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Case Report

Molecular genetic characterization of a prenatally detected 1.484-Mb Xq13.3-q21.1 duplication encompassing *ATRX* and a literature review of syndromic intellectual disability and congenital abnormalities in males with a duplication at Xq13.3-q21.1

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ABSTRACT

Objective: We present prenatal diagnosis of dup(X)(q13.3q21.1) in a male fetus and molecular genetic analysis in three generations and a literature review of syndromic intellectual disability and congenital abnormalities in males with a duplication at Xq13.3-q21.1.

Case report: A 35-year-old, primigravid woman underwent amniocentesis at 18 weeks of gestation because of advanced maternal age. The woman and her mother were phenotypically normal, and there was no intellectual disability in the maternal family. Cytogenetic analysis of cultured amniocytes revealed a karyotype of 46,XY. Simultaneous array comparative genomic hybridization (aCGH) analysis on uncultured amniotic fluid incidentally detected a 1.484-Mb microduplication of Xq13.3-q21.1 encompassing *ATRX*. Subsequent aCGH analysis on fetal blood, maternal blood and grandmother's blood revealed the same 1.484-Mb dup(X)(q13.3q21.1). Prenatal ultrasound findings were unremarkable with no growth restriction and no short stature. After genetic counseling of syndromic intellectual disability in males with *ATRX* duplication, the woman elected to terminate the pregnancy. The fetus postnatally manifested hypoplastic male external genitalia, clinodactyly, hypertelorism, midface hypoplasia, epicanthic folds and micrognathia.

Conclusion: Simultaneous aCGH analysis on uncultured amniotic fluid in addition to conventional cytogenetics at amniocentesis is practical and may help in detecting unknown familial inheritance of subtle X chromosome aberrations.

Introduction

ATRX [Online Mendelian Inheritance in Man (OMIM) 300032] is located at Xq21.1 and encodes X-linked helicase 2, which is a chromatin-remodeling factor. Loss-of-function of mutations or deletions of *ATRX* are associated with X-linked dominant α-thalassemia/mental retardation syndrome or ATRX syndrome (OMIM 301040), and X-linked recessive mental retardation-hypotonic facies syndrome (OMIM 309580). Partial duplication of the *ATRX* gene has been reported to cause ATRX syndrome [1,2].

Duplication of the X chromosome involving Xq13.3-q21.1 encompassing *ATRX* in a male has been reported to be associated

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with X-linked mental retardation phenotype including mental retardation, short stature, facial dysmorphism, cryptorchidism and a small penis [3–13]. Prenatal diagnosis of dup(X)(q13.3q21.1) is very rare. Here, we present our experience of prenatal diagnosis and family investigation of familial inheritance of dup(X)(q13.3q21.1) in three generations.

Case report

A 35-year-old, primigravid woman was referred to the hospital at 21 weeks of gestation for genetic counseling of familial Xq13.3-q21.1 duplication in the male fetus. The woman underwent amniocentesis at 18 weeks of gestation because of advanced maternal age. Cytogenetic analysis of cultured amniocytes revealed a karyotype of 46,XY. Simultaneous array comparative genomic hybridization (aCGH) analysis on uncultured amniotic fluid incidentally detected a 1.484-Mb microduplication of Xq13.3-q21.1 encompassing *ATRX*. Subsequent aCGH analysis on maternal blood revealed the same Xq microduplication, indicating a familial inheritance. There was no intellectual disability in the maternal family. Prenatal ultrasound findings were unremarkable with no growth restriction and no short stature. After counseling of the association of dosage increase of *ATRX* with X-linked syndromic intellectual disability in male probands under such a circumstance, the woman elected to terminate the pregnancy. The fetus postnatally manifested hypoplastic male external genitalia, clinodactyly, hypertelorism, midface hypoplasia, epicanthic folds and micrognathia. Cytogenetic analysis of the fetal blood revealed a karyotype of 46,XY, and aCGH analysis on the DNA extracted from the fetal blood using CytoChip ISCA Array (Illumina, San Diego, CA, USA) revealed a result of arr Xq13.3q21.1 (75,500,269–76,984,168) × 2.2 encompassing three OMIM genes of *MAGEE1*, *FGF16* and *ATRX* (Fig. 1). The woman had a karyotype of 46,XX, and aCGH analysis of the DNA extracted from her blood using CytoChip ISCA Array (Illumina, San Diego, CA, USA) revealed a result of arr Xq13.3q21.1 (75,500,269–76,984,168) × 3.3 encompassing three OMIM genes of *MAGEE1*, *FGF16* and *ATRX* (Fig. 2). The woman's mother had a karyotype of 46,XX, and aCGH

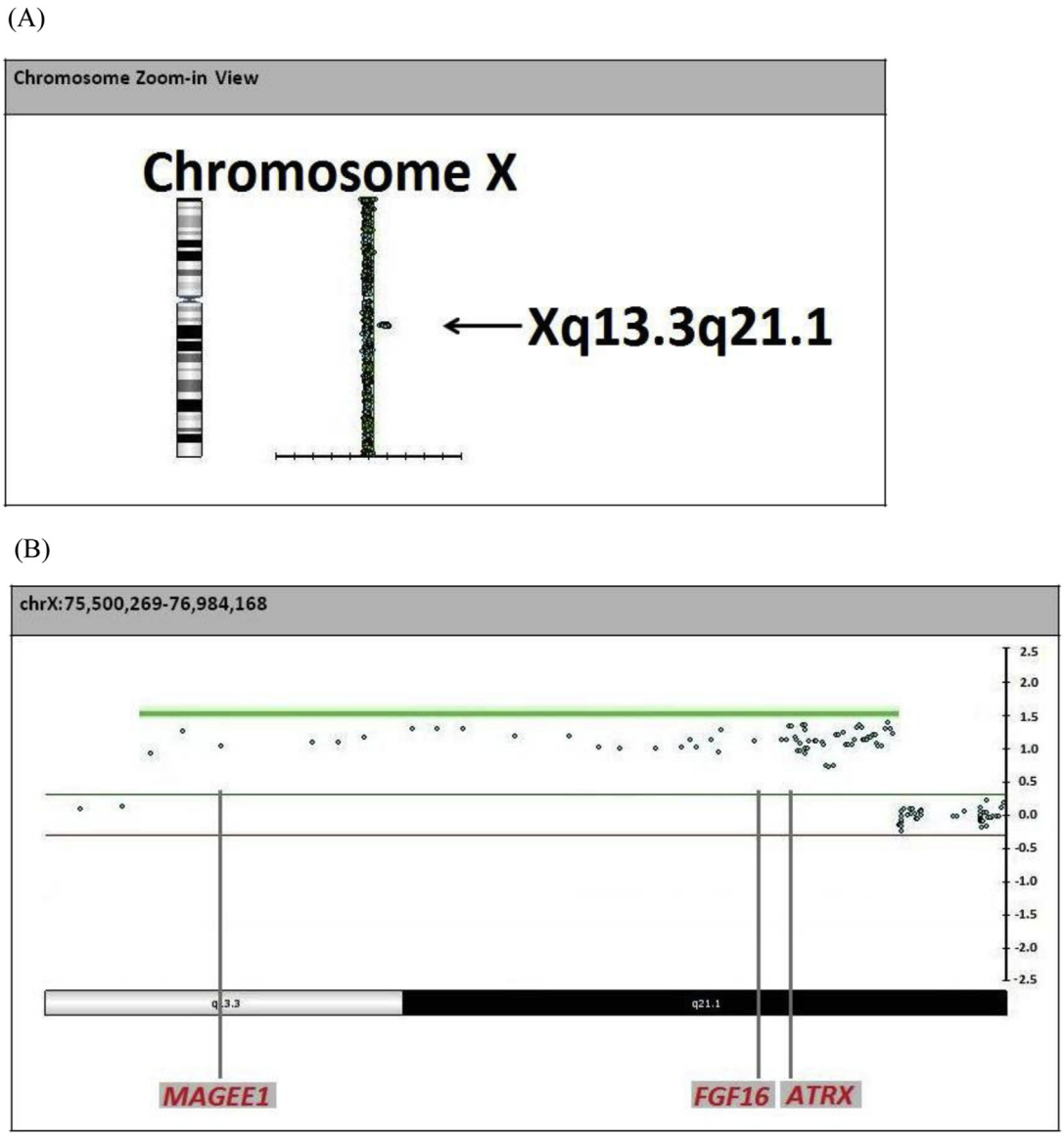

Fig. 1. (A) and (B). The fetus carries a 1.484-Mb duplication of Xq13.3-q21.1 encompassing ATRX.

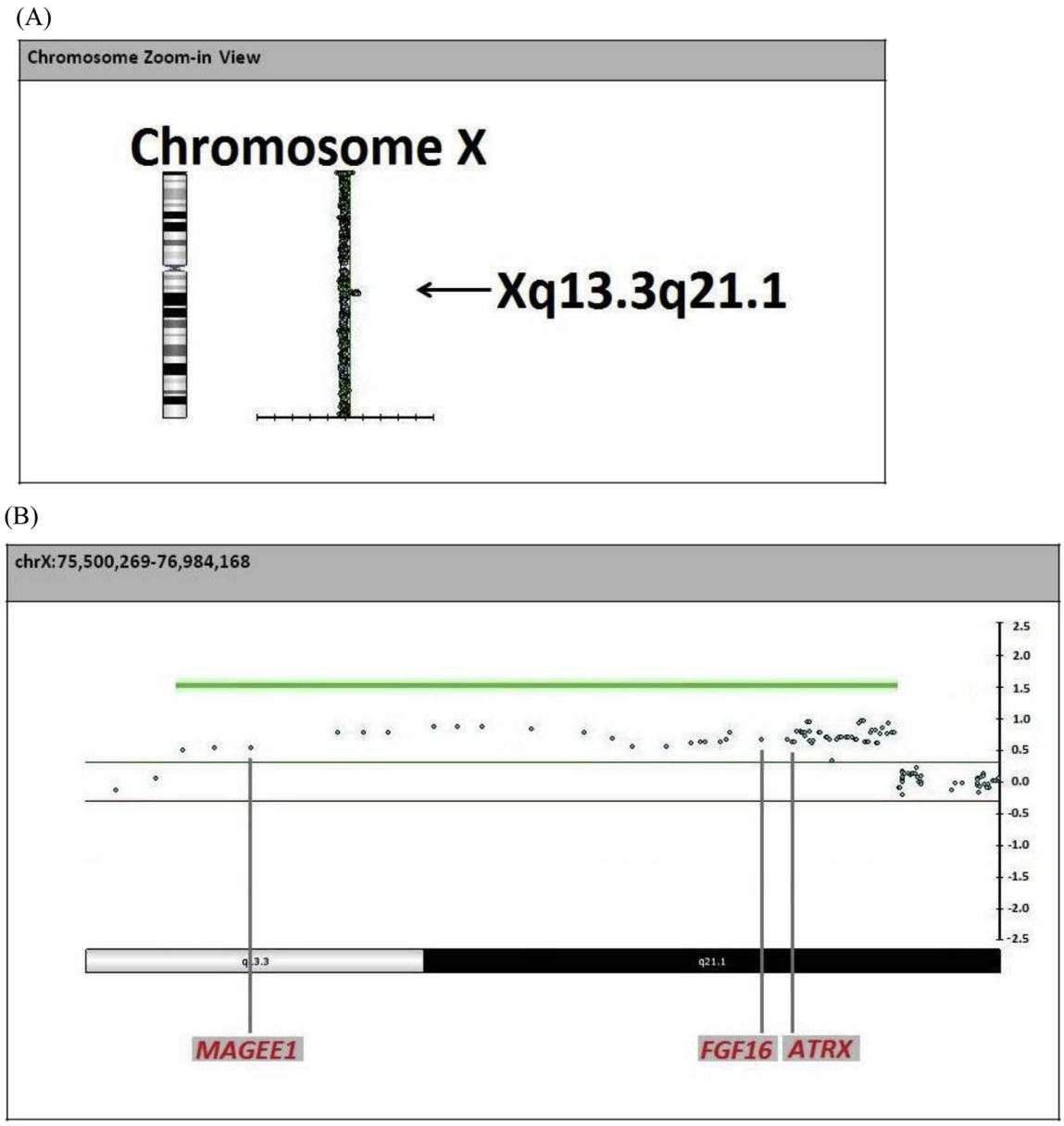

Fig. 2. (A) and (B). The mother of the fetus carries a 1.484-Mb duplication of Xq13.3-q21.1 encompassing ATRX.

analysis of the DNA extracted from her blood using CytoChip ISCA Array (Illumina, San Diego, CA, USA) revealed a result of arr Xq13.3q21.1 (75,500,269–76,984,168) × 3.0 encompassing three OMIM genes of *MAGEE1*, *FGF16* and *ATRX* (Fig. 3). Both the mother and the maternal grandmother of the fetus carried a 1.484-Mb duplication of Xq13.3-q21.1 encompassing *ATRX* but presented no phenotypic abnormalities. The woman's brother and her maternal uncle were phenotypically normal, had the karyotype of 46,XY, and carried no Xq13.3q21.1 duplication by aCGH analysis.

Discussion

Sparkes et al. [3] reported a *de novo* insertional translocation of Xq13q24 into the X chromosome in a baby boy with multiple congenital anomalies and low birth weight. Steinbach et al. [4] reported dup(X)(q13q22) in a psychomotoric retarded boy and his healthy, short-statured mother. Vejerslev et al. [5] reported familial dup(X)(q13.1q21.2) in a 10-month-old boy with severe mental retardation, short stature, hypoplastic genitalia, cryptorchidism, facial dysmorphism and broad thorax, and in phenotypically normal female carriers for at least three generations. Cremers et al. [6] reported dup(X)(q13q22) in a boy with muscular hypotony, growth retardation, psychomotor retardation, cryptorchidism and Pelizaeus-Merzbacher disease. Thode et al. [7] reported maternally derived dup(X)(q13.1q21.1) in three males with marked short stature, severe intellectual handicap and an unusual facial appearance. Yokoyama et al. [8] reported maternally derived dup(X)(q13.3q21.2) in a 2-year-and-8-month-old boy with marked severe growth failure, mental retardation, and facial and genital abnormalities. Shapira et al. [9] reported dup(X)(q13.3q21.2) in a 4-year-old boy with growth and mental retardation, growth hormone deficiency, compensated primary hypothyroidism, facial dysmorphism, hypoplastic genitalia and hypotonia, and

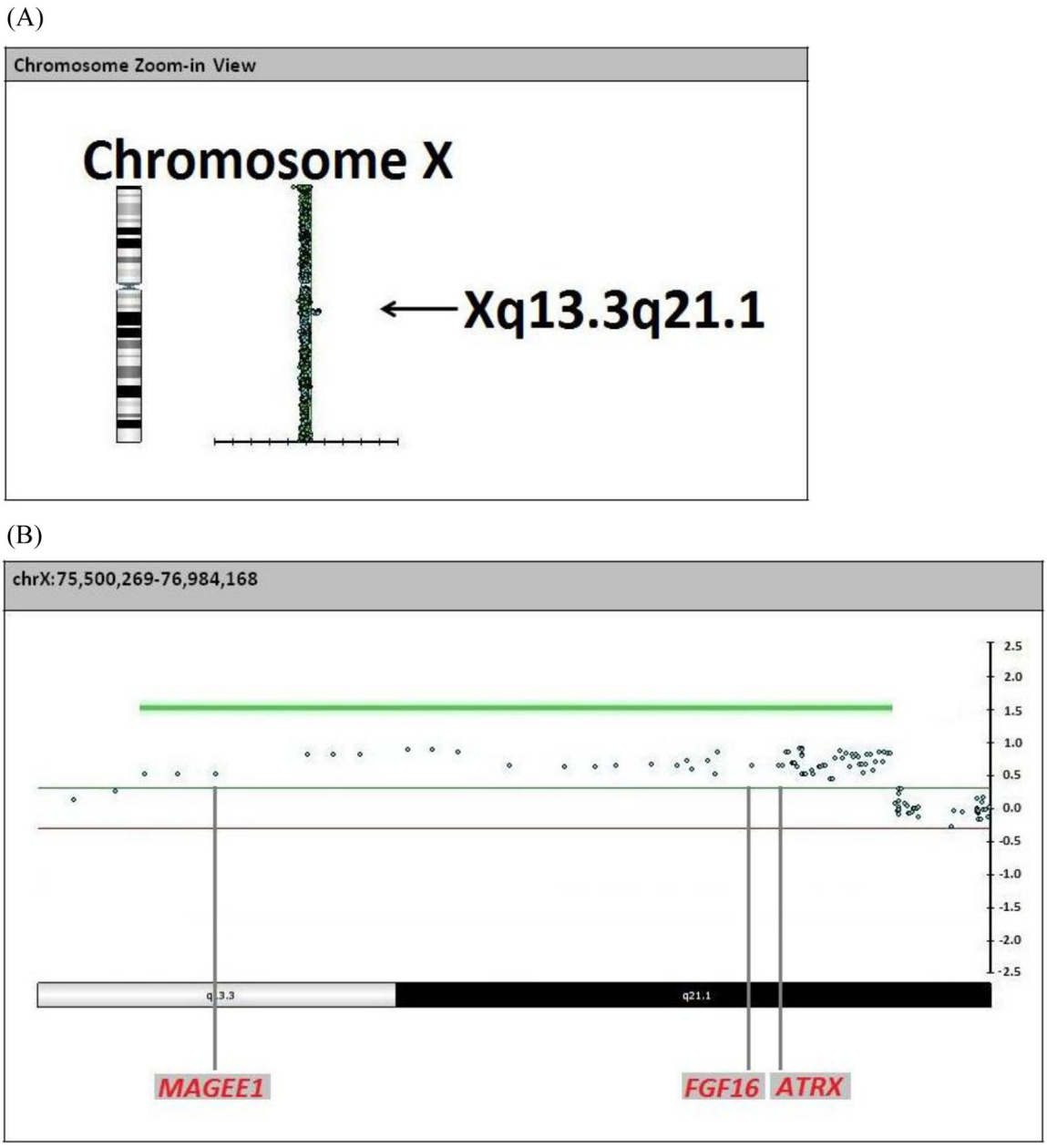

Fig. 3. (A) and (B). The maternal grandmother of the fetus carries a 1.484-Mb duplication of Xq13.3-q21.1 encompassing ATRX.

mosaicism of dup(X)(q13.3q21.2) in his mother's X chromosome. Hou [10] reported dup(X)(q13.2q21.2) in a 2-year-old boy with hypotonia, gastroesophageal reflux, laryngomalacia, recurrent infections, IgG4 deficiency, dysgenesis of the corpus callosum, proximal renal tubular acidosis and nephrolithiasis, and his normal healthy mother and his sister who had suffered from nephrolithiasis. Lugtenberg et al. [11] reported a *de novo* 7-Mb dup(X)(q13.2q21.1) encompassing *ATRX* and *SLC16A* in a 26-year-old man with mental retardation, minor facial and genital anomalies, short stature and broad thorax. Sismani et al. [12] reported a prenatally ascertained, maternally inherited 14.8-Mb dup(X)(q13.2q21.31) in a male fetus with increased nuchal translucency, ventriculomegaly and polyhydramnios on prenatal ultrasound. Martínez et al. [13] reported maternally derived dup(X)(q13q21.1) and dup(X)(q13.2q21.31) encompassing *ATRX* respectively in two unrelated males with severe intellectual disability, absent expressive speech, early hypotonia, behavior problems, postnatal growth deficiency, microcephaly, cryptorchidism and facial dysmorphism.

Pregnant women who carry a duplication at Xq13.3-q21.1 will have a 50% chance of passing the aberrant X chromosome to male offspring with a risk of syndromic intellectual disability and congenital abnormalities. Prenatal diagnosis of a duplication at Xq13.3-q21.1 is uncommon. Carrió et al. [14] first reported prenatal diagnosis of dup(X)(q13q22) through conventional cytogenetics by chorionic villus sampling in a pregnancy conceived by a 28-year-old woman who was known to be a carrier of dup(X)(q13q22) and had delivered two male preterm infants with multiple malformation syndrome including pterigium colli, congenital heart disease and ambiguous genitalia and the same dup(X)(q13q22). Sismani et al. [12] reported prenatal diagnosis of dup(X)(q13.2q21.31) through conventional cytogenetics by amniocentesis because of abnormal

prenatal ultrasound and a subsequent detection of the maternal carrier status.

The present case adds to the list of prenatal diagnosis of a duplication of Xq13.3-q21.1 in a male fetus in a not known at-risk pregnancy. The peculiar aspect of this case is the incidental detection of a subtle familial interstitial Xq duplication by simultaneous aCGH analysis on uncultured amniotic fluid at amniocentesis because of advanced maternal age. Our presentation provides evidence that simultaneous aCGH analysis on uncultured amniotic fluid in addition to conventional cytogenetics at amniocentesis is practical and may help in detecting unknown familial inheritance of subtle X chromosome aberrations.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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