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Cytogenetic Study of Turner Syndrome and Its Variants

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ABSTRACT The principle objective of the present study was to investigate postnatal variants of Turner syndrome by cytogenetic study. Total of 1530 cases were referred to the researchers laboratory for cytogenetic analysis (karyotyping), out of which 61 cases of Turner syndrome (TS) diagnosed between March 2005 and January 2014. The most observed karyotype was classic 45,X (49.2 %) followed by iso(X) and iso(X) mosaic each (9.8 %) and least case of number one (1.6 %) was recorded with ring (Xr). Interestingly two cases of Robertsonian translocation t(13;14) were noticed which are considered to be rare. On the basis of clinical features of TS, such as primary or secondary amenorrhea with short stature, the confirmation was done by chromosomal analysis, karyotyping and FISH.

INTRODUCTION

Turner syndrome (TS) is the only sex chromosome disorder in which complete absence of X-chromosome is compatible with life. The loss of one of the sex-chromosomes in Turner Syndrome occurs after zygote has formed or after fusion of gametes (Eduardo et al. 2011; Bispo et al. 2013). The frequency is 1 in 2500 in live births (Bondy et al. 2007). It is estimated that 3 % of all human fertilization are 45, X (Urbach and Benvenisty 2009). Turner syndrome clinical features include short stature, gonadal dysgenesis, primary or secondary amenorrhea, fertility, cardiac and renal problems. Mosaic TS is associated with infertility, secondary amenorrhea and recurrent abortions (Kammoun et al. 2008).

In recent studies, Mazzaschi et al. (2014) have revealed that cytogenetic findings can be usedfor observed phenotypic features in Turner syndrome. Similarly, Demirhan et al. (2014) havestudied the frequency and types of chromosomal abnormalities in Turkish women with amenorrhea and concluded that primary and secondary amenorrhea could be due to chromosomal aberrations in TS.

According to published cytogenetic reports, chromosome monosomy (45, X) is found in 45-55% of cases, other karyotypes with structural changes in X chromosomes are 25-30% including iso-chromosome of long arm, mosaic isochromosome, deletion and ring.

In an attempt to correlate variation in TS the cytogenetic study was carried out in large samples (2005-2014) and it was compared with clinical analysis to find out genotypic and phenotypic correlations.

MATERIAL AND METHODS

The case records of pediatrics and female patients who underwent karyotyping (G- Banding) of peripheral blood lymphocytes were analyzed from March 2005 to January 2014. All these patients referred with clinical features having short stature and primary or secondary amenorrhea.

The cytogenetic study having cell culture from phytohemagglutinin-stimulated peripheral blood lymphocytes using standard conventional method. At least 25 metaphases were studied for karyotyping. G- banding was performed to identify individual chromosomes. The automatic scanning system (Axioimager Z_2 – Carl - Zeiss) and karyotyping software (IKAROS, Germany) was used to make karyotype. Interphase Fluorescence in situ Hybridization (FISH) analysis was performed using fresh slide, the procedure followed as per instruction given by company. Cytogenetic nomenclature followed according to guidelines from the International System for Human Cytogenetics Nomenclature (ISCN 2009, 2013).

RESULTS

Sixty-one patients with Turner syndrome were identified diagnostically during the nine years from 2005 to 2014. The karyotyped distribution of 61 patients is presented in Table 1.The-

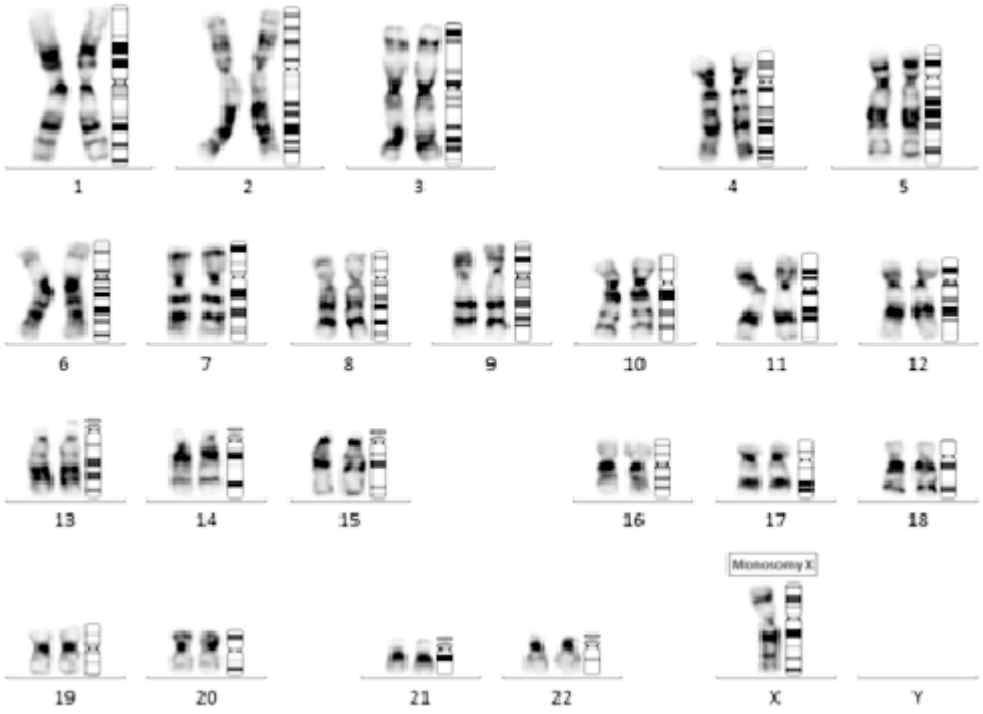
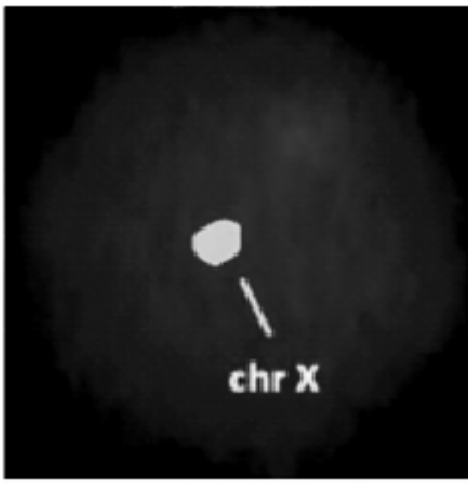
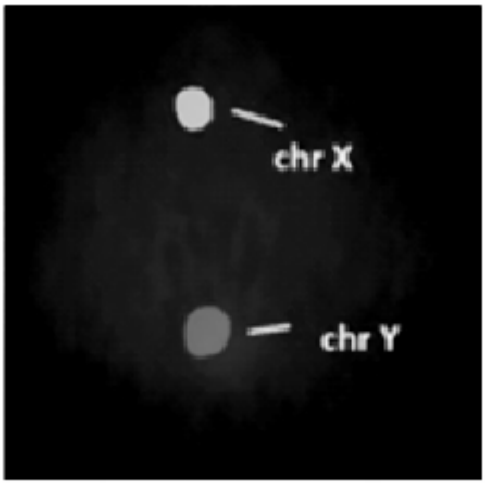


Fig. 1. Karyotype of patient shows classic Turner syndrome 45,X



Interphase cell showing 1 Green signal indicated by an arrow, (55%)



Interphase cell showing 1 Orange and 1 Green signal indiaed by an arrow, (45%)

Fig. 2. Interphase FISH shows mosaic Turner syndrome 45 X 155/46 XV1451

Table 1: Turner syndrome variants - Distribution of karyotypes in 61 cases

S. No.	*Karyotype group*	*Karyotype patients*	*No*	*%*
1	Classic Turner Syndrome	45, US, X	30	49.2
2	Iso Chromosome (X)	46 Xi (X) (q10), 46,Xi,X(910)	6	9.8
3	Iso (X) mosaic	45, X / 46, X iso (Xq)	6	9.8
4	47, XXX mosaic	45, X / 47, XXX	4	6.6
5	46XX, mosaic	45, X / 46 XX	3	4.9
6	46 XY, mosaic	45, X / 46 XX	3	4.9
7	Autosomal translocation	46, XX, rob (13;14); 46 XY, rob (13;14)	1+1}	3.3
8	Inversion	45, X, inv(q) (p11; 12)	2	3.3
9	Ring	45, X / 46 X, r	1	1.6
10	Complex mosaic	a) 46, X del (Xq 13) / 45, X	1	6.6
		b) 45, X / 46, X, add (Xq)	1	
		c) 46, X add (Xp) / 45, X	1	
		d) 45, XX, der (14), t(14;15) (q32;q11.2),-15	1	

most common was classic TS with 30 patients (49.2%). The age of was ranged from 7 days to 22 years old. In most cases TS was diagnosed at age of puberty. The mean age was13 ± 2 years.

In 85% of all cases short stature was the most frequent phenotypic features. The short statue was observed more in number with monosomy as compared to other abnormalities. The other

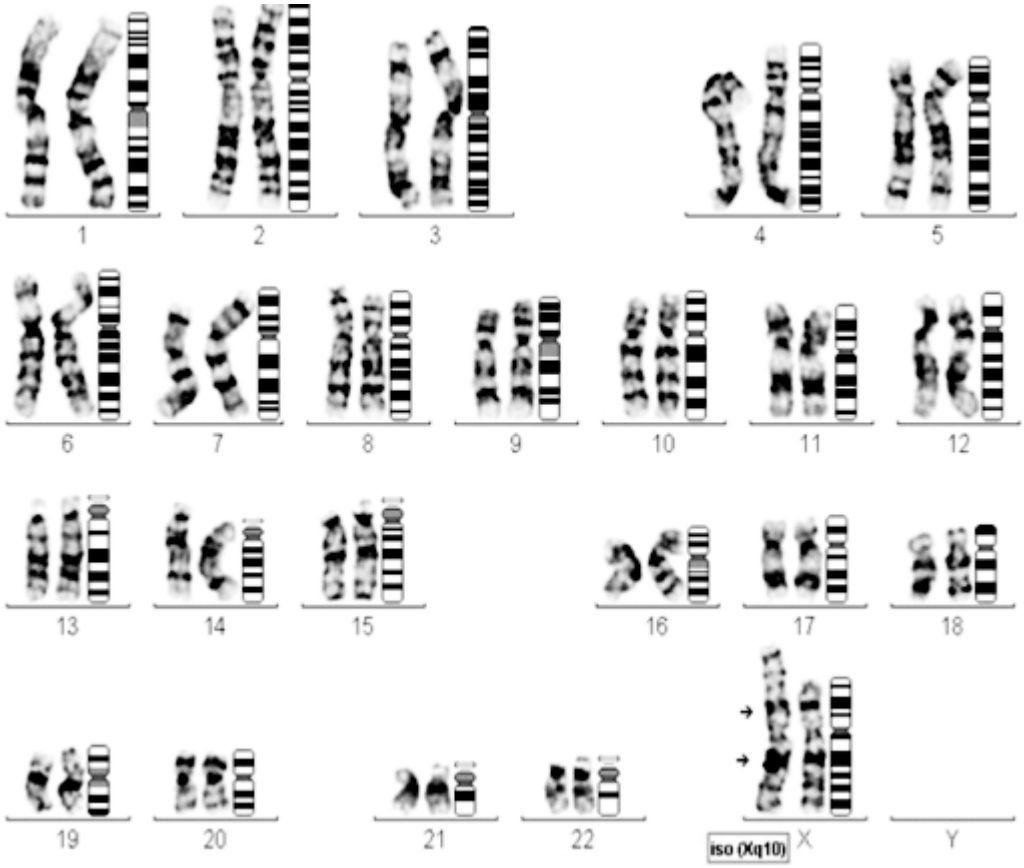


Fig. 3. Karyotype of patient shows 46.X,i(X)(q10)

important characteristics was primary and/or secondary amenorrhea more in case of monsomy as compared to those of mosaic and translocation.

The karyotype of typical classic TS is shown in Figure 1 where there is monosomy X. However, Figure 2 shows interphase FISH with mosaicism having chromosome complement of 45,X (55)/46, XY (45). In the study the researchers found structural changes inX-chromosome (Fig. 3) which was present in 19.6% having chromosome complement of 46, X, i(X)(q10).

The researchers have also recorded two cases with autosomal Robertsonian translocation such as 45, XXrob(13;14) and 46,XY, rob(13;14) which are rare in nature. One case each of inversion45,X,inv(9)(p11q12) and a ring with mosaic 45,X/46Xr respectively was also recorded (Table 1).

DISCUSSION

Turner Syndrome (TS) is the consequence of complete or partial absence of one X – chromosome in a female with short stature and gonadal dysgenesis (Bharath et al. 2010). The frequency is 1 in 2500 in live births based on data from Europe, Japan and United States (Bondy et al. 2007). TS is a chronic disease associated with a wide range of malformations with varying frequencies in different populations mainly related to X-chromosome rearrangements.

Molecular studies have shown that the maternal X is retained in two-third of patients withTS and paternal X in the remaining one- third. More than one-half of all patients with TS have mosaic chromosome complement (Zneimer 2014). The molecular mechanism(s)responsible for gonadal failure with X-chromosome deletions could involve the loss of putative ovarian determinant gene(s) necessary to be present in two copies during ovarian development (Meenakshi et al. 2014).

In the present cytogenetic analysis of 61 TS patients is in good agreement with previously published reports (Djordjevic et al. 2010; Elleuch et al. 2010; Bispo et al. 2013). In the present study, out of 1530 cases which referred for chromosomal analysis, the researchers noticed 61 cases of TS, out of which 50 % with 45, X classic TS followed by iso(X) and mosaic iso(X).

The researchers also found two cases of rare chromosome rearrangements of balanced translocation with TS. They are X- monosomy with balanced Robertsonian translocation t(13;14). Earlier Krajinovic et al. (1994) and Silva et al. (2006) havealso reported four cases of X- monosomy and Robertsonian translocation of t(13;14). Further, the researchers also found one case each of inversion and airing which are normally found with X- monosomy in varying frequencies.

In conclusion, it was observed that the patients with 45, X karyotyped exhibit more severe phenotypes than those with mosaicism. TS is a chromosomal disorder and frequently it is being misdiagnosed, therefore, it is suggestive that any female with short stature and primary or secondary amenorrhea, with or without phenotypic features should be confirmed by chromosomal analysis. Early recognition and timely investigation will improve their quality of life.

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