Rare Types of Turner Syndrome: Clinical Presentation and Cytogenetics in Five Cases

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ABSTRACT

Turner Syndrome occurs in one out of every 5000 live female births and the diagnosis is usually based on the clinical presentation. In the last 9 years, 17 of 1681 patients who underwent cytogenetic evaluation to investigate uncertain chromosomal anomaly had Turner syndrome. Ten of the patients were the 45,X (classic) type, 2 patients were 46,X,i(Xq), 1 patient was 46,X,der(X)del(X)(p22.1) del(X)(q26), and 4 were mosaic (2 were 45,X/46,XY and the other 2 were 45,X/47,XXX). Detailed clinical evaluations of these patients are presented.

Keywords: Turner Syndrome, isochromosome X, X deletion, mosaicism, cytogenetics

Clinical Presentation

Patient 1

On admission to the Department of Child Health and Diseases, this 10-year-old girl was complaining of short stature. Physical examination revealed her height to be 119 cm (< 3% on the percentile curve by age for girls), and her weight to be 29 kg (10th-25th percentile). She had edema of the hands and feet, short hands and fingers, and a low-posterior hairline (**Image 1**). Results of the examination of her external genitalia appeared to indicate labial synechiae. Abdominal ultrasonic imaging revealed a horseshoe kidney. Radiographic imaging of her hands and wrists showed epiphyseal development to be within normal limits. Her karyotype was determined to be 46,X,i(Xq) (**Figure 1**). Her short stature was treated with medical therapy by a pediatric endocrinologist; her height increased to 132 cm in the following 15 months.

Patient 2

A 24-year-old woman with secondary amenorrhea was referred to a gynecological and obstetric outpatient clinic. Results of her physical and gynecological examinations included a height of 136 cm, weight 42 kg, drooping eyelids, micrognathia, low-set ears, koilonychia (ie, concave nails), a broad chest, low-set and widely spaced nipples, a depressed nasal bridge, short fingers and toes, and edema of the hands and feet. This patient did not consent to being photographed. Her karyotype was determined to be 46,X,i(Xq) (**Figure 2**).

Patient 3

A 14-year-old girl with short stature was referred to a pediatric outpatient clinic with a diagnosis of Turner Syndrome (TS). Results of her physical examination showed her height to be 149 cm (< 3rd percentile) and her weight to be 54 Kg (50th percentile). Other signs of TS were cubitus valgus, a low-posterior hairline, a broad chest with widely spaced nipples, multipigmented nevi, high, arched palate, and hypergonadotropic hypogonadism (**Image 2**). She had amenorrhea and incomplete breast development. An abdominal ultrasonic examination revealed her uterus to be 18 mm × 9 mm; the right ovary was absent and the

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Abbreviations

TS, Turner Syndrome; GTG banding, giemsa-trypsin banding; PCR, polymerase chain reaction; FSH, follicle-stimulating hormone; LH, luteinizing hormone; AML, acute myeloid leukemia; FISH, fluorescence in situ hybridization

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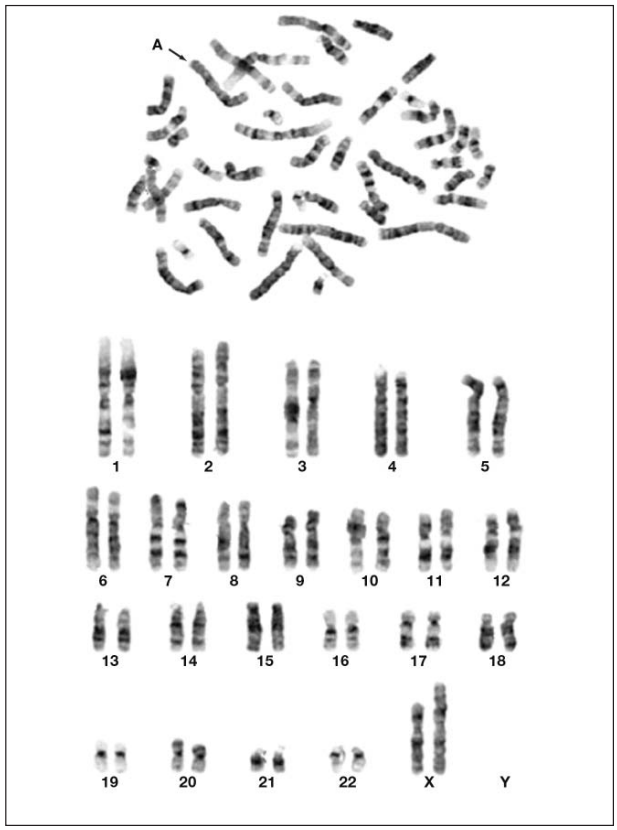


Figure 1

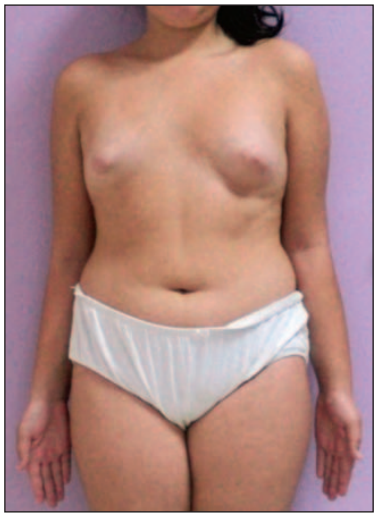
Chromosomic photograph from patient 1 (original magnification, ×100). Isochromosome X (arrow).

Image 1

Photograph of patient 1. Note her widely spaced nipples, swollen hands, and cubitus valgus. She also has short stature; however, her neck is of normal length and circumference.

Image 2

Photograph of patient 3. Note her cubitus valgus, broad chest with widely spaced nipples, and multipigmented nevi. She also has a low-posterior hairline and short stature.



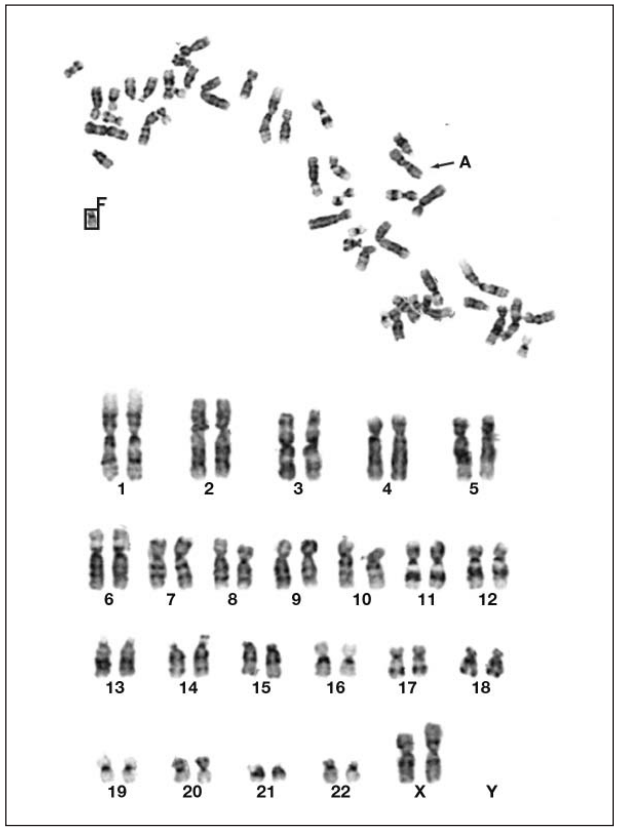


Figure 2

Chromosomic photograph from patient 2 (original magnification, ×100). Isochromosome X (arrow).

Figure 3

Chromosomic photograph from patient 3 (original magnification, ×100). **A**, Normal X chromosome (black arrow). **B**, deleted X chromosome (red arrow).

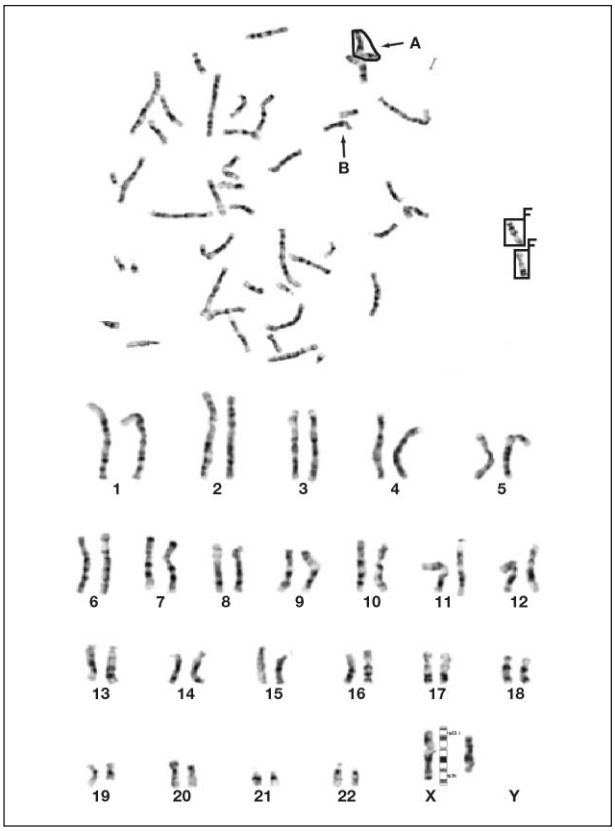
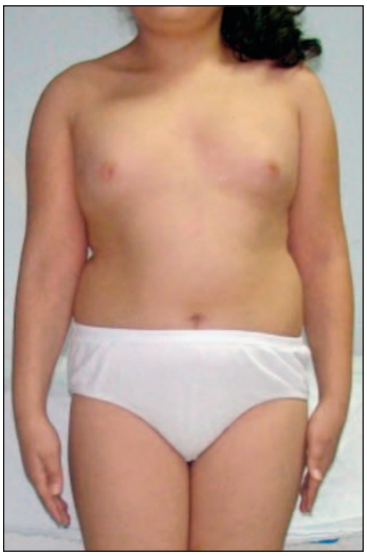


Image 3

Photograph of patient 4. Note her widely spaced nipples and short neck. She also has short stature.



left ovary was 14 mm in diameter with anechoic spaces. Review of her medical record revealed past surgery for polyps. She also had asymptomatic hypothyroidism. Her karyotype was determined to be 46,X,der(X)del(X)(p22.1)del(X)(q26) (**Figure 3**).

Patient 4

This 12-year-old girl presented with short stature. Results of her physical examination revealed cubitus valgus, widely spaced nipples, height of 118 cm (< 3rd percentile), and weight of 35 kg (**Image 3**). Pelvic ultrasonographic imaging revealed a right renal stone, small uterus, and absent ovaries. Alkaline phosphatase and lactate dehydrogenase were elevated (755 and 444 IU/L, respectively). Her karyotype was determined to be 45,X/46,XY (70%/30%) (**Figure 4A** and **4B**); also, molecular analysis of her blood lymphocytes confirmed the presence of the SRY (sex-determining region on the Y chromosome) gene.

Patient 5

The patient, referred to our laboratory with a diagnosis of TS from a pediatric outpatient clinic of another institution, was age 7 years and had a height and weight of 110 cm and 22 kg, respectively. Her clinical findings were short stature, webbed neck, flat nasal bridge, widely spaced nipples, dark brown nevi, cubitus valgus, and edema of the hands and feet (**Image 4**). Abdominal ultrasonographic imaging revealed a horseshoe kidney and a 17.0 X 4.7 mm right ovary that contained a 6.8 X 3.0 mm anechoic cyst. The left ovary was not visualized. Cytogenetic analysis was performed on peripheral blood at the time she was admitted to our institution. Her karyotype was determined to be 45,X/47,XXX (35%/65%) (**Figure 5A** and **5B**).

Cytogenetic and Molecular Studies

After obtaining medical and family histories, a blood sample was obtained from each patient for cytogenetic studies. Standard chromosomal analysis was performed by using giemsa-trypsin (GTG) banding; karyotyping of prepared lymphocyte

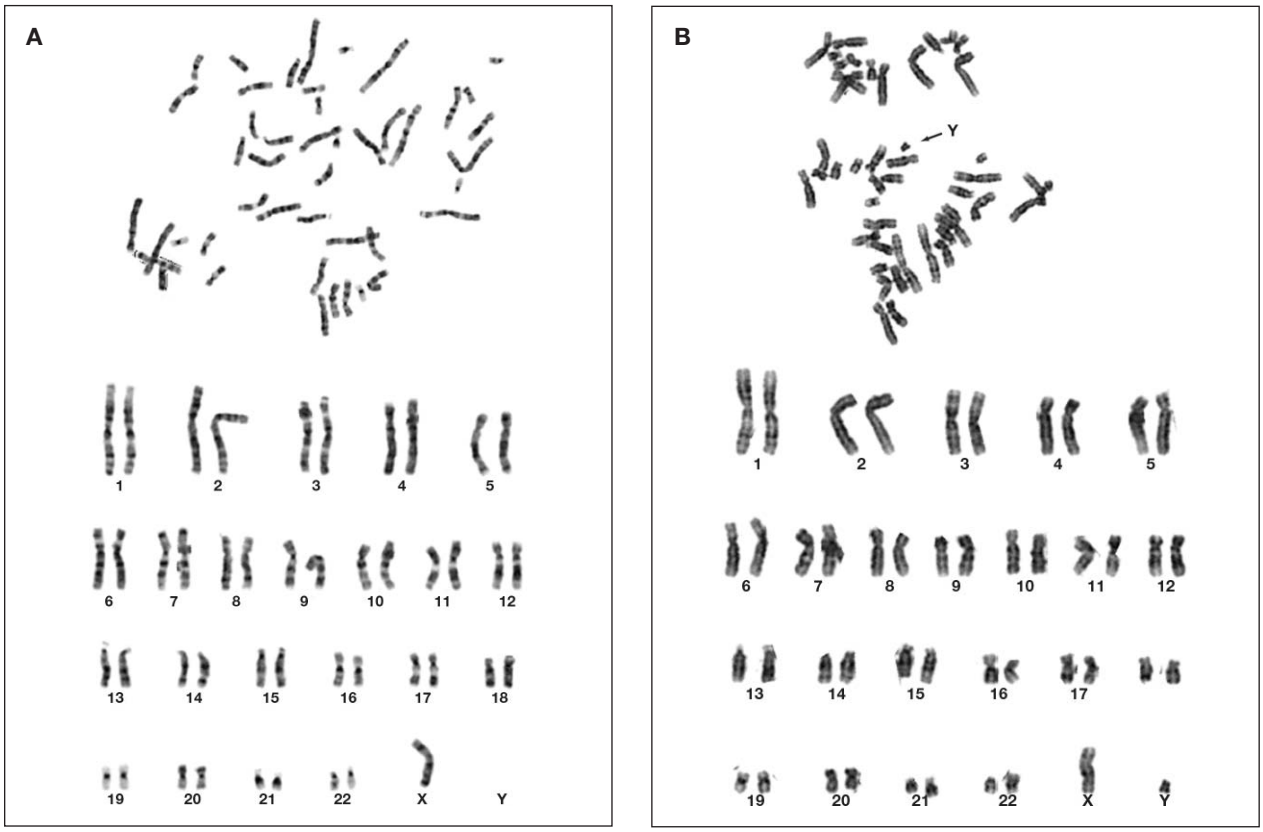
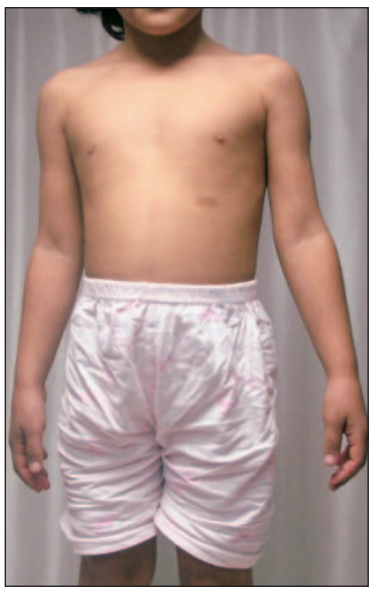


Figure 4

Chromosomic photograph from patient 4 (original magnification, ×100). **A**, 45,X karyotype; **B**, 46,XY karyotype (arrow).

Image 4

Photograph of patient 5. Note her webbed neck, flat nasal bridge, widely spaced nipples, dark brown nevi, cubitus valgus, and edema of the hands and feet. She also has a flat nasal bridge and short stature.



cultures was performed according to the International System for Human Cytogenetic Nomenclature's 1995 protocol.[1] Metaphases were examined in 50 cells; chromosome analyses of the parents were carried out using the GTG banding technique. The SRY (OMIM 480000) gene was amplified by polymerase chain reaction (PCR), using genomic DNA from peripheral blood. The DNA was isolated using a High Pure PCR Template Preparation Kit (F. Hoffmann-La Roche Ltd, Indianapolis, IN). The PCR reactions were completed in a total volume of 100 µL, including extracted DNA, 2 µL each of forward and reverse primers, 10 µL dNTP mix, 10 µL PCR buffer, 10 µL magnesium chloride, and 1 µL Taq DNA polymerase. Thermal cycling was performed as follows: initial activation at 95°C for 2 minutes, followed by 35 cycles of denaturation at 95°C for 45 seconds, annealing at 57°C for 1 minute, and extension at 72°C for 1.5 minutes, with a final extension at 72°C for 7 minutes. The PCR amplification products were separated by 2% agarose gel electrophoresis and

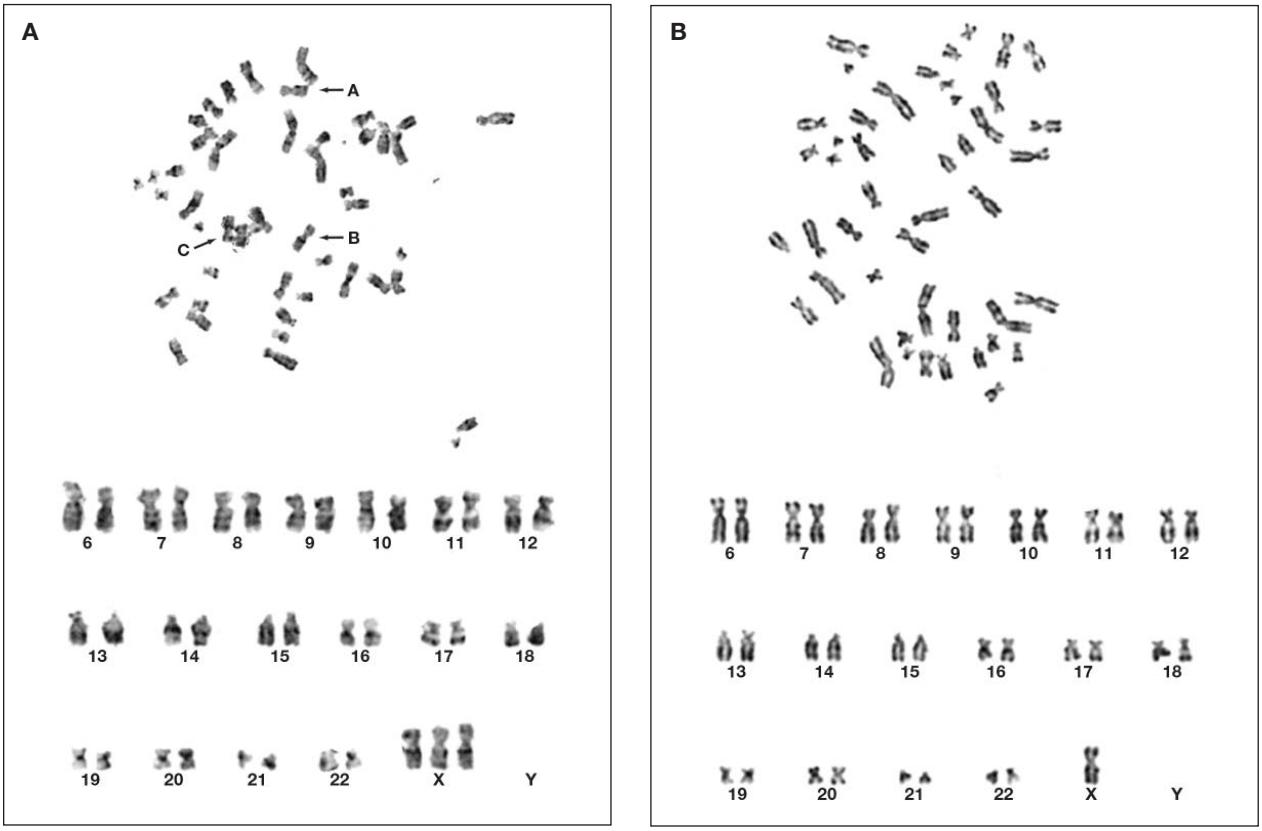


Figure 5

Chromosomic photograph from patient 5 (original magnification, ×100). **A**, 47,XXX; X chromosomes (arrows). **B**, 45,X chromosome.

visualized under ultraviolet transillumination (Vilber-Lourmat, Marne-la-Vallée, France).

Discussion

Turner Syndrome is characterized cytogenetically by X chromosome monosomy, the presence of an abnormal X chromosome, or mosaicism of a 45,X cell line with another cell line, which might be 46,XX, 46,XY or have an abnormal sex chromosome rearrangement.[2] The incidence of Turner syndrome is approximately 1 in 5000 newborn girls;[2] 97% of the TS conceptions are spontaneously aborted.[2] On chromosomal analysis, the percentage occurrences of the various karyotypes observed in TS are 45,X (50%); 45,X/46,XX (20%); 46,X,i(Xq)(15%); 46,X,r(X) or 46,X,del(X)(10%); and others (5%).[3] Sybert and McCauley[4] observed occurrences of 46,X,i(Xq) (7%); 45,X/46,X,i(Xq) (8%); 45,X/46,X,+ring (6%); 45,X/46,X,+mar (1%); 45,X/46,XY or 46,X,Yvar/Ydel (7%); 45,X/46,XX/47,XXX (3%); 45,X/46,XX (13%); 46,X,Xp (short-arm deletions) (2%); 46,X,Xq (interstitial long-arm deletions) (2%); and others (6%).

The 45,X cell line arises from meiotic nondisjunction or anaphase lagging during spermatogenesis or oogenesis or from postzygotic error. Clinical manifestations vary and may be subtle; they usually include short stature, webbed neck, broad chest with widely spaced nipples, cubitus valgus, congenital lymphedema, lack of spontaneous pubertal development resulting from ovarian sex hormone insufficiency, a low-posterior hairline, misshapen or rotated ears, narrow palate with crowded teeth, hyperconvex nails, multipigmented nevi, and cardiac malformation.[5]

An isochromosome is a structurally abnormal chromosome consisting of 2 short or 2 long arms; the abnormal transverse misdivision of the centromere

(ie, centric fission) yields unbalanced chromosomal constitution, monosomy for the missing arms, and trisomy for the duplicated arms.[6] This formation may also occur due to the more complex U-type exchange, resulting in acentric or dicentric products. The process of isochromosomization may occur in the premeiotic gamete during meiotic cell divisions or in postzygotic cell divisions of a normal or trisomic conceptus.[7]

Mosaicism is the presence of 2 or more cell lines with different chromosomal constitutions in the affected individuals. The cell lines are derived due mostly to postzygotic mitotic nondisjunction; they are represented as, for example, 45,X/47,XXX/46,XX/46,XY.[8] The chromosome constitution is also clinically significant in this syndrome. Individuals with i(Xq) show characteristics similar to individuals with classical 45,X. However, patients with a deletion of Xp have short stature and congenital malformations, and those with a deletion of Xq often display only gonadal dysfunction.[9]

In our institution, 17 of the 1681 patients who underwent cytogenetic evaluation to investigate uncertain chromosomal anomalies between 2003 and 2011 displayed the TS phenotype. Ten of those 17 patients had the 45,X type; 2 had 46,X,i(Xq); 1 had 46,X,der(X) del(X)(p22.1)del(X)(q26); and 4 had mosaicism (2 had 45,X/46,XY and the other 2 had 45,X/47,XXX). The patients with the classic 45,X TS karyotype were excluded from the study. Two cases, of 45,X/46,XY and 45,X/47,XXX, respectively, were reported previously[10,11] and details of these cases are presented in the discussion section. All variations of the TS karyotype in our patients were clinically evaluated. We report here on the 5 cases with TS-karyotype variations; their parents all possess normal karyotypes.

46,X,i(Xq) Karyotype

We compared the characteristics of the patient with 46,X,i(Xq) karyotype with the other cases displaying that karyotype that have been reported in the literature. The 46,X,i(Xq) karyotype is found in 7% to 17% of individuals with TS.[4,12] Some reports[9,13,14] have indicated that patients with the 46,X,i(Xq) karyotype have characteristics similar to those observed in classical TS. Those reports claim that the risks for hypothyroidism and mild mental retardation are higher in these patients than in the healthy population. Comparing the patient with isochromosome Xq with individuals who have the 45,X type of TS, the probability of partially developed nipples and mental retardation was higher but the probability of a low-posterior hairline, neck webbing, and hypoplastic nails was lower.[15] Patients with i(Xq) have similar characteristics to those with classical 45,X. However, patients with a deletion of Xp have short stature and congenital malformations. Those with deletion of Xq often only have gonadal dysfunction.[9] Sybert and McCauley[4] have reported the 46,X,i(Xq) karyotype in 7% of patients with TS. The clinical anomalies in the i(Xq) type TS are cardiac disease, renal malformation, menstrual disorders, mental retardation, and edema. In our report, the rate of occurrence of isochromosome Xq is 12% (2 of 17 patients), which is comparable to the rates reported in the literature (ie, 7-17%).[4,12] Patient 1 with i(Xq) was admitted to the pediatric service at another institution for investigation of short stature; it was revealed that she also has a horseshoe kidney, labial synechiae, and edema on her hands and feet. Patient 2 with i(Xq) had secondary amenorrhea and short stature. We observed no mental retardation in either of these patients. We found that the isochromosome i(Xq) form of TS was generally milder than classic TS. A female with short stature, but without typical clinical findings of TS, should be evaluated for this chromosomal form.

46,XX,del(X)(p22.1;pter)(q26;qter) Karyotype

Sybert and McCauley[4] reported the rate of occurrence of the 46,XX,del(Xp) karyotype as 2%; they reported menstrual disorders and renal malformation as the most frequently observed clinical abnormalities. Ranke and colleagues[16] reported the rate of the Xp-deletion form of TS as 1.3%. Elsheikh and colleagues[17] reported the rate of Xp-deletion TS as 1.5%, with clinical findings similar to those of classical TS; Xq-deletion TS was reported as 3%, and clinical findings were varied.

Calvano and colleagues[18] reported a case of 45,X/46,X,del(Xq)/46,X,idic(Xq)-karyotype TS in a 35-year-old woman referred for secondary amenorrhea. She had experienced menarche at age 13 years and irregular menstrual cycles for the following 2 years, with no subsequent spontaneous menstrual cycles. Menstruation had occurred only after initiation of estrogen and progesterone therapy, when the patient was 15 years of age. Her secondary sexual characteristics developed normally after initiation of hormone treatment. Clinical examination revealed short stature (150 cm) but no other typical markers of TS. Pelvic sonographic imaging revealed utero-ovarian hypoplasia. Plasma levels of estradiol and progesterone were low; in our study, the levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were increased. Also in our study, the frequency of deletion-

X-chromosome TS is 6%, which is higher than the frequency reported by Sybert and McCauley[4] and Elsheikh and colleagues,[17] but lower than that reported by Graham and colleagues.[3] Our case was different due to Xp and Xq deletions; the phenotype was different from the case reported on by Elsheikh and colleagues.[17] Our patient displayed suppressed sexual development, as did the patient reported on by Calvano and colleagues.[18] Wong and colleagues[19] reported observing deletion of Xq23 in the bone marrow of a patient with acute myeloid leukemia (AML). However, in our case, the cytogenetic and clinical characteristics are unique: the 46,X,der(X)del(X)(p22.1)del(X)(q26) karyotype was observed in the peripheral blood. Our case is the first of its kind reported in the literature, to our knowledge.

45X/46,XY (70%/30%) Karyotype

Sybert and McCauley[4] reported the frequency of 45,X/46,XY karyotype TS as 7%; in our study the frequency of this karyotype was 12%. Nishi and colleagues[20] observed that the frequency of the Y chromosome sequences in patients with TS varies from 0% to 61% depending on the molecular methodology used; in their cases the most frequent karyotype was 45,X (54%) followed by mosaicism involving structural aberration of X chromosome. Ganguly and Sahni[21] reported that only 1% of the 45,X conceptions were viable, indicating the necessity of mosaicism with X or Y chromosome. Fernández-García and colleagues[22] performed G banding, FISH, and PCR for SRY in 41 cases of TS and reported 2 cases with Y chromosome mosaicism and 4 cases with 45,X.[23] 45,X/46,XY mosaic patients exhibit a wide phenotypic spectrum, including normal females, females with TS, males with mild hypospadias, and male or female pseudohermaphrodites.[23] In more than 90% of this group a normal male phenotype had been found. However, diagnoses in this postnatal group was likely biased by ascertainment because usually, phenotypically abnormal individuals were referred for cytogenetic studies.[23] Akbas and colleagues[10] reported the case of a 7-year-old phenotypic female with 45,X/46,XY TS. The patient had short stature, a webbed neck, a broad chest with widely spaced nipples, syndactyly of toes, horseshoe kidney and cardiac malformation. In our series of TS patients, the frequency of 45X/46,XY mosaicism was 12% (2 of 17), which is higher than the frequency observed in other studies.[4,21,22] In our patients, although 30% of the cells were 46,XY, the phenotype was female. The most important factor in determining the formation of male phenotype is the SRY gene on Y chromosome, but the 30% XY cell fraction we observed in our patients was not sufficient to create male phenotype. This observation was consistent with other studies showing different proportions of XY mosaicism. Derbent and colleagues[24] stated that 45,X/46,XY mosaic karyotype produces a wide range of phenotypes, from normal female to TS to male. Our cases, along with those reported by others, suggest that a low degree of XY mosaicism may produce a mild TS phenotype.[11] Although the SRY gene is necessary for the formation of male phenotype, in two of our cases the presence of SRY did not produce a male phenotype.

45X/47,XXX(35%/65%) Karyotype

Sybert and McCauley[4] reported the frequency of 45,X/46,XX and 45,X/46,X/46,XXX karyotype TS as 13% and 3%, respectively. The clinical abnormalities observed were cardiac disease, renal malformation, menstrual disorders, mental retardation, and edema.[4] The 45,X/47,XXX type of mosaicism is rare. Abnormalities such as short stature, renal insufficiency, craniofacial dysmorphism, ovarian dysgenesis, and learning disabilities are observed in most individuals with TS; patients with the 45,X/47,XXX karyotype also have learning difficulties but have average stature, normal cranium and head circumference, and normal renal ultrasonic findings with normal uterus and ovaries. In individuals with TS who possess the 45,X/47,XXX karyotype, TS manifestations are generally mild.[25] The clinical features of patient 5 in our series, whose 45,X/47,XXX mosaicism was reported previously,[26] are mostly consistent with cases previously described in the literature.

Akbas and colleagues[11] reported a case involving a patient seen by a gynecologist at the age of 17 with menometrorrhagia. She reported that her menarche had occurred 1.5 months previously; menstrual bleeding had sporadically continued without cessation since that time. Physical examination revealed her height and weight to be 132 cm and 45 kg, respectively. She displayed some symptoms of TS, such as multiple nevi, particularly on her face, and short stature. She had short fingers and edema of her hands and feet. Her breasts were small and undeveloped; they were assessed to be at stage 2 on the Tanner scale. She had minimal pubic and axillary hair. During a pelvic exam, she expressed intolerable discomfort during bimanual examination. However, her external genitalia appeared to be normal; no active bleeding was observed. Using transabdominal ultrasonic imaging, her uterus was determined to be 6 cm in length, with an endometrial

thickness of 7.5 mm. Her adnexa were free of masses; no distinct ovaries could be visualized by ultrasonic imaging. Her karyotype was 45X/47,XXX (66%/33%); the frequency of 45,X/47,XXX was 2 of 17 (12%), which was lower than the frequency reported by Sybert and McCauley.[4] Clinical stigmata that were associated with 47,XXX mostly resemble classical TS but are milder. Patient 5 in our series and the patient reported by Akbas and colleagues[11] had a similar proportion of 45,X cells (35% and 33%, respectively).

We believe that possible differences in the viability of cells with 45,X and 47,XXX have resulted in these 2:3 and 1:3 ratios after mosaicism has emerged. Patient 5 has milder characteristics than in the case reported by Tauchmanovà and colleagues.[26] Their finding depends on the fact that the 45,X cell fraction is lower, whereas in our subject, the 47,XXX cell fraction was higher. This observation supports the theory that patients with 45,X/47,XXX mosaicism demonstrate the phenotypes and related syndromes in proportion with the degree of mosaicism. Patient 5, who has 45,X/47,XXX mosaicismcm demonstrates one of very few cases reported with the clinical and cytogenetic characteristics described above.

We present the clinical and cytogenetic findings in several cases of TS, a rare genetic disease. Although the clinical symptoms of TS can be variable, the common characteristic in our cases was short stature. The clinical findings in these patients resemble typical TS; however, the clinical course was milder in our patients. Because physical examination, electrocardiographic readings, and chest X-ray examinations did not reveal heart disease or cardiac abnormalities, we did not perform detailed evaluations of cardiac function. LM

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