

CASE REPORT

Advanced paternal age effect on trisomy X syndrome

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ABSTRACT

Advanced parental age is a risk factor for chromosomal abnormalities in their offspring. Trisomy X or Triple X syndrome has previously been reported with advanced maternal age. Here we report two (2) cases of Trisomy X with paternal age as risk factor. Generally, Trisomy X individuals show variable physical and psychological manifestations. However, both cases reported here have advanced paternal age as a risk factor; 55 years old (46 years old at conception) for Case 1 with patient having right eye squint, beaked nose, Posterior Misalignment Type Ventricular Septal Defect (PMVSD) and small Patent Ductus Arteriosus (PDA) with failure to thrive and 49 years old (45 years old at conception) for Case 2 with speech delay and protruding tongue. In view of that, advanced paternal age could possibly contribute the accumulation of de novo mutations in germ line mosaicism.

Keywords: Trisomy X, 47,XXX, Advanced paternal age, Cytogenetic, Germ line mosaicism

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such as Down syndrome and Patau syndrome have also been associated with advanced paternal age as a risk factor. The incidence of Trisomy X which involve the sex chromosome is one (1) in 1000 in females. Previously Trisomy X syndrome has been reported to be associated with advanced maternal age, however there are few reports of its association with advanced paternal age. Here we report on two (2) patients diagnosed with Trisomy X syndrome. The blood samples of these patients were sent to our laboratory for chromosomal analyses for suspected syndromic abnormalities.

INTRODUCTION

Advanced parental age poses a risk to transmit new mutations to their offspring from the accumulation of de novo mutations in the germ line (germ line mosaicism), which in men are four (4) times faster than women and the statistical relationship of paternal age at conception and offspring's biological sequel to paternal age effects (1). A German obstetrician-gynaecologist, Weinberg (1912) first proposed paternal age effects and subsequently confirmed by Penrose in 1955 (2) and this phenomenon of advanced paternal age is defined as individuals aged 40 years or older during conception.

In Trisomy X, there is additional number of chromosomes, instead of the normal XX. With Trisomy X individuals, the chromosome is 47,XXX instead of 46,XX in the normal individuals. Other Trisomy cases

CASE REPORT 1

Patient one (1) is nine-year-old Malay female child, product of non-consanguineous marriage. The father is 55 years old (46 years old at conception) and mother 37 years old (28 years old at conception) (Table II). There is no history of chromosomal abnormalities in the other siblings. However, one female sibling (child number three) died at age of one week while there was history of two other abortions in the mother. This patient has dysmorphic features, with right eye squint, beaked nose, Posterior Misalignment Type Ventricular Septal Defect (PMVSD) and small Patent Ductus Arteriosus (PDA) with failure to thrive (Table I). Chromosome analysis was requested because of these reasons. The karyotype results reveal 47,XXX in 21 metaphases that examined with 400 ISCN bphs resolution (Figure 1).

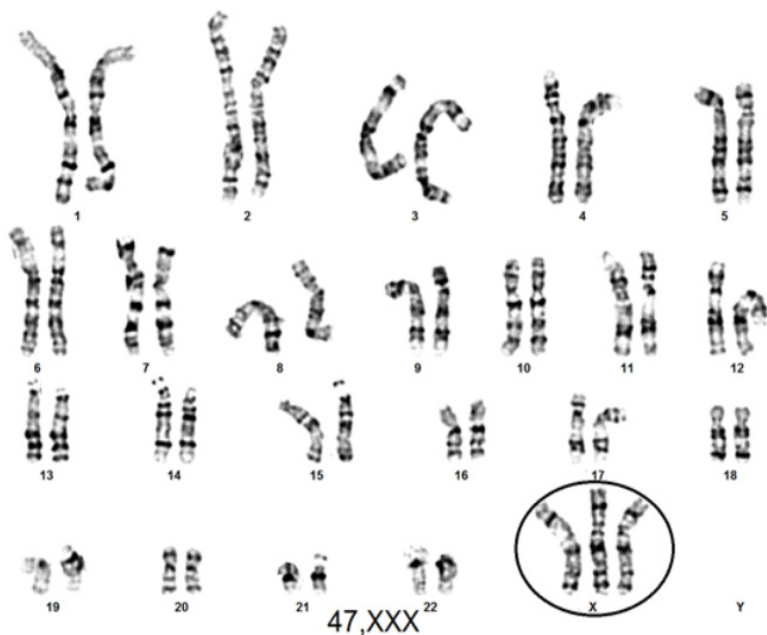


Figure 1: Case 1 karyotyping showed an extra X chromosome

CASE REPORT 2

Patient two (2) is four-year-old Malay female, youngest of six (6) children. The father is 49 years old (45 years old at conception) and the mother is 42 years old (38 years old at conception) (Table I). There is non- consanguineous and no known history of chromosomal disorder in the family. However, the mother has Thalassemia trait.

Other family members are not screened for Thalassemia. Clinical observation such as speech delay and protruding tongue was observed in the proband. The working diagnosis was Down syndrome since the physical abnormalities resemble this syndrome (Table II). The karyotype results reveal 47,XXX in 23 metaphases that examined with 400 ISCN bphs resolution (Figure 2).

Table I: The parental age profile of both patients

Patient	Father's Age	Mother's Age	Family History
Case 1	55 (46)	37 (28)	NA
Case 2	49 (45)	42 (38)	Mother has B-Thal trait, other family members not screen.

Table II: Clinical features and diagnosis of both cases

Patient	Clinical features/	Clinical Diagnosis	Chromosome Analysis
Case 1	Right eye marked divergent squint Nose beaked PMVSD with non systolic murmur	Failure to thrive with PMVSD, small PDA and subtle dysmorphism	47, XXX
Case 2	speech delay protruding tongue	Down Syndrome	47, XXX



Figure 2 : Case 2 karyotyping showed an extra X chromosome

DISCUSSION

Based on the previous cases reported on Triple X syndrome, the most common clinical features are speech delays, motor delays and learning disabilities. In this report, the clinical and psychological manifestation of Trisomy X were variable for each patient as described in Table I and II. The maternal age of patient 2 is 42 years old (38 years old at conception) years old and more advanced as compared to mother of patient 1. It is grossly unfair if no interaction occurs between paternal age and maternal age since it seems equitable to assume a positive correlation between the two factors is that the older men have a child with older women. However, both cases presented with advanced paternal age with incidence of abnormality of chromosome may be related to the semen quality such as semen volume, lower sperm motility, and a decreased percent of normal sperm (3). Studies have reported that quality of sperm from advanced paternal age associated with a mosaic germ line mutation which is significantly transmitted to their off springs (3). There is a possible contribution from mosaic germ line mutation involved in abnormal reproductive outcomes such as a high risk of non-disjunction, and the origin of chromosomal meiotic non-disjunction appears to vary considerably between parents and among chromosomes. Furthermore, as reported earlier, in 1000 off springs associated with non-disjunction from maternal during meiosis I include Trisomy 15, 16 and 22, while Trisomy 7 and 18 resulted in meiosis II (4). For paternal cases, 100% of XXY, Trisomy 2 and Trisomy 22 originated in meiosis I, whereas 100 % of XXX, XYY and Trisomy 15 originated during meiosis II (5). According to several evidences on parental age effects on the production of sperm and egg cells in females are predominant in the first stage of meiosis. Furthermore, genetically defective sperm would carry a mutation not only in the germ tissues but also carried to all somatic cells.

CONCLUSION

Although there is still limited research to prove advanced

paternal age with sperm quality especially in incidence of chromosomal abnormalities and post-mitotic cells that are vulnerable to genetic defects, some indirect observation of cases resemblance to these does relate to this inference. More studies are needed in this specific field and of similar cases to elucidate the scientific explanation to better understand the mechanism behind it.

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REFERENCES

1. De Meyer T, Rietzschel ER, De Buyzere ML, De Bacquer D, Van Crielinge W, De Backer GG, Gillebert TC, Van Oostveldt P, Bekaert S. Paternal age at birth is an important determinant of offspring telomere length. *Human molecular genetics*. 2007 Sep 19;16(24):3097-102.
2. Weinberg W. Zur vererbung des zergwuchses. *Arch. Rassen-u. Gesel. Biolog.*. 1912;9:710-8.
3. Delhanty JD. Inherited aneuploidy: germline mosaicism. *Cytogenetic and genome research*. 2011;133(2-4):136-40.
4. Eichenlaub-Ritter U. Parental age-related aneuploidy in human germ cells and offspring: A story of past and present. *Environmental and molecular mutagenesis*. 1996;28(3):211-36.
5. Hassold T, Hunt P. To err (meiotically) is human: the genesis of human aneuploidy. *Nature Reviews Genetics*. 2001 Apr;2(4):280.