VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2023, vol. 94, no. 3, 188–190

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2021.0225

Prenatal diagnosis and molecular cytogenetic characterization of Xp22.32p22.31 microduplication in a Chinese family

Weixin Cui[1*], Xi Li[2*], Yan Jin[3], Juan Zhang[4]

[1]Department of Obstetrics, Maternal and Child Health Hospital of Hubei Province, Wuhan, Hubei, PR China
[2]Department of Gastroenterology, Peking University Shenzhen Hospital, Shenzhen, Guangdong, PR China
[3]Department of of child Health Care, Maternal and Child Health Hospital of Hubei Province, Wuhan, Hubei, PR China
[4]Department of Stomatology, Maternal and Child Health Hospital of Hubei Province, Wuhan, Hubei, PR China
[*]these authors contributed equally to this work

ABSTRACT

Objectives: To explore the relationship between Xp22.32p22.31 microduplication and mental retardation identifiable by chromosomal G-banding and chromosomal microarray analysis (CMA).

Material and methods: Chromosomal G-banding, CMA, and physical and mental examinations were performed on four members of a Chinese family.

Results: The mother and one baby had the same microduplication (arr[GRCh37] Xp22.32p22.31(5970505-6075215)x2), and the baby had mental retardation.

Conclusions: Xp22.32p22.31 microduplication in males could cause mental retardation. Combination of NIPT, prenatal ultrasound, chromosomal G-banding and CMA has high accuracy in risk assessment for prenatal diagnosis.

Key words: prenatal diagnosis; Xp22.32p22.31 microduplication; chromosomal microarray analysis; mental retardation

Ginekologia Polska 2023; 94, 3: 188–190

INTRODUCTION

Neuroligin 4 X-linked (NLGN4X) represents a critical X-linked postsynaptic scaffolding protein affecting excitatory synapsis development and maintenance, which is involved in multiple neuropsychiatric pathologies, including cognitive impairment, autism spectrum disorders (ASD), anxiety, attention deficit hyperactivity disorder (ADHD) and Tourette's syndrome. The NLGN4X gene is located on the X chromosome (Xp22.3). Chromosomal rearrangements, including duplications and deletions, could cause diverse genetic diseases [1].

Xp22.32p22.31 microduplication represents a common finding in clinical cytogenetics [2, 3]. The clinical significance of Xp22.32p22.31 microduplication remains unclear. We report a prenatal diagnosis case with a family in which the mother and one child had Xp22.32p22.31 microduplication, and this child further developed mental retardation. The mother was a carrier of the microduplication with normal phenotype. The above findings may help delineate the phenotypic features of Xp22.32p22.31 microduplication, suggesting a pathogenetic cause for mental retardation.

MATERIAL AND METHODS

Case report

This study had approval from the Ethics Committee of Maternal and Child Health Hospital of Hubei Province. The guardians of the children provided signed informed consent.

Corresponding author:
Juan Zhang
Department of Stomatology, Maternal and Child Health Hospital of Hubei Province, Wuhan, Hubei, PR China
e-mail: zhangjinhuahk@126.com

Received: 09.08.2021 Accepted: 19.11.2021 Early publication date: 18.03.2022

In 2017, a 36-year-old, gravida 1, para 0 woman with diamniotic twin pregnancy was submitted to amniocentesis for cytogenetics and chromosomal microarray analysis (CMA) at gestation week 18 since noninvasive prenatal testing (NIPT) suggested high odds of sex chromosome aneuploidy. The parents had no family history of chromosomal aberrations or congenital anomalies. No sign of spontaneous abortion was found in early pregnancy. The totality of prenatal laboratory indexes were within respective normal ranges, and the patients had normal karyotypes.

Cytogenetic assessment of G-band metaphases obtained from amniotic fluid cells after culture was performed. Chromosome samples were prepared by the G-banding method (resolution, 300–400 bands). In total, 20 metaphases were examined for both fetuses, and karyotyping followed the ISCN 2016 nomenclature [4].

Chromosomal Microarray Analysis (CMA) of uncultured amniotic fluid cells was carried out with the Affymetrix CytoScan 750 K chip, which encompasses 550 k nonpolymorphic and 200 k SNP markers, with a probe spacing averaging 4.1 kb.

RESULTS

The karyotypes of both fetuses were 46, XY. The CMA result of fetus A was normal, but that of fetus B revealed a 105-kb chromosomal duplication, arr[GRCh37] Xp22.32p22.31 (5970505-6075215)x2 (Fig. 1). Then, CMA examination of the parents was performed. Parental CMA showed the father was normal, while the mother had a duplication of the same region as fetus B.

Ultrasound revealed no dysmorphisms or intrauterine growth restriction (IUGR). At 24 weeks of gestation, fetus A had an estimated fetal weight of 660 g, an abdominal circumference of 19.5 cm, a head circumference of 21.9 cm, a femur length of 4.2 cm and a fetal heart rate of 150 bpm; fetus B had an estimated fetal weight of 630 g, an abdominal circumference of 19.1 cm, a head circumference of 21.2 cm, a femur length of 4.0 cm and a fetal heart rate of 145 bpm [5]. The parents were comprehensively examined, and no overt anomalies were identified.

The parents were told that Xp22.32p22.31 microduplication in males could be associated with mental retardation in genetic counseling. However, they decided to continue the pregnancy. At pregnancy week 36, two male babies were delivered vaginally. After childbirth, both babies underwent comprehensive physical exams, which were unremarkable. At the age of two years, both babies underwent Gessell examination: baby A was normal (Development Quotient, DQ = 91), while baby B had mental retardation (DQ = 69). The IQs (Intelligence Quotients) of babies A and B were 105 and 73, respectively.

DISCUSSION

Xp22.32p22.31 microduplication could be tightly associated with both specific epilepsy genes and brain maturation events. However, discordant findings have been reported for the pathogenicity of Xp22.32p22.31 microduplication, which is considered in some instances to have unspecified function or to be benign [6], and in others to induce developmental abnormalities such as autism, cognitive impairment,

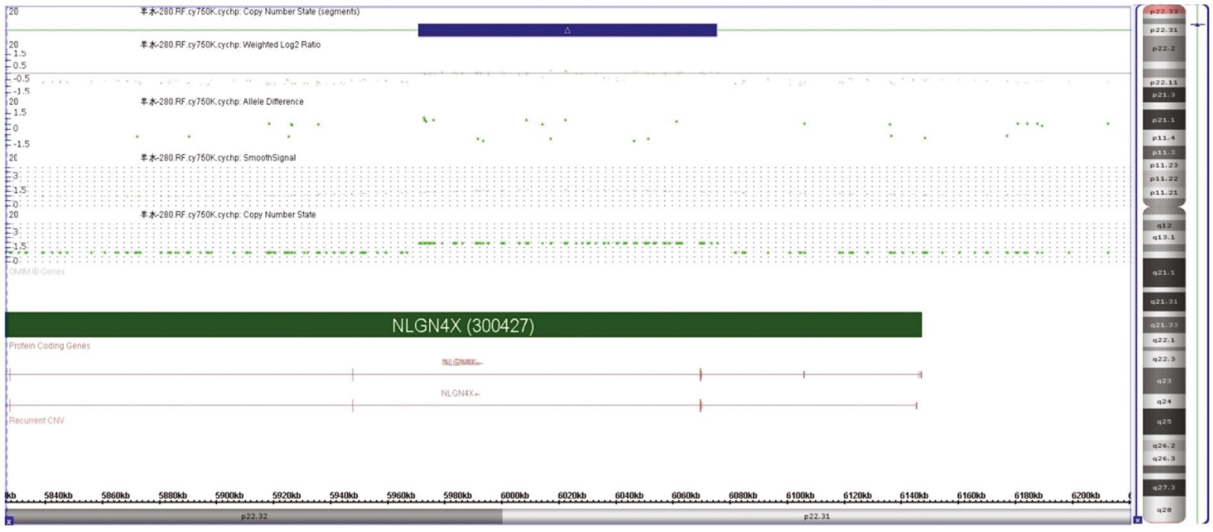

Figure 1. CMA revealed the Xp22.32p22.31 microduplication (arr[GRCh37] Xp22.32p22.31(5970505-6075215)x2)

hypotonia and eating disorders [7, 8]. Cognitive impairment and learning troubles in baby B suggest a probable pathogenic role for Xp22.32p22.31 microduplication.

Even if the clinical importance of this rearrangement remains debatable, its possible pathogenetic role has been recently suggested, although it may require further genetic factors [7]. The phenotype varies and is common in neurobehavioral diseases, with seizures found in 3–44% of cases [9, 10]. Cognitive impairment ranges between mild and severe mental retardation, with associations with autism spectrum disorder, speech and reading troubles, dyslexia, and attention deficit hyperactivity disorder in some affected individuals.

In addition, these phenotypic differences might be associated with further genetic modifiers, including decreased penetrance, distinct genes in the duplication region and position effect [11]. Additionally, X chromosome inactivation may also significantly affect the occurrence of this duplication [12].

As shown above four members of a family were examined, and one child had maternally inherited Xp22.32p22.31 microduplication associated with cognitive disability and mental retardation while his mother was asymptomatic. Xp22.32p22.31 microduplication in males could cause mental retardation and must be taken seriously.

Combination of NIPT, prenatal ultrasound, chromosomal G-banding and CMA has high accuracy in risk assessment for prenatal diagnosis [13].

Ethics approval and consent to participate

This study had approval from the Ethics Committee of Maternal and Child Health Hospital of Hubei Province. The guardians of the children provided signed informed consent.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Kopp N, Amarillo I, Martinez-Agosto J, et al. Pathogenic paternally inherited NLGN4X deletion in a female with autism spectrum disorder: Clinical, cytogenetic, and molecular characterization. Am J Med Genet A. 2021; 185(3): 894–900, doi: 10.1002/ajmg.a.62025, indexed in Pubmed: 33369065.
2. Li F, Shen Y, Köhler U, et al. Interstitial microduplication of Xp22.31: Causative of intellectual disability or benign copy number variant? Eur J Med Genet. 2010; 53(2): 93–99, doi: 10.1016/j.ejmg.2010.01.004, indexed in Pubmed: 20132918.
3. Du Y, Lin J, Lan L, et al. Detection of chromosome abnormalities using current noninvasive prenatal testing: A multi-center comparative study. Biosci Trends. 2018; 12(3): 317–324, doi: 10.5582/bst.2018.01044, indexed in Pubmed: 29952350.
4. McGowan-Jordan J, Simons A, Schmid M. An International System for Human Cytogenomic Nomenclature. Karger, Basel 2016.
5. Oğlak SC, Bademkıran MH, Obut M. Predictor variables in the success of slow-release dinoprostone used for cervical ripening in intrauterine growth restriction pregnancies. J Gynecol Obstet Hum Reprod. 2020; 49(6): 101739, doi: 10.1016/j.jogoh.2020.101739, indexed in Pubmed: 32251738.
6. Baldwin EL, Lee JY, Blake DM, et al. Enhanced detection of clinically relevant genomic imbalances using a targeted plus whole genome oligonucleotide microarray. Genet Med. 2008; 10(6): 415–429, doi: 10.1097/GIM.0b013e318177015c, indexed in Pubmed: 18496225.
7. Liu P, Erez A, Nagamani SC, et al. Copy number gain at Xp22.31 includes complex duplication rearrangements and recurrent triplications. Hum Mol Genet. 2011; 20(10): 1975–1988, doi: 10.1093/hmg/ddr078, indexed in Pubmed: 21355048.
8. Faletra F, D'Adamo AP, Santa Rocca M, et al. Does the 1.5 Mb microduplication in chromosome band Xp22.31 have a pathogenetic role? New contribution and a review of the literature. Am J Med Genet A. 2012; 158A(2): 461–464, doi: 10.1002/ajmg.a.34398, indexed in Pubmed: 22140086.
9. Olson H, Shen Y, Avallone J, et al. Copy number variation plays an important role in clinical epilepsy. Ann Neurol. 2014; 75(6): 943–958, doi: 10.1002/ana.24178, indexed in Pubmed: 24811917.
10. Addis L, Sproviero W, Thomas SV, et al. Identification of new risk factors for rolandic epilepsy: CNV at Xp22.31 and alterations at cholinergic synapses. J Med Genet. 2018; 55(9): 607–616, doi: 10.1136/jmedgenet-2018-105319, indexed in Pubmed: 29789371.
11. Alvarado DM, Aferol H, McCall K, et al. Familial isolated clubfoot is associated with recurrent chromosome 17q23.1q23.2 microduplications containing TBX4. Am J Hum Genet. 2010; 87(1): 154–160, doi: 10.1016/j.ajhg.2010.06.010, indexed in Pubmed: 20598276.
12. Carrel L, Willard HF. X-inactivation profile reveals extensive variability in X-linked gene expression in females. Nature. 2005; 434(7031): 400–404, doi: 10.1038/nature03479, indexed in Pubmed: 15772666.
13. Chen CP, Hung FY, Chern SR, et al. Prenatal diagnosis of mosaicism for trisomy 7 in a single colony at amniocentesis in a pregnancy with a favorable outcome. Taiwan J Obstet Gynecol. 2019; 58(6): 852–854, doi: 10.1016/j.tjog.2019.09.022, indexed in Pubmed: 31759541.