Novel Insights from Clinical Practice

HORMONE RESEARCH IN PÆDIATRICS

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Trisomy of the Short Stature Homeobox-Containing Gene (SHOX) due to Duplication/Deletion of the X Chomosome: Clinical Implications on the Stature

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Established Facts

- Stature is a complex trait related to growth-modulating genes.
- SHOX is a homeobox gene located in the short arm of the pseudoautosomal region 1 (PAR1) of the sex chromosomes (Xp22.3 and Yp11.3) and its dosage effect (haploinsufficiency-overdosage) on the stature has been frequently evaluated.
- The enhancing effect of SHOX gene triplication in combination with estrogen deficiency has been proposed as a factor leading to tall stature.

Novel Insights

- In 2 of our patients, SHOX gene triplication resulted from an abnormal X chromosome with Xp duplication and partial Xq deletion.
- Patient 1 is a teenager girl with tall stature and behavioral abnormalities who entered puberty spontaneously. In this case, SHOX gene triplication is associated with tall stature and even preserved gonadal function.
- Patient 2 is a girl with mild Turner syndrome (TS) phenotype, gonadal dysgenesis and normal stature at 6.8 years but with a steady deterioration (SDS –2.94 at 16.5 years). Despite the extra copy of SHOX associated with gonadal dysgenesis, growth retardation was finally present.
- In light of these cases, we suggest that SHOX overdosage per se, without estrogen deficiency, may in some cases induce excessive height, and the combination of an extra copy of the SHOX gene with estrogen deficiency might not always be necessarily followed by tall stature.

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Key Words
Genetic overdosage · Gonadal dysgenesis · Haploinsufficiency, SHOX gene · Psychiatric disturbances · SHOX gene · Tall stature · Turner phenotype · Xp duplication

Abstract
Background: The karyotypes of 2 patients with abnormal stature and different phenotypes revealed one similar structural abnormality in the X chromosome by conventional cytogenetic studies and fluorescence in situ hybridization analysis (FISH). FISH strongly suggested the presence of two copies of the SHOX gene in the der(X) chromosome. ***Patients and Results:*** Patient 1 is a teenager girl with tall stature, behavioral disturbances and normal pubertal development. The abnormal X chromosome was present in all cells studied. Parent's karyotypes were normal. Patient 2 is a girl with gonadal dysgenesis, mild Turner syndrome phenotype and short stature. The karyotype was a mosaic 45,X/46,X,r(X) and der(X) chromosome presented in most metaphases of the cell lines. Parent's karyotypes were normal. Nearly all duplication of Xp and partial deletion of the long arm (Xq) from Xq27 or Xq21 to Xqter, in cases 1 and 2, respectively, were observed. In both patients, duplication of Xp translocated to deleted Xq occurred leading to a triplication of the pseudoautosomal region 1 (PAR1) where the SHOX gene is located (Xp22.3). ***Conclusions:*** We propose that in some cases of trisomy for the SHOX gene, the effect of overdosage per se may affect the stature, even in patients with preserved ovarian function (case 1), and that estrogen deprivation may not always be a contributor for tall stature (case 2).

Introduction

A structurally abnormal X chromosome with Xp duplication concomitant with partial Xq deletion is a rare event. In the few cases reported to date, a very tall stature has been a frequent clinical finding [1–3].

Rao et al. [4] cloned the SHOX gene (short stature homeobox-containing gene) located on PAR1 of the sex chromosomes in Xp22.3 and Yp11.3. This gene was also identified by Ellison et al. [5] and named PHOG (pseudoautosomal homeobox-containing osteogenic gene).

The SHOX gene is most strongly expressed in bone marrow fibroblasts, implying that SHOX plays a positive role in human skeletogenesis and thus in final height determination [6, 7]. Since X inactivation is not complete for several loci in Xp22.3, SHOX is expressed on the inactive as well as the active X and Y chromosomes. For this reason, genes on PAR1 are presented in two active copies indicating a dosage effect of the SHOX gene in cases with aberrations in sex chromosomes.

Deletions on PAR1 implicating SHOX gene haploinsufficiency were first related to short stature and Léri-Weill syndrome [8]. Also, subtle distal deletion in Xpter or Ypter was subsequently demonstrated in patients with idiopathic short stature and normal gonadal function or in patients with TS [9].

On the other hand, overdosage caused by SHOX gene triplication has mainly been related to patients with tall stature, long limbs and gonadal dysgenesis [2]. It is also known that most of the patients carrying triple X syndrome and triple dosage of PAR1 have tall stature and normal gonadal function [10].

In this study, 2 girls with an abnormal X chromosome resulting in SHOX gene triplication are reported and the enhancing effect of overdosage on their heights is evaluated.

Case Reports

Case 1

This girl was referred at 14 years of age due to excessive height. She is the 2nd child of healthy and unrelated parents. Her brother is 190 cm tall and her half brother from the same mother 175 cm, both being healthy. Her mother and father's heights are 167 and 185 cm, respectively, providing a target height for the patient of 170 cm (SDS 1.52). She was born at term after a normal pregnancy with a length of 55 cm (SDS 2.77) and a weight of 3,550 g. Infancy was uneventful. She had menarche at 12 years of age and she always had regular menses every 25 days. Since early childhood she had several behavioral problems which were difficult to control and she was institutionalized some time before the evaluation. At presentation, she measured 184 cm (SDS +4.31) and weighed 119.2 kg, having a body mass index of 35.21 kg/m^2. Breast and pubic hair were adult. Pelvic echography showed a normal uterus and ovaries. Nuclear magnetic resonance imaging of the central nervous system was normal. Laboratory studies (LH, FSH, TSH, T4, T3, IGF1, IGFBP-3 and estrogen plasma levels) were within the normal range (table 1). Besides her tallness and psychiatric disorder, no clinical signs of excess growth hormone secretion were present. Normal gonadal function and no further increase in height were noted at a follow-up examination at the age of 18.25 years (fig. 1).

Case 2

She was a 6.8-year-old girl referred to a pediatric endocrinologist to study her thyroid function. She was born to healthy nonconsanguineous parents after an uncomplicated term pregnancy. Her birth weight was 2,800 g (SDS –1.15). Her mother and father's heights are 148 and 169.5 cm, respectively, providing a target

height for the patient of 152.5 cm (SDS –1.34). Her healthy 12-year-old brother is 143 cm tall. She complained of frequent otitis media. At examination, she was 113.5 cm tall (SDS –1) and weighed 25 kg (SDS 1.22), and had mild TS phenotype, cubitus valgus, hypoplastic nails (fig. 2a) and hypertension. No malformations were found by renal, cardiologic and gynecological ultrasonography. At a follow-up examination at 9.4 years of age, her height was 123 cm (SDS –1.24), and bone age was 8.10 years. Laboratory investigations revealed a high FSH level (table 1). At 10.6 years of age, her height was 127 cm (SDS –1.42) and her weight 36 kg (SDS 0.39), with a body mass index of 21.56 kg/m^2. Growth velocity was 3.5 cm/year (fig. 2b). She was started on recombinant human growth hormone (rhGH) therapy at the age of 11.1 years. During the 14-month rhGH treatment (first 10 months 0.81 U/kg/week, last 4 months 0.95 U/kg/week), growth velocity increased only 2.5 cm/year compared with the untreated previous level. Her growth response, the development of alterations in glucose metabolism and her continuous need for hypotensive medication led to discontinuation of rhGH treatment at the age of 12.3 years. At the age of 13.8 years, FSH was 89.9 mIU/ml, LH 17.2 mIU/ml and estrogen 9.2 pg/ml. At 14.9 years of age she received hormone replacement therapy with conjugated estrogen (0.3 mg/day), which was increased at the age of 16.0 years (0.623 mg/day). At her last clinic visit at the age of 16.5 years, her height was 142.5 cm (SDS –2.94), weight 57 kg (SDS 0.44), bone age 15 years and Tanner stage 4.

Cytogenetic Studies

PHA-stimulated peripheral blood lymphocytes were cultured at 37°C for 72 h in McCoy's 5A medium plus 10% fetal calf serum and harvested for metaphase conventional preparations [12]. GTG-banding was achieved by the trypsin-Giemsa method [13], C [14]- and R-banding was performed using a fluorescence method with acridine orange or by heat-Giemsa staining [15]. In order to study late replication and high resolution, fluorodeoxyuridine and bromodeoxyuridine were added to some synchronized peripheral blood cultures according to a technique modified by Yunis [16].

Fluorescence in situ hybridization (FISH) studies [17] were carried out on peripheral blood lymphocyte cultures using:

- whole X-chromosome painting (wcpX) with spectrum orange label;
- DXZ1 spectrum green probe to centromere region X(p11.1–q11.1);
- dual-color fluorescence using KAL spectrum orange/DXZ1 spectrum green control probe which hybridizes proximal to SHOX at Xp22.3, and
- wcpY probe spectrum orange which hybridizes on PAR1.

All the probes were analyzed and photographed using an epifluorescence microscope.

Results

Case 1

G-banding showed an abnormal X chromosome with Xp duplication (Xp11.3-pter) translocated to partially Xq deleted (Xq27-qter) in all cells studied (n = 100; fig. 3a).

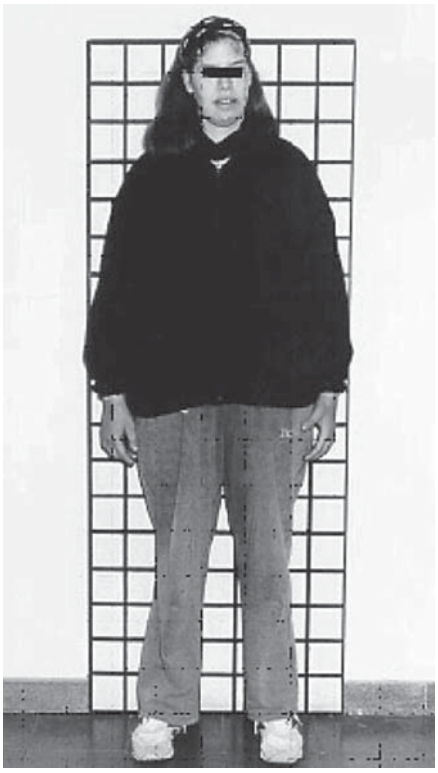


Fig. 1. Patient 1 aged 16 years.

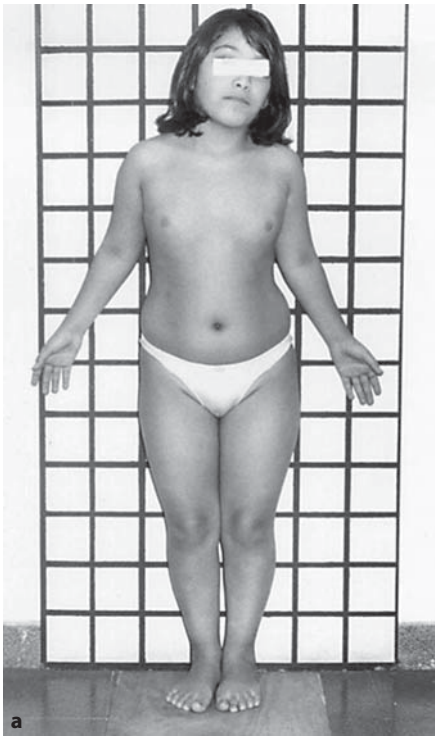
Late replication was observed by R-banding (fig. 3b). The ideograms with breakpoints on Xp and Xq are shown in figure 3c.

FISH showed that wcpX probe homogeneously stained both X chromosomes (fig. 3d). KAL and wcpY probes indicated three hybridization signals (fig. 3e, f). According to the 2009 International System for Human Cytogenetic Nomenclature [18], the karyotype was identified as: 46,X,der(X)(pter-q27::p11.3-pter),ish der(X)(wcp+,DXZ1+,KAL++,PAR1++). The parents' karyotypes were normal.

Case 2

The patient's karyotype in over 100 metaphases studied presented mosaicism with three cell lines: 46,X,der(X)(pter-q21::p11.4-pter)[70]/45,X [20]/46,X,r(X)(p11.4q21)[10].

FISH with wcpX hybridized completely the X chromosomes in all cell lines (fig. 4a, b). The KAL probe showed three hybridization signals (fig. 4c). Three copies of the SHOX gene were identified in most cells (n = 70), and only one copy, resulting in a monosomy-haploinsufficiency of the PAR1-SHOX gene, in the remainder (n = 30). The parents' karyotypes were normal.



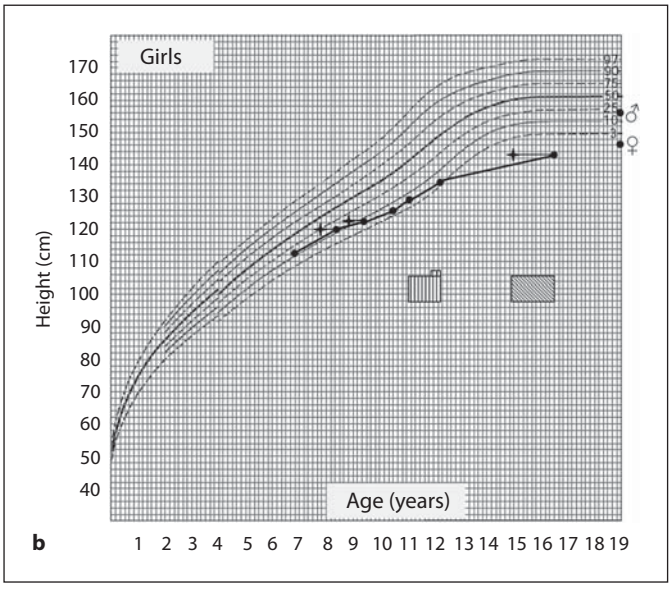


Fig. 2. a Patient 2 aged 10.6 years. **b** Growth chart of patient 2 in relation to an Argentinean normal growth chart [11] showing the effect of rhGH therapy (▥) on her growth curve. ● = Height; ✦ = Bone age; ▧ = estradiol treatment.

Table 1. Clinical and hormonal values

	Patient 1	Patient 2	Normal range
WBC, $\times 10^9$/l	7.5		4.4–11.0
Hemoglobin, mmol/l	1.78	2.39	1.86–2.48
Hematocrit	0.37		0.38–0.42
ESR, mm/h	28.0		
Glucose, mmol/l	4.83	4.88	3.33–6.11
Total cholesterol, mmol/l	3.33	4.21	3.38–6.37
Triglycerides, mmol/l	1.37	1.66	0.4–1.81
HDL cholesterol, mmol/l	0.97	1.36	1.03–1.55
LDL cholesterol, mmol/l	1.45	2.09	1.82–4.14
BUN, mmol/l	9.28		3.57–17.85
Creatinine, μmol/l	82.21	43.32	70.72–123.76
TSH, mU/l	0.7	4.78	0.5–6.5
T4, nmol/l	83.67	162.18	77.23–180.20
T3, pmol/l	1,812.60	2,734.26	1,228.88–3,379.42
Anti-TPO, kIU/l	0.3	<0.5	<20
LH (basal), IU/l	1.8	17.2[a]	1.1–6.3
LH (30 min after LHRH), IU/l	19.6		
LH (60 min after LHRH), IU/l	22.6		
FSH (basal), IU/l	2.1	20[b], 89.9[a]	2.5–10
FSH (30 min after LHRH), IU/l	3.8		
FSH (60 min after LHRH), IU/l	4.7	1.45–3.59	
Estradiol, pmol/l	187.22	33.77[c]	110.13–385.46
IGF-I, nmol/l	28.50		15.56–63.15
IGFBP-3, mg/l	3.20		2.1–7.4

[a] Age: 13.8 years. [b] Age: 9.4 years. [c] Age: 11.1 years.

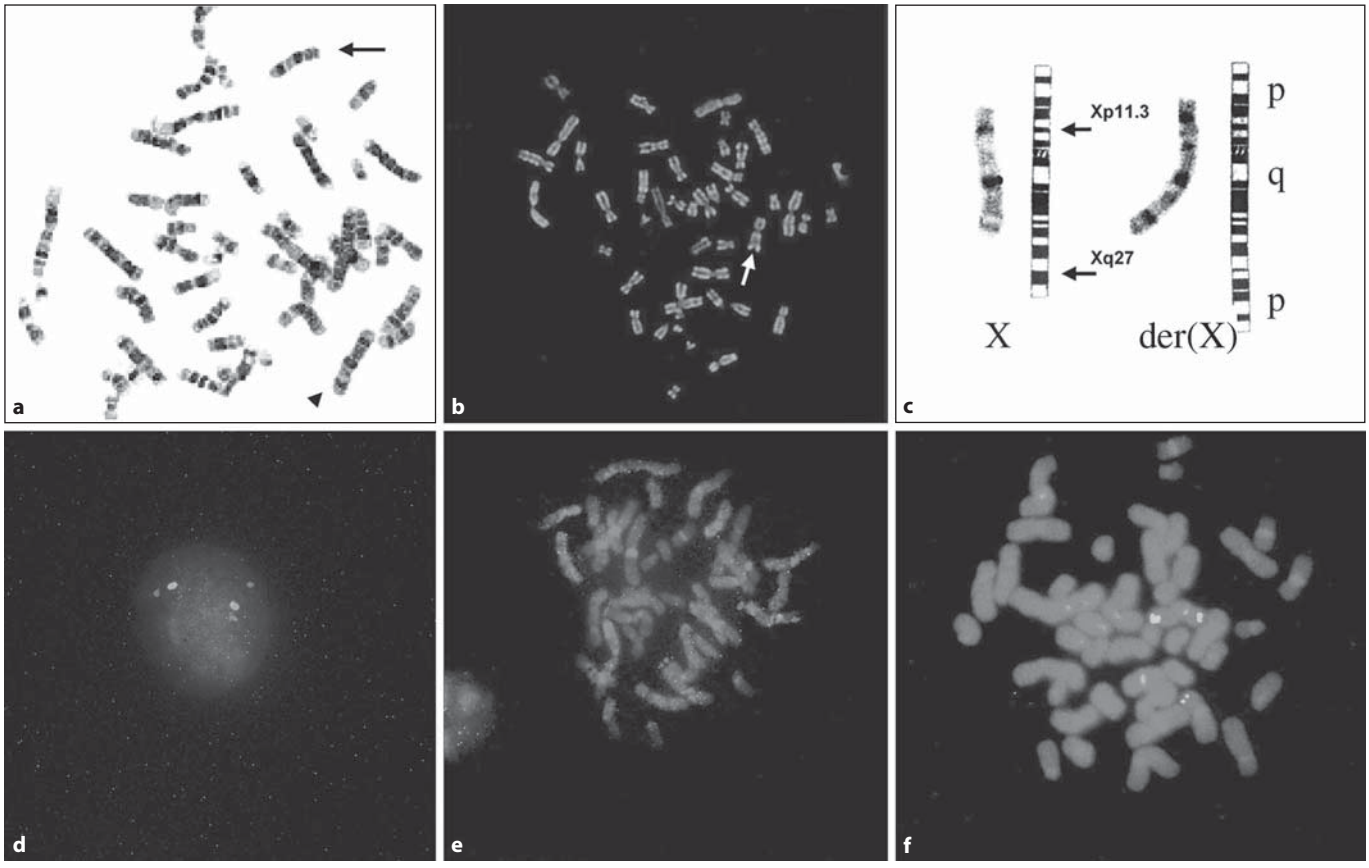


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Fig. 3. Patient 1. **a** Standard analysis of G-banded chromosomes showed extra Xp translocated to Xq of one X chromosome (arrow indicates the normal X chromosome and arrowhead the abnormal X chromosome). **b** Late replication by R-banding was demonstrated in the abnormal X chromosome (white arrow). **c** G-banding of the normal (left) and the abnormal (right) X chromosomes and their ideograms with diagrammatic representation of the abnormal X chromosome. **d–f** FISH using DXZ1 (X-α satellite; **d**), the KAL probe (**e**) and wcpY (whole Y painting; **f**). **d** One green signal was present in each X centromere in interphase nucleus indicating that the abnormal chromosome was monocentric. The red signals (KAL probe) indentified the Kallman locus (Xp22.3) showing only one at the normal X and two at the abnormal X chromosome. **e** One red signal in the normal X chromosome and two red signals at both ends of the structurally abnormal X chromosome indicate triplication of the SHOX gene. DXZ1 probe (green signals) served as a control probe for X chromosome in metaphase cells. **f** One orange signal was present in the normal X chromosome and two orange signals in the abnormal X chromosome indicating triplication of PAR1 in metaphase cells.

Discussion

The SHOX gene, which is known to be an important growth-determining factor in human beings, maps on the distal part of PAR1 of sexual chromosomes (Xp22.3 and Yp11.3) [4]. Moreover, Xq13–q22 and Xq22–q26 map genes which play a positive role on gonadal development [19]. The typical clinical signs as short stature, somatic malformations and gonadal dysgenesis present in patients with TS are caused by total or partial haploinsufficiency of one of the X chromosomes [20]. In this report we present 2 patients with different phenotypes but a similar abnormality – Xp duplication and partial Xq deletion – in the X chromosome in both karyotypes, and both had evidence suggesting triple dosage of the SHOX gene.

The first literature reports on this condition involved 2 patients with tall stature and gonadal dysgenesis. They presented an X chromosome with Xp duplication translocated on partially deleted Xq. The altered X chromosomes with breakpoints on Xq24 or Xq28 in each case were analyzed by conventional cytogenetic analysis [1, 21]. Later on, Binder et al. [3] reported a patient with tall stature, gonadal dysgenesis and stigmata of TS with a monocentric X-chromosomal aberration with nearly

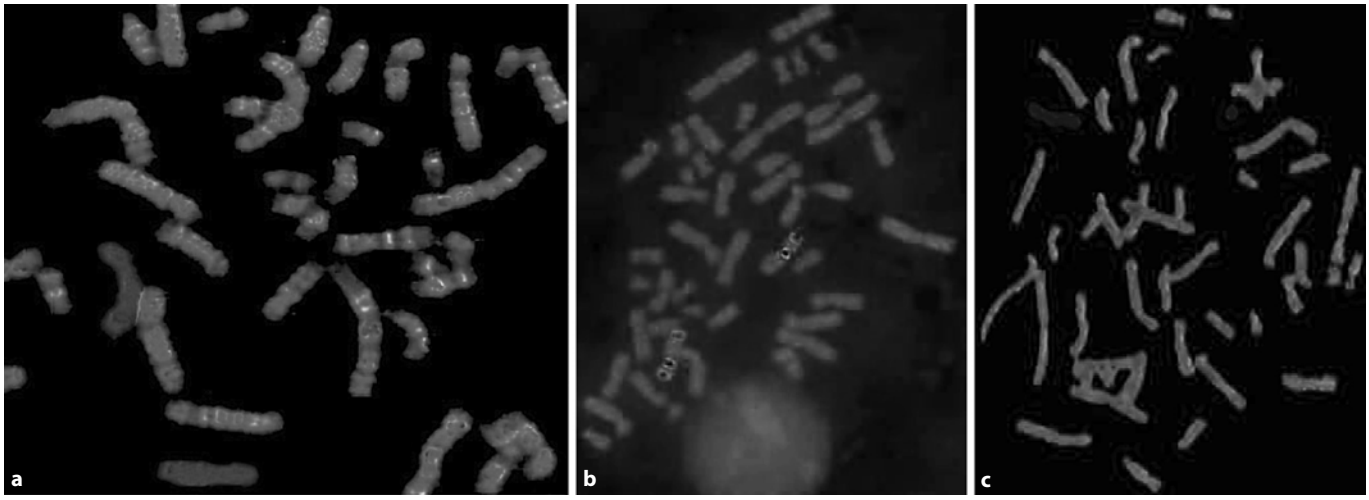

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Fig. 4. Patient 2. FISH using wcpX (whole X painting probe; **a**, **b**) and KAL probe (**c**). FISH hybridized completely to both X chromosomes in metaphase cells (red signals; **a**) and to normal and X-ring chromosomes in metaphase cells (red signals; **b**). **c** One red signal in the normal X chromosome and two red signals at both ends of the structurally abnormal X chromosome indicate triplication of Xp22.3. DXZ1 probe (X-α satellite; green signals) served as a control probe in metaphase cells.

complete Xp duplication and loss of Xq from Xq21.2 to Xqter in all metaphases studied. By FISH using KAL and DXZ1 probes they confirmed triple dosage of the SHOX gene suggesting that the overdosage might be implicated in the overgrowth. Ogata et al. [2] reported a patient with tall stature, no TS phenotype and gonadal dysgenesis with 46,X,der(X)(pter-q13 or q21::p11.4 or p21.1-pter) [60%]/45,X[40%] karyotype. They proposed that neither SHOX overdosage nor estrogen deficiency alone were sufficient to express tall stature, while their combination allowed a continued growth with a higher final height in patients with gonadal dysgenesis. That combination was the key to diagnosis, suggesting that SHOX gene functions as a repressor of growth plate fusion, counteracting the skeletal-maturing effects of estrogens [22, 23]. In 2008 a new patient with tall stature, gonadal dysgenesis, no Turner stigmata, poor breast development after estrogen replacement and a karyotype with an extra copy of the SHOX gene was described [24]. On the other hand, Adamson et al. [25] reported the case of a woman with normal stature, gonadal dysgenesis and trisomy of the SHOX gene resulting from a crossover event of one maternal X chromosome containing balanced pericentric inversion (p21q21). Kanaka-Gantenbein et al. [26] studied a teenager with triple dosage of the SHOX gene, tall stature, psychotic disorder and normal ovarian function. Further, a patient with normal stature, premature ovarian failure and three copies of the SHOX gene was also recently reported [27].

We hereby present 2 cases of SHOX gene triplication with different phenotypes. Case 1 had tall stature without estrogen deficiency and case 2 a mild TS phenotype, gonadal dysgenesis with subsequent estrogen deficiency and normal stature at 6.8 years, but with a steady deterioration (SDS –2.94 at 16.5 years).

Based on the literature reports and the present study, we suggest that the combination of both SHOX gene triplication and estrogen deficiency is not necessarily a condition leading to tall stature. The literature concerning that proposal is controversial. Some of the patients reported have a heterogeneous phenotype and certain variants in the karyotypes were also observed. Besides it would be important to consider a role of the X-inactivation center, where genes mapping near the breakpoints in the der(X) are also affected [28]. In our first case, Xp duplication with triple SHOX dosage was possibly responsible for her tall stature. The SHOX overdosage did neither affect her endocrine functions nor estrogen action on growth plate fusion, since she had her menarche at a normal age and ceased growing accordingly having attained her tall final height at 14 years of age. It might also be possible that trisomy of the ASMT gene located on PAR1 (Xp22.3) and NLGN4 genes (Xp22.32) would be implicated in her behavior, since hemizygous deletions or

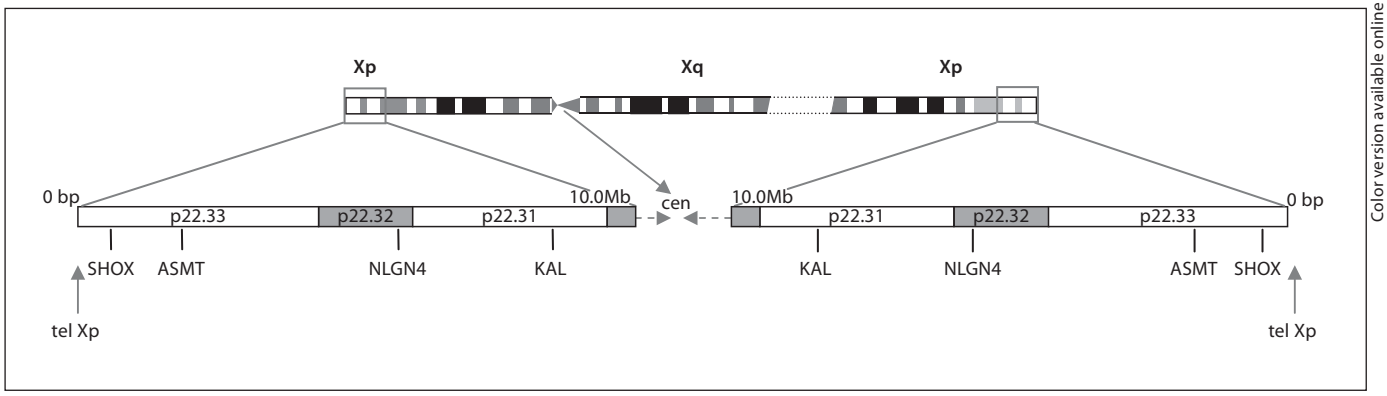

Fig. 5. Schematic representation of the chromosomal locations of genes between Xpter-Xp22.31 in the abnormal X chromosome with Xp duplication. SHOX is localized at the telomere proximal end of the major pseudoautosomal region PAR1 on the short arm of the X chromosome.

mutations of them have clinical significance in individuals with autism spectrum disorders [29, 30] (fig. 5). In the second case, the mosaicism should be considered as responsible for her short stature, gonadal dysgenesis and other stigmata of TS.

To sum up, we propose that SHOX overdosage may express overgrowth even in the presence of preserved ovarian function. The overdosage effect on height in patients with gonadal dysgenesis is not always clear, since in these cases the combination with estrogen deficiency may not always lead to tall stature. On the contrary, lack of estrogen actions, impeding the pubertal growth spurt, is considered an important contributor to the short stature of TS patients.

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