Taiwanese Journal of Obstetrics & Gynecology 56 (2017) 385–389

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

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

Chih-Ping Chen [a, b, c, d, e, f, *], Hoi-Kin Yip [g], Liang-Kai Wang [a], Schu-Rern Chern [b], Shin-Wen Chen [a], Shih-Ting Lai [a], Peih-Shan Wu [h], Wayseen Wang [b, i]

[a] *Department of Obstetrics and Gynecology, MacKay Memorial Hospital, Taipei, Taiwan*
[b] *Department of Medical Research, MacKay Memorial Hospital, Taipei, Taiwan*
[c] *Department of Biotechnology, Asia University, Taichung, Taiwan*
[d] *School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan*
[e] *Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan*
[f] *Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[g] *Department of Obstetrics and Gynecology, Cardinal Tien Hospital, Xindian, New Taipei City, Taiwan*
[h] *Gene Biodesign Co. Ltd, Taipei, Taiwan*
[i] *Department of Bioengineering, Tatung University, Taipei, Taiwan*

A R T I C L E I N F O

Article history:
Accepted 23 March 2017

Keywords:
ATRX
Prenatal diagnosis
Xq13.3-q21.1 duplication
Xq duplication

A B S T R A C T

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

* Corresponding author. Department of Obstetrics and Gynecology, MacKay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei 10449, Taiwan. Fax: +886 2 25433642, +886 2 25232448.

E-mail address: cpc_mmh@yahoo.com (C.-P. Chen).

http://dx.doi.org/10.1016/j.tjog.2017.04.023
1028-4559/

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

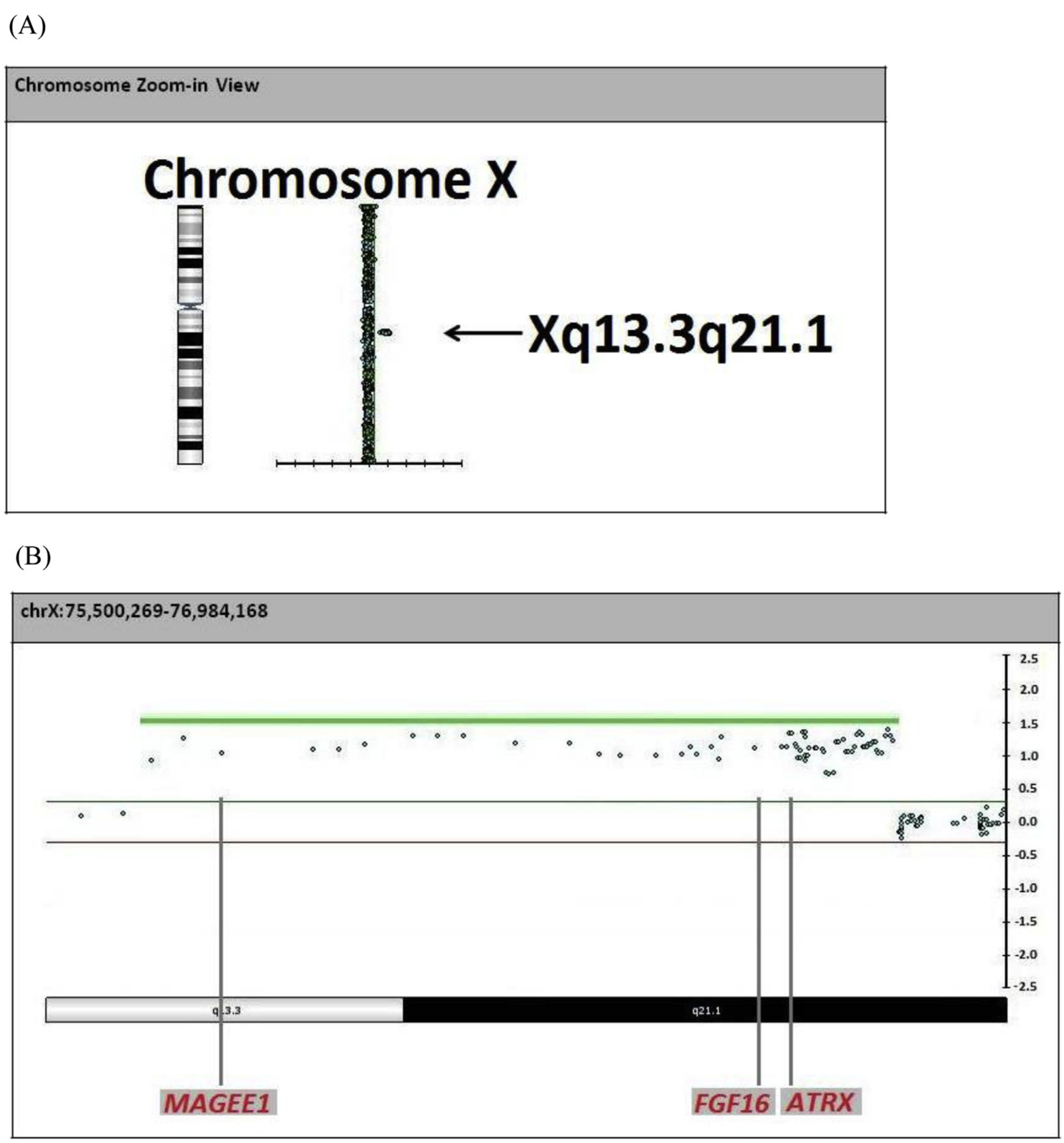

Fig. 1. (A) and (B). The fetus carries a 1.484-Mb duplication of Xq13.3-q21.1 encompassing ATRX.