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Association of Parental Origin with Phenotypic Profile in Turner Syndrome

Sayee Rajangam[1], **Vallabhajosyula Ranganath**[2*] **and Leelavathy N**[3]

[1]*Department of Anatomy, International Medical School, Bangalore, India*

[2]*PUGSOM, Perdana University, Selangor, Malaysia*

[3]*Department of Anatomy, Oxford Medical College, Bangalore, India*

[*]**Corresponding author:** Ranganath V, Associate Professor, Hall 'D', Level 1, MAEPS building, MARDI complex, University Putra Malaysia, 43400, Selangor, Malaysia, Tel: +60137955485; E-mail: ranganath@perdanauniversity.edu.my

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Abstract

Objective: The objective of the study is to report the association between the phenotype of the Turner syndrome with that of its karyotype and the parental origin of the X. 181 female referred to division of human genetics, St. John's Medical College with different referral reasons are included in 1st phase of the study to observe the karyotype, upon obtaining the consent. Families of probands with confirmed pure or mosaic (more than 10% of mosaic status) karyotype of Turner stigmata are requested to participate in 2nd phase of study to determine the parent of origin. 20 families agreed and gave the consent for the study.

Material and Method: The Karyotype analsyis was carried by GTG banding method automated karyotyping system. The parental origin was determined by X chromosome specific short tandem repeat (STR) markers. 23 Turner stigmata features were listed in the proforma. The secondary measure is to observe the associated Turner stigmata with the determined karyotype and the parental origin.

Results: In 11 female probands, one had X structural abnormality (45,X/46,X,i(Xq)); 2 had X-mosaicism (45,X/46,XX) and 8 had 45,X. The determined parental origin of X was maternal in 8 (72.7%) and paternal in 3 (27.2%).

23 phenotypic features of Turner stigmata were tabulated. The features were further categorized as general observations, classical features of TS, features based on ultrasound findings and behavior. Percentage analysis indicated that a higher concordance of phenotype and behavior in proband with maternal X.

Conclusion: In the present study, the Turner syndrome features were seemed to be associated with the maternal origin of X in Turner syndrome.

Keywords: Karyotype; Phenotypic profile; Turner syndrome; Cardiovascular disorders; Visual acuity

Introduction

Normal female possesses XX chromosome one derived from mother (Xm) and other from father (Xp). Turner syndrome (TS), an sex chromosomal aneuploidy seen in female with 45,X karyotype in more than 50%; 30% to 40% are mosaic and the rest with structural changes. The most commonly seen structural chromosomal abnormality is isochromosome formation followed by ring formation and the other types [1]. Molecular studies have shown that approximately 60% to 80% of monosomy is due to absence of paternally derived X that occur either during mitosis in the embryo or meiosis in the father [2]. The phenotypic clinical profile in TS is variable for unknown reasons. It is speculated that the variability depends on origin of X. Retrospective studies indicate that the socio-cognitive features, social IQ and other behavioural activities in TS are associated with Xp (paternally derived) suggesting the existence of expression of genes of different genetic loci from the parent's X [3-6]. Association of parental origin with cardiovascular disorders [7], high degree of social activity, verbal and communications skills, visual acuity and memory are reported [8].

The findings from the existing literature clearly depict the variability of clinical profile with reference to parental origin primarily on socio-cognitive profile. There exists some paucity in literature to associate the karyotype, clinical profile with parental origin and correlation of the findings. Thus, the present study, attempted to correlate the phenotype with genotype i.e., the karyotype and the parental origin of X in TS.

Material and Method

The Sample consisted 181 female individuals referred to division of Human Genetics, Department of Anatomy, SJMC, Bangalore, with primary amenorrhea (PAm) as the main chief complaint and the other complaints were such as TS (?), Secondary Amenorrhea (SA), Bad Obstretric History (BOH), Primary Infertility (PI), Growth Retardation (GR), Ambiguous Genitalia (AG), Multiple Congenital Anomalies (MCA), Primary Ovarian Failure (POF), Sexual Infantilism and Very Obese. At the time of referral, a clinical proforma was documented to report the expressed phenotypic features of the proband. With the informed consent, cytogenetic analysis was performed by conventional karyotyping method (Peripheral lymphocyte culture) and automated karyotyping system (Applied Biosystems).

The consent to determine the parental origin was obtained after karyotype confirmation. 20 TS female and families have given consent for parental origin detection. DNA was extracted from the proband and parents by modified phenol-chloroform method (Thangraj et al.) [9]. Quantification of DNA was carried by gel electrophoresis method. X chromosome specific STR (Short Tandem Repeat) markers of definite primer length used to amplify the DNA of proband and parents under specific PCR settings (BIORAD). The amplified product was subjected to GENE SCAN (Applied Biosystems 3730) for parental origin determination. The results of GENE SCAN was analyzed and interpreted in GENEMAPPER (ABI Prism Linkage mapping sets v2.5 user's manual)

The listed phenotypic features that were documented are correlated with karyotype and the originated X. A percentage analysis was carried out to report the entire documented and observed data.

Sl.No	Karyotype	n 11; %	Xm n 8; %	Xp n 3; %
1	45,X	8; 72.72	6; 75	2; 25
2	45,X/46,XX	2; 18.18	1; 50	1; 50
3	45,X/46,X,i(Xq)	1; 9.09	1; 100	-

Table 1: TS: Parental origin vs. karyotype (n11).

Results

The parental origin could be determined in 11 (55%) families with TS proband. Maternal origin of the X chromosome was confirmed in 72.7% (8) and paternal in 27.3% (3).

Table 1 shows the determined karyotype of 11 TS probands with the parental origin of X. 45,X karyotype was observed in 72.72% (8) cases; out of which 75% (6) showed maternally derived X (Xm) and 25% (2) paternally derived X (Xp).

Sl.no	Features	TS (11)	
		Xm (8)	Xp (3)
1.	Chief complaints at the time of referral		
	Primary amenorrhea (PA)	4	1
	?TS	2	-
	Short Stature	1	1
	Dysmorphic features	1	-
	Infertility		1
2.	Age at the time of referral (in years)		
	0-10	1	1
	11-20	7	1
	21-30		2
3.	Birth order		
	1	4	-
	2	2	2
	3	1	1
	10	1	-
4.	Maternal age at conception (in years)		
	16-20	4	2
	21-30	4	1
5.	Paternal age at conception (in years)		
	21-30	3	-
	31-40	5	2
	41-50	-	1
6.	Consanguinity		
	1st cousin	-	1
	Uncle-neice	2	-
7.	Education		
	Secondary schooling	5	1
	Preuniversity education	1	-
	Graduation	-	2
8.	Behaviour		
	Normal	5	3
	Subnormal	3	-
9.	Height (in cms)		
	<120	1	1
	120-140	4	-
	>140	3	2
10.	Stature		
	Short	4	2
11.	Low hair line	2	-
12.	Webbed neck	4	-
13.	Lymphedema	1	-
14.	Breast development		
	Hypoplastic	2	2
	Not developed	5	1
15.	Far apart nipple position	2	1
16.	Axillary hair growth		
	Absent	5	2
	Scanty	1	1
17.	Shield shaped chest	2	-
18.	Cubitus valgus	3	-
19.	Pubic hair growth		
	Absent	5	1

	Scanty	1	2
20.	Ultrasound findings		
	Hypoplastic uterus	3	1
	Infantile uterus	2	-
	Streak gonads	4	1
21.	Not attained menarche	6	3
22.	Karyotype		
	45,X	6	2
	45,X/46,XX	1	1
	45,X/46,X,i(Xq)	1	-

Table 2: TS parental origin with general and clinical features.

X-mosaicism, the next common karyotype in TS was present in 2 and the parental origin was of equal percentage. The structural anomaly for X i.e.' iso chromosome for Xq was observed in one and the normal X of that case was found to be maternal. The features that were framed in the TS proforma were listed in Table 2. The observed TS features are tabulated against the determined parental origin. The interesting observation was the behavior of TS probands. Subnormal behavior was observed in 3 TS probands with Xm. All the TS female with Xp showed normal behavior. The documented TS stigmata such as low hair line, webbed neck, lymphedema, cubitus valgus, absence of axillary and pubic hair growth (secondary sexual character), hypoplastic and infantile uterus, streak gonads was high in Xm derived TS probands. Abnormality of paramesonephric derivatives are confirmed by ultrasound findings.

Discussion

The investigations to determine the parental origin were carried out either on single case or in a number of selective cases with 45,X or X-mosaicism or X-structural abnormality. Boczkowski in 1966 [10] based on Xg blood grouping, determined the maternal origin of single X in one patient; Schinzel et al. [11] in 1993 with X-linked molecular probes, reported the maternally originated X in one patient; Krajinovic et al. [12] in 1994 based on polymorphic microsatellite markers determined the paternally derived X in one patient; Pasarell et al. [13] in 1999 with PCR based polymorphic microsatellite markers, determined the maternally and paternally derived X in two cases and da Silva et al. [14] in 2006 reported the maternally derived X in one patient based on PCR based polymorphic microsatellite markers. A high percentage was noticed for maternally derived X. It was observed from the literature that the reported percentage of maternally derived X. The observations of the present study were within the reported range for each category. The observations of the present study for maternally derived X (Xm) (72%, 8) and paternally derived X (Xp) (28%, 3) were similar to the study by Mathur et al. [15] (72% Xm; 28% Xp). The findings of the maternal origin of 72% in the present study may be interpreted that a higher percentage of paternal X might have been lost from the normal female (46,XX) or male (46,XY) zygote.

The parental origin of X was determined mostly in probands with 45,X, because the incidence of that karyotype in TS is around 40 to 50%. The reported range of Xm with 45,X was 36.70 [5] to 68.75% [16] and for Xp with 45,X, the range was 12.76 [5] to 20.37% [17]. The observations of the present study, 54.5% Xm and 18.18% Xp with 45,X karyotype was within the reported range.

Association of TS stigmata with Xm was observed to be on higher side than the reported finding from the literature. It was observed in the present study that except for the reproductive system, TS with Xm or Xp origin did not manifest any abnormal systemic features. As stated in literature [8,15] in the present study too, the association OF the pheotypic features and parental origin was minimal, with more concordance with Xm

In the present study, features were categorized into 23 groups that are gathered from proforma (two parts for ultra sound findings – uterus and ovary). The calculated total numbers of 23 features are multiplied for the sample of 11 was 264. Irrespective of the parental origin, the TS females manifested 54.1% of the abnormal TS features. Out of which, with Xm [8], the manifestation of phenotypic features was 73.42% and with Xp [3], it was 26.57%.

The observation of 54.1% of the manifestation of TS features, in the present study, could be interpreted that, in Indian women, the severity of the features were more associated with Xm. From, the findings it could be opined, that out of the listed features, in case scoring is carried out, any suspected TS with 50% scoring and above might have X and a similar prediction could be applied for Xp. From the findings, it is seen, thus, a TS diagnostic criteria has emerged for the individuals with TS in India.

Conclusion

In TS, out of 11, structural abnormality of X was observed in one with the determined karyotype of 45,X/46,X,i(Xq); 2 had X-mosaicism (45,X/46,XX) and the remaining 8 had 45,X. Parental origin of X was determined in 11 cases. The maternal origin in TS was 72.7% [8] and paternal in 3 (27.2%). On correlation, in TS, it was observed that ≥ 50% of probands with maternally derived X, showed high degree of TS Stigmata which can correlated with chief complaint and age at the time referral. The 23 features were listed from TS proforma showed the manifestation of 54.16% of abnormal TS features irrespective of parental origin. Out of which, with Xm [8], the manifestation of phenotypic features was 73.42% (105/143) and with Xp [3], it was 26.57%

The observations of features in TS, could be interpreted that, in Indian women, the severity of the features were associated with TS females with Xm.

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