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Research Letter

Molecular cytogenetic characterization and prenatal diagnosis of familial Xp22.33 microdeletion encompassing short stature homeobox gene in a male fetus with a favorable outcome

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Dear Editor,

A 34-year-old, gravida 1, para 0, woman underwent amniocentesis at 18 weeks of gestation because of advanced maternal age. She had a body height of 150 cm. Her husband was 38 years old and had a body height of 170 cm. The woman had a family history of short stature. Her elder sister had a body height of 148 cm, and her parents had a body height of 145 cm. However, her brother had a body height of 165 cm. Amniocentesis revealed a karyotype of 46,XY. Array comparative genomic hybridization (aCGH) analysis of amniotic fluid revealed a result of arr Xp22.33 (581,803–795,716) × 0–1 mat with a 213.9-kb Xp22.33 microdeletion encompassing only one Online Mendelian Inheritance in Man (OMIM) gene of short stature homeobox (*SHOX*). Multiplex ligation-dependent probe amplification-P018 (SALSA MLPA Probemix P018 SHOX; MRC-Holland, Amsterdam, The Netherlands) analysis of the DNA extracted from the amniotic fluid and parental blood confirmed maternal transmission of the heterozygous *SHOX* deletion. The father did not have any *SHOX* deletion. The mother had a karyotype of 46,XX. An aCGH analysis of the DNA extracted from the maternal blood using CytoChip ISCA Array (Illumina, San Diego, CA, USA) revealed a result of arr Xp22.33 (553,160–1,232,886) × 1.3 with a 679.7-kb Xp22.33 microdeletion encompassing four genes including the OMIM gene of *SHOX* (Figure 1). The father had a karyotype of 46,XY. An aCGH analysis of the DNA extracted from the paternal blood revealed a result of arr (1–22) × 2, X × 1, Y × 1. The prenatal ultrasound findings were unremarkable. The parents elected to continue the pregnancy, and a normal male baby was delivered at 39 weeks of gestation with a body weight of 3126 g (>97th centile), body length of 49.5 cm (25–50th centile), head circumference of 32.5 cm (5–15th centile), and chest circumference of 31 cm. The cord blood had a karyotype of 46,XY. An aCGH analysis of the cord blood revealed a result of arr Xp22.33 (581,741–1,232,886) × 0.7 with a 651.1-kb Xp22.33 microdeletion encompassing four genes including the OMIM gene of *SHOX* (Figure 2). Metaphase fluorescence *in situ* hybridization analysis of 20 cultured lymphocytes obtained from the cord blood using the bacterial artificial chromosome probes RP11-808D8 (877,516–1,060,527) specific for Xpter (Xp22.33) crossing over with Ypter (Yp11.2) and RP11-943J20 (Xq11.1; 63,613,179–63,792,988) showed an Xp22.33 deletion, but no Yp11.2 deletion, in all 20 cells (Figure 3). Metaphase fluorescence *in situ* hybridization analysis of 20 cultured lymphocytes obtained from the maternal peripheral blood using

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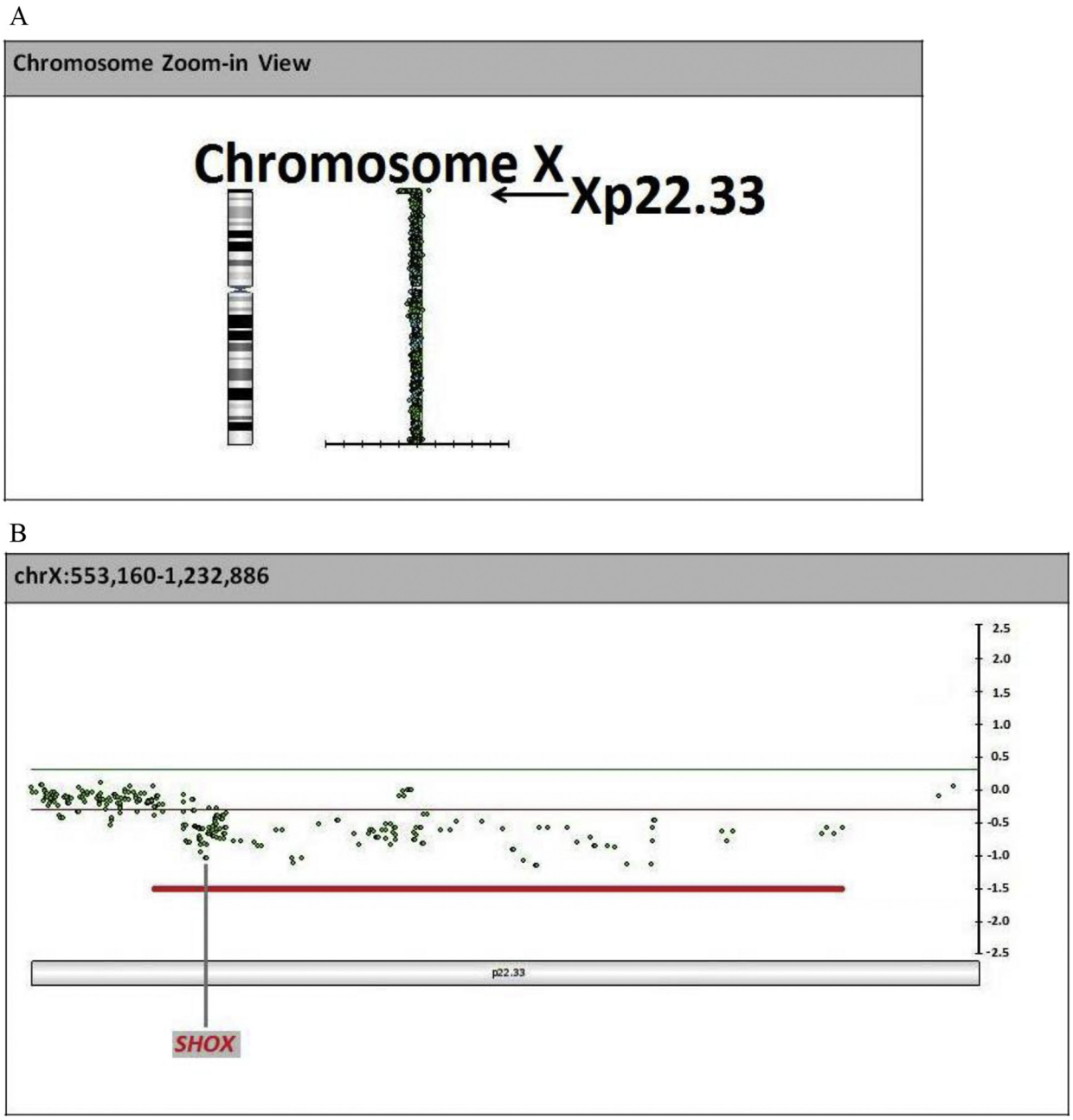

Figure 1. Array comparative genomic hybridization analysis of the DNA extracted from maternal peripheral blood shows a 679.7-kb Xp22.33 microdeletion (553,160–1,232,886) encompassing *SHOX*. (A) Chromosome zoom-in view and (B) chromosome X. SHOX = short stature homeobox.

the bacterial artificial chromosome probes RP11-808D8 and RP11-943J20 showed a heterozygous Xp22.33 deletion in all 20 cells (Figure 4).

SHOX (OMIM 312865) (Xp22.33) encodes SHOX protein and is a pseudoautosomal homeobox-containing osteogenic gene. *SHOX* deficiency disorders include idiopathic familial short stature (OMIM 300582); Leri–Weill dyschondrosteosis (LWD) (OMIM 127300), which is inherited in a pseudoautosomal dominant pattern and has the classic clinical triad of short stature, mesomelia (the middle portion of a limb is shortened in relation to the proximal portion), and Madelung deformity (abnormal alignment of the radius, ulna, and carpal bones at the wrist); and Langer mesomelic dysplasia (OMIM 249700), which is inherited in a pseudoautosomal recessive pattern resulted from *SHOX* nullizygosity due to biallelic *shox* deficiency and has severe short stature and severe skeletal dysplasia [1]. In case of LWD, short stature is noted in early childhood, mesomelia is evident in school-aged children, and Madelung deformity typically develops in mid-to-late childhood [1].

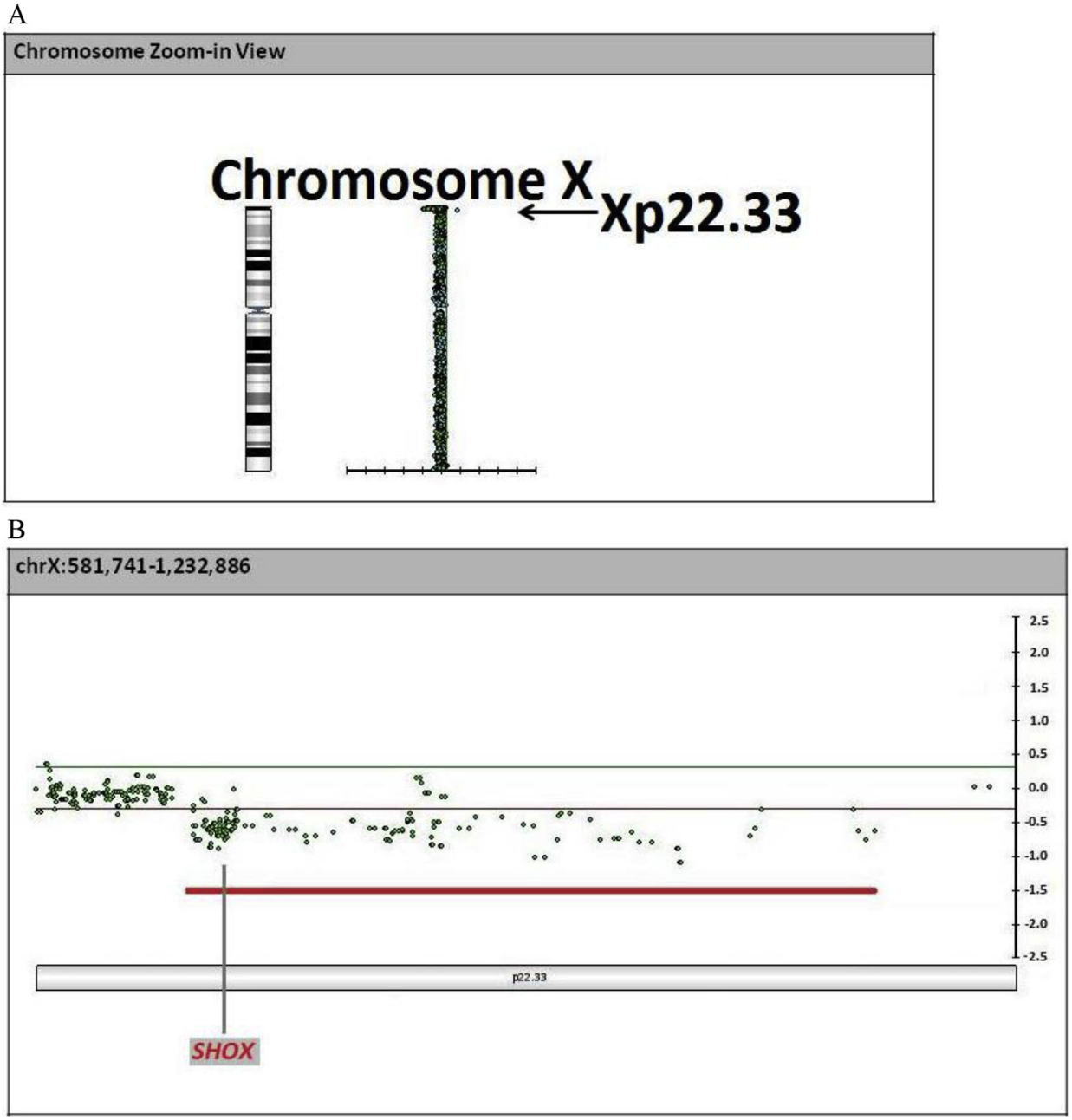

Figure 2. The aCGH analysis of the DNA extracted from cord blood shows a 651.1-kb Xp22.33 microdeletion (581,741–1,232,886) encompassing *SHOX*. (A) Chromosome zoom-in view and (B) chromosome X. aCGH = array comparative genomic hybridization; SHOX = short stature homeobox.

Differential diagnosis of isolated short stature and LWD caused by *SHOX* deficiency includes Turner syndrome in females, idiopathic short stature in both sexes, LWD caused by pathogenic variants other than *SHOX* deficiency, and trauma, infection, or tumors in the distal radial growth plate [1].

The peculiar aspect of the present case is the incidental detection of familial transmission of Xp22.33 microdeletion encompassing *SHOX* during prenatal genetic diagnosis because of advanced maternal age. The present case provides evidence that prenatal diagnosis of Xp22.33 microdeletion encompassing *SHOX* can be associated with a favorable outcome. Recombinant human growth hormone therapy is effective in the treatment of patients with *SHOX* deficiency [1–18]. Prenatal diagnosis of familial *SHOX* deficiency provides the affected fetus an opportunity for early recognition of the disorder as well as early medical treatment in childhood.

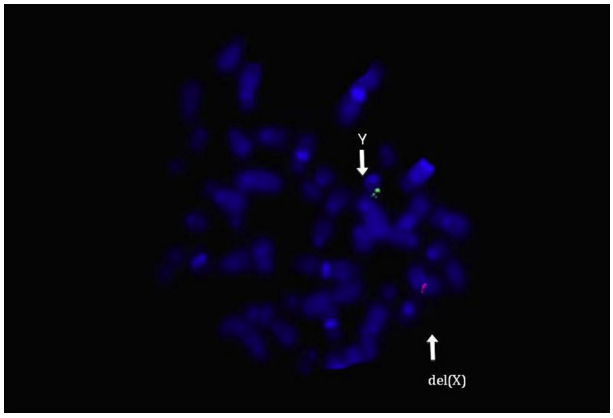

Figure 3. Metaphase fluorescence *in situ* hybridization on the cord blood lymphocytes using the Xp22.33- and Yp11.2-specific probe of RP11-808D8 (Xp22.33 and Yp11.2; 877,516–1,060,527; fluorescein isothiocyanate, spectrum green) and the Xq11.1-specific probe of RP11-943J20 (Xq11.1; 63,613,179–63,792,988; Texas Red, spectrum red) shows one green signal in the Y chromosome and only one red signal in the del(X) chromosome with Xp deletion. del = deletion.

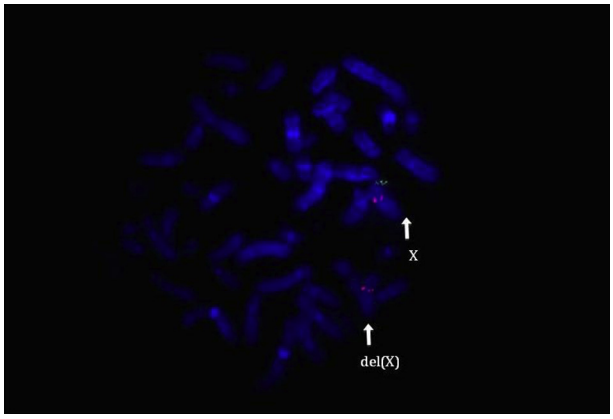

Figure 4. Metaphase FISH on the maternal peripheral blood lymphocytes using the Xp22.33- and Yp11.2-specific probe of RP11-808D8 (Xp22.33 and Yp11.2; 877,516–1,060,527; FITC, spectrum green) and the Xq11.1-specific probe of RP11-943J20 (Xq11.1; 63,613,179–63,792,988; Texas Red, spectrum red) shows one green signal and one red signal in the X chromosome and only one red signal in the del(X) chromosome with Xp deletion. del = deletion; FISH = fluorescence *in situ* hybridization; FITC = fluorescein isothiocyanate.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

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