RESEARCH NOTE

A mother with variant Turner syndrome and two daughters with trisomy X: a case report

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Introduction

Though fertility among mosaic Turner syndrome women has been reported, spontaneous pregnancy is rare with risk of miscarriages and chromosomal abnormalities (Rizk and Deb 2003). We report an unusual family in which a mother with mosaic 45,X[13]/46,X,add(X)(?q26)[17] gave birth to two children bearing 47,XX,add(X)(q26)mat. Both children, aged 12 years old and 9 years old, presented with learning disabilities and subtle dysmorphism. The mother has premature menopause but did not have learning disability or dysmorphism. Whole chromosome painting revealed that the abnormal chromosome X in both sisters was duplicated chromosome X, which was inherited from their mother.

Turner syndrome is characterized by absence of all or part of one X chromosome from all or some cell lines affecting approximately 1 in 2500 live births (Rizk and Deb 2003). Features include short stature, gonadal dysgenesis, primary amenorrhoea, decreased fertility and anomalies of cardiac, renal and endocrine origin. Mosaic Turner syndrome is associated with infertility, secondary amenorrhoea and recurrent abortions (Kammoun *et al*. 2008). Spontaneous conception among Turner syndrome patients is extremely rare with cases reported mainly in mosaics. About 30% of these pregnancies have a normal outcome while the rest are complicated by chromosomal abnormalities such as recurrence of X chromosome defect in female offspring and trisomy 21, stillbirths, foetal malformations and recurrent abortions (Rizk and Deb 2003).

Trisomy X is a common female chromosome abnormality, occurring in approximately 1 in 1000 births. It has a variable phenotype and includes learning disabilities, speech delays, behavioural problems, seizures, genitourinary abnormalities and premature ovarian failure (Tartaglia *et al*. 2010).

We report a family in which a mother with variant Turner syndrome conceived without artificial assistance and gave birth to two daughters with trisomy X. To our knowledge, this has never been reported before.

Case report

Two sisters aged 12 and 9 were referred for learning disabilities. The elder sister was born after an uneventful pregnancy at full term with a birth weight of 2.6 kg. She had frequent albeit transient choking on feeds postnatally and recurrent febrile seizures from 10 months to two years. She had global developmental delay and was noted to have learning disability since six years of age. Her intelligence quotient (IQ) evaluation using comprehensive test of nonverbal intelligence (CTONI) showed a score of 80. Although currently independent in activities of daily living, she could only identify body parts and objects and had poor expressive and receptive speech. She also had behavioural problems, mainly in the form of temper tantrums, overfamiliarity with strangers and aggressive behaviour, which seemed to worsen as she grew older.

Her head circumference was small (2nd centile) while her height and weight were both at 50th centile. She had some dysmorphic features including full cheeks, right auricular pit, tapering long digits, mild hypertelorism and lateral deviation of toes. Examination of her other systems were essentially normal.

The younger sister was born term, vaginally, with a birth weight of 3 kg. There were no antenatal or postnatal complications and she had attained normal early developmental

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milestones. She had features of attention deficit hyperactivity disorder (ADHD) and poor school performance, although better than her sibling. Her IQ evaluation using CTONI showed a score of 83. Her growth parameters were all below 5th centile and she had subtle dysmorphism i.e. mild clinodactyly and lateral deviation of third toes. Systemic review did not reveal any abnormalities.

Chromosomal analysis of both sisters showed 47 XXX with one of the chromosome X being abnormal (figure 1). Karyotyping of the mother revealed 13 cells with 45,X and 17 cells with 46 X, (add) X in which there is an additional material of unknown origin at the long arm of one of the X chromosomes (figure 2). Whole chromosome paint (WCP) using X chromosome probes confirmed that the additional material originated from chromosome X. Thus, the mother's karyotype was consistent with variant Turner syndrome. Both her daughters inherited this aberrant X chromosome. The father refused to consent for chromosomal analysis.

Their mother had premature menopause at 35 years of age and required hormonal replacement therapy. She had no learning disabilities or dysmorphism. However, she has a twin sister who also had premature menopause at 35. Her twin sister has only child, a 10 year old daughter, who has

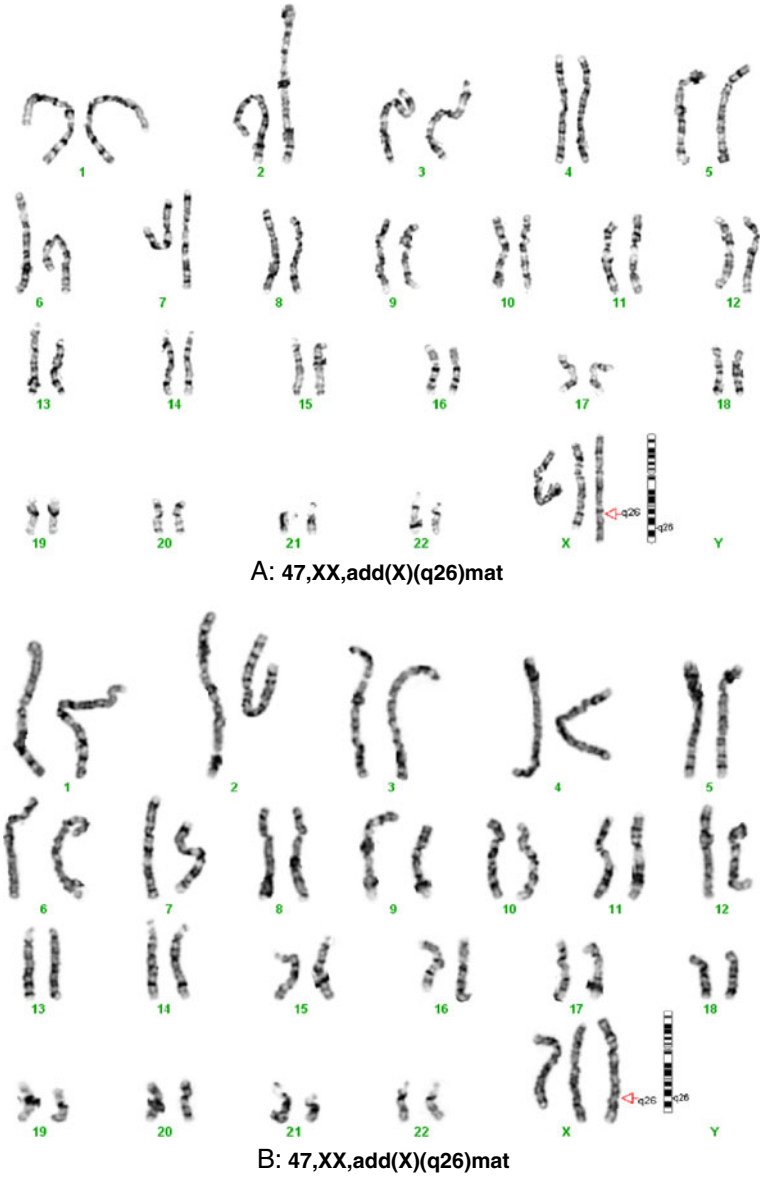

Figure 1. Chromosome analysis of (A) elder daughter and (B) younger daughter. The arrows show an extra chromosome X with additional material of unknown origin on the long arm (q26).

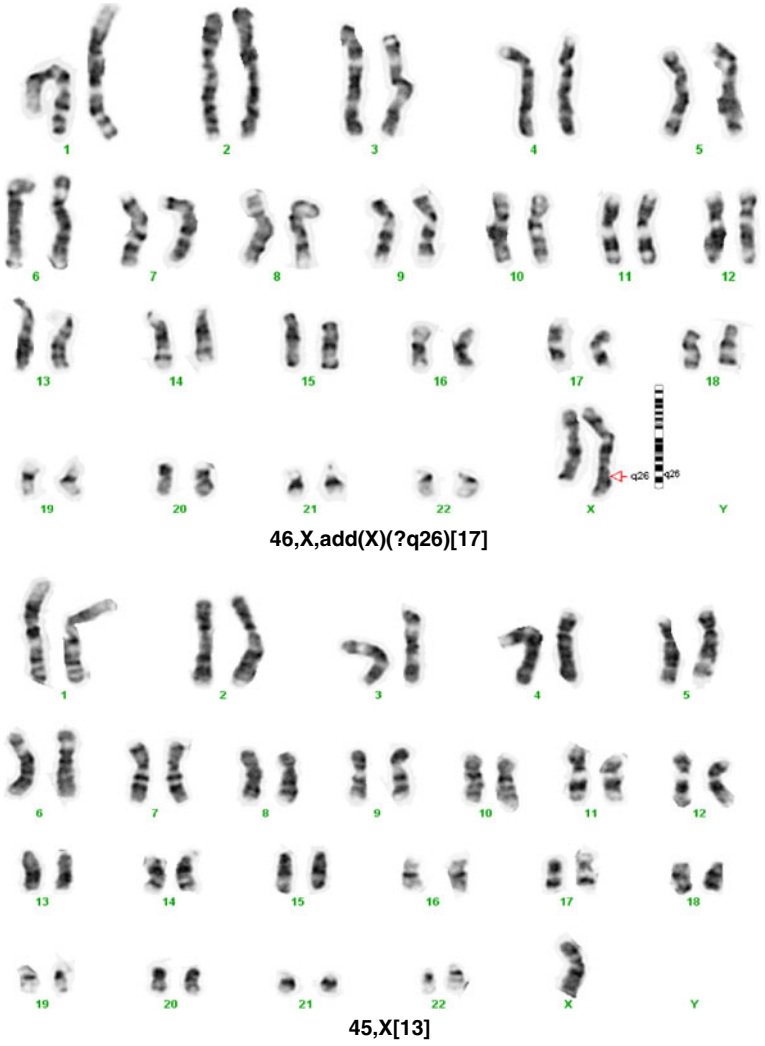

Figure 2. Chromosome analysis of the mother. Of the 30 cells examined, 13 cells showed a 45,X karyotype and the remaining 17 cells showed additional material of unknown origin at the long arm of one chromosome X (q26).

normal cognitive function. Both her twin as well as her twin's daughter have not had their chromosomes analysed.

Discussion

Pregnancies resulting from spontaneous ovulation and fertilization in Turner syndrome patients are extremely rare, occurring in about 2% of cases. It can occur in patients with mosaic karyotype containing 46XX cell line or in patients with structural abnormalities of chromosome X in which the genes thought to control ovarian function are spared (Tarani *et al*. 1998). Mosaicism (45,X/46,XX; 45,X/46,XY; 45,X/47,XXX) constitutes 16% of the karyotypic abnormalities in Turner syndrome (Rizk and Deb 2003).

In about 30% women with mosaic Turner syndrome, spontaneous puberty can occur due to partial ovarian function (Su *et al*. 2006). As they are often phenotypically normal and can have spontaneous conception similar to our index case, they are rarely detected during adolescence. Had it not been for her two daughters presenting with learning disability, behavioural problems and dysmorphism, which warranted chromosomal analysis, this mother's mosaic karyotype would have been detected a little later when she presented with premature menopause at 35 years of age.

In patients with successful pregnancies, complications are high. A review of 13 pregnancies in six women with Turner syndrome in Rome, Italy, (Tarani *et al*. 1998) revealed six abortions and eight livebirths of which four had chromosomal and physical abnormality. In 160 pregnancies involving 74 women with Turner syndrome, 20% had chromosomal abnormalities, which included Down and Turner syndromes among others (Tarani *et al*. 1998). However, to our knowledge, there were no reports of patients with mosaic Turner

with abnormal chromosome X undergoing spontaneous pregnancy with two daughters inheriting the abnormal chromosome X.

The retained fertility among women with variant Turner syndrome is presumably due to partial synapsis occurring at meiosis in 46,X, abnormal X oocytes, resulting in equal frequencies of gametes carrying either normal X or abnormal X chromosome under 1:1 segregation (Gardner and Sutherland 2001). However, this family has clearly demonstrated another outcome whereby nondisjunction during meiosis I resulting in trisomy X, which included the abnormal X chromosome, in the offsprings. This is consistent with the fact that 90% of nondisjunctions leading to trisomies X arise from an error during maternal meiosis, at least half during meiosis I division (Thomas *et al*. 2000). It is interesting that this has occurred twice in the same family. Recurrent trisomy X has been reported but it was shown to be secondary to nondisjunction at meiosis II together with reduced recombination (Reish *et al*. 2004). The latter is compatible with Angell's hypothesis of reduced pairing during meiosis I and premature chromatids separation before meiosis I is completed. The presence of duplicated X chromosome in this family may have interfered with pairing during meiosis I, thus leading to recurrent trisomy that included the abnormal X chromosome. It would be interesting to define the exact nature of the duplicated X to determine how reduced pairing could have occurred in this family. Alternatively, nondisjunction in paternal meiosis II could have led to the same outcome in the offspring if 24, XX sperm fertilized the 23, abnormal X ovum. However, recurrence of the same abnormal karyotype in both siblings and the fact that most trisomies X arise in maternal meiosis make this explanation less likely.

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