

RESEARCH

Open Access



Prenatal diagnosis and genetic counseling of a uniparental isodisomy of chromosome 8 with no phenotypic abnormalities

Chunjiao Yu^{1†}, Ying Tian^{2†}, Liang Qi^{3†} and Bo Wang^{4*}

Abstract

Background: Uniparental disomy (UPD) refers to an epigenomic abnormality in which both copies of, or a part of, a homologous pair of chromosomes are inherited from one parent. UPD arises via a number of mechanisms, including monosomic and trisomic rescue (in embryonic development), incomplete segregation of chromosomes, and mitotic recombination.

Case presentation: A 34-year-old, gravida 2, para 0 woman underwent amniocentesis at 18 weeks of gestation because the noninvasive prenatal testing (NIPT) showed the highly possibility of trisomy chromosome 8. GTG-banding karyotype analysis was performed on cultured amniocytes. Chromosomal microarray analysis (CMA), fluorescence in situ hybridization (FISH), whole-exome sequencing (WES) on uncultured amniocytes were performed.

Results: CMA detected a 29.4 Mb uniparental isodisomy of chromosome 8, arr 8p23.3p12(168484_29427840) × 2 hmz [GRCh37(hg19)]. FISH, WES and ultrasound examination showed no abnormal. At the 36-month checkup, the baby was developing normally.

Conclusion: Combination of NIPT, prenatal ultrasound, karyotype analysis, CMA, FISH, WES and genetic counseling will prove a more accurate risk assessment for the prenatal diagnosis of UPD.

Keywords: Uniparental disomy, Noninvasive prenatal testing, Chromosomal microarray analysis, Fluorescence in situ hybridization, Whole-exome sequencing

Introduction

Uniparental disomy (UPD) refers to an epigenomic abnormality in which both copies of, or a part of, a homologous pair of chromosomes are inherited from one parent [1]. UPD arises via a number of mechanisms, including monosomic and trisomic rescue (in embryonic development), incomplete segregation of chromosomes, and mitotic recombination [2].

UPD can be grouped into cases with pure isodisomy, pure heterodisomy and such with mixed iso-/heterodisomy. Also, one must distinguish UPD of a whole haploid chromosome set, UPD of one whole chromosome, and UPD of a part of a chromosome—a segmental UPD; the latter subtype is normally explained to be the consequence of a chromosomal rearrangement rescue-event [3]. UPD can be associated with human diseases through disruption of the normal allelic expression of genes that undergo genomic imprinting, homozygosity for an autosomal recessive trait, or due to incomplete (cryptic) trisomic rescue. Most often UPD is considered as a molecular genetic problem, but in some latest researches, it is affirmed and substantiated by corresponding data that UPD is a chromosomal disorder in the first place [4].

*Correspondence: wangbo1005@163.com

[†]Chunjiao Yu, Ying Tian, Liang Qi these authors contributed equally to this work

⁴ Department of Clinical Laboratory, Maternal, Child Health Hospital of Hubei Province, Wuhan, Hubei, People's Republic of China
Full list of author information is available at the end of the article



UPD does not affect the number or the structure of chromosomes and therefore escapes karyotype analysis [5], but it can be detected by SNP-based CMA technology, microsatellite analyses or trio exome sequencing (ES) [6]. Here we present the first case with paternal isodisomy 8 showing no phenotype [7].

Methods

Patients and samples

A 34-year-old, gravida 2, para 0 woman underwent amniocentesis at 18 weeks of gestation because NIPT showed the highly possibility of trisomy chromosome 8. GTG-banding karyotype analysis was performed on cultured amniocytes. CMA, FISH, WES on uncultured amniocytes were performed.

Results

Cytogenetic analysis of the cultured amniocytes revealed a normal karyotype of 46,XX. CMA on uncultured amniocytes was performed using the Affymetrix CytoScan 750 K chip, which includes 550 k non-polymorphic markers and 200 k SNP markers. CMA detected a 29.4 Mb iso-UPD of chromosome 8, arr 8p23.3p12(168484_29427840) × 2 hmz [GRCh37(hg19)] (Fig. 1). The parental karyotypes and CMA analysis were

normal. Microsatellite analyses suggested paternal UPD for chromosome 8.

All prenatal laboratory data were within normal range. Ultrasound examination showed no facial dysmorphisms or intrauterine growth restrictions (IUGRs) (At 25 weeks of gestation, estimated fetal weight 700g, abdominal circumference 19.9 cm, head circumference 22.1 cm, femur long 4.3 cm and fetal heart rate 145 bpm) in the fetus [8]. After genetic counseling, we performed WES and FISH on uncultured amniocytes. The Novaseq6000 platform (Illumina, San Diego, USA), with 150 bp pair-end sequencing mode, was used for sequencing the genomic DNA of the family. The sequencing reads were aligned to the human reference genome (hg38/GRCh38) using the Burrows-Wheeler Aligner tool. WES revealed no homozygous mutations of any known recessive pathogenic genes for inherited disorders on chromosome 8p23.3p12. Interphase FISH analysis on uncultured amniocytes using the probe of CEP-8 revealed monosomy chromosome 8 in 5/200 cells and trisomy chromosome 8 in 3/200 cells.

The parents decided to continue the pregnancy. At 40 weeks of gestation, a 3350-g female infant was delivered naturally. Apgar scores were 8/9/9. The infant received a complete physical examination with normal findings. At the 36-month checkup, the baby was

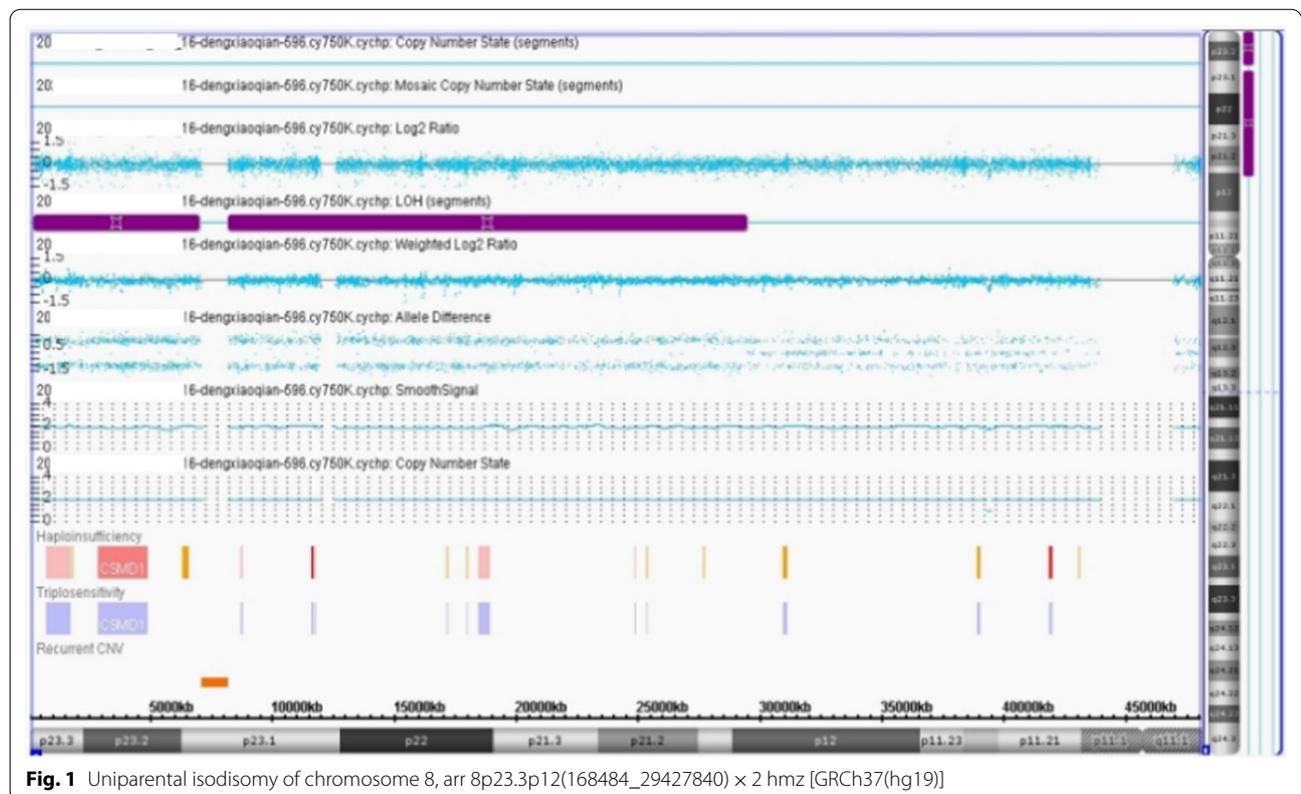


Fig. 1 Uniparental isodisomy of chromosome 8, arr 8p23.3p12(168484_29427840) × 2 hmz [GRCh37(hg19)]

developing normally(head circumference 51 cm, height 99 cm, weight 14.5 kg, Intelligence Quotient, IQ=115).

Discussion

In contrast to numeric or structural chromosomal aberration, UPD does not affect the number or the structure of chromosomes and therefore escapes cytogenetic detection [5]. But it can be detected by SNP-based CMA technology and microsatellite analyses. SNP-based CMA consist of sets of oligonucleotides specific for polymorphisms in the genome. Although an oversimplification, each SNP has 2 different oligo sets, one for each allele, which when hybridized with sample DNA give a signal intensity relating to copy number and a SNP call referring to the allele in the sample, which can either be AA, BB, or the heterozygous call AB.

It must be stressed, that in SNP-based CMA only isodisomy can be detected and is normally blind for heterodisomy [7]. Microsatellite analyses or trio exome sequencing (ES) can detect pure isodisomy, pure heterodisomy, mixed iso-/heterodisomy and segmental UPD [6].

In this study, NIPT showed the highly possibility of trisomy chromosome 8. It is speculated that UPD of chromosome 8 may be caused by trisomy rescue.

UPD can be associated with human diseases through disruption of the normal allelic expression of genes that undergo genomic imprinting, homozygosity for an autosomal recessive trait, or mosaicism aneuploidy. UPD could lead to various clinical phenotypes due to either homozygosity of recessive mutations or aberrant patterns of imprinting. Imprinting disorders alter epigenetic regulation and DNA methylation and histone modifications [9]. The widespread use of SNP-based CMA technology and microsatellite analyses have facilitated UPD detection. For the majority of chromosomes, UPD is without clinical consequence. However, for chromosomes 6, 7, 11, 14, 15, and 20, there are parent-of-origin or imprinting differences in gene expression in the context of UPD, which may lead to phenotypic abnormalities [10].

There are very few examples of paternal UPD8 in the literature, we present the first case with paternal isodisomy 8 showing no phenotype. We found some cases of paternal UPD8 with phenotypic abnormalities [7], the nosogenesis of most cases is the homozygote state of recessive pathogenic gene [11–16], but in other cases the cause is unknown [17]. There are several suspected recessive pathogenic genes for inherited disorders on chromosome 8p23.3p12 such as *XKR6*, *MIRS97* [18], *RP1L1* [19] and *PPP1R3B* [20]. In our case, no pathogenic mutations or homozygous recessive pathogenic genes were detected by CMA and WES.

Conclusions

To summarize, we report a case of paternal UPD for chromosome 8 with a normal phenotype. Combination of NIPT, prenatal ultrasound, karyotype analysis, CMA, FISH, WES and genetic counseling will prove a more accurate risk assessment for the prenatal diagnosis of UPD.

Abbreviations

UPD: Uniparental disomy; CMA: Chromosomal microarray analysis; NIPT: Noninvasive prenatal testing; FISH: Fluorescence in situ hybridization; WES: Whole-exome sequencing; IUGRS: Intrauterine growth restrictions.

Acknowledgements

We thanked all the participants and the families in this study for their cooperation.

Author contributions

CY and YT are responsible for clinical diagnosis and treatment. LQ is responsible for pathological examination. BW is responsible for genetic testing and thesis writing.

Funding

There was no funding available for this study.

Availability of data and materials

All relevant data and material is included in this publication.

Declarations

Ethics approval and consent to participate

The research was approved by the Ethics Committee of Maternal and Child Health Hospital of Hubei Province. All patient guardians gave informed consent to the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department of Prenatal Diagnosis Center, Maternal, Child Health Hospital of Hubei Province, Wuhan, Hubei, People's Republic of China. ²Department of Obstetrics, Maternal, Child Health Hospital of Hubei Province, Wuhan, Hubei, People's Republic of China. ³Department of Ophthalmology, Maternal, Child Health Hospital of Hubei Province, Wuhan, Hubei, China. ⁴Department of Clinical Laboratory, Maternal, Child Health Hospital of Hubei Province, Wuhan, Hubei, People's Republic of China.

Received: 19 February 2022 Accepted: 22 March 2022

Published online: 26 April 2022

References

- Robinson WP. Mechanisms leading to uniparental disomy and their clinical consequences. *BioEssays*. 2000;22:452–9.
- Brian AW, Paola EL, Matthew WJ, Cheng L, David G, David CJ, Fiona MR, Faith ED, Gareth JM. Integration of global SNP-based mapping and expression arrays reveals key regions, mechanisms, and genes important in the pathogenesis of multiple myeloma. *Blood*. 2006;108:1733–43.
- Liehr T. Cytogenetic contribution to uniparental disomy (UPD). *Mol Cytogenet*. 2010;3:8. <https://doi.org/10.1186/1755-8166-3-8>.
- Liehr T. Uniparental disomy is a chromosomal disorder in the first place. *Mol Cytogenet*. 2022;15:5. <https://doi.org/10.1186/s13039-022-00585-2>.

5. Eggermann T. Prenatal detection of uniparental disomies (UPD): Intended and incidental finding in the era of next generation genomics. *Genes*. 2020;11:1454–65.
6. Scufns J, Keller-Ramey J, Dyer L, Douglas G, Torene R, Gainullin V, Juusola J, Meck J, Retterer K. Uniparental disomy in a population of 32,067 clinical exome trios. *Genet Med*. 2021;23:1101–7. <https://doi.org/10.1038/s41436-020-01092-8>.
7. Liehr T. Cases with uniparental disomy. 2022. <http://cs-tl.de/DB/CA/UPD/0-Start.html>. Accessed 01 Jan 2022.
8. Süleyman CO, Muhammed HB, Mehmet O. 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.
9. Zhang C, Hao SJ, Zhang QH, Liu FR, Zhou BB, Xuan F, Xing W, Chen X, Wang Y, Ma PP, Cao ZF, Xi Ma. Maternal UPD of chromosome 7 in a patient with Silver-Russell syndrome and Pendred syndrome. *J Clin Lab Anal*. 2020;34:e23407–11.
10. Gaudio DD, Shinawi M, Astbury C, Tayeh MK, Deak KL, Raca G, et al. Diagnostic testing for uniparental disomy: a point to consider statement from the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2020;22:1133–41.
11. Benlian P, Foubert L, Gagné E, Bernard L, De Gennes JL, Langlois S, Robinson W, Hayden M. Complete paternal isodisomy for chromosome 8 unmasked by lipoprotein lipase deficiency. *Am J Hum Genet*. 1996;59:431–6.
12. Matsubara K, Kataoka N, Ogita S, Sano S, Ogata T, Fukami M, Katsumata N. Uniparental disomy of chromosome 8 leading to homozygosity of a CYP11B1 mutation in a patient with congenital adrenal hyperplasia: Implication for a rare etiology of an autosomal recessive disorder. *Endocr J*. 2014;61:629–33.
13. Guerrero-López R, Giráldez BG, Verdú A, Carrascosa-Romero MC, Ortega-Moreno L, Sánchez-Martín G, García-Muñoz Guren S, Pardal-Fernández JM, Serratosa JM. A new case of spinal muscular atrophy with progressive myoclonic epilepsy associated with a homozygous mutation in ASAH1. *Europ J Hum Genet*. 2014;21:232.
14. Giráldez BG, Guerrero-López R, Ortega-Moreno L, Verdú A, Carrascosa-Romero MC, García-Campos Ó, García-Muñozguren S, Pardal-Fernández JM, Serratosa JM. Uniparental disomy as a cause of spinal muscular atrophy and progressive myoclonic epilepsy: Phenotypic homogeneity due to the homozygous c.125C>T mutation in ASAH1. *Neuromuscul Disord*. 2015;25:222–4.
15. Šafka Brožková D, Paulasová Schwabová J, Neupauerová J, Sabová J, Krůtová M, Peřina V, Trková M, Laššuthová P, Seeman P. HMSN Lom in 12 Czech patients, with one unusual case due to uniparental isodisomy of chromosome 8. *J Hum Genet*. 2017;62:431–5.
16. Ashraf AP, Hurst ACE, Garg A. Extreme hypertriglyceridemia, pseudohyponatremia, and pseudoacidosis in a neonate with lipoprotein lipase deficiency due to segmental uniparental disomy. *J Clin Lipidol*. 2017;11:757–62.
17. Papenhausen P, Schwartz S, Rishog H, Keitges E, Gadi I, Burnside RD, Jaswaney V, Pappas J, Pasion R, Friedman K, Tepperberg J. UPD detection using homozygosity profiling with a SNP genotyping microarray. *Am J Med Genet A*. 2011;155:757–68.
18. Nihan HA, Özlem YC, Herbert S, Thomas S, Server HC, Zuhai Y. De novo 8p23.1 deletion in a patient with absence epilepsy. *Epileptic Disord*. 2017;19(2):217–21.
19. Hiraoka M, Ishikawa A, Matsuzawa F, Aikawa SI, Sakurai A. A variant in the RP1L1 gene in a family with occult macular dystrophy in a predicted intrinsically disordered region. *Ophthalmic Genet*. 2020;41(6):599–605.
20. Niazi RK, Sun J, Have CT, Hollensted M, Linneberg A, Pedersen O, Nielsen JS, Rungby J, Garup N, Hansen T, Gjesing AP. Increased frequency of rare missense PPP1R3B variants among Danish patients with type 2 diabetes. *PLoS ONE*. 2019;14(1):e0210114.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

