

SHOX haploinsufficiency and overdosage: impact of gonadal function status

Tsutomu Ogata, Nobutake Matsuo, Gen Nishimura

Abstract

Since its discovery in 1997, knowledge about the *SHOX* gene has rapidly increased. In this review, we summarise clinical features and diagnostic and therapeutic implications in *SHOX* haploinsufficiency and overdosage. *SHOX* haploinsufficiency usually results in mesomelic short stature and Turner skeletal features, including Madelung deformity with puberty, in subjects with normal gonadal function. Thus, identification of early or mild signs of Madelung deformity is pivotal for the diagnosis, and gonadal suppression therapy may serve to mitigate the clinical features. By contrast, *SHOX* overdosage usually leads to long limbs and tall stature resulting from continued growth into the late teens in subjects with gonadal dysgenesis. Thus, the combination of tall stature and poor pubertal development is the key to diagnosis, and oestrogen therapy can help the prevention of unfavourably tall stature as well as the induction of sexual development. These findings, in conjunction with skeletal assessment in Turner syndrome and expression analysis during human embryogenesis, imply that *SHOX* functions as a repressor for growth plate fusion and skeletal maturation in the distal limbs and, thus, counteracts the skeletal maturing effects of oestrogens.

(J Med Genet 2001;38:1-6)

Keywords: *SHOX*; oestrogens; clinical features; practical implications

The distal ends of Xp and Yp are composed of 2.6 Mb of DNA sequences that are identical in the X and Y chromosomes.¹ This particular region is named the short arm pseudoautosomal region (PAR1), where the X and the Y chromosomes recombine during male meiosis.¹ Genes on the PAR1 escape X inactivation and, therefore, are present in two active copies in both males and females.¹ Since Xp terminal deletions invariably result in short stature irrespective of the breakpoints² and small Yp terminal deletions lead to short stature,³ it has been suggested that a growth gene resides in the PAR1, and that haploinsufficiency of the

growth gene causes short stature as a dominant phenotype.²

In 1997, Rao *et al*⁴ cloned a novel gene from the distal part of the PAR1 and named it *SHOX* for short stature homeobox containing gene. This gene was also identified by Ellison *et al*⁵ and termed *PHOG* for pseudoautosomal homeobox containing osteogenic gene. *SHOX* is expressed from an inactive X chromosome as well as an active X and a normal Y chromosome, indicating that *SHOX* exerts the dosage effect in sex chromosome aberrations, as expected.⁴ In addition, *SHOX* is most strongly expressed in bone marrow fibroblasts, implying that *SHOX* has a certain role in bone growth and maturation (however, *SHOX* expression has not been examined in several critical tissues such as chondrocytes or osteocytes).^{4,5} Furthermore, expression analysis in human embryos has shown that *SHOX* is exclusively expressed in the developing limbs and in the first and second pharyngeal arches, suggesting that it is involved in mesomelic short stature and skeletal features in Turner syndrome.⁶

In this review, we summarise clinical features and diagnostic and therapeutic implications in *SHOX* haploinsufficiency and overdosage.

SHOX haploinsufficiency

PATIENTS

SHOX haploinsufficiency is common to sex chromosome aberrations associated with terminal Xp or Yp deletions. To define the clinical features in *SHOX* haploinsufficiency, however, it is necessary to identify patients with intragenic *SHOX* mutations or microdeletions involving *SHOX* as the sole impaired disease gene. To date, such mutations or microdeletions have been shown in more than 100 patients, including 29 Japanese patients in whom sufficient clinical data are available^{4,6-11} (unpublished data). The Japanese patients are familial in 17 cases from seven pedigrees and sporadic in 12 cases, and consist of three prepubertal boys, seven adult males, eight prepubertal girls, five pubertal girls, and six adult females. All patients with proven *SHOX* haploinsufficiency have low-normal to severe short stature and lack demonstrable non-skeletal Turner features or definitive biochemical abnormalities. In addition, all pubertal or adult patients have normal gonadal function.

Department of
Paediatrics, Keio
University School of
Medicine, 35
Shinanomachi,
Shinjuku-ku, Tokyo
160-8582, Japan
T Ogata
N Matsuo

Department of
Radiology, Nasu Chuo
Hospital, Ohtawara
324-0036, Japan
G Nishimura

Correspondence to:
Dr. Ogata,
t-ogata@po.iijnet.or.jp

SKELETAL FEATURES

Skeletal features are highly variable but can be classified into several groups, on the basis of the combination of short fourth metacarpals and/or cubitus valgus, which appears in ~40% of Turner patients, and Madelung deformity and/or mesomelia characteristic of Léri-Weill dyschondrosteosis (LWD), which occurs in ~7% of Turner patients.^{10,12} For example, the 29 Japanese patients are divided into the following: (1) five patients with no discernible abnormalities; (2) one patient with short fourth metacarpals and borderline cubitus valgus but without demonstrable Madelung deformity or mesomelia; (3) three patients with Madelung deformity and/or mesomelia of various degrees but without recognisable short fourth metacarpals or cubitus valgus; and (4) 20 patients with both short fourth metacarpals and/or cubitus valgus and Madelung deformity and/or mesomelia of various degrees (fig 1). In addition, genu valgum and relatively short lower limbs are clinically discernible in all patients with overt LWD, and tibial exostosis was detected in one of four patients with LWD with radiographs of the knees and lower legs. These findings indicate that *SHOX* haploinsufficiency causes not only mesomelic short stature but also Turner skeletal features in the limbs,¹⁰ and that most patients with *SHOX* haploinsufficiency have features of LWD to a variable extent, although there may be an ascertainment bias in that patients with the LWD phenotype are predominantly studied for *SHOX* haploinsufficiency.

Limb skeletal features are more severe in females than in males and become evident with puberty.^{10,13-15} In this context, two matters are noteworthy. First, short fourth metacarpals in Turner syndrome are often associated with radiologically discernible premature fusion of the epiphysis,^{15,16} and Madelung deformity is primarily ascribed to premature fusion of the medial half of the distal radial and ulnar growth plates.¹⁷ In addition, bone maturation in Turner syndrome is relatively advanced in metacarpal and distal radioulnar regions.¹⁸ These findings, in conjunction with *SHOX* expression in the developing limbs,⁶ suggest that *SHOX* functions as a repressor for growth plate fusion and skeletal maturation in the distal limbs, so that *SHOX* haploinsufficiency results in premature growth plate fusion and

relatively advanced skeletal maturation in such regions. Second, skeletal maturation in normal subjects is primarily caused by gonadal oestrogens in both sexes,¹⁹ and serum oestrogen concentration is higher in females than in males and increases with puberty in both sexes.²⁰ Thus, it has been suggested that gonadal oestrogens exert a maturational effect on skeletal tissues that are susceptible to unbalanced premature growth plate fusion and skeletal maturation because of *SHOX* haploinsufficiency, facilitating the development of skeletal lesions in a female dominant and pubertal tempo influenced fashion.¹⁰ In agreement with this, severe skeletal features are usually manifested by early maturing females who are exposed to gonadal oestrogens from a relatively early age.¹⁰ Furthermore, this notion would explain why the prevalence of skeletal lesions in Turner syndrome remains roughly 40% for short metacarpal and cubitus valgus and only about 7% for Madelung deformity, because gonadal oestrogen production is usually severely compromised in Turner syndrome.¹⁰ Although Turner patients treated with oestrogens rarely have Madelung deformity, this would be because of oestrogen therapy usually being started from the late teens with a low dosage.²¹ However, a hitherto unknown modifying factor(s) other than oestrogens would also be relevant to the development of skeletal lesions, because skeletal features are still variable among age and sex matched patients.

In Turner syndrome, skeletal anomalies also frequently appear in the faciocervical region.¹² In this context, the presence of high arched palate in two adult Japanese females and short neck in three German patients^{6,10} (unpublished data) together with *SHOX* expression in the first and second pharyngeal arches,⁶ suggests that *SHOX* haploinsufficiency is also relevant to Turner skeletal features in the faciocervical region. However, since the prevalence of faciocervical skeletal anomalies is apparently low as compared with that of limb skeletal anomalies, it appears that, in Turner syndrome, a deformational effect of cystic hygroma and facial oedema on the developing skeletal tissues also contributes to the development of faciocervical skeletal features.¹⁰



Figure 1 Radiographs of the hands and wrists in patients with proven *SHOX* haploinsufficiency and normal gonadal junction. (A) Normal skeletal appearance in a 15 year old boy. (B) Short fourth metacarpal in a 14 year old girl. (C) Moderate Madelung deformity in a 13 year old girl. (D) Short fourth metacarpal and severe Madelung deformity in an 18 year old girl.

GROWTH PATTERN

Prenatal growth appears to be compromised in *SHOX* haploinsufficiency. The mean SD score is -1.1 for birth length and -0.6 for birth weight.¹⁰ Since the mean SD score is -1.01 for birth length and -1.20 for birth weight in Turner syndrome,²² *SHOX* haploinsufficiency may account for most of the birth length reduction and roughly half of the birth weight reduction in 45,X Turner syndrome.

Postnatal growth primarily depends on the presence or absence of overt LWD. Most patients without overt LWD continue to grow along the -2 SD growth curve throughout the growth period (fig 2).¹⁰ The magnitude of height deficit (about 2 SD) is compatible with the estimation that *SHOX* haploinsufficiency decreases adult height by about 12 cm in the absence of overt LWD,²³ because 12 cm approximates the magnitude of 2 SD of the adult height in the normal population. Consistent with the relatively mild statural effect of *SHOX* haploinsufficiency (about 2 SD) as compared with the magnitude of normal height variation (± 2 SD, that is, 4 SD), *SHOX* haploinsufficiency permits normal height in patients with a high genetic height potential (tall parental height).¹⁰ Furthermore, the growth pattern with an apparently normal growth rate, which is similar to that of normal variant short stature, appears to be characteristic of *SHOX* haploinsufficiency, because most diseases affecting linear growth are usually associated with a reduced growth rate.²⁴

By contrast, patients with overt LWD, though they usually grow along the -2 SD growth curves before puberty, show an obvious downward growth shift with puberty (fig 2).¹⁰ It is likely that prepubertal growth is relatively well preserved because of dormant gonadal function, whereas pubertal growth is compro-

mised because of production of gonadal oestrogens facilitating growth plate fusion.

SHOX haploinsufficiency alone is unlikely to explain the growth failure and the growth pattern in 45,X Turner syndrome.² In 45,X Turner syndrome, the mean adult height is about 20 cm lower than that of normal females, and the linear growth is accompanied by a reduced growth rate beginning from early childhood in the absence of discernible LWD.²² Here, it is noteworthy that 45,X is associated with gross chromosome imbalance, because chromosome imbalance, irrespective of the increase or decrease of chromosomal material, has been suggested to result in global developmental defects including growth failure.²⁵ Although 45,X Turner patients usually have gonadal dysgenesis, gonadal oestrogen deficiency is unlikely to influence adult height or childhood growth pattern.²⁶ Thus, the remaining growth deficit and the reduced growth rate from early childhood in 45,X Turner syndrome appears to be the result of chromosome imbalance.

DIAGNOSTIC IMPLICATIONS

The above clinical findings provide some indications for the selection of patients to be examined for *SHOX* haploinsufficiency. First, skeletal assessment implies that *SHOX* haploinsufficiency is usually detected in patients with the LWD phenotype and is obviously rare in patients with no skeletal abnormalities or in those with short metacarpals and/or cubitus valgus only. This would be further supported by the following findings: (1) of the five Japanese patients with no skeletal abnormalities, three are prepubertal children who may manifest skeletal features with puberty, so that definitive normal skeletal findings are manifested by only two adult males

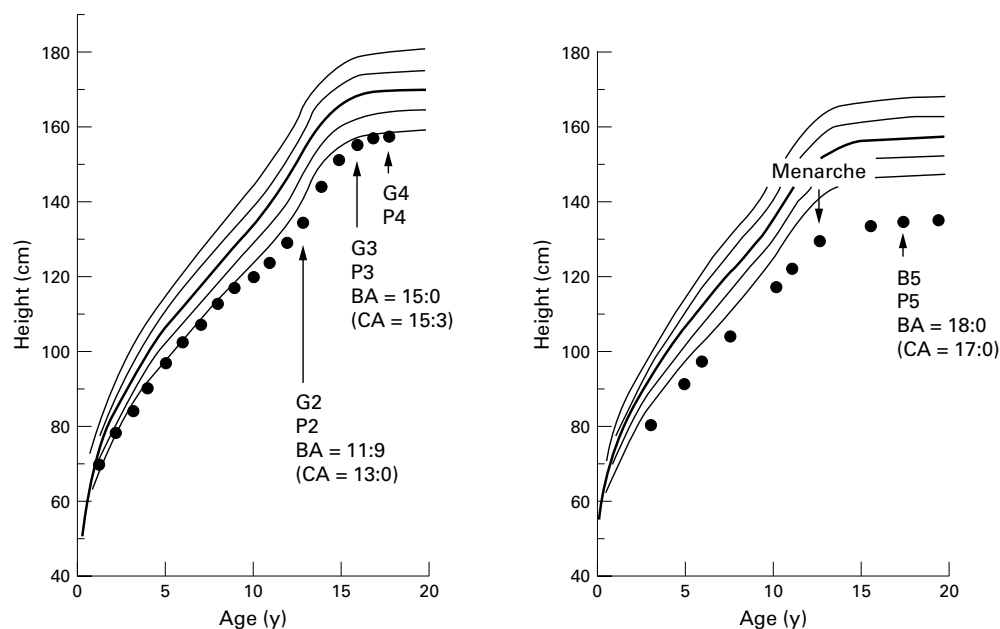


Figure 2 Growth charts in patients with proven *SHOX* haploinsufficiency and normal gonadal function.¹⁰ The actual heights are plotted on the sex matched standard longitudinal growth curves (mean, ± 1 SD, and ± 2 SD) for Japanese children. Pubertal stage is indicated according to the classification of Tanner (G: genitalia; B: breast; P: pubic hair). Bone ages (BAs) are given together with chronological ages (CAs) at the time of BA determination. (Left) A boy without recognisable skeletal abnormalities (see fig 1A). (Right) A girl with both short fourth metacarpal and Madelung deformity (see fig 1D).

with borderline short stature ascertained through familial study of the probands with Madelung deformity; (2) we could identify a single prepubertal girl with *SHOX* mutation and she began to show mild Madelung deformity with puberty (unpublished data); (3) although Rao *et al*¹ found a family with a heterozygous *SHOX* nonsense mutation by analysing 91 patients with short stature, and Binder *et al*¹¹ found a girl with *SHOX* deletion by studying 68 patients with short stature, re-examination of such patients has shown mild skeletal features in most of them^{6 11}; and (4) we have not identified *SHOX* haploinsufficiency in eight subjects with short stature who exhibit short metacarpals and/or cubitus valgus but lack Madelung deformity (unpublished data). Second, growth assessment suggests that most patients with *SHOX* haploinsufficiency usually have borderline short stature (around -2 SD) and grow along the standard growth curves before puberty. These findings imply that *SHOX* haploinsufficiency should primarily be looked for in patients with Madelung deformity and/or mesomelia, and that the proband's family members should also be examined if they have no discernible skeletal features or short stature. By contrast, *SHOX* haploinsufficiency is quite unlikely in patients with no evidence of Madelung deformity or mesomelia, especially in those with severe short stature (<3 SD) accompanied by a reduced height velocity.

For the detection of *SHOX* haploinsufficiency, therefore, it is critical to identify characteristic skeletal features. In particular, it is of practical importance to recognise early or mild signs of Madelung deformity on hand and wrist radiographs that are almost invariably obtained for bone age evaluation in children with short stature. For this purpose, it is necessary to observe carefully several indications of Madelung deformity such as metaphyseal lucency and epiphyseal hypoplasia at the ulnar border of the distal radius, decreased carpal angle, angulation of the distal radius and ulna, and subluxation of the distal ulna.²⁷ In our experience, the first signs of Madelung deformity are often exhibited by metaphyseal lucency and epiphyseal hypoplasia of the medial side of the distal radius in prepubertal patients and by decreased carpal angle in pubertal or adult patients (fig 3). When such findings are suspected, radiographs of the distal limbs should be obtained, to examine characteristic features such as radial curvature and/or shortening and tibial deformity.

In the analysis of *SHOX* haploinsufficiency, it is noteworthy that microdeletions involving *SHOX* are much more prevalent than intragenic *SHOX* mutations. For example, of 29 Japanese patients, 28 patients have microdeletions, and only a single patient has an intragenic mutation¹⁰ (unpublished data) and similar data have also been published.^{7-9 11} The high prevalence of microdeletions would be consistent with repetitive sequences such as subtelomeric interspersed repeats being abundantly present around *SHOX*,²⁸ because unequal crossing over between homologous chro-



Figure 3 Early and mild signs of Madelung deformity. (A) Metaphyseal lucency and mild epiphyseal hypoplasia of the medial side of the distal radius in an 8 year old boy. (B) Decreased carpal angle in addition to angulation of the distal radius and epiphyseal hypoplasia of the medial side of the distal radius in a 15 year old girl.

mosomes or an intrachromosomal recombination is prone to occur in such a region. Thus, it is recommended that FISH analysis should be performed first and when *SHOX* deletion is excluded intragenic mutation should be searched for.

THERAPEUTIC IMPLICATIONS

For *SHOX* haploinsufficiency, two therapeutic interventions can be considered. First, since growth hormone (GH) therapy is effective in Turner syndrome despite the absence of GH deficiency,²⁹ it may also be advantageous in *SHOX* haploinsufficiency. To date, beneficial short term effects have been reported in three patients.^{11 30} Second, since gonadotrophin releasing hormone analogue (GnRHa) therapy can suppress gonadal oestrogen production, it may serve to prevent or mitigate the development of skeletal features. The assessment of GH and GnRHa therapy awaits further and future clinical studies.

SHOX overdose

PATIENTS

SHOX overdose can be caused by structural, as well as numerical, abnormalities of the sex chromosomes. In this context, females with 46,X, idic(Xq-) (=46,X,der(X)t(Xq;Xq))³¹⁻³⁴ (unpublished data) and 46,X,der(X)(pter→q21::p11→pter) (=46,X,der(X)t(Xp;Xq))³⁵⁻³⁷ are noteworthy, because they have a unique combination of *SHOX* overdose (one on the normal X chromosome and two on both ends of the derivative X chromosome) and oestrogen deficiency owing to gonadal dysgenesis. This combination shows a sharp contrast to the association of *SHOX* haploinsufficiency with normal gonadal oestrogen production.

SKELETAL FEATURES

Skeletal data are fragmentary in each individual patient. Taken together, however, it is likely that the combination of *SHOX* overdose and oestrogen deficiency leads to long metacarpals, large hands and feet, and long limbs³¹⁻³⁷ (unpublished data). Since *SHOX* is expressed in the distal limbs, this phenotype can be explained by the *SHOX* dosage effect

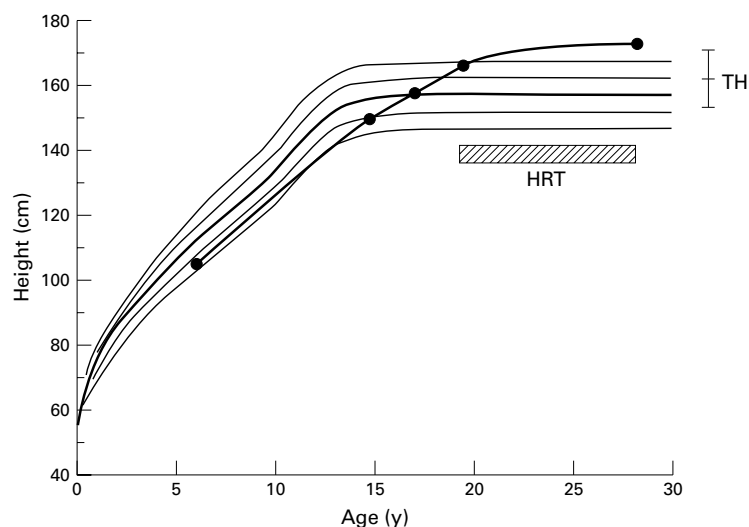


Figure 4 Growth curve in a female with 46,X,der(X)(pter→q21::p11→pter) accompanied by proven SHOX overdosage and complete gonadal dysgenesis.³⁶ The growth curve of the female is depicted on the standard growth curves for Japanese females (mean, ± 1 SD, and ± 2 SD). Target height (TH, a child's final height as predicted from the parental height) is shown, together with target range (95% confidence interval of target height) indicated by the vertical bar. HRT: hormone replacement therapy.

which could be exaggerated because of the delayed growth plate fusion resulting from gonadal oestrogen deficiency. This idea would also explain why relative tall stature in Klinefelter patients is almost totally the result of increased leg length,³⁸ because Klinefelter patients have three copies of *SHOX* and hypogonadism.

GROWTH PATTERN

Long term growth pattern is available in only a few patients^{36,37} (unpublished data). Collectively, they grow along the normal height standard curves in the prepubertal period and continue to grow with a nearly constant height velocity throughout the pubertal period of normal subjects, attaining tall adult height (above +2 SD) (fig 4). The white adult height is 174.8 (SD 4.6 cm) (n=5) for females with apparently non-mosaic 46,X,idi(Xq-) and primary amenorrhoea untreated until their late teens (over 17 years old).³⁶

Two factors are relevant to the tall stature. One is the *SHOX* duplication on the derivative X chromosome, because *SHOX* has a dosage effect on the adult height.² The other is gonadal dysgenesis, because gonadal oestrogen deficiency permits a prolonged growth period. Each factor alone appears to be insufficient to explain the tall stature. For example, the white adult height is 167.9 (SD 7.7) cm (n=19) for females with 47,XXX accompanied by three copies of *SHOX* and relatively well preserved oestrogen production, 164.3 (SD 7.7) cm (n=22) for females with 46,XX gonadal dysgenesis accompanied by two copies of *SHOX* and gonadal oestrogen deficiency, and 162.2 (SD 6.0) cm for normal females accompanied by two copies of *SHOX* and gonadal oestrogen production.² Thus, the tall stature in females with 46,X,idi(Xq-) and 46,X,der(X)(pter→q21::p11→pter) appears to be the result of the synergistic effects of the two factors.³⁶

The growth pattern is similar to that in oestrogen resistance or aromatase deficiency, which is free from biological effects of both gonadal and extragonadal oestrogens.¹⁸ This suggests that an extra copy of *SHOX* has the potential to override the skeletal maturation effect of extragonadal oestrogens, because *SHOX* is likely to function as a repressor for skeletal maturation.

DIAGNOSTIC IMPLICATIONS

SHOX overdosage should be looked for in females with tall stature and gonadal dysgenesis, especially in those with continued growth into the late teens. In addition, large hands and feet and long limbs represent a further indication for *SHOX* overdosage.

THERAPEUTIC IMPLICATIONS

There are two therapeutic implications. First, oestrogen replacement therapy is effective in preventing unfavourable tall stature as well as inducing pubertal development. Second, although GH therapy has widely been used in Turner syndrome,²⁹ it may be unnecessary in females with the unique combination.

Summary

Current data indicate that there is a striking contrast in clinical features between patients with the association of *SHOX* haploinsufficiency with normal gonadal function and those with the combination of *SHOX* overdosage and gonadal dysgenesis. This is consistent with the notion that *SHOX* functions as a repressor for growth plate fusion and skeletal maturation in the distal limbs and counteracts the skeletal maturing effects of oestrogens. Further clinical studies in patients with *SHOX* abnormalities will permit a better definition of the phenotypic spectrum and better diagnostic and therapeutic applications.

SHOX sequence analysis was carried out in collaboration with Dr Rappold, Institute of Human Genetics, Heidelberg University, Germany.

- Rappold GA. The pseudoautosomal regions of the human sex chromosomes. *Hum Genet* 1993;92:315-24.
- Ogata T, Matsuo N. Sex chromosome aberrations and stature: deduction of the principal factors involved in the determination of adult height. *Hum Genet* 1993;91:551-62.
- Davis RM. Localisation of male determining factors in man: a thorough review of structural anomalies of the Y chromosome. *J Med Genet* 1981;18:161-95.
- Rao E, Weiss B, Fukami M, Rump A, Niesler B, Mertz A, Muroya K, Binder G, Kirsch S, Winkelmann M, Nordsiek G, Heinrich U, Breuning MH, Ranke MB, Rosenthal A, Ogata T, Rappold G. Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome. *Nat Genet* 1997;16:54-63.
- Ellison JW, Wardak Z, Young MF, Robey PG, Laig-Webster M, Chiong W. PHOG, a candidate gene for involvement in the short stature of Turner syndrome. *Hum Mol Genet* 1997;6:144-7.
- Clement-Jones M, Schiller S, Rao E, Blaschke RJ, Zuniga A, Zeller R, Robson SC, Binder G, Glass I, Strachan T, Lindsay S, Rappold GA. The short stature homeobox gene *SHOX* is involved in skeletal abnormalities in Turner syndrome. *Hum Mol Genet* 2000;9:695-702.
- Belin V, Cusin V, Viot G, Girlich D, Toutain A, Mencia A, Vekemans M, Merrer ML, Munnich A, Cormier-Daire V. *SHOX* mutations in dyschondrosteosis (Leri-Weill syndrome). *Nat Genet* 1998;19:67-9.
- Shears DJ, Vassal HJ, Goodman FR, Palmer RW, Reardon W, Superti-Furga A, Scambler PJ, Winter RM. Mutation and deletion of the pseudoautosomal gene *SHOX* cause Leri-Weill dyschondrosteosis. *Nat Genet* 1998;19:70-3.

- 9 Schiller S, Spranger S, Schechinger B, Fukami M, Merker S, Drop SL, Troger J, Knoblauch H, Kunze J, Seidel J, Rappold GA. Phenotypic variation and genetic heterogeneity in Leri-Weill syndrome. *Eur J Hum Genet* 2000;**8**:54-62.
- 10 Kosho T, Muroya K, Nagai T, Fujimoto M, Yokoya S, Sakamoto H, Hirano T, Terasaki H, Ohashi H, Nishimura G, Sato S, Matsuo N, Ogata T. Skeletal features and growth patterns in 14 patients with haploinsufficiency of SHOX: implications for the development of Turner syndrome. *J Clin Endocrinol Metab* 1999;**84**:4613-21.
- 11 Binder G, Schwartz CP, Ranke MB. Identification of short stature caused by SHOX defects and therapeutic effect of recombinant human growth hormone. *J Clin Endocrinol Metab* 2000;**85**:245-9.
- 12 Lippe BM. Primary ovarian failure. In: Kaplan SA, ed. *Clinical pediatric endocrinology*. Philadelphia: Saunders, 1990:325-66.
- 13 Lichtenstein JR, Sundaram M, Burdge R. Sex-influenced expression of Madelung's deformity in a family with dyschondrosteosis. *J Med Genet* 1980;**17**:41-3.
- 14 Dawe C, Wynne-Davies R, Fulford GE. Clinical variation in dyschondrosteosis: a report on 14 individuals in 8 families. *J Bone Joint Surg Br* 1982;**64**:377-81.
- 15 Lubin MB, Gruber HE, Rimoin DL, Lachman RS. Skeletal abnormalities in the Turner syndrome. In: Rosenfeld RG, Grumbach MM, eds. *Turner syndrome*. New York: Marcel Dekker, 1988:281-300.
- 16 Preger L, Steinbach HL, Moskowitz P, Scully AL, Goldberg MB. Roentgenographic abnormalities in phenotypic females with gonadal dysgenesis. *AJR Radium Ther Nucl Med* 1968;**125**:899-912.
- 17 Henry A, Thorburn MJ. Madelung's deformity. *J Bone Joint Surg Br* 1967;**49**:66-73.
- 18 Even L, Bronstein V, Hochberg Z. Bone maturation in girls with Turner's syndrome. *Eur J Endocrinol* 1998;**138**:59-62.
- 19 MacGillivray MH, Morishima A, Conte F, Grumbach M, Smith EP. Pediatric endocrinology update: an overview. *Horm Res* 1998;**49**(suppl 1):2-8.
- 20 Angsusingha K, Kenny FM, Nankin HR, Taylor FH. Unconjugated estrone, estradiol and FSH and LH in prepubertal and pubertal males and females. *J Clin Endocrinol Metab* 1974;**39**:63-8.
- 21 Grumbach MM, Conte FA. Disorders of sex differentiation. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR, eds. *Williams textbook of endocrinology*. 9th ed. Philadelphia: Saunders, 1998:1303-425.
- 22 Brook CGD, Murset G, Zachmann M, Prader A. Growth in children with 45,XO Turner's syndrome. *Arch Dis Child* 1974;**49**:789-95.
- 23 Curry JR, Magenis RE, Brown M, Lanman JT Jr, Tsai J, O'Lague P, Goodfellow P, Mohandas T, Bergner EA, Shapiro LJ. Inherited chondrodysplasia punctata due to a deletion of the terminal short arm of an X chromosome. *N Engl J Med* 1984;**311**:1010-15.
- 24 Reiter EO, Rosenfeld RG. Normal and aberrant growth. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR, eds. *Williams textbook of endocrinology*. 9th ed. Philadelphia: Saunders, 1998:1427-507.
- 25 Epstein CJ. *The consequences of chromosome imbalance: principles, mechanisms, and models*. Cambridge: Cambridge University Press, 1986.
- 26 Grumbach MM, Styne DM. Puberty: ontogeny, neuroendocrinology, physiology, and disorders. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR, eds. *Williams textbook of endocrinology*. 9th ed. Philadelphia: Saunders, 1998:1509-25.
- 27 Langer LO Jr. Dyschondrosteosis, a heritable bone dysplasia with characteristic roentgenographic features. *AJR* 1965;**95**:178-88.
- 28 Rouyer F, de la Chapelle A, Andersson M, Weissenbach J. An interspersed repeat sequence specific for human subtelomeric regions. *EMBO J* 1990;**9**:505-15.
- 29 Betts PR, Butler GE, Donaldson MDC, Dunger DB, Johnston DI, Kelnar CJ, Kirk J, Price DA, Wilton P. A decade of growth hormone treatment in girls with Turner syndrome in the UK. *Arch Dis Child* 1999;**80**:221-5.
- 30 Shanske A, Ellison J, Vuguin P, Dowling P, Wasserman J, Heinrich J, Saenger P. Deletion of the pseudoautosomal region in a male with a unique Y;13 translocation and short stature. *Am J Med Genet* 1999;**82**:34-9.
- 31 Therman E, Sarto GE, Patau K. Apparently isodicentric but functionally monocentric X chromosome in man. *Am J Hum Genet* 1974;**26**:83-92.
- 32 Dewald G, Spurbeck JL, Gordon H. Replication patterns of three isodicentric X chromosomes and an isochromosome in human lymphocytes. *Am J Med Genet* 1978;**1**:445-60.
- 33 Robertson J, Faed MJW, Lamont MA, Crowder AM. Isodicentric X chromosome in a moderately tall patient with gonadal dysgenesis: lack of effect of functional centromere on inactivation pattern. *J Med Genet* 1982;**19**:463-5.
- 34 Rivera H, Rivas F, Garcia-Esquivel L, Moller M, Cantú JM. Ovarian dysgenesis due to an idic(X)(q2803). *Ann Genet* 1987;**30**:98-100.
- 35 Lepping KA, Brown CJ, Bressler SL, Gustashaw K, Pagon RA, Willard HF, Distèche CM. Mapping of the distal boundary of the X-inactivation center in a rearranged X chromosome from a female expressing XIST. *Hum Mol Genet* 1993;**7**:883-7.
- 36 Ogata T, Kosho T, Wakui K, Fukushima Y, Yoshimoto M, Miharu N. Short stature homeobox-containing gene duplication on the der(X) chromosome in a female with 45,X/46,X,der(X), gonadal dysgenesis, and tall stature. *J Clin Endocrinol Metab* 2000;**85**:2927-30.
- 37 Binder G, Eggermann T, Enders H, Ranke MB, Dufke A. Tall stature, gonadal dysgenesis and stigmata of Turner syndrome due to structurally altered X chromosome. In: *The 5th International Turner Syndrome Meeting: Optimizing Health Care for Turner Patients in the 21st Century*, March 23-26, 2000, Naples, Italy.
- 38 Schibler D, Brook CGD, Kind HP, Zachmann M, Prader A. Growth and body proportion in 54 boys and men with Klinefelter's syndrome. *Helv Paediatr Acta* 1974;**29**:325-35.