CASE REPORT

Prenatal Diagnosis and Genetic Counseling of a Maternally Inherited Chromosome 15q11.2q13.1 Duplication in a Chinese Family

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ABSTRACT

Background • Maternally inherited chromosomal duplications in the region of 15q11.2q13.1 have been associated with neurodevelopmental disorders and other clinical manifestations. Prenatal diagnosis of such duplications is crucial for providing accurate genetic counseling and guiding clinical management decisions.

Objective • This study aims to present the prenatal diagnosis and genetic counseling of a maternally inherited 15q11.2q13.1 duplication.

Case Presentation • A 38-year-old gravida 1, para 0 woman underwent amniocentesis at 16 weeks of gestation due to advanced maternal age. Karyotype analysis was performed on cultured amniocytes, and chromosomal microarray analysis (CMA) was conducted on uncultured amniocytes.

Results • The karyotype analysis of the cultured amniocytes revealed a normal karyotype of 46, XX. CMA identified a 4.21 Mb maternally inherited chromosomal duplication in the region of 15q11.2q13.1 (arr[GRCh37]15q11.2q13.1(23,894,550_28,107,154)x3).

Conclusions • Copy number variants (CNVs) and unbalanced chromosomal abnormalities (UBCA) identified in prenatal cases require careful consideration and accurate interpretation to determine their potential harm or harmlessness compared to the norm. The combination of prenatal ultrasound, karyotype analysis, CMA, and genetic counseling proves helpful in the prenatal diagnosis of CNVs and UBCA. (*Altern Ther Health Med.* 2023;29(7):462-464).

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INTRODUCTION

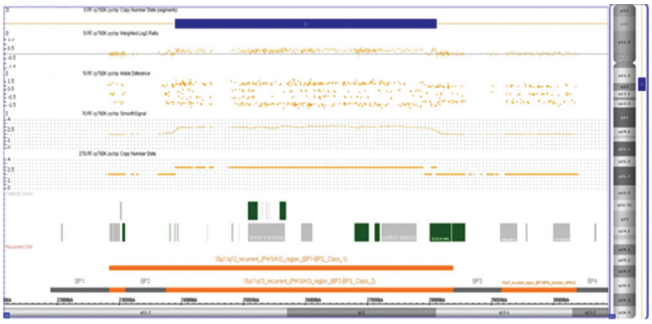
Copy number variants (CNVs) play a significant role in normal genetic variation and pathogenic genomic alterations. Unbalanced chromosome abnormalities (UBCA) involve the gain or loss of large genomic regions, often with minimal clinical impact on the affected individuals. While conventional karyotyping provides a comprehensive overview of the entire genome and identifies structural and numerical chromosome abnormalities, chromosomal microarray analysis (CMA) utilizes array technology to detect chromosome abnormalities.[1] CMA has the advantage of detecting rearrangements longer than 5Mb, which may be missed by conventional karyotyping,[2] while conventional karyotyping remains the method of choice for detecting balanced translocations.[3]

Clinical phenotypes associated with chromosome 15q11-q13 duplications exhibit significant variability and are less well-defined. Affected individuals can present with a range of manifestations, including normal development, autism, developmental delay, mental retardation, or short stature.[4] The phenotypic spectrum varies widely and is influenced by the parent of origin of the duplication. Maternal inheritance is more commonly associated with an abnormal phenotype, whereas paternal inheritance is often associated with a normal phenotype.[5] This study presents the prenatal diagnosis and genetic counseling of a maternally inherited 15q11.2q13.1 duplication.

CASE PRESENTATION

A 38-year-old woman, gravida 1, para 0, underwent amniocentesis at 16 weeks of gestation due to advanced maternal age. Her husband was 37 years old, and there was no family history of congenital disabilities or genetic diseases. Prenatal ultrasound, chromosomal microarray analysis (CMA) on uncultured amniocytes, karyotype analysis of the cultured amniocytes, and genetic counseling were conducted.

Figure 1. Chromosomal microarray analysis (CMA) detected a 4.21 Mb chromosomal duplication in the region of 15q11.2q13.1 (arr[GRCh37]15q11.2q13.1(23,894,550_28,107,154)x3).



Note: The orange arrow indicates the duplicated region.

MANAGEMENT AND OUTCOME

Cytogenetic analysis of the cultured amniocytes revealed a normal karyotype of 46, XX. Using the Affymetrix CytoScan 750K chip, which includes 550k non-polymorphic markers and 200k SNP markers, CMA on uncultured amniocytes detected a 4.21 Mb chromosomal duplication in the 15q11.2q13.1 region. According to the International System of Cytogenomic Nomenclature 2020 (ISCN 2020),[6] this duplication is reported as arr[GRCh37] 15q11.2q13.1(23,894,550_28,107,154)x3 (Figure 1).

Subsequently, both CMA and conventional karyotyping were performed using peripheral blood samples from the parents, and their karyotypes were found to be normal. The CMA results indicated that the mother had the same microduplication as the fetus. A comprehensive physical examination of the parents was conducted, and no abnormalities were identified. At 26 weeks of gestation, an ultrasound examination revealed intrauterine growth restriction (IUGR) in the fetus. Following genetic counseling, the parents made the decision to terminate the pregnancy, and a female fetus was delivered. DNA methylation analysis on cord blood confirmed a maternal origin of the 15q11.2q13.1 gene dosage. Postnatal cytogenetic analysis on cord blood, umbilical cord, and placenta yielded results consistent with the prenatal diagnosis.

DISCUSSION

The 15q11–q13 chromosomal region in humans is known to be involved in various constitutional rearrangements, including deletions and duplications. These rearrangements often occur at five recurrent breakpoints, designated as BP1–BP5, which correspond to the location of low-copy repeats.[7] Among the rearrangements, paternally and maternally derived deletions in the 15q11-13 region are well characterized and associated with Prader-Willi syndrome and Angelman syndrome, respectively.[8] However, the clinical phenotypes associated with duplications in this region are less well understood and exhibit significant variability. Affected individuals can range from having normal phenotypes to presenting with autism, developmental delay, mental retardation, or epilepsy.[9]

In the case of the family discussed in this report, the chromosomal duplication of 15q11.2q13.1 involved the BP2-BP3 regions,[10] which contain important functional genes such as NDN (OMIM:602117), SNRPN (OMIM:182279), and UBE3A (OMIM:601623), among others. NDN and SNRPN are imprinted genes expressed from the paternal allele in the human brain and other tissues.[11] Deletion or mutation of the paternal copy of NDN and SNRPN leads to Prader-Willi syndrome (PWS), characterized by hypotonia, mental retardation, short stature, hypogonadotropic hypogonadism, and small hands and feet. UBE3A, on the other hand, is an imprinted gene expressed from the maternal allele in the human brain and other tissues. Deletion or mutation of the maternal copy of UBE3A causes Angelman syndrome (AS), characterized by mental retardation, movement or balance disorders, ataxia, hypotonia, epilepsy, absence of speech, excessive laughter, and distinctive facial features.[2-12]

The chromosome 15q11.2q13.1 duplication syndrome shares clinical features that overlap with Angelman syndrome. It has been observed that a normal phenotype is more commonly associated with paternal inheritance of the duplication, while maternal inheritance is linked to autism, developmental delay, mental retardation, or epilepsy.[9] Given that the fetus, in this case, had the same microduplication as the mother and ultrasound examination revealed intrauterine growth restriction (IUGR), the parents made the decision to terminate the pregnancy.

CONCLUSION

In conclusion, we have presented a case of maternally inherited 15q11.2q13.1 duplication. Our case provides evidence that these maternally inherited microduplications can be associated with intrauterine growth restriction (IUGR), developmental delay, mental retardation, autism, and epilepsy. The detection of chromosomal microdeletions and microduplications can be challenging using conventional cytogenetic methods. However, the number of reported cases has significantly increased with the application of molecular genetic techniques, particularly array-based methods. Unbalanced chromosome abnormalities have been reported in various euchromatic regions of human autosomes. However, it is important to note that not all carriers of these microdeletions or microduplications present with the typical clinical manifestations due to variable expressivity and incomplete penetrance. When considering UBCA and CNVs, it is crucial to consult databases and the latest literature to provide patients with up-to-date genotype-phenotype correlation information. The combination of prenatal ultrasound, karyotype analysis, chromosomal microarray analysis, and genetic counseling proves to be valuable in the prenatal diagnosis of chromosomal microdeletions and microduplications. Our findings contribute to the growing body of knowledge on the clinical implications and diagnostic approaches for chromosomal microdeletions and microduplications, emphasizing the importance of a multidisciplinary approach in prenatal care.

DECLARATIONS
The Ethics Committee of Shiyan Maternal and Child Health Hospital approved the research.

CONSENT FOR PUBLICATION
All patient guardians gave informed consent to the publication of this study.

AVAILABILITY OF DATA AND MATERIALS
Please contact the corresponding author for data requests.

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

AUTHOR CONTRIBUTIONS
Long He Chun He contributed equally to this work.

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