

**45,X/47,X,i(X)(q10),i(X)(q10)/46,X,i(X)(q10)**  
**Isochromosome Xq in Mosaic Turner syndrome**

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**ABSTRACT** A 17-year old female has been referred for karyotyping and genetic counseling. Proband had primary amenorrhea, short stature and poorly developed secondary sexual characteristics. Ultrasound scanning showed hypoplastic uterus and gonadal dysgenesis. Chromosomal analysis revealed the mosaic status for the isochromosome formation in the long arm of X, i(Xq). Proband had 3 cell lines. Her karyotype: 45,X(4%)/ 47,X,i(X)(q10), i(X)(q10)(8%)/ 46,X,i(X)(q10)(88%). Proband has expressed X numerical anomaly for the constitutional X structural anomaly. Proband and family were counseled about education, career, appropriate medical management and hormonal therapy.

## INTRODUCTION

Isochromosome is defined as the structurally abnormal chromosome consisting of either two short or long arms, because of the abnormal transverse misdivision of the centromere (centric fission), resulting in unbalanced chromosomal constitution, monosomy for the missing and trisomy for the duplicated arms (Young 2005). The formation may also be because of the more complex U-type exchange resulting in acentric or dicentric products. The process of isochromosome may occur in pre meiotic gamete, during meiotic cell divisions or in post zygotic cell divisions of a normal or trisomic conceptus (Gardner and Sutherland 2004). The symbol 'i' is in use to indicate the isochromosomal status (ISCN 2005).

Mosaicism is the presence of two or more cell lines with different chromosomal constitutions in the affected individuals. The cell lines mostly are derived due to post zygotic mitotic non disjunction and for example represented as 45,X/47,XXX/46,XX. The number of the cell lines or the percentage may be given in bracket and

the normal diploid karyotype is written last (Turnpenny and Pellard 2005; ISCN 2005).

Turner syndrome (TS) was first described in 1938 and the chromosomal cause was established in 1959. It is a case of the X chromosomal aneuploidy, that is monosomy status compatible with relatively normal growth and development (Turner 1938; Ford et al. 1959). TS incidence is around 1 in 5000 newborn females, even though 97% of the TS conceptions are spontaneously aborted.

On chromosomal analysis, the percentage occurrence 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%) (Graham et al. 2007)

In this article we report the observed mosaic karyotype for the isochromosome formation in the long arm of X in referred individual with primary amenorrhea.

## CASE REPORT

Proband female, 17-years old was 3<sup>rd</sup> born to non-consanguineous parents aged 42 and 50 years respectively. Family history was non-significant. Her younger sister 15 years old had attained menarche at 12 years.

Proband was of normal built. Her weight was 32 kg and her height 4' 4". Her secondary sexual features were poorly developed: scanty axillary hair, absent pubic hair, hypoplasia of breast and child voice. Short stature and primary amenorrhea were the chief complaints at the time of referral.

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## Investigations

*Ultra Sound Scanning:* Bilateral non-visualised ovaries and hypoplastic uterus.

*Chromosomal Analysis:* GTG banded peripheral lymphocyte culture.

*Karyotype:* 45,X(4%)/47,X,i(X)(q10), i(X)(q10)(8%)(qter→q10::q10→qter) (qter→q10::q10→qter)/46,X,i(X)(q10) (qter→q10::q10→qter) 88% (Fig. 1).

The presence of the 3 cell lines and the 2 times the i(Xq) was reconfirmed.

## DISCUSSION

Proband has expressed TS phenotype and the genotype. The 2 cell lines of 45, X and 46, X,i(Xq) fall under the 15 to 50% of the reported karyotypes in TS. Moreover, the mosaic nature of X is also the most viable karyotype in sex chromosomal aneuploidy. The distinguishing feature is the presence of the 3<sup>rd</sup> cell line with double (i.e. two times the isochromosome for the long arm of X). This finding may be the first report, since no such case is seen in the literature.

## X Inactivation

In normal females, in early embryonic development, one of the two Xs is randomly and permanently inactivated in nearly all somatic cells and it is ensured that females like males may have one functional copy of the X, it is also known that in normal female with two Xs, not all the genes are inactivated. During the reproductive period, in spite of the X inactivation, some loci are functionally disomic. For example, genes in Xp22 in the pseudoautosomal region and in the critical regions in Xq13→q27 may not be inactivated.

## Mechanisms

Most of the i(Xq)s are isodicentric or pseudoisodicentric, because the activity from one of the centromeres is suppressed. In X chromosome, the mechanism of the formation is the U-type exchange and reunion between the sister chromatids of the X and frequently associated with 45, X cell line. The absence of the normal cell line in mosaic state indicates that i(Xq) may be predominantly of meiotic origin (James et al. 1997 cited in Ferguson-Smith and Simonic 2007).

## Molecular Correlation to X

X chromosome belonging to the C group of chromosomes, spans 153 million bps of DNA and forms 5% of the total DNA in the cells of women and 2.5% in men. Even though, 2000 genes in the human genome have been attributed to X it is considered to be 'gene poor chromosome' because it is composed primarily of repeated segments of DNA, which do not code for proteins of any known function. 165 and 243 genes loci have been located to the 88 and 115 regions in the short and long arms of X (McKusick and Amberger 2002; Graham et al. 2007).

The critical region in X, Xq13→q27 has 127 genes and the candidate genes for gonadal dysgenesis include RPS4X and DIAPH2 on Xq and DFRX4 located at Xp11.4. A popular candidate gene on the X long arm is the human homolog of the *Drosophila melanogaster* gene diaphanous (dia). This gene causes sterility in male and female flies. Sequence comparisons between 'dia' and the human EST (expressed sequence tag) DRE25 has revealed a significant homology. DRE25 also maps to human Xq21-22, a region important for ovarian maintenance. *Drosophila* 'dia' is member of a family of proteins, which establish the cell polarity, govern the cytokinesis and reorganize the actin, cytoskeleton. Studying the familial premature ovarian failure in Xq21; autosome translocation, it was found to be associated with the disruption of DRE25 (Simpson and Elias 2003). XPNPEP2 encodes Xaa-Pro aminopeptidase (metallo-protease) that hydrolyzes proline bonds. XPNPSP2 was disrupted in Xq translocation and Xq25 was the region involved (Simpson and Elias 2003).

In 45,X Turner syndrome, the haplo-sufficiency for SHOX gene (short stature homeo-box containing gene) in Xp may account for the short stature. Likewise, from the critical region in Xq, functional monosomy may result in primary or secondary ovarian failure and affect ovarian and uterine cycles (Gardner and Sutherland 2004).

The i(Xq) appearing as the metacentric chromosome consists of the isologous arms, which are structurally identical and contain the same genes. Almost all 46, X,i(Xq) individuals manifest streak gonads. Complete ovarian failure and partial ovarian failure have been reported in 91% and 9% of cases with i(Xq) individuals. Short stature and TS stigmata are also found to be frequent. The almost complete lack of gonadal

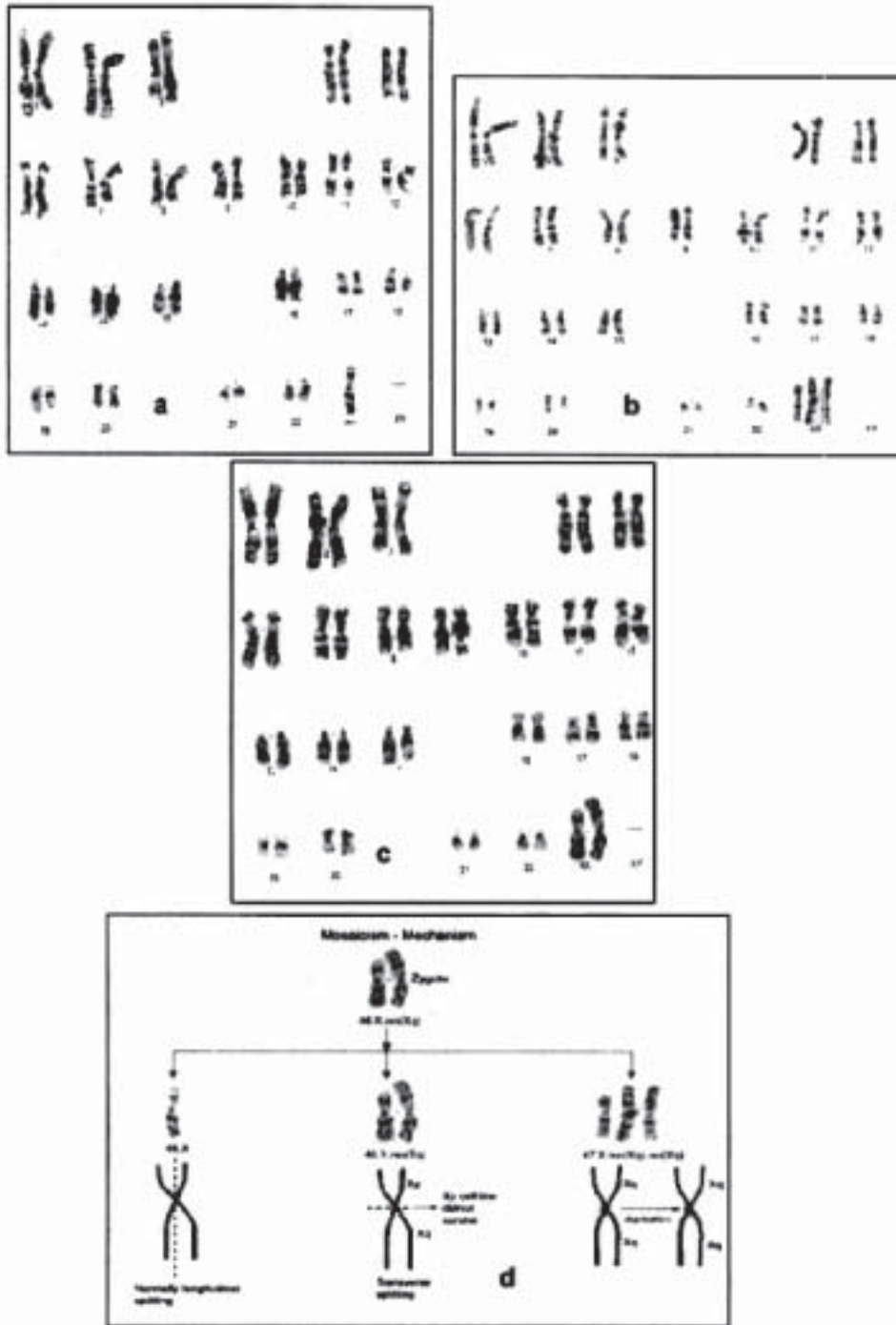


Fig. 1. a. 45, X(4%)/ b. 47,X,i(X)(q10), i(X)(q10)(8%)/ c. 46,X,i(X)(q10)(88%) d. Diagrammatic representation – isochromosome formation and non-disjunction from 46,X,i(X)(q10) female zygote.

development in 46, X, i(Xq) contrasts with 46,X,del(Xp11) about 50% of whom menstruate or develop breasts (Simpson and Elias 2003).

### Present Study

Proband has showed both the numerical and structural anomaly for the X chromosome. X centromere instead of the longitudinal separation has undergone transverse separation. Thereby, the short and the long arms have resulted in the formation of the isochromosome. The isochromosome for the long arm has been preferentially retained. The higher percentage of the isochromosome for the X long arm has indicated that the proband, as the zygote, may have started with 46, X,i(Xq) cell line. The structural anomaly may have tried to correct itself by non-disjunction resulting in the other 2 cell lines 45, X and its counterpart the 47,X,i(X)(q10),i(X)(q10). The isochromosome belonging to the 45-cell line category naturally has been included in the 47 cell lines.

In the present study, the female proband has manifested the features of TS, because in spite of the 3 cell lines and the X structural anomaly, as per the rule of selective Lyonization, the abnormal X may have undergone the X inactivation phenomenon. In the proband, if the genes in Xq are transcribed, then it will result in functional trisomy and pentasomy that is 3 times the products in the predominant 46,X,i(Xq) and 5 times in 47,X,i(Xq) cell lines. In all the 3 cell lines there definitely exists the functional monosomy for the products from the short arm of X. Thus, proband has shown short stature and gonadal dysgenesis reflecting the functional monosomy for the stature as well as the amenorrhea. In the proband, the bigenic or allelic products have not been transcribed. Hence, for all practical purposes she must have been genotypically and phenotypically functioning as TS.

It is to be noted that these lines have been considered from the peripheral lymphocyte culture.

### Genetic Counseling

Proband and her parents were communicated

about diagnosis, prognosis, education and career (after Harper 2004). Then, hormonal assay for thyroid hormones-T3, T4, thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH) and lutenising hormone (LH) were advised. The clinical management by hormonal therapy, and referral to the endocrinologist were provided. Symptomatic management in the presence of any medical conditions was informed. Follow up for the marriage and reproductive options were emphasized.

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