

CLINICAL REPORT

Prenatal diagnosis of Prader-Willi syndrome due to uniparental disomy with NIPS: Case report and literature review

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FUNDING INFORMATION

This work was supported by Grant AAAA-A18-118053190010-5 of Ministry of Healthcare of the Russian Federation.

Abstract

Background: PWS is challenging to diagnose prenatally due to a lack of precise and well-characterized fetal phenotypes and noninvasive markers. Here we present the case of prenatal diagnosis of Prader-Willi syndrome, which was suspected with whole-genome NIPS.

Methods: Whole-genome noninvasive prenatal screening showed a high risk for trisomy 15. Amniocentesis followed by FISH analysis and SNP-based chromosomal microarray was performed.

Results: Simultaneous analysis of maternal and fetal samples with SNP microarrays demonstrated maternal uniparental disomy (UPD).

Conclusion: The presented case is the first case of PWS described in detail, which was suspected by NIPS results. It demonstrates that the choice of confirmation methods concerning the time needed is crucial for the right diagnosis. We suppose that prenatal testing of UPD is essential for chromosome regions, which play a key role in the appearance of various gene-imprinting failure syndromes like PWS or AS.

KEYWORDS

NIPS, Prader-Willi syndrome, rare trisomy, trisomy 15, UPD

1 | INTRODUCTION

Noninvasive prenatal DNA screening (NIPS) is getting more widespread in clinical practice. It is recommended for pregnant women regardless of the risk group according to conventional screening (Anthony et al., 2016). The use of shallow whole-genome sequencing for NIPS allows analysis of all chromosome aneuploidies; hence the value of reporting such findings remains controversial. Some authors state that rare autosomal aneuploidies can suggest an increased risk of fetoplacental disease and be beneficent for pregnancy management (Chatron et al., 2019; Pertile et al., 2017; Scott et al., 2018). Others argue

that pregnancy outcomes in case of increased risk for rare autosomal trisomies are not as adverse as expected (He, Liu, Xie, Liu, & Li, 2019). American College of Medical Genetics and Genomics does not recommend screening for rare autosomal aneuploidies as information about the significance of such findings is limited (Anthony et al., 2016). There are no recommendations for the follow up of the patients with a high risk of rare trisomy. However, for some conditions only whole-genome NIPS results allow us to detect risk prenatally.

Here we present the case of prenatal diagnosis of Prader-Willi syndrome, which was suspected with whole-genome NIPS.

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2 | MATERIALS AND METHODS

2.1 | Ethical compliance

Informed written consent was obtained from the patient.

2.2 | Clinical report

A 43-year-old woman (gravida 4, para 1) was referred to the laboratory for NIPS because of the advanced maternal age. Results of 1st trimester screening indicated low risk for common trisomies: trisomy 21 risk 1:679, trisomy 18 risk 1:1663, trisomy 13 1:5216 (PAPP-A 1,414 MoM, bHG 0,799 MoM). NIPS was performed at 13 weeks of gestation and showed a high risk for trisomy 15 (Figure 1). Fetal fraction estimated from SNP markers was 9.4%, fetal fraction estimated from chromosome 15 was 6%.

As the ratio of fetal fraction estimated from chromosome 15 and SNP markers was 0.64, we could suggest that not all the trophoblast cells have trisomy 15. So, the obtained NIPS results can be explained by chromosomal mosaicism that can be confined to the placenta or affect the fetus too.

Mosaicism formation is a result of nondisjunction error during mitotic cell division or during meiosis, followed by a postzygotic correction of aneuploidy. The latter can result in uniparental disomy (UPD) if a wrong chromosome is lost during the correction. Furthermore, fetal mosaicism should be excluded.

2.3 | NIPS

Noninvasive prenatal DNA screening was performed using an in-house developed protocol with Ion S5 XXL sequencer. Sequencing data analysis was conducted with an in-house developed software.

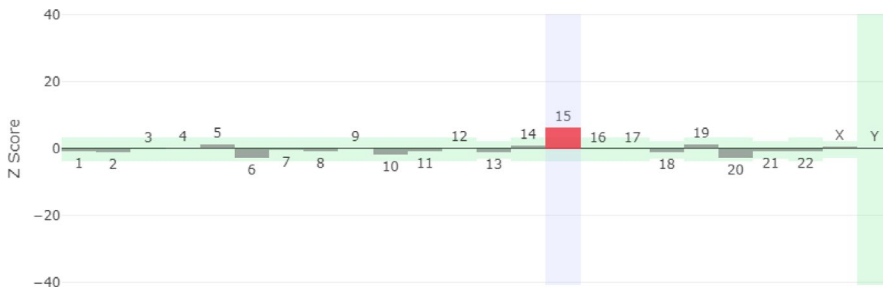


FIGURE 1 NIPS results revealed high risk for trisomy 15.

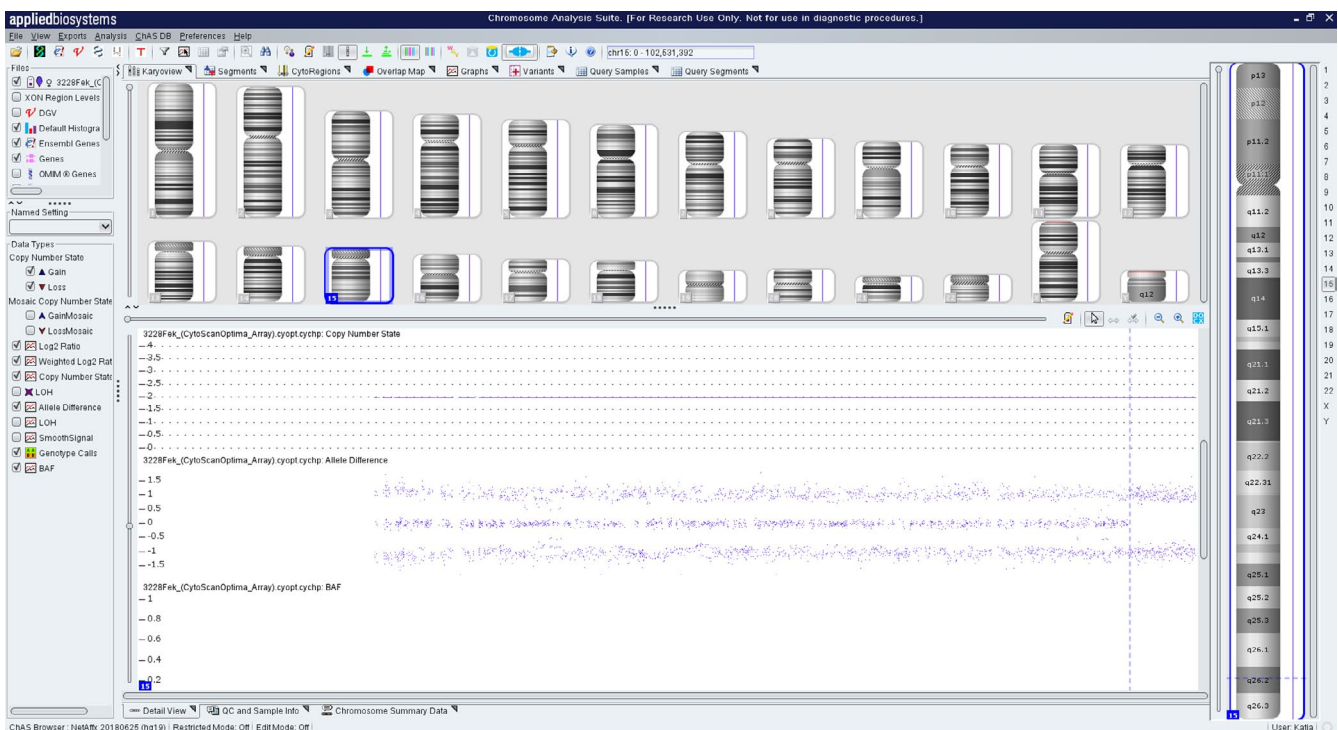


FIGURE 2 Molecular karyotyping arr[hg19] 15q26.2q26.3(95 806 550-102 395 843)x2 hmz.

2.4 | Analyses during pregnancy

As the 15th chromosome is involved in imprinting syndromes the patient was informed about this risk. After consultation with the geneticist, the patient decided to undergo invasive diagnosis. At 16–17 gestation weeks, amniocentesis followed by FISH (probes SE D15Z4, Kretech Diagnostics, Netherlands) analysis and SNP-based chromosomal microarray (CytoScan Optima Array Affymetrix, Santa Clara, CA) was performed.

2.5 | Analyses after pregnancy termination

We analyzed SNRPN gene promoter methylation in amniotic fluid and fetal muscle using sequence-based quantitative

methylation analysis SeQMA (Dikow et al., 2007). Amniotic fluid of a fetus without karyotype abnormalities obtained during the routine invasive procedure was used as a control.

Four spaced placental samples were collected and FISH analysis of 300 nuclei was performed for each sample.

3 | RESULTS

As the 15th chromosome is involved in imprinting syndromes the patient was informed about this risk. After consultation with the geneticist, the patient decided to undergo invasive diagnosis at 16–17 gestation weeks. FISH analysis revealed two copies of chromosome 15 in all 100 nuclei. Molecular karyotyping showed normal karyotype arr[hg19] 15q26.2q26.3 (95 806

FIGURE 3 Comparison of maternal and fetal genotypes for chromosome 15. Solid line—fraction of genotypes within 50 SNP-window where both alleles are identical to the maternal allele demonstrates the presence of maternal heterodisomy in the 15q11.1q26.2 region. Dash line—fraction of homozygous genotypes in fetus within 50 SNP-window demonstrates the presence of loss of heterozygosity region on the end of the chromosome.

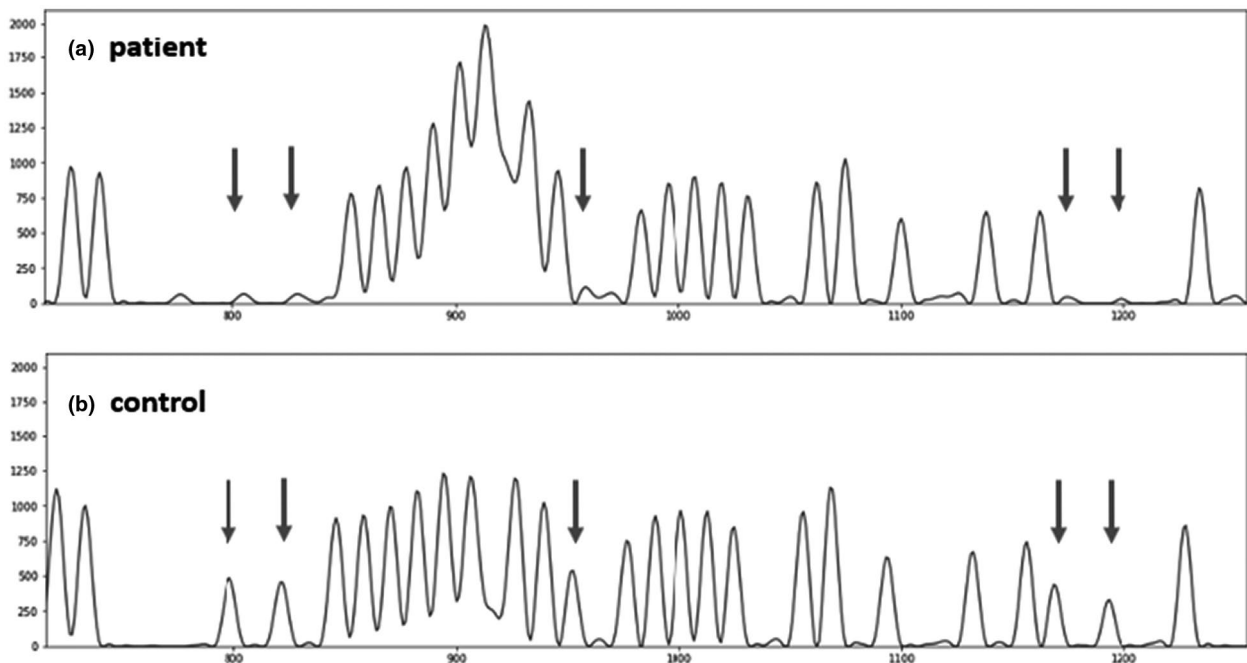
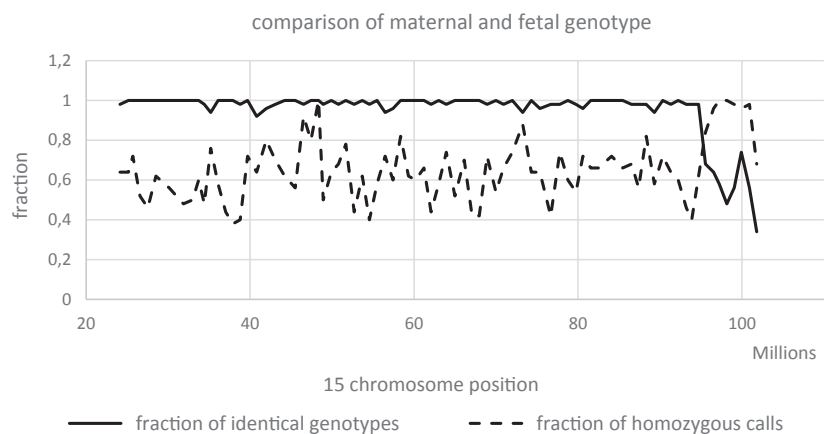


FIGURE 4 T-peak raw data in SeQMA analysis. Capillary electropherograms of T-peaks in the SNRPN-promoter region are used for the SeQMA assay on bisulfite-treated DNA. Arrows indicate cytosine residues in CpG dinucleotides of the original sequence. Other peaks were either original thymine or non-CpG cytosine residues. (a) Hypermethylated CpG cytosines in DNA from a PWS patient escape bisulfite transformation and no peak signal is generated in the SeQMA assay (b) Control DNA showing a 50% reduction in peak signal indicating one methylated allele.

550-102 395 843)x2 hmz with a 6.5 Mb loss of heterozygosity region on the end of the chromosome (Figure 2). To exclude or confirm UPD we carried out the molecular karyotyping of maternal blood cells. Comparison of maternal and fetal genotypes of 15th chromosome demonstrated the presence of maternal heterodisomy in the 15q11.1q26.2 region and maternal homodisomy in the 15q26.2q26.3 region upd(15)mat.arr[hg19] 15q11.1q26.2(22 809 980-95 806 550)x2 htz, 15q26.2q26.3(95 806 550-102 395 843)x2 hmz (Figure 3). Both copies of 15-th chromosome were of maternal origin which means that fetus had UPD of maternal origin that leads to Prader-Willy syndrome (Buiting et al., 1995).

On the request of the patient pregnancy was terminated at 21st gestation week with small cesarean section for placenta previa.

After pregnancy termination, four spaced placental samples were collected. Mosaic 15th chromosome trisomy was detected in all samples, with 3-70% of trisomic nuclei in different samples.

Methylation analysis is recommended as a first-tier test if PWS is suspected (Ramsden, Clayton-Smith, Birch, & Buiting, 2010). So, after the termination of pregnancy, we analyzed SNRPN gene promoter methylation in amniotic fluid and fetal muscle. Methylation analysis was not performed during pregnancy due to time limitations. Patient methylation analysis has shown no T-peak signal for CpG cytosines, which corresponds to hypermethylation in DNA (Figure 4).

4 | DISCUSSION

At present, PWS is challenging to diagnose prenatally due to a lack of precise and well-characterized fetal phenotypes. Fetal hypomobility, polyhydramnios, and abnormal extremity positions are observed in pregnancies with PWS fetuses. Some noninvasive tests allow detection 15q11.2-q13 microdeletion, which accounts for approximately 75% of PWS cases, and it is possible to confirm with chromosomal microarray, which is routinely performed in prenatal diagnosis lab, however only whole genome test can help detect the risk for trisomy 15 and suspect the possibility of the UPD.

We have found nine published cases of high-risk of trisomy 15 detected with whole-genome NIPS with documented pregnancy outcomes (Bayindir et al., 2015; Chatron et al., 2019; Chen et al., 2019; He et al., 2019; Pertile et al., 2017; Scott et al., 2018). In four out of nine cases, babies with normal phenotypes were born. In three cases, UPD was detected, and in two cases, true fetal mosaicism. Thereby more than a half of described cases had an adverse pregnancy outcome. Some authors mentioned that UPD was excluded as SNP microarrays were used for prenatal diagnosis (He et al., 2019). However, prenatal examination with SNP microarrays

of fetus alone with no parental samples can miss cases of hetero-UPD as described in Dong et al. (2019).

This is the first case of PWS, which was suspected using NIPS results. It demonstrates that the choice of confirmation methods concerning the time needed is crucial for the right diagnosis. DNA methylation test for the SNRPN gene promoter is usually used postnatally for Prader-Willi syndrome diagnosis. Hence it is not a standard test for prenatal diagnosis lab; it could be used for prenatal diagnosis if available. In case of usage of SNP microarrays as a confirmation method, additional examination of at least one parental sample with additional data analysis is obligatory for such clinical cases. We suppose that prenatal testing of UPD is essential for chromosome regions, which play a key role in the appearance of various gene-imprinting failure syndromes like PWS or AS.

ACKNOWLEDGEMENTS

This study was supported by grant AAAA-A18-118053190010-5 from the Ministry of Healthcare of the Russian Federation.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

SJ was involved in bioinformatic data analysis, drafting of the article, critical revision of the article, and final approval of the version to be published. DT and SG were involved in developing the idea, critical revision of the article, and final approval of the version to be published. SO was involved in the cytogenetic analysis, critical revision of the article, and final approval of the version to be published. GA and TK performed NIPS, were involved in critical revision of the article, and final approval of the version to be published. MK performed molecular karyotyping, was involved in critical revision of the article, and final approval of the version to be published. BI was involved in patient management, critical revision of the article, and final approval of the version to be published.

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How to cite this article: Shubina J, Barkov IY, Stupko OK, et al. Prenatal diagnosis of Prader-Willi syndrome due to uniparental disomy with NIPS: Case report and literature review. *Mol Genet Genomic Med*. 2020;8:e1448. <https://doi.org/10.1002/mgg3.1448>