SHORT COMMUNICATION

48,XXXX, A RARE ANEUPLOIDY

Kaur A[1,*], Pandhi M[2], Singh JR[1]

***Corresponding Author:** Anupam Kaur, Centre for Genetic Disorders, Guru Nanak Dev University, 143005 G.T. Road, Amritsar, India; Tel.: +91-183-2258802/2258809, Ext. 3277; Fax: +91-183-2258863; University Fax: 2258820; E-mail:anupamkaur@yahoo.com

ABSTRACT

The 48,XXXX chromosome constitution is a rare aneuploidy which shows some peculiar manifestations in affected females. This first report from India of tetrasomy X with bilateral, typical, complete coloboma of iris, shows the importance of chromosomal investigation and fluorescent *in situ* hybridization (FISH) in females with mental retardation and dysmorphic features.

Key words: Tetrasomy, Mental retardation, Coloboma of iris

INTRODUCTION

The first two females with the 48,XXXX karyotype were reported in 1961 [1]. Only about 50 cases have been described since [2], mostly as isolated reports. We report the first documented case from India and its distinctive features.

CLINICAL REPORT

MM9 was 13 years of age at the time of investigation, had moderate mental retardation (IQ-43), and was attending the Red Cross School for Mentally Challenged at Amritsar, India. A detailed pedigree analysis and evaluation of the clinical findings was undertaken. She was a full-term first-born of a 17-year-old mother and a 23-year-old father. She had a high forehead, flat nasal bridge, small ears, hypertelorism, divergent strabismus, bilateral, typical, complete coloboma of iris (6 o'clock position), extending up to the ciliary border, long philtrum, short neck, short fifth finger and a height of 162.8 cm (Figure 1). The skull radiograph was suggestive

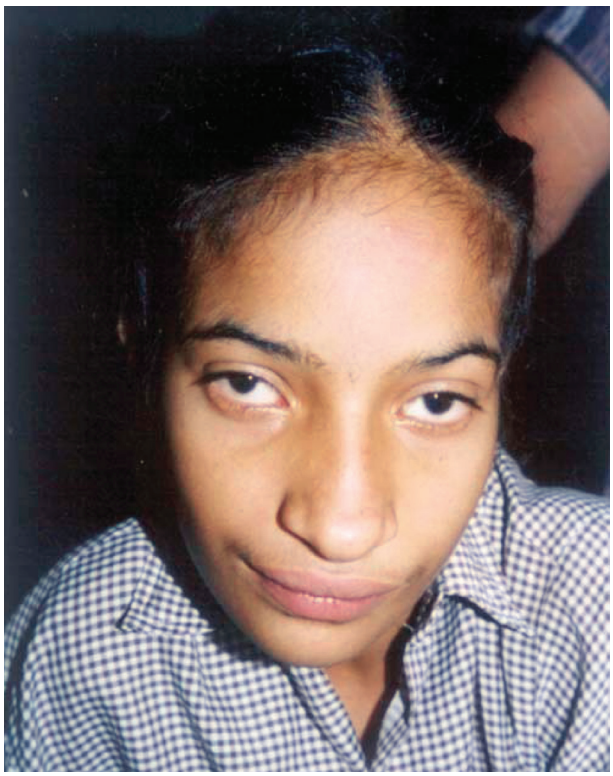

Figure 1. Facial features of a 48,XXXX female.

1 Centre for Genetic Disorders, Guru Nanak Dev University, Amritsar, 143005, India

2 Medical Service Provider, Rudhiana, Gurdaspur, India

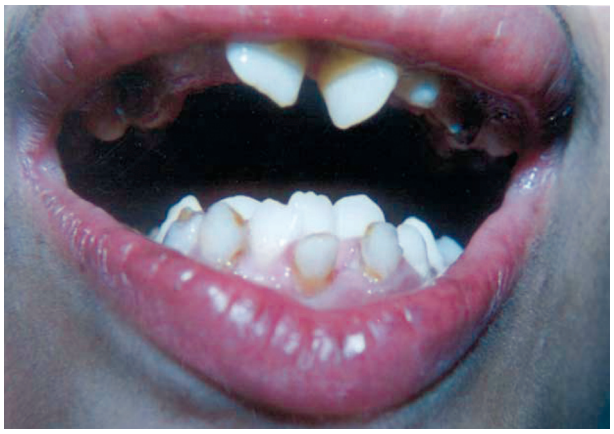

Figure 2. Taurodontism in 48,XXXX female.

perplasia (Figure 2). Ultrasonography of the abdomen showed normal results. Her uterus measured 6.5 × 2.5 cm. The ovaries were of normal size and she had a normal menstrual history. The serum levels of IgM, IgG and IgA were within normal limits. She showed delay in comprehensive and expressive speech. Her karyotype showed a non mosaic, chromosomal constitution of 48,XXXX (Figure 3). The karyotypes of her parents and her younger brother showed normal chromosomal constitution. For the fluorescent *in situ* hybridization (FISH) analysis, 500 interphase lymphocyte nuclei were scanned, and four signals were seen with the CEP-X probe (Figure 4). Her father had a history of head injury

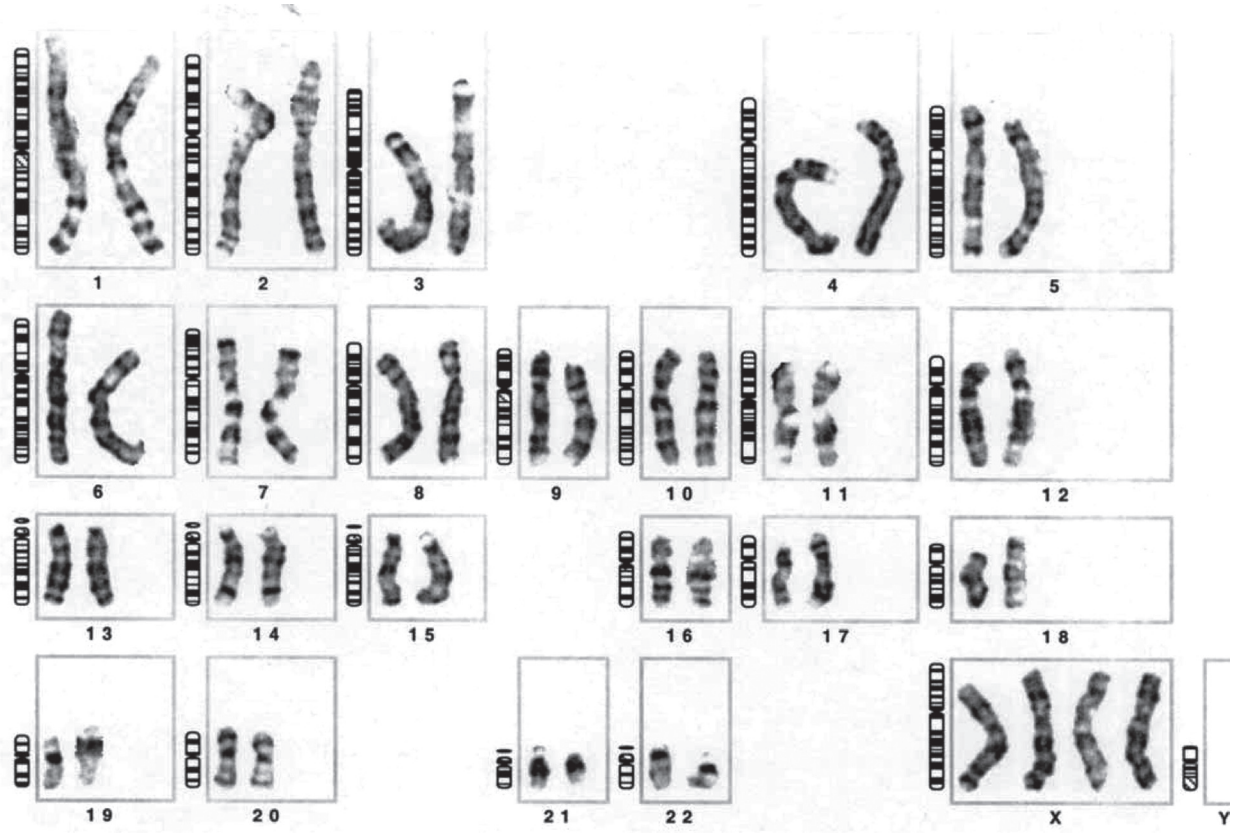

Figure 3. Karyotype showing 48,XXXX constitution.

of intracranial tension and bitemporal narrowing. The X-ray report did not indicate radioulnar synostosis, while elbow and wrist radiographs suggested her bone age to be 12 to 14 years. Her teeth were irregular and placed in two rows with gingival hyand subsequent seizures. He had been taking phenytoin at the time of her conception.

Cytogenetic and Molecular Analysis. Chromosomal preparations were made from phytohemagglutinin-stimulated peripheral lymphocytes

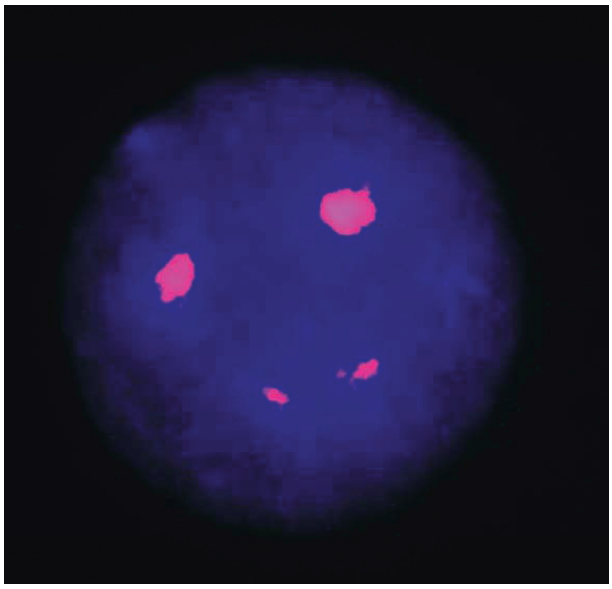

Figure 4. CEP X showing four X chromosome signals.

using RPMI1640 medium and standard culturing technique with modifications [3]. Chromosomal analyses were performed on all four family members. Chromosomal banding was done by Trypsin-Giemsa GTG banding. Consent was obtained from the parents before investigations began. From the patient, 100 metaphases were examined for numerical and structural chromosomal abnormalities and karyotyped, 500 interphase nuclei were scored for FISH which was performed with a CEP-X probe (spectrum orange) according to the manufacturer's instructions (Vysis UK Ltd., now part of Abbott Molecular, Des Plaines, IL, USA). After hybridization, a rapid wash procedure was followed. Chromosomes were counter stained with 4'-6-diamidino-2-phenylindole (DAPI) and viewed by using triple band-pass filter and Quips Smart Capture Imaging Software (Vysis UK Ltd.).

DISCUSSION

The distinctive clinical finding of the subject was bilateral, typical, complete coloboma of iris extending up to the ciliary border. This has not been previously reported in cases with the 48,XXXX constitution. Individuals with 48,XXXX have been described as pleasant, friendly, cooperative, aggressive and emotionally labile [4]. Our patient was shy with an IQ of 43. Mental retardation is characteristic of 48,XXXX with an average IQ of 60 (range 30-70). Major psychological/psychiatric studies [5] suggest that schizophrenic symptoms may be more frequent in subjects with tetrasomy X, than in the general population. The phenotype in tetrasomy X is very heterogeneous, the presence of extra sex chromosomes having a detrimental effect on growth, development and the general phenotype. Most often the skeletal, cardiac and gonadal systems are affected, with a varying degree of facial dysmorphism and speech impairment [4]. Cammarata *et al.* [6] reported midface hypoplasia, hypertelorism, upslanting palpebral fissures, epicanthal folds, low nasal bridge, micrognathia, short neck, clinodactyly of fifth finger and metaphyseal enlargement of long bones in 48,XXXX patients. Most of these features were present in our patient. Linden *et al.* [4] described a patient with facial asymmetry, delayed development and poor motor coordination.

The loss of an X chromosome results in short stature and often in primary ovarian failure [7], whereas an extra X chromosome is responsible for increased height. Tall stature is common in tetrasomy X females, with an average height of 169 cm [4]. Our patient was 162.8 cm (average height 156 cm, for Indian females of 16+ years) [8] and had normal menarche. Three 48,XXXX women have given birth to children with a normal karyotype, with trisomy and with omphalocele, respectively [9]. Half of the cases with 48,XXXX have normal menarche and menopause, while the rest have menstrual dysfunction [9-11].

The errors in meiosis I influence the likelihood of error in meiosis II and in early mitotic division. In most if not all cases, chromosome tetrasomy is attributed to successive non disjunctional events involving the same parent [12]. In most cases, additional chromosomes are derived from one parent and the other parent contributes a single X or Y chromosome.

This 48,XXXX syndrome can be diagnosed best by karyotyping, and most cases are ascertained because of clinical findings. Fluorescent *in situ* hybridization is used successfully to detect aneuploidies and to confirm the results of chromosomal analyses. The reporting of more cases can elucidate the clinical phenotype in females with tetrasomy X. Furthermore, molecular studies in such cases should reveal the effect of an extra X chromosome on growth and facial dysmorphism.

ACKNOWLEDGMENT

This study was supported by DBT grants (BT/ TF/ 09/21/90) to JRS.

REFERENCES

1. Carr DH, Barr ML, Plunkett ER. An XXXX sex chromosome complex in two mentally defective females. Canadian Med Assoc J 1961; 84: 131-137.

2. Chromosomal Variation in Man Online http://jws-edck.wiley.com:8096/Borgaonkar/cytocat.nsf

3. Kaur A, Mahajan S, Singh JR. Cytogenetic investigation in mentally retarded individuals. Int J Hum Genet 2003; 3(1): 13-16.

4. Linden MG, Bender BG, Robison A. Sex chromosome tetrasomy and pentasomy. Pediatrics 1995; 96(4, Pt. 1): 672-682.

5. Delsi LE, Friedrich U, Wahlstrom J, Boccio-Smith A, Forsman A, Eklund K, Crow T J. Schizophrenia and sex chromosome anomalies. Schizophr Bull 1994; 20(3): 495-505.

6. Cammarata M, Simone P, Graziano L, Giuffre M, Corsello G. Rare sex chromosome aneuploidies in humans. Report of six patients with 48,XXYY, 49,XXXXY and 48,XXXX karyotypes. Am J Med Genet 1999; 85(1): 86-87.

7. Rooman RP, Van Driessche K, Du Caju MV. Growth and ovarian function in girls with 48,XXXX karyotype--patient report and review of the literature. J Pediatr Endocrinol Metab 2002; 15(7): 1051-1055.

8. Agarwal KN, Saxena A, Bansal AK, Agarwal DK. Physical growth assessment in adolescence. Indian Pediatr 2001; 38(11): 1217-1235.

9. Hara S, Haywood BD, Davis KK, Sherill MV, Blackshear A, Crump EP. A black female with the 48,XXXX chromosome constitution. Am J Mental Deficiency 1975; 79(4): 464-466.

10. Bergmann E. Manifestation familiale du karyotype triplo X. Communication preliminaire. J Genet Hum 1961; 10: 370-371.

11. Blackstone RD, Grinzaid KS, Saxe DF. Reproduction in 48,XXXX women. Am J Med Genet 1994; 52: 379.

12. Hassold T, Pettay D, May K, Robinson A. Analysis of non-disjunction in sex chromosome tetrasomy and pentasomy. Hum Genet 1990; 85(6): 648-650.