A Fetus with Maternal Uniparental Disomy on Chromosome 20: Case Report with Genetic Analysis and Prenatal Diagnosis

Li-Qing Hu, Zhen Deng, Shu-Na Li, Wu-Yan Huang, Lei Li, Ge-Fei Xiao, Qi-Zhi Xiao

Department of Medical Genetics and Prenatal Diagnosis (Zhuhai Institute of Medical Genetics), Zhuhai Center for Maternal and Child Health Care, Zhuhai, Guangdong, China

SUMMARY

Background: A fetus with increased copy number of chromosome 20 was identified by NIPT. Here we utilize several genetic tests and analyses to illuminate the etiology of such aneuploidy.

Methods: Amniotic fluid cells were extracted from pregnant woman and sent for karyotype and chromosomal microarray analysis (CMA). Trio pedigree analysis was conducted with Chromosome Analysis Suite and uniparental disomy (UPD)-tool software.

Results: CMA identified consistent results, which were 2 regions of homozygosity: arr[GRCh37]20p12.2q11.1 (11265096_26266313)hmz and arr[GRCh37]20q11.21q13.2(29510306_54430467)hmz. The trio pedigree analysis discovered that the fetal chromosome 20 was the entire maternal UPD mosaic with isodisomy and heterodisomy.

Conclusions: When a large segment of chromosome is homozygous, appropriate genetic tests are required to find the potential mechanisms for UPD formation.

KEYWORDS
uniparental disomy, chromosomal microarray analysis, confined placental mosaicism, genetic mechanism, case report

HIGHLIGHTS
1. Two novel and rare maternal uniparental disomy on chromosome 20
2. Different genetic tests/analyses are used to illuminate the UPD formation
3. Supporting confined placental mosaicism might cause false positive in NIPT

INTRODUCTION

Uniparental disomy (UPD) means the homologous chromosomes of somatic cells come from the same parent [1]. The mechanisms of the UPD formation include trisomy rescue, monosomy duplication, gamete complementation, and errors after fertilization [2]. UPD on
most chromosomes are asymptomatic, but UPD on chromosomes 6, 7, 11, 14, 15, and 20 might cause diseases [3]. Maternal UPD on chromosome 20 [UPD(20)mat] could cause Mulchandani-Bhoj-Conlin syndrome (MBCS), an uniparental disomy disorder of growth retardation with similar phenotypes related to Silver-Russell syndrome (SRS) [4]. Here we report the clinical and genetic information of a fetus with rare UPD(20)mat, providing clues and basis for prenatal diagnosis and counseling, aims to increase the detection rate of such UPD and imprinting disorder.

**CASE REPORT**

The case was from the Prenatal Diagnosis Center of Zhuhai Women’s and Children's Hospital. All information was obtained with informed consent from the fetus's parents and approved by the ethics committee. At the 15th week of pregnancy, the peripheral blood of the pregnant women was drawn for non-invasive prenatal test (NIPT). Extraction of cell-free fetal DNA (cfDNA) and construction of DNA nano ball was performed according to the standard operating procedure and reagents of NIFTY<sup>®</sup> (BGI, Shenzhen, China). The next-generation sequencing (NGS) was performed on BGI-SEQ-500, and data analysis was performed using corresponding protocols and software. NIPT indicated low risk (-3 < Z score < 3) of trisomy 21 (T21, Z score = 1.065), trisomy 18 (T18, Z score = 0.455), and trisomy 13 (T13, Z score = 0.570), but increased copy number of chromosome 20 was found (Figure 1).

Amniotic fluid cells were extracted and cultured in the medium produced by Guangzhou Heneng Biotechnology Co., Ltd. Lymphocytes in peripheral blood were extracted and cultured with the kit produced by Guangzhou Baiyunshan Baidi Biomedical Co., Ltd. Both amniotic fluid cells and lymphocytes were analyzed using routine G-banding karyotype. The karyotype was described according to the standards of the International System for Human Cytogenetic Nomenclature (ISCN 2020), but no abnormality was found for the karyotype. About 6 - 10 mL of amniotic fluid was extracted in a sterile centrifuge tube for chromosomal microarray analysis (CMA). Genomic DNA was extracted and purified with kit produced by Xiamen Zhishan Co., Ltd., and the following steps were performed according to the standard protocol of Affymetrix HD kit (ThermoFisher Co., Ltd., USA). All data was analyzed with the Chromosome Analysis Suite (ChAS) software, which found two regions of homozogosity (ROH, 15.0 Mb and 24.9 Mb) on chromosome 20 (Figure 2): arr[GRCh37]20p12.2q11.11(11265096-26266313) hzm and arr[GRCh37]20q11.21q13.2(29510306-54430467) hzm, involving 244 genes in the Online Mendelian Inheritance in Man, such as **RRBP1, SNX5, and MGMT**.

The peripheral blood of the parents was drawn for further trio CMA, the UPD-tool software was used to investigate whether the ROH was UPD and the origin [5]. UPD analysis of the pedigree suggested that the case was actually a whole maternal UPD with uniparental homodisomy and uniparental heterodisomy supplemental figures (Figure S1).

At the 22 weeks and 3 days of pregnancy, the ultrasound showed that the actual development of the fetus was 1 week later than the gestational age (breach presentation, birth weight was 423 ± 62 g), with umbilical cord around neck (supplemental figures; Figure S2). The length of maternal cervix was longer than 3.0 cm. The fetus was induced at the 26 weeks and 2 days of pregnancy, the skin and placental tissues were collected for CMA to verify the results of NIPT and amniocentesis. CMA results were consistent in skin tissue of the induced fetus and amniotic fluid cells (two ROH on chromosome 20), while it revealed trisomy 20 in the placental tissue (supplemental figures; Figure S3).

**DISCUSSION**

NIPT is based on high-throughput sequencing to evaluate the risk of common fetal chromosomal aneuploidy, using cfDNA fragments from maternal peripheral plasma. The cfDNA is mainly derived from the placenta, and confined placental mosaicism is one of the major factors causing false positive in NIPT [6]. Our study suggests that the increased copy number of chromosome 20 (identified by NIPT) of this case is due to the mosaic maternal UPD of homodisomy and heterodisomy. UPD is usually caused by two non-disjunction events during meiosis and mitosis. The homologous chromosomes fail to separate in meiosis I phase, which would cause uniparental heterodisomy. Sister chromatids fail to divide into daughter cells in meiosis II will result in uniparental homodisomy. Gametes produced by meiotic non-disjunction might be nullid (containing no copy of the affected chromosome) or disomy (containing two copies of the affected chromosome). After fertilization with normal haploid gamete, the chromosomes of the affected zygote might be trisomy or monosomy [7].

The genetic mechanism of UPD in this case has been analyzed above. Through the CMA and UPD-tool analysis of the case, we verified that it was a mosaic maternal UPD with uniparental homodisomy and heterodisomy in the whole chromosome 20. UPD is a kind of chromosomal abnormality, which can cause physiological dysfunction, embryo abortion, miscarriage, and so on. Different from genetic diseases such as microdeletions and microduplications, the occurrence of UPD is mostly not the result of inheriting the genetic defects of parents, it is rather related to abnormalities during meiosis, fertilization, and mitosis [8].

There are multiple methods to investigate the genetic information of UPD, such as karyotype analysis, gene chip, genome sequencing, and partial detection such as quantitative fluorescent polymerase chain reaction (QF-PCR), fluorescence in situ hybridization (FISH), and so
Figure 1. Increased copy number of chromosome 20 was indicated by NIPT.

NIPT - Non-invasive prenatal testing.

Figure 2. Two ROH identified by CMA from amniotic fluid cells.

ROH - region of homozygosity, CMA - chromosomal microarray analysis.
The combination of NIPT, high-resolution rate karyotyping and CMA are effective methods that can complement each other. UPD analysis can also be used to confirm noninvasive or prenatal ultrasound findings. A clear understanding of the mechanism of UPD formation could help figure out the period and possible forms of mutation, as well as judging the reproductive process, and providing genetic counseling to patients more comprehensively.

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