



CASE REPORT

An isodicentric X chromosome with gonadal dysgenesis in a lady without prominent somatic features of Turner's syndrome. A case report



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Isodicentric X chromosomes in general have phenotypes characteristic of the resultant X deletions. Gonadotropin levels in Turner's syndrome (TS) girls are high, but have a normal biphasic pattern. Here, we report a 21-year-old lady with primary amenorrhea. Clinical examination revealed a short neck but no other typical stigmata of Turner's syndrome. The levels of gonadotropin were not raised to post-menopausal levels. A chromosome study showed a 45,X/46,X,idic(X)(q22) karyotype. She was diagnosed as having Turner's syndrome.

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Introduction

Turner's syndrome (TS) results from whole or partial monosomy of the X chromosome and is mediated by

haploinsufficiency of genes that normally escape X-inactivation. Half of all TS patients have the karyotype of 45,X. Mosaicism for a normal 46,XX cell population occurs in approximately 15% of girls with TS.¹ The major clinical findings in TS patients include short stature, pre-pubertal ovarian failure leading to the absence of secondary sexual characteristics and infertility and also craniofacial abnormalities which include high arched palate, low posterior hairline and low set ears.^{2,3} Most girls with TS receive the diagnosis in mid-childhood when investigating short

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stature. Patients with isodicentric X with Xq deletions are phenotypically very different from those with isodicentric X with Xp deletion, which can be associated with Turner's syndrome stigmata. Gonadotropins have been reported to be elevated in the majority of these girls with TS, because of gonadal dysgenesis.

Here, we report a 21-year-old lady with gonadal dysgenesis and normal stature whose karyotype is 45,X/46,X,idic(X)(q22).

Case report

An otherwise healthy, 21-year-old lady, was admitted because of primary amenorrhea. She was the healthy product of an uncomplicated term pregnancy, born to a 25-year-old mother and a 29-year-old father. As far as is known, there was no family history of anosmia and delayed sexual development. Her academic performance ranked in the middle of her class. She had a brother aged 23, who was of normal development.

Rapid weight gain, with a rate of more than 5 kg/semester, was noted when she was a junior high school student. She had a good appetite, without polydipsia. Breast development had occurred at the age of 16, but she could not recall the exact time when pubic hair grew initially. There was no cold or heat intolerance, galactorrhea, headache, or anosmia.

On examination, her vital signs were normal. Her weight was 94.8 kg, height 157.7 cm, and body-mass index (the weight in kg divided by the square of the height in m) was 38.1. She had a short neck and acanthosis nigricans. Breasts and external genitalia were consistent with Tanner stage III development (Fig. 1). The remainder of the examination was unremarkable. A pelvic ultrasound examination revealed a small uterus and ovaries.

Endocrine studies showed an elevated follicle-stimulating hormone (FSH) level (23.1 IU/L) and low estradiol (28.2 pg/mL) and progesterone (0.42 ng/mL) levels. The luteinizing hormone (LH) level of 9.18 IU/L and testosterone level of 0.716 ng/mL were within normal limits. The insulin-like growth factor I (IGF-1) level of 126 ng/mL was low. The levels of other pituitary hormones were within the normal ranges. A thyrotropin-releasing hormone (TRH) test revealed normal thyroid-stimulating hormone (TSH) and prolactin responses. A luteinizing hormone releasing hormone (LHRH) test showed an excessive LH response and delayed down-sloping of both FSH and LH levels (Table 1). Clomiphene challenge evoked no elevation of gonadotropin. Estradiol and progesterone did not respond to human chorionic gonadotropin (hCG) administration. The bone age was equal to chronologic age. Magnetic resonance image (MRI) revealed no morphological abnormality of the pituitary gland and hypothalamus. An analysis of 40 metaphase cells from short-term lymphocyte cultures showed 30 cells to have a 45,X chromosome pattern and 10 cells with a 46,X,idic(X) with deletions distal to Xq22 (46,X,idic(X)(q22)) chromosome complement (Fig. 2). Her father presented with a normal karyotype. Her mother's karyotype was 45,X[8%]/46,XX[92%] (a total of 34 cells were examined). None of the parental karyotypes had this unbalanced aberration in the proband.



Figure 1 The patient has short neck, Tanner stage III breast development.

Discussion

Isodicentric X chromosomes are uncommon. The formation of isodicentric chromosomes presumably occurs by end-to-end fusion of chromatids after a break, with subsequent loss of an acentric fragment.⁴ Isodicentric X chromosomes in general have phenotypes characteristic of the resultant X deletions. The short stature—homeobox (*SHOX*) gene, located in the region of Xp, is responsible for the skeletal features.⁵ The lymphogenic gene for soft tissue and visceral stigmata has been assigned to the X-specific region in the middle part of Xp.⁶ Therefore, loss of the short arm (Xp) results in short stature and the typical skeletal change of TS. On the other hand, the long arm (Xq) deletions confer primary or secondary ovarian failure, in part as a result of loss of premature ovarian failure (*POF*) gene, located in the region of Xq.⁵ Our patient, who has one X chromosome

Table 1 The results of LHRH test.

	0 Min	30 Min	60 Min	90 Min	120 Min
FSH (IU/L)	23.4	41.6	37.1	37.9	37.5
LH (IU/L)	6.75	47	34	31.7	25.2

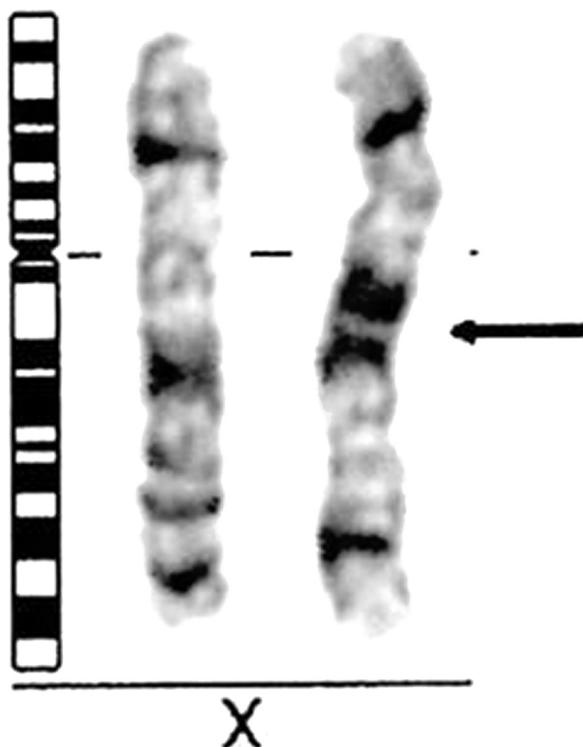


Figure 2 Karyotype of the normal chromosome X and isodicentric X chromosome from the patient. The dicentric region is indicated by the arrow.

containing complete duplication of Xp and a partial deletion of Xq, presents with primary amenorrhea, short neck, and hypoplastic gonads, without other typical stigmata of TS. This is probably due to the fact that, in spite of the presence of a 45, X cell line, the cells containing a second abnormal X chromosome had a positive effect on the phenotype.

For this patient (and her parents), we only performed classic karyotyping with Giemsa (G-banding) and were therefore unable to investigate the issue of skewed X inactivation. Although it is very likely that the aberrant X chromosome is preferentially inactivated,⁷ we would like to address that the most critical gene responsible for short stature in common Turner syndrome, *SHOX*, resides in the pseudoautosomal region of Xp and escapes X inactivation.⁵ We reason, albeit without experimental proof, that for those cells with the 46,X,idic(X)(q22) karyotype, there are actually three active copies of *SHOX*. The combination of the triple dosage of *SHOX* gene caused the normal growth of our patient with the derivative X chromosome. The clinical picture of our patient resembles that of pure gonadal dysgenesis probably due to the missing part of the Xq.

There are at least 56 mega base pairs (Mb) and 740 genes in the deleted Xq region. The most studied gene in this region is the premature ovarian failure-1 (*POF1*) gene located at Xq26.⁸ Correlations between other genes and Turner syndrome presentations are largely unexplored. Petkovic et al reported that a patient, whose karyotype is 45,X/46,X,psu idic(X)(q22.3), exhibited a clinical picture in striking contrast to that observed in our patient; she had moderate growth retardation.⁹ There might be two

explanations for the phenotypic difference between our case and the case presented by Petkovic et al. Firstly, Petkovic et al reported the break point at Xq22.3, but our resolution was not high enough and therefore we only reported Xq22 as the breakpoint. The whole Xq22 is a 10.4 Mb region containing more than 120 genes. It is possible that some critical genes might reside in this region and account for the phenotypic differences between these two cases. Secondly, in general, phenotypic predictions for any given case based on the karyotype are unreliable in Turner syndrome patients.¹ The predictions for patients with isodicentric X chromosomes have been among the most difficult, evidenced by the high variations of phenotypes in this kind of patients in several review papers.^{6,10,11} Tsai et al (2006) reviewed nine patients with de novo 45,X/46,X,idic(Xq) reported in the literature.¹² Only seven patients have typical Turner stigmata. Most reported patients were ascertained at later ages due to reproductive concerns or atypical development of sexual characteristics.

Gonadal dysgenesis is a cardinal feature of TS. Gonadotropin has been reported to be elevated in the majority of these girls with TS because of gonadal dysgenesis.¹³ The amplitudes of FSH and LH pulses are increased^{14,15} because negative feedback from estrogen is lacking.^{16,17} In this case, the levels of gonadotropin were not raised to postmenopausal levels. In the 1970s, Conte et al demonstrated that gonadotropin levels in TS girls are high, but have a normal biphasic pattern.¹⁸ Their levels are increased during the first 2 years of life and then decline gradually. Between the fifth and 10th year of age, gonadotropin levels are low, even in those with gonadal dysgenesis, indistinguishable from those in normal girls. Then, they rise to castrate levels around the usual age for puberty. Girls with X mosaicism had the lowest gonadotropin levels during puberty, particularly when bilateral ovaries were detected.¹⁹ These authors concluded that gonadal function is not the primary determinant of the pattern of gonadotropin secretion from infancy through adolescence, but does affect the amounts of gonadotropin secreted. In patients with TS, ovarian volume was negatively correlated with LH and FSH values and this shows that even low estradiol levels can modulate the function of their pituitary-gonadal-axis as in normal patients.²⁰

Our report presents the patient with gonadal dysgenesis and normal stature whose karyotype is 45,X/46,X,idic(X)(q22). Although almost all patients of Turner's syndrome have somatic stigmata, the cytogenetic abnormality is more important for diagnosis than the Turner's phenotype in these patients. Turner syndrome patients with 45,X/46,X,idic(X) can have highly variable presentations, depending on the distribution of mosaic cells, chromosomal inactivation pattern, position effects, or the patient's age. Therefore, Turner syndrome should be considered in patients with amenorrhea in spite of no typical somatic stigmata.

References

1. Sybert VP, McCauley E. Turner's syndrome. *N Engl J Med* 2004; 351:1227–38.
2. Lippe B. Turner syndrome. *Endocrinol Metab Clin North Am* 1991;20:121–52.

3. Zinn AR, Page DC, Fisher EM. Turner syndrome: the case of the missing sex chromosome. *Trends Genet* 1993;**9**:90–3.
4. Therman E, Sarto GE, Patau K. Apparently isodicentric but functionally monocentric X chromosome in man. *Am J Hum Genet* 1974;**26**:83–92.
5. Rao E, Weiss B, Fukami M, Rump A, Niesler B, Mertz A, et al. Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome. *Nat Genet* 1997;**16**:54–63.
6. Ogata T, Matsuo N. Turner syndrome and female sex chromosome aberrations: deduction of the principal factors involved in the development of clinical features. *Hum Genet* 1995;**95**:607–29.
7. Leppig KA, Distèche CM. Ring X and other structural X chromosome abnormalities: X inactivation and phenotype. *Semin Reprod Med* 2001;**19**:147–57.
8. Persani L, Rossetti R, Cacciatori C. Genes involved in human premature ovarian failure. *J Mol Endocrinol* 2010;**45**:257.
9. Petkovic I, Barisic I, Bago R. Cytogenetic evaluation, fluorescence in situ hybridization, and molecular study of psu idic(X)(pter₁÷q22.3::q22.3÷pter) chromosome aberration in a girl with moderate growth retardation. *Croatian Med J* 2003;**44**:494–9.
10. Dalton P, Coppin B, James R, Skuse D, Jacobs P. Three patients with a 45, X/46, X, psu dic(Xp) karyotype. *J Med Genet* 1998;**35**:519.
11. Ranke MB, Saenger P. Turner's syndrome. *The Lancet* 2001;**358**:309–14.
12. Tsai AC, Fine CA, Yang M, Walton CS, Beischel L, Johnson JP. De novo isodicentric X chromosome: 46, X, idic(X)(q24), and summary of literature. *Am J Med Genet A* 2006;**140**:923–30.
13. Pasquino AM, Passeri F, Pucarelli I, Segni M, Municchi G. Spontaneous pubertal development in Turner's syndrome. Italian Study Group for Turner's Syndrome. *J Clin Endocrinol Metab* 1997;**82**:1810–3.
14. Ross JL, Loriaux DL, Cutler Jr GB. Developmental changes in neuroendocrine regulation of gonadotropin secretion in gonadal dysgenesis. *J Clin Endocrinol Metab* 1983;**57**:288–93.
15. Hosoda A, Fujieda K, Matsuura N, Okuno A, Yuri K. Age-related change of pulsatile gonadotropin secretion in Turner syndrome. *Pediatr Res* 1991;**29**:196–200.
16. Mauras N, Rogol AD, Veldhuis JD. Specific, time-dependent actions of low-dose ethinyl estradiol administration on the episodic release of growth hormone, follicle-stimulating hormone, and luteinizing hormone in prepubertal girls with Turner's syndrome. *J Clin Endocrinol Metab* 1989;**69**:1053–8.
17. Nathwani NC, Hindmarsh PC, Massarano AA, Brook CG. Gonadotrophin pulsatility in girls with the Turner syndrome: modulation by exogenous sex steroids. *Clin Endocrinol (Oxf)* 1998;**49**:107–13.
18. Conte FA, Grumbach MM, Kaplan SL. A diphasic pattern of gonadotropin secretion in patients with the syndrome of gonadal dysgenesis. *J Clin Endocrinol Metab* 1975;**40**:670–4.
19. Mazzanti L, Cacciari E, Bergamaschi R, Tassinari D, Magnani C, Perri A, et al. Pelvic ultrasonography in patients with Turner syndrome: age-related findings in different karyotypes. *J Pediatr* 1997;**131**:135–40.
20. Conte FA, Grumbach MM, Kaplan SL, Reiter EO. Correlation of luteinizing hormone-releasing factor-induced luteinizing hormone and follicle-stimulating hormone release from infancy to 19 years with the changing pattern of gonadotropin secretion in agonalad patients: relation to the restraint of puberty. *J Clin Endocrinol Metab* 1980;**50**:163–8.