Case Report

Isochromosome X mosaicism in a child with Kabuki syndrome phenotype: A rare cytogenetic association

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Isochromosome is a structurally unbalanced chromosome consisting of two short arms or two long arms, which are derived by abnormal centromere division or sister-chromatid exchange. Most autosomal isochromosomes are unusual, while those involving sex chromosomes are common. Kabuki syndrome (KS, OMIM 147920) is a multiple malformation/mental retardation syndrome of unknown etiology. A conventional cytogenetic study on lymphocytes from a 4-year-old girl with physical features suggestive of KS was found to have mosaicism for isochromosome for the long arm of the X. Although most manifestations present in this patient have been described before, this report is a rare association of clinical and cytogenetic findings in this syndrome. A genome-wide analysis and a larger number of patient groups studied could improve our understanding of the genetic basis of KS.

Key words: Cytogenetic, isochromosome X, Kabuki syndrome, mental retardation, mosaicism, multiple malformation

Introduction

Isochromosome is a structural chromosome aberration consisting of two short arms or two long arms, which are derived by abnormal centromere division or sister-chromatid exchange.[1] Kabuki syndrome (KS, OMIM 147920) was described in 1981 by two Japanese groups [Niikawa *et al*. and Kuroki *et al*.] as a multiple congenital anomaly/mental retardation syndrome of unknown etiology. More than 350 affected individuals have been reported. The phenotypic features (regardless of ethnic origin) resemble the make-up of actors in Kabuki (traditional Japanese theater).[2] Here, we report a patient with Kabuki syndrome (KS) phenotype and mosaicism for 45,X/46,X,i(X)(q10) present in the peripheral lymphocytes.

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Case Report

A 4-year-old female child was referred to the medical genetics out patient clinic for investigation of dysmorphic features and developmental delay. She was the second child of natural conception to nonconsanguineous parents. She was born after 40 weeks of gestation by caesarean section. There was no history of antenatal problems, exposure to drugs or medical illness during pregnancy. Her mother and father were 27 and 31 years old, respectively, at conception. The child was born 8 years after marriage, and the pedigree analysis revealed mental retardation in the paternal first cousin. Her elder 10-year-old female sibling is normal.

On physical examination at 4 years of age, her height was 97.2 cm (25th centile), weight 15 kg (25th centile) and head circumference 49 cm (appropriate for age). She had epicanthic folds, blue sclera, long palpebral fissures, everted lower eye lids, long eye lashes, large ears, high arched palate, open mouth, mild fifth finger clinodactyly, persistent fetal finger pads and single palmar crease on the right side, with mild learning disability.

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Her electrocardiogram was within normal limits. Her renal ultrasound was performed, and it was normal. Intelligence quotient (IQ) assessment revealed borderline range (IQ of 82). Hearing assessment (BERA) showed severe bilateral hearing loss.

Cytogenetics

Metaphase chromosome preparation from the proband was made from phytohemagglutinin-stimulated peripheral blood lymphocytes cultured for 72 h and stained with Giemsa (GTG banding at approximately 550-band stage) according to the standard techniques. Of the 50 metaphases analyzed, 28 cells showed 45,X and 22 cells showed 46,X,i(X)(q10). Chromosome analysis showed mosaicism for 45,X and one normal X chromosome and an isochromosome for the long arm of one X chromosome. Parental chromosome analysis was normal [Figures 1 and 2a and 2b].

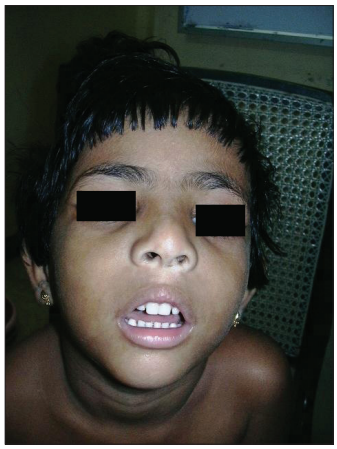

Figure 1: Clinical photograph of the proband

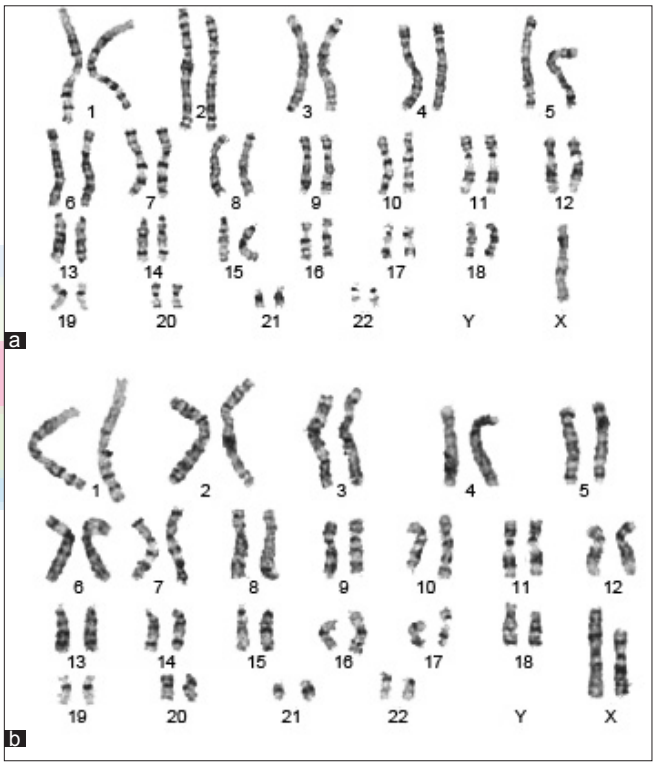

Figure 2: (a) Chromosome analysis showing one of the mosaic karyotypes, 45,X. (b) Chromosome analysis showing one of the mosaic karyotypes for isochromosome for the long arm of the X

Discussion

With the above clinical picture [Figure 1], a clinical diagnosis of KS was made. KS is a rare disorder. The name is suggested because of characteristic facies that resembles those of the makeup of actors in traditional Japanese art form. The etiology of this condition is currently unknown. Most cases of KS are sporadic, and an autosomal dominant inheritance with marked variability of expression from parent to child transmission has been suggested.[3-5]

Because the etiology of this condition is not clear and diagnostic testing is currently not available, it is generally agreed that the characteristic facial gestalt is necessary to make this diagnosis. Based on the clinical findings by Niikawa *et al.* in 62 patients diagnosed with KS, five major manifestations were defined, namely: distinctive facial features (eversion of the lower lateral eyelid, arched eyebrows with the lateral one-third dispersed or sparse, depressed nasal tip and prominent ears) in 100% of their patients, skeletal anomalies (deformed spinal column with or without sagittal cleft vertebrae and brachydactyly V) in 92% of their patients, dermatoglyphic abnormalities (fingertip pads, absence of digital triradius c and/or d and increased digital ulnar loop and hypothenar loop patterns) in 93% of their patients, mild to moderate mental retardation in 92% of their patients and postnatal growth deficiency in 83% of their patients. The minor features described in this condition are cardiovascular anomaly, cleft lip and/or cleft palate, scoliosis, deformed vertebra/rib, blue sclerae, kidney/urinary tract malformation, premature thelarche, hearing loss, lower lip pits, cryptorchidism, preauricular pits,

hip dislocation and seizures. There have also been a number of less-frequent findings reported in KS, including visceral abnormalities and susceptibility to frequent infections.[6] In our case, facial dysmorphism, dermatoglyphic abnormalities, minor features (blue sclera, hearing loss) and mild learning disability were found.

Various autosomal chromosome aberrations have been reported in patients with KS, including an interstitial duplication of 1p [dup(1)(p13.1p22.1)], an inherited balanced translocation between chromosomes 3 and 10 [t(3;10)(p25;p15)], an inherited paracentric inversion of the short arm of chromosome 4 [inv(4)(p12pter)], a partial 6q monosomy with partial 12q trisomy [der(6) t(6;12)(q25.3;q24.31)], an inherited pseudodicentric chromosome 13 and an inherited balanced translocation involving 15q and 17q [t(15;17),(15q;21q)]. Milunsky and Huang (2003) found 8p22-8p23.1 duplication in six unrelated individuals with KS by the comparative genomic hybridization technique. Studies of Miyake *et al*. did not confirm 8p22-8p23.1 duplication in the 28 patients with a similar condition.[7]

Sex chromosome aberrations found in association with KS that have been reported are pericentric inversion of the Y chromosome, ring Y, ring X and 45, X. X-chromosome aberrations have been reported frequently in individuals with KS, which have led some authors to postulate that KS may be due to abnormalities involving the pseudoautosomal region of the X chromosome. Based on the expression of interferon regulatory factor 6 (IRF6) gene product along the medial edge of the fusing palate, tooth buds, hair follicles, genitalia and skin throughout the body, Armstrong *et al*. hypothesized that some of the features found in KS are due to the involvement of the IRF6 gene pathway. Cho KH reported a mosaic karyotype of isochromosome X in one patient with KS; this cytogenetic aberration was observed in our patient also. Isochromosome for the long arm of the X is found in 12–20% of the patients with Turner syndrome,[8-10] but isochromosome Xq has not been reported in 48 individuals with KS studied by Armstrong *et al*.

This case has been reported because of the rare association of clinical and cytogenetic findings, which, to our knowledge, is the first cytogenetic report from India. Further genome-wide analysis and a larger number of patient groups need to be examined before postulating a role for mosaic isochromosome Xq in the causation of KS.

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