CASE REPORT

A Case of Maternal Uniparental Disomy of Chromosome 6 with Intrauterine Growth Restriction

Liulian Feng, BD; Yefei Ma, MD; Yang Xu, BD

ABSTRACT

Background • Uniparental disomy (UPD) is a well-known epigenomic anomaly characterized by the inheritance of both copies of a homologous pair of chromosomes (or part thereof) from the same parent. This genetic condition can have significant implications for prenatal diagnosis and management.

Case Presentation • We present a case of a 29-year-old gravida 1 para 0 female who underwent amniocentesis at pregnancy Week 19 due to a high possibility of trisomy chromosome 6, as indicated by noninvasive prenatal testing (NIPT). However, fluorescence in situ hybridization (FISH) and whole-exome sequencing (WES) revealed no abnormalities. Subsequently, chromosomal microarray analysis (CMA) detected uniparental disomy of chromosome 6. Additionally, an ultrasound examination at 28 weeks of gestation revealed intrauterine growth restriction (IUGR). Given these findings, the parents made the decision to terminate the pregnancy.

Conclusions • The combination of genetic counseling, FISH, karyotype analysis, WES, CMA, NIPT, and prenatal ultrasound can provide valuable insights for the prenatal diagnosis of UPD. These diagnostic approaches play a crucial role in identifying and managing cases of UPD, primarily when associated with intrauterine growth restrictions. (*Altern Ther Health Med.* 2023;29(7):447-449).

Liulian Feng, BD; Yang Xu, BD; Department of Obstetrics and Gynecology, Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University, Edong Healthcare Group, Huangshi, Hubei, PR China. **Yefei Ma, MD,** College of Life Science and Technology, Huazhong University of Science and Technology, Hongshan, Wuhan, Hubei, PR China.

Corresponding author: Yang Xu, BD
E-mail: fengliulian@yeah.net

BACKGROUND

Uniparental disomy (UPD) refers to the inheritance of both homologous chromosomes of a pair from a single parent. UPD has been reported for nearly all human chromosomes.[1] It occurs through various mechanisms, including monosomic and trisomic rescue during embryonic development, incomplete segregation of chromosomes, and mitotic recombination.[2] UPD does not alter the number or structure of chromosomes, making it undetectable through karyotype analysis.[3] However, advances in technology such as SNP-based chromosomal microarray (CMA), microsatellite analyses, or trio exome sequencing (ES) enable the detection of UPD.[4] In this report, we present a rare case of partially maternal UPD involving chromosome 6 and intrauterine growth restriction (IUGR)[5] to contribute to the existing literature and enhance our understanding of this genetic anomaly.

CASE PRESENTATION

A 29-year-old primigravida woman underwent amniocentesis at pregnancy Week 19 due to a high possibility of trisomy of chromosome 6 based on NIPT results. FISH, CMA, and WES were performed on uncultured amniocytes. Additionally, G-banding karyotype analysis was conducted on cultured amniocytes.

G-banding Karyotype Analysis

The G-banding karyotype analysis of the cultured amniocytes revealed a normal karyotype of 46, XY (Figure 1).

Chromosomal Microarray Analysis (CMA)

CMA was performed on uncultured amniocytes using the Affymetrix CytoScan 750K chip, which includes 200k SNP markers and 550k non-polymorphic markers. CMA detected uniparental disomy of chromosome 6, specifically arr 6q23.2q25.2(135035371_154781155)×2 hmz and 6q11.1q14.1(61972917_82044615)×2 hmz [GRCh37(hg19)] (Figure 2). The couple involved in this case is not closely related, and both parental karyotypes and CMA analysis were normal.

Figure 1. The karyotype of 46, XY. Figure 1 depicts the G-banding karyotype analysis results, demonstrating a normal karyotype of 46, XY. The image visually represents the chromosomal structure and arrangement observed in the analyzed sample.

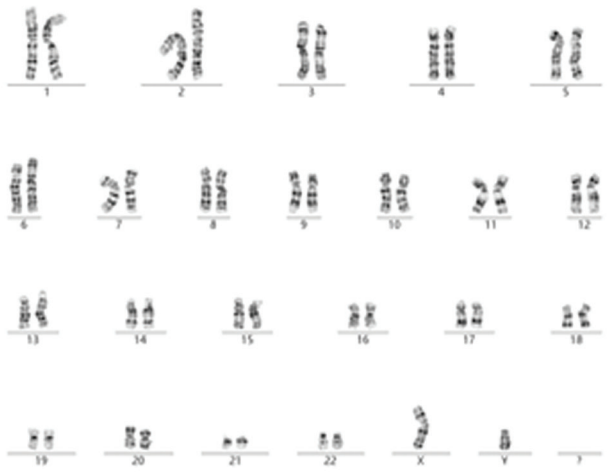
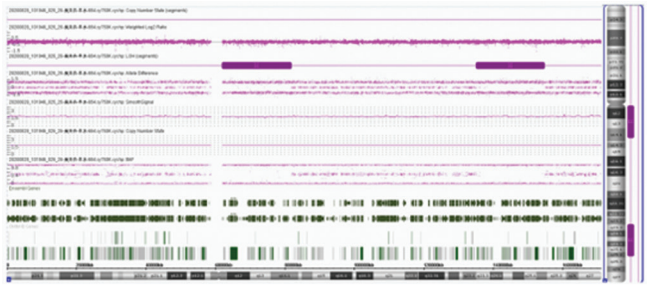


Figure 2. Uniparental disomy of chromosome 6, arr 6q23.2q25.2(135035371_154781155)×2 hmz and 6q11.1q14.1 (61972917_82044615)×2 hmz[GRCh37(hg19)] Figure 2 illustrates the results of Chromosomal Microarray Analysis (CMA) using the Affymetrix CytoScan 750K chip. The CMA analysis detected uniparental disomy of chromosome 6, specifically at regions 6q23.2q25.2 (135035371_154781155)×2 hmz and 6q11.1q14.1 (61972917_82044615)×2 hmz [GRCh37(hg19)]. The figure provides a visual representation of the chromosomal regions affected by the uniparental disomy, aiding in the understanding and interpretation of the molecular findings.



Maternal and Virology Studies

Maternal TORCH analysis and amniotic fluid virology studies, including PCR for CMV and parvovirus B19, yielded negative results.

Microsatellite Analysis

Microsatellite analyses indicated maternal uniparental disomy for chromosome 6.

Ultrasound Examination

Ultrasound examination revealed intrauterine growth restriction (IUGR) in the fetus at 28 weeks of gestation. The estimated fetal weight was 650g, abdominal circumference 19.1cm, head circumference 21.1cm, femur length 4.2cm, and fetal heart rate 155 bpm.[6]

Fluorescence In Situ Hybridization (FISH) and Whole-Exome Sequencing (WES)

Following genetic counseling, FISH and WES were performed on uncultured amniocytes. The Novaseq6000 platform (Illumina, San Diego, USA) was used for genomic DNA sequencing with 150 bp pair-end sequencing mode. The sequencing reads were aligned to the human reference genome (hg38/GRCh38) using the Burrows-Wheeler Aligner tool. WES did not reveal any homozygous mutations of known recessive pathogenic genes associated with inherited disorders on chromosome 6. Interphase FISH on uncultured amniocytes using the CEP-6 probe showed trisomy chromosome 6 in 2/200 cells and monosomy chromosome 6 in 4/200 cells.

Noninvasive Prenatal Testing (NIPT)

The high possibility of trisomy of chromosome 6 was indicated by NIPT in this study. It is hypothesized that these trisomy/monosomy chromosome 6 cells may result from trisomy rescue. However, it is important to note that the proportion of these trisomy/monosomy cells is very low, and their overall impact is minimal.

Termination of Pregnancy and Autopsy Results

After genetic counseling, the parents decided to terminate the pregnancy, resulting in the delivery of a male fetus. DNA microsatellite analysis on cord blood and placenta confirmed a maternal origin of chromosome 6. Interphase FISH analysis on the placenta revealed monosomy chromosome 6 in 34/1000 cells and trisomy chromosome 6 in 26/1000 cells. The autopsy findings were consistent with the ultrasound diagnosis.

DISCUSSION

UPD can be classified into three categories: pure heterodisomy, pure isodisomy, and mixed hetero-/isodisomy. Additionally, UPD can involve a whole haploid chromosome set, an entire chromosome, or a segment of a chromosome, known as segmental UPD, which is often attributed to a chromosomal rearrangement rescue event.[7] While UPD is generally considered a molecular genetic problem, recent research has provided evidence that UPD is primarily a chromosomal disorder.[8] UPD can be associated with human diseases through three mechanisms: (1) Homozygosity for an autosomal recessive trait: UPD can result in the inheritance of two copies of a mutant gene from one parent, leading to homozygosity and manifestation of the associated recessive trait; (2) Disruption of normal allelic expression of genes undergoing genomic imprinting: Imprinting disorders can arise when UPD affects imprinted genes, altering their normal expression patterns and causing phenotypic abnormalities; (3) Incomplete (cryptic) trisomic rescue: UPD can occur as a

result of trisomy rescue, where an embryo with a trisomy spontaneously eliminates one of the extra chromosomes. This rescue event can lead to UPD and potentially contribute to the development of certain genetic conditions.[7-8]

Unlike numerical or structural chromosomal aberrations, UPD does not alter the number or structure of chromosomes, making it undetectable through cytogenetic methods.[3] However, microsatellite analyses and SNP-based CMA can identify UPD. SNP-based CMA employs oligonucleotide sets specific for polymorphisms in the genome. Each single nucleotide polymorphism (SNP) has two oligo sets, one for each allele. When hybridized with sample DNA, they generate a signal intensity corresponding to the copy number and an SNP call indicating the allele present in the sample (AA, BB, or heterozygous AB).[9] It is important to note that SNP-based CMA primarily detects isodisomy and is less effective in detecting heterodisomy.[8] On the other hand, microsatellite analyses and trio exome sequencing can identify pure isodisomy, pure heterodisomy, mixed iso-/heterodisomy, and segmental UPD.[4]

NIPT indicated the high possibility of trisomy of chromosome 6 in this study. It is hypothesized that this UPD may be caused by trisomy rescue. UPD can lead to various clinical phenotypes, including homozygosity for autosomal recessive traits, mosaic aneuploidy, or disruptions in the normal allelic expression of genes undergoing genomic imprinting. Imprinting disorders involve alterations in epigenetic regulation, DNA methylation, and histone modifications [10]. The widespread use of microsatellite analyses and SNP-based CMA has facilitated the detection of UPD. While UPD generally has no clinical consequences for most chromosomes, certain chromosomes (6, 7, 11, 14, 15, and 20) exhibit parent-of-origin or imprinting differences in gene expression that can result in phenotypic abnormalities.[11]

Paternal uniparental disomy of chromosome 6 (upd(6) pat) is associated with (intrauterine) growth restriction and transient neonatal diabetes mellitus.[12] In contrast, maternal uniparental disomy of chromosome 6 (upd(6)mat) is a rare finding, and its clinical relevance is currently uncertain.[5] Most cases of upd(6)mat are associated with intrauterine growth restriction, preterm delivery, congenital malformations,[1,13-15] and autosomal recessive hereditary diseases (involving genes on chromosome 6),[16-17] but other clinical features are not commonly observed.[18] Some researchers suggest that upd(6) mat has no impact on the health of carriers unless a recessive gene mutation is activated.[19]

Therefore, upd(6)mat is considered a biomarker rather than a direct cause of clinical features. When an upd(6)mat is detected, it indirectly indicates the cause of the phenotype, but UPD itself is not the underlying cause.[1] IUGR was previously associated with maternal and paternal uniparental disomy of chromosome 6.[20] However, confirming this association has been challenging due to the rarity of upd(6) mat and the etiology is not well understood. The findings presented in this paper further support previous reports regarding an association between upd(6)mat and IUGR.

CONCLUSION

In summary, we report a rare case of maternal uniparental disomy involving chromosome 6 with intrauterine growth restriction. The combination of genetic counseling, FISH, karyotype analysis, WES, CMA, NIPT, and prenatal ultrasound can significantly aid in the prenatal diagnosis of UPD. Our findings underscore the importance of utilizing these techniques to enhance the accuracy and effectiveness of UPD detection.

AVAILABILITY OF DATA AND MATERIALS

All relevant data and material is included in this publication.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE.

The Ethics Committee of Huangshi Central Hospital approved the research. Patient guardians gave informed consent to the study.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

All authors have made equal contributions to this work.

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