck, cubitus valgus, Barnet sign and limitation of elbow extension. Her mesomelic short stature and Turner skeletal phenotypes are shown in Fig. 1; the growth chart of the patients is shown in Fig. 2. Her endocrinological findings were within normal range (Table 1). Chromosomal analysis



	Case 1	Case 2	Case 3
age (yr)	7	14	43
age at menarche	prepuberty	12 years old, regular	14 years old, irregular
height-arm span (cm)	10	20	5
shortening of 4th metacarpal bone	–	–	–
Carpal angle (°)	126	92	108
Madelung deformity	++	+++	+

Fig. 4 Radiographs of the hand and forearms in case 1 at the age of 7 yr (left), case 2 at the age of 14 yr (middle), and case 3 at the age of 43 yr (right).

of peripheral lymphocytes using G-banding revealed 46,X,del(X)(p22.3). She also demonstrated SHOX haplosufficiency in FISH analysis.

Case 3 (mother of the proband)

Case 3 was examined at 43 yr of age. Her height was 147 cm (–2.2 SD) and she weighed 48 kg (–0.7 SD). Her arm span was 142 cm. The upper-to-lower segment ratio was 1.35 (+2.3 SD). Her menarche occurred at the age of 14 and, thereafter, menstruation was irregular. She received fertility treatment for pregnancy. Her menstruations were few and her last period had occurred 1 yr ago. She had a short neck and broad chest, however she did not show cubitus valgus or mesomelic features. Her endocrinological findings are shown in Table 1. Her serum TSH level was slightly elevated with normal free thyroxine, and antithyroid antibodies were positive. A high serum FSH level with a low estradiol level indicated ovarian failure and early menopause. Chromosomal analysis of peripheral lymphocytes revealed 45,X [9] / 46, X, del(X) (p22.3) [11], indicating mosaic Turner syndrome. FISH analysis also revealed SHOX

haploinsufficiency of both karyotypes.

Radiological findings

The radiographs of the left arm of the 3 cases are displayed in Fig. 4. Case 1 revealed radial bowing and shortening despite before puberty. Case 2 showed severe radial bowing and shortening, decreased carpal angle, angulation of the distal radius and dorsal subdislocation of the distal ulnar. Case 3 showed mild radial bowing and decreased carpal angle and had the least pronounced features of the 3 cases.

Discussion

We describe different skeletal phenotypes of a mother and two daughters with SHOX haploinsufficiency. In some cases, women with Xp deletions are fertile, and the deleted chromosome can be transmitted to offspring. In the literature, families in which the mother showed the mosaic karyotype 45,X / 46,X del(X)(p21.1 or 21.2) and transmitted the deleted X chromosome to daughters have been reported (5, 6), whereas reports of the families with the mosaic del(X)(p22.3) are not found.

Clinical studies of patients with SHOX haploinsufficiency reveal not only short stature but also Turner skeletal features such as short metacarpals, cubitus valgus, and Madelung deformity characteristic of LWD (7). The Madelung wrist deformity likely originates with disorganized growth of part of the radial epiphysis, leading to radial bowing, premature fusion of the epiphysis, dorsal dislocation of the ulna, and wedged carpal bones (8). Variation of the manifestation of Madelung deformity has been observed even within the same LWD family (4), however the skeletal features tend to be more severe in females than in males and become more obvious after puberty (7). It has been suggested that gonadal estrogen exerts a maturational effect on skeletal tissue that is susceptible to unbalanced premature fusion of the growth plates because of SHOX haploinsufficiency, facilitating the development of skeletal lesions in a female-dominant and age-influenced fashion (7).

On the other hand, Turner syndrome reveals SHOX haploinsufficiency due to structural alteration of one X chromosome, but rarely presents with Madelung deformity (9). To explain this finding, it has been proposed that an estrogen deficiency in Turner syndrome might prevent premature and irregular closure of the epiphyseal cleft which is thought to be a main pathological factor in the manifestation of LWD (7).

In the present case, it is possible that the mother's mild skeletal features resulted from impairment of gonadal estrogen production and delayed pubertal tempo, because of mosaic Turner syndrome. Moreover, phenotypic heterogeneity and intrafamilial variability are frequently found in haploinsufficiency syndromes including LWD (10). Dosage effects often have a highly variable phenotype, at least in human populations, and a variety of genetic and non-genetic factors may be responsible for this phenomenon. The proband showed unbalanced premature fusion of the distal radius despite before puberty. These findings suggest the existence of other factors besides estrogen contributing to premature fusion. Ross *et al.* reported radial lucencies, which appear to be an antecedent of Madelung deformity, were found in some of their prepubertal female and male LWD patients (11). They supposed that girls with Turner syndrome could be protected from developing Madelung deformity by their gonadal estrogen deficiency, and by the modifying effects of loss of nonpseudoautosomal growth genes (11).

In conclusion, the different skeletal phenotypes of the mother and her daughters with SHOX haploinsufficiency might be due to the mild gonadal estrogen deficiency found in the mother, which was caused by mosaic Turner syndrome, and the phenotypic variability of SHOX haploinsufficiency.

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