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Frequencies and distributions of sex chromosome abnormalities in females with the Turner phenotype: a long-term retrospective study in the southern region of Turkey

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Background/aim: The genetic background of Turner syndrome (TS) is highly variable. The correlation between genotype and phenotype is not yet well understood. The aim of this study was to describe the frequencies and distributions of Turner karyotypes and to discuss the phenotype/genotype relation in a very large group of individuals with TS.

Materials and methods: The karyotype results of 248 female participants were evaluated retrospectively.

Results: Of 248 females with the Turner phenotype, 14.5% had normal karyotypes and 85.5% had Turner karyotypes. About 72.2% of the abnormalities were numerical aberrations and 27.8% were structural aberrations. The most frequent karyotype was monosomy X, which was found in 135 females (63.7%), followed by 44 mosaics (21%), 40 isochromosomes of the long and short arms of chromosome X (19.1%), and 17 deletions of the short and long arms of chromosome X (8.0%). One case of Robertsonian translocation and one case of mosaic TS with marker chromosome were detected.

Conclusion: This study shows the frequency and distribution of karyotypes in females with TS. There is great value to be gleaned from studies of females with TS in furthering our understanding of the atypical clinical features associated with TS. Studies involving genetic analyses will be necessary to examine gene expression profiles in girls with TS and identify potential candidate genes underlying the atypical clinical features associated with TS.

Key words: Turner syndrome, monosomy X, Turner phenotype

1. Introduction

TS is defined as the total or partial absence of the second sex chromosome in females (1). Its incidence is 1 in every 1850 newborn girls, although it is higher at the moment of fertilization. It is estimated to affect approximately 3% of all female fetuses (2). However, there appears to be a high fetal wastage with only 1% of these embryos surviving to term (3). TS is accepted as the one of the most common chromosomal abnormalities. The prevalence of TS cases diagnosed postnatally seemed to be decreasing in recent birth cohorts. On the other hand, the prevalence of TS cases diagnosed prenatally was found as 11% of all abnormal karyotypes in our amniocentesis laboratory (4) (unpublished data). The X chromosome in 45,X TS is of maternal origin in 85% of cases (5–7), indicating the presence of an error in the paternal sperm.

The pathogenesis of the TS phenotype is complex and quite variable, even among women with the same karyotype; however, there are some common clinical features: low stature, gonadal dysgenesis, and anatomic malformations such as cubitus valgus. In addition, the Turner phenotype can be associated with other less frequent characteristics such as cardiovascular congenital defects, renal alterations, or aorta anomalies. A specific neurophysiologic profile that can include selective nonverbal deficiencies such as alterations of the sight-space capacity and low capacity of abstraction can also be associated with the Turner phenotype (8–11). Mental deficiency is not a characteristic of TS. These varying phenotypic expressions are associated with different karyotypes. Most authors believe that growth retardation, ovarian failure, and other physical abnormalities are separate and have distinct genetic effects. Growth failure may result from the deficiency of X-linked gene(s), perhaps together with nonspecific effects of aneuploidy. Both the embryonal lethality and the Turner phenotype are considered the result of a haploinsufficiency of genes found on both sex chromosomes (X and Y). Numerous studies have shown that 4%–20% of women with TS present a Y chromosome (12). Although clinical features of TS have primarily been explained by the dosage

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effects of the short stature homeobox-containing gene (*SHOX*) and the putative lymphogenic gene together with chromosomal effects leading to nonspecific features, several matters remain to be determined (13).

The genetic background of TS is also highly variable. Cytogenetically, the syndrome is characterized by sex chromosome monosomy (45,X), which is present in 50%–60% of cases. The other cases present mosaicism, with a 45,X cell line accompanied by one or more other cell lines with a complete or structurally abnormal X or Y chromosome. The structural abnormalities include isochromosomes, deletions, and ring chromosomes. Although TS is generally considered to affect only females, a Y chromosome may also be present (as mosaic karyotype 45,X/46,XY). However, the 45,X/46,XY karyotype can result in a variety of different phenotypes besides TS, including normal males (14,15).

Here we present the results of the postnatal prevalence of sex chromosome abnormalities in 248 females with the Turner phenotype and the relation between the karyotypes and phenotypes in a large group of individuals with TS, in the scope of a long-term retrospective study in the southern region of Turkey.

2. Materials and methods

The diagnosis of TS is made on the basis of chromosomal analysis. The patients in this study were retrospectively evaluated females who possessed a risk for TS and were referred to postnatal chromosome analysis. Participants included 248 females showing clinical features such as short stature, gonadal failure, pterygium, Sphinx face, primary/secondary amenorrhea, infertility, micrognathia, cubitus valgus, abnormal ears, low posterior hairline, short neck, short fourth metacarpal, webbed neck, spina bifida, kyphoscoliosis, nevus pilosus, lymphedema of the hands and feet, nail dysplasia, scoliosis, mental retardation, hypothyroidism, developmental concerns, bicuspid aortic valve, gastrointestinal and feeding problems, and poor short-term memory and attention span (Figure 1). Patients seen and diagnosed in the Departments of Pediatric Endocrinology and Diabetes and Urology were referred to the Department of Medical Biology and Genetics, Faculty of Medicine, Çukurova University for cytogenetic analysis between the years of 1982 and 2012. The age of the analyzed population ranged between 5 months and 36 years and the average age was 14.4 years. Standard techniques for the cultivation of lymphocytes from the peripheral blood of patients were used and the preparations were treated with trypsin to obtain G-banding. The analyses were performed on ≥50 cells. Evaluation of karyotypes was done according to the 2005 International System for Human Cytogenetic Nomenclature standards.

3. Results

A total of 248 females with TS were analyzed cytogenetically. Karyotype results were divided into seven categories: monosomy X, mosaic monosomies of X, isochromosomes X, deletions of chromosome X, duplications of X, and having a marker chromosome and Y chromosome. The frequencies and distributions of X chromosome aberrations detected are shown in the Table. Some abnormalities of the X chromosome are shown in Figure 2. The karyotype results were normal (46,XX) in 14.5% of 248 females. However, chromosomal aberrations were detected in 85.5% of the females. About 72.2% of the abnormalities were numerical aberrations (45,X, mosaic, and others), and 27.8% were structural aberrations (isochromosome, deletions, and duplication of the X chromosome) (Table). Numerical aberrations were the most common aberrations (approximately 72%) and usually consisted of pure Turner and mosaic cases. TS is defined by the partial or complete absence of the X chromosome. 45,X monosomy is the most common karyotype (approximately 64%) among the numerical aberrations for TS. Seven percent of all abnormalities were true mosaics (45,X/46,XX) and the other 13% were labeled as partial mosaic abnormalities (this includes both numerical partial mosaic aberrations and structural partial mosaic aberrations). Interestingly, one case of Robertsonian translocation between chromosome 14 and 15 [44,X,robt(14;15] and another case of mosaic TS with marker chromosome (45,X/46,X,+mar) were detected also. As shown in the Table, approximately 28% of females with TS have structural anomalies. Several karyotypic variations were seen. Those variations included short or long arm deletions, the isochromosome of the long arm of the X chromosome, and structural mosaics in combination with cell lines such as 45,X and 46,XX. Structural anomalies were divided into three categories: isochromosomes, deletions, and duplications of the X chromosome. Among structural anomalies, isochromosomes of X were encountered predominately (19% of all anomalies, 67.8% of all structural anomalies). The second most common karyotypes seen among structural anomalies were deletions (8% of all anomalies), composing 13.6% of all structural anomalies detected. For example, deletion (X) denotes a terminal and distal Xp deletion with breakage at Xp11, Xp21, Xp22, or Xp26. Deletions for Xq were determined with breakage around regions Xq11, Xq13, Xq21, Xq25, and Xq26. Duplications included two cases of mosaic duplications of chromosome X [45,X/46,X,dup(X)(q21-q26)] karyotypes and their frequency was 0.94% of all anomalies.

4. Discussion

The Turner phenotype is quite variable, even among women with the same karyotype. The correlation between

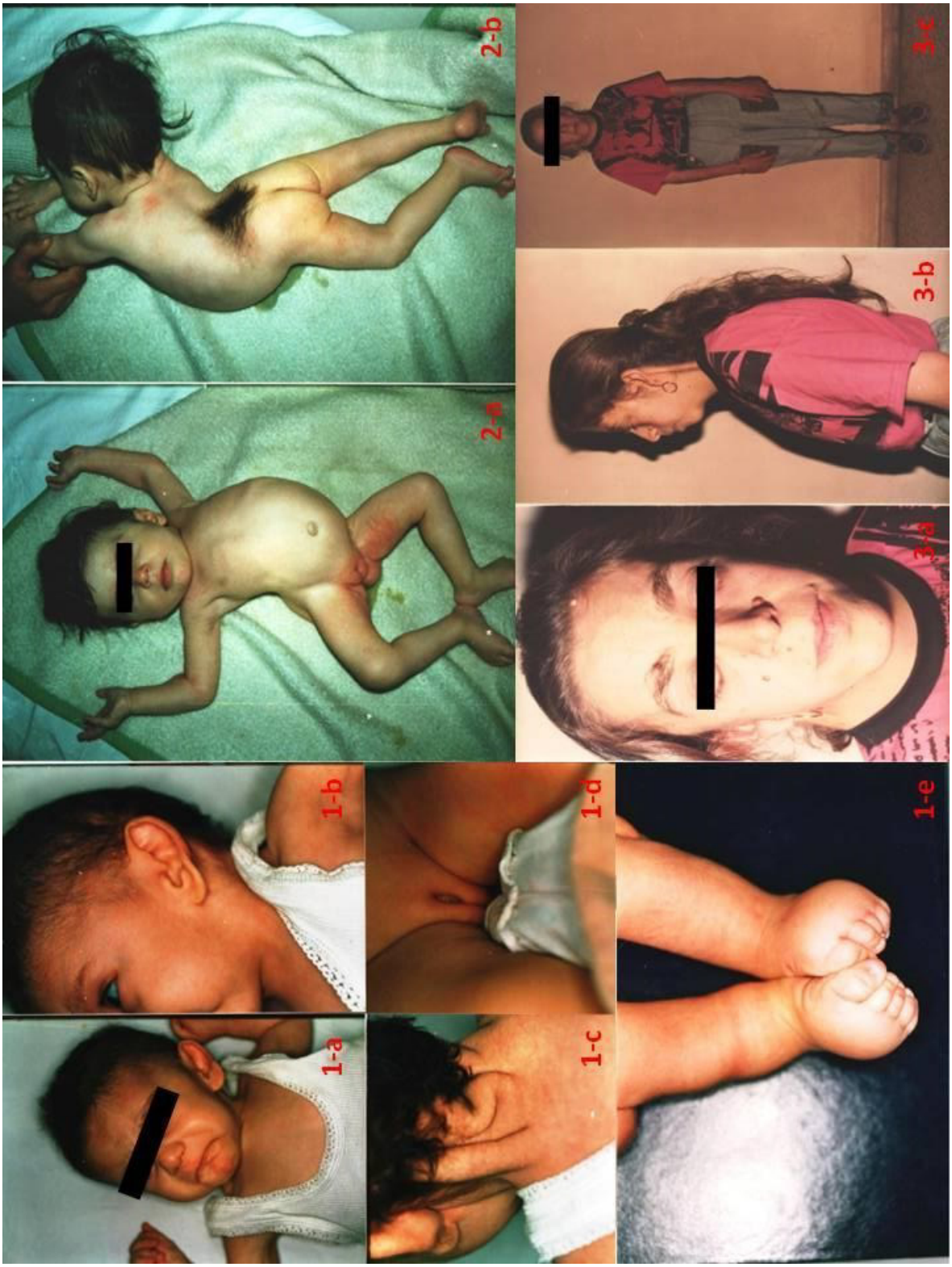

Figure 1. 1-a) Note increased carrying angle of arms; 1-b) abnormal ears, low posterior hairline; 1-c) redundant nuchal skin, webbed neck; 1-d) gonadal dysgenesis, external genitalia of the patient; 1-e) puffiness of the feet. 2-a) Short stature, short neck, spina bifida; 2-b) kyphoscoliosis, nevus pilosus, low posterior hairline in two 2-year-old infants with TS; 3-a) Sphinx face, multiple nevus, multiple pterygium, 3-b, 3-c) short stature (gonadal failure, primary amenorrhea, infertility) in a 26-year-old woman with TS.

Table. Frequencies and distributions of the karyotypes in a Turkish population of 248 females showing TS symptoms.

Cytogenetic category	Karyotype	No. of cases	Frequency in all cases (%)	Frequency in anomalies (%)
Normal	46,XX	36	14.5	-
Abnormal	45,X and the others	212	85.5	Frequency in anomalies (%)
Abnormal				-
Numerical abnormalities of chromosome X Pure Turner (monosomy X)	45,X		133	62.73
Monosomy X with marker chromosome	45,X/46,X,+mar		1	0.47
Turner with Robertsonian translocation of chromosome 14 and 15	44,X,robt(14;15)		1	0.47
Total			135	63.67
Mosaic Turner with numerical aberrations of X	45,X/46,XX		15	7.07
Partial numerical aberrations				
Mosaic XY females with long arm of chromosome X	45,X/47,XY,+Xq		1	0.47
Mosaic Turner with abnormalities of short arm of chromosome X	45,X/46,XXp+		1	0.47
Mosaic Turner with long arm of chromosome Y	45,X/46,XX/46,XYq		1	0.47
Total			18	8.49
Structural abnormalities of chromosome X **Isochromosome X** Isochromosome of long arm of chromosome X	46,X,i(Xq)		17	8.01
Isochromosome of long arm of chromosome X in mosaic form	45,X/46,X,i(Xq)		19	8.96
Isochromosome of short arm of chromosome X in mosaic form	45,X/46,X,i(Xp)		1	0.47
Isochromosome of long arm of chromosome X in mosaic form (three cell lines)	45,X/46,XX/46,X,i(Xq)		2	0.94
Isochromosome of long arm of chromosome X with duplication in mosaic form	45,X/46,X,i(Xq),dup(Xq11-q13)		1	0.47
Total			40	19.05
Deletion of chromosome X short arm (p) deletions				
Pure	46,X,del(Xp)		2	0.94
Partial	46,X,del(X)(p11-p14)		1	0.47
Partial	46,X,del(X)(p22.1-pter)		3	1.41
Partial	46,X,del(X)(p21)		1	0.47
Partial	46,X,del(X)(p11-pter)		1	0.47
Mosaic partial	45,X/46,XX,del(X)(p22-pter)		2	0.94
Mosaic pure	45,X/46,X,del(Xp)		1	0.47
Long arm (q) deletions				
Pure	46,X,del(Xq)		1	0.47

Table. (Continued).

Partial	46,X,del(X)(q21-qter)		1	0.47
Partial	46,X,del(X)(q26)		1	0.47
Partial	46,X,del(Xq25)		1	0.47
Mosaic partial	45,X/46,X,del(Xq13)		1	0.47
Mosaic partial	45,X/46,X,del(X)(q26-qter)		1	0.47
Total			17	8.01
Duplication of chromosome X				
Mosaic	45,X/46,X,dup(X)(q21-q26)		2	0.94
Total				28.11

genotype and phenotype is not yet well understood, but generally patients with a 45,X karyotype tend to have a more severe phenotype than those who are mosaic with a normal cell line (16). Patterns of TS ascertainment are changing. An example of some variabilities in TS phenotypes is illustrated in Figure 1, which depicts two 2-year-old infants and a 26-year-old woman with the 45,X karyotype. As a humble contribution to the literature regarding TS, we examined karyotypic findings in 248 females with the Turner phenotype. Of these females, 14.5% had a normal karyotype (46,XX) and the rest had karyotypes compatible with the Turner karyotype, of which 72% were carriers of numerical aberrations and only 28% were carriers of structural aberrations (Table). Interestingly, as we said, 14.5% of the females had normal karyotypes (46,XX). How can a normal karyotype cause the Turner phenotype? Females with normal karyotypes might be impacted by two mechanisms. One possible mechanism is that the patients have clinical findings compatible with TS, but, in essence, the observed clinical findings may be related to other syndromes. Therefore, clinicians may evaluate patients falsely. The other one is that it has been hypothesized that the physical manifestations of TS are due either to the absence of two normal sex chromosomes before X chromosome inactivation or to haploinsufficiency of genes in the pseudoautosomal regions of the X or Y chromosome, as well as to aneuploidy itself (17). Effective X-linked gene haploinsufficiency in TS is also influenced by the "parent of origin" of the intact chromosome X, as the expression of some X chromosome genes differs systematically depending on which parent the chromosome is inherited from through a process known as imprinting (18). Whether an imprinted gene will be expressed or not depends on its parental origin (19,20). Individuals who retain the maternal X chromosome (Xmat) may demonstrated greater impairments compared to those with the paternal X chromosome (Xpat) (21–23). Some studies have observed individuals with Xpat rather than Xmat to have poorer outcomes (24). The results of another study suggested that each parent-of-origin TS subgroup might be associated with a particular profile of deficits (25).

The most frequent karyotype in TS is 45,X. In a routine TS case, the syndrome is characterized by pure monosomy X, which is present in 50%–70% of cases (16,26–28). In the present study, the most prevalent karyotype was 45,X monosomy and its frequency was recorded as approximately 64% of all abnormal karyotypes (Table; Figure 2). This result is in agreement with other reports. Monosomy X results from nondisjunction as a result of failure of the sex chromatids to separate during meiosis in the parental gametes or in the early embryonic divisions (29). In 75%–85% of the cases of monosomy X, the X chromosome is of maternal origin, indicating that it is the paternal sex chromosome that has been lost (30,31).

Hildenbrand et al. (32) reported a patient with TS and a 45,X/46,X,+mar karyotype who developed unilateral gonadoblastoma. We also detected one case of 45,X/46,X,+mar in our study in which the patient had short stature, deficit of the bicuspid aortic valve, and deficits of short-term memory and attention span. Congenital cardiac anomalies are common in females with TS. Some studies indicated that structural cardiac anomalies are most prevalent in women with pure 45,X monosomy and tend to be less common in those with an isochromosome Xq karyotype. Deficit of the bicuspid aortic valve is the most common congenital malformation affecting the heart (33–35). It is usually an isolated abnormality, but, as we said, we can encounter congenital cardiac anomalies in TS cases, so our finding is consistent with the literature. Additionally, a significant number of females with TS have deficits in specific areas of intellectual performance. This may be reflected by poor arithmetic skills, difficulty with constructional tasks, poor sense of direction, and difficulty in learning to drive (36,37). We also observed these findings in some cases.

Mosaicism can be defined as the presence of a 45,X cell line accompanied by one or more other cell lines with a complete or structurally abnormal X or Y chromosome.

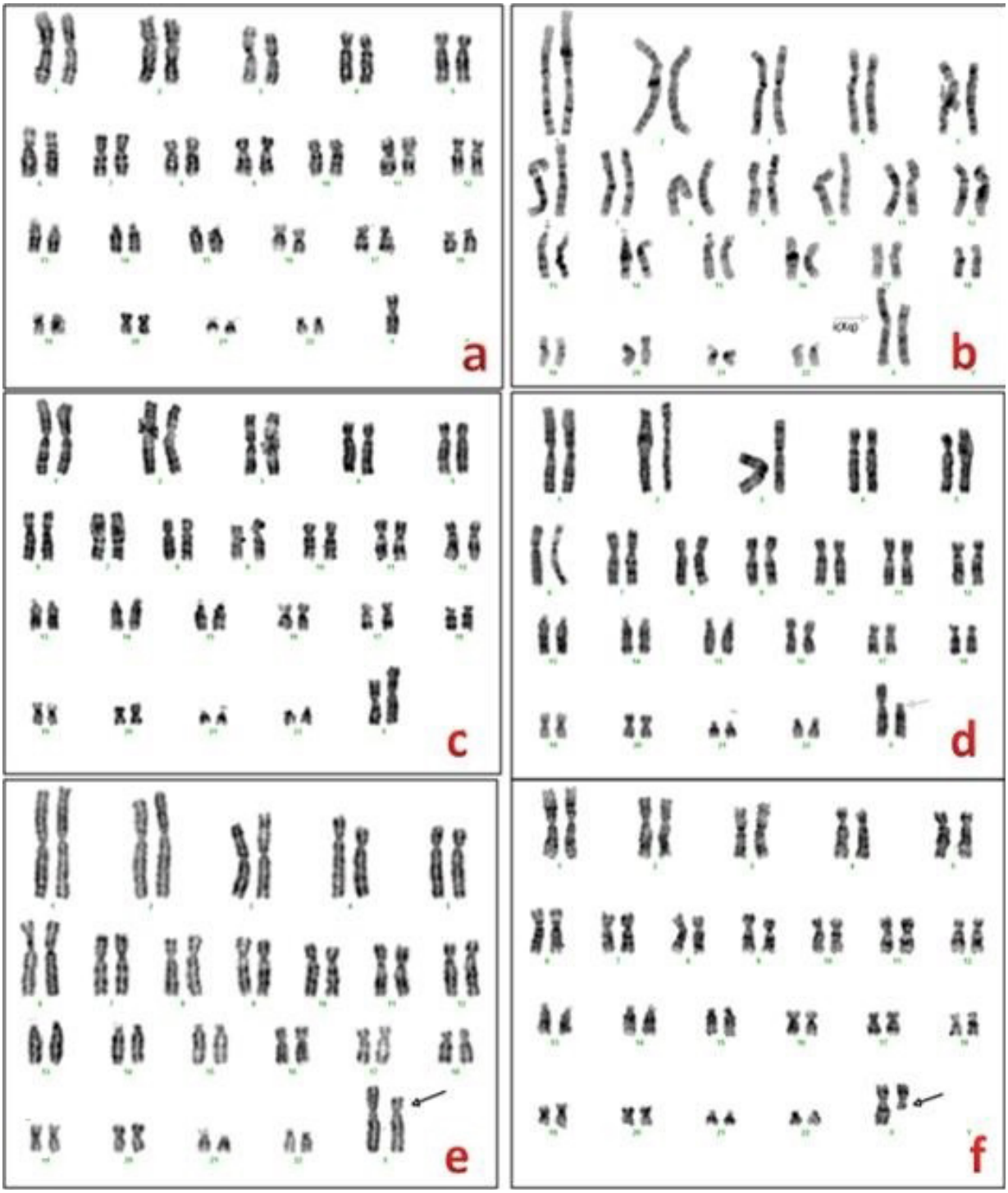

Figure 2. Karyotypes showing 45,X (a), i(Xq) (b), dup(Xp) (c), del(Xp) (d), 46,X,del(X)(p22-pter) (e), and 46,XX,del(X) (q13-qter) (f) chromosome constitutions in some metaphases from females with TS.

The karyotype 45,X/46,XX accounts for roughly 15% of TS cases, and the other mosaic karyotypes contribute to TS cases to a lesser degree (5,38). In our study, the second most common karyotypes seen among all anomalies were mosaicism, accounting for 21% of all chromosome anomalies detected. Our findings and many other reports indicate that mosaicism tends to show moderate outcome (17,39,40).

Females with TS can also have a mosaic pattern with additional Y chromosome material (45,X/46,XY). Approximately 6% of women with TS have 45,X/46,XY mosaicism (41) and such women also have an increased risk of developing gonadoblastoma (42). Although the identity of the gene (or genes) linked to gonadoblastoma has not been established yet, there is evidence indicating that these genes are located near the centromere of the Y chromosome (43,44). We also detected a case of mosaic TS with the long arm of the Y chromosome (45,X/46,XX/46,XYq). Because the diagnosis of TS by definition only includes phenotypic females, the Y chromosome is either defective or the dosage of the Y-containing cell line is very low or restricted to nongonadal tissues. Hence, the development of the default female phenotype is becoming possible. Loss of the testis-determining factor (*SRY*) gene locus on the short arm of the Y chromosome also leads to the phenotype of TS, even without a 45,X cell population.

Structural X chromosome abnormalities are thought to occur as a result of breakages in the X chromosome with subsequent reunion of X chromosome sequences. TS may also occur if a second sex chromosome, usually the X chromosome, is present but has a structural abnormality. These structural abnormalities include a partial deletion of the X chromosome [del(X)] or an isochromosome in which the short arm is lost while the long arm is duplicated [46,X,i(Xq)]. The most frequently occurring karyotypes are 45,X, karyotypes with an isochromosome of Xq or Xp. In our study, the second most common karyotype seen among all anomalies was isochromosome Xp-q, accounting for 19% of all chromosome anomalies detected in our study. Isochromosome Xq is associated with autoimmune disorders and deafness, but congenital abnormalities were conspicuously absent (5). Genes located on the proximal region of the short arm of the X chromosome are also important for normal ovarian function and development and the haploinsufficiency of these genes is thought to be implicated in the pathogenesis of gonadal dysgenesis associated with TS (45). In agreement with this, our cases suggest that the pathogenesis of gonadal dysgenesis occurred in females with TS with i(Xp). The presence of isochromosome Xq suggests an increased risk for hypothyroidism and inflammatory bowel disease (46,47).

Deletions involving the short or long arm of the X chromosome were also found among our cases and the frequency was approximately 8% of all abnormal karyotypes. However, the majority (65%) of deletions were deletions of the short arm (Table). This suggests that there is a relationship between especially the Xp deletion and the Turner phenotype. The short arm distal to the Xp11, Xq13–25, and Xq26–28 regions of the X chromosome are accepted as vital regions for normal ovarian development (48,49). Additionally, deletion of 31 genes that escaped from X inactivation, mapped to the short arm of chromosome X, is known to account for most of the Turner phenotypes (50).

In conclusion, this study illustrates the frequency and distribution of karyotypes causing TS, and we hope to make a contribution to the literature about this syndrome. We also think that our findings will contribute to further understanding of the relative contributions of chromosome X dosage effects and genetic imprinting on the clinical features associated with TS. Studies involving molecular genetic analysis will be necessary to examine gene expression profiles in females with TS and to identify potential candidate genes underlying the atypical clinical features associated with TS. The normal karyotypes with the TS phenotype may be due to haploinsufficiency of those X chromosome genes that escape from inactivation. Most children with TS are under the care of specialists. It has been proposed that adults should also be followed in multidisciplinary specialty clinics. On the basis of our own experience, we believe that the affected females must be referred to specialists.

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