Noninvasive prenatal testing aids identification of tetrasomy 18p: A case report

Yuko Tamaki a,⁎, Yukiko Katagiri a, Nahomi Umemura a, Naoki Takeshita b, Mineto Morita a

a Department of Obstetrics and Gynecology, Toho University Omori Medical Center, Japan
b Department of Obstetrics and Gynecology, Toho University Sakura Medical Center, Japan

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Tetrasomy 18p syndrome (Online Mendelian Inheritance in Man 614290) is a rare chromosomal disorder that is seen in approximately 1 in every 180,000 live births. It is caused by the presence of isochromosome 18p, which is a supernumerary marker composed of two copies of the short arms of chromosome 18. Isochromosome 18p is one of the most commonly observed isochromosomes. We report tetrasomy 18p syndrome diagnosed prenatally after noninvasive prenatal testing (NIPT) was positive for trisomy 18. Tetrasomy 18p was finally diagnosed by G-banding and fluorescence in situ hybridization of chromosome 18p, before invasive confirmatory testing the karyotype findings by NIPT showed an increase in the DNA fragments from chromosome 18p, indicating duplication of chromosome 18p. NIPT can detect not only trisomy 13, 18, and 21, but also structural chromosomal anomalies, such as deletions and duplications. An NIPT report “positive for trisomy 18” indicates the possibility of tetrasomy 18p, and detailed analysis of NIPT data can reveal subchromosomal copy number variations, to a certain extent, before definitive diagnostic testing.

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1. Introduction

The utility and the clinical validity of cell-free fetal DNA screening for trisomies are well recognized all over the world. In Japan, clinical studies of screening for trisomy 13, 18, and 21 in high-risk pregnancies have been performed, though these studies have mostly involved older women. Moreover, sex-chromosome aneuploidies and genome-wide copy number variations have not been examined in such studies [1]. Genome-wide screening for copy number variations using cell-free DNA in maternal plasma is technically possible [2], and some companies are now offering genome-wide screening. However, the validity of genome-wide screening from cell-free fetal DNA has not yet been established.

In this case report, we describe a fetus with suspected tetrasomy 18p detected by noninvasive prenatal testing (NIPT).

2. Case

A healthy, 41-year old, gravida 1 woman became pregnant after a single blastocyst transfer was made due to her husband with oligozoospermia. Her medical history was unremarkable. The woman’s younger brother was known to have a ventricular septal defect. The woman opted for NIPT at 12+6 weeks of gestation because of an elevated nuchal translucency thickness (about 4 mm) and her age. We explained about the objectives and limitations of NIPT, and differences from invasive testing at genetic counseling. Peripheral blood was collected, DNA was extracted, and massive parallel sequencing [3,4] (MaterniT21 Plus) was performed using Illumina HiSeq 2000 (San Diego, United States). The sequencing data were used to calculate the Z-scores for trisomies 21, 18, and 13, which represent robust assessments of normalized chromosomal representation compared with the euploid genome. NIPT produced a positive result for chromosome 18, which was considered to indicate a high possibility of trisomy 18. Amniocentesis was carried out at 15+6 weeks of gestation. An ultrasound scan showed the biparietal diameter to be within normal range and no major anomalies. The result indicated 47,XY,+i(18)(p10)[20] (Fig. 1). Fluorescence in situ hybridization of chromosome 18p with a telomeric probe produced 4 signals, sufficient for a diagnosis of tetrasomy 18p. The pregnancy was terminated at 19+4 weeks on parental request.

⁎ Corresponding author at: Department of Obstetrics and Gynecology, Toho University Omori Medical Center, 6-11-1 Omori-nishi, Ota-ku, Tokyo 143-8541, Japan.
E-mail addresses: yishihara@med.toho-u.ac.jp (Y. Tamaki), yukikonk@med.toho-u.ac.jp (Y. Katagiri), nahomi.ume@med.toho-u.ac.jp (N. Umemura), ntakesit@med.toho-u.ac.jp (N. Takeshita), mmorita@med.toho-u.ac.jp (M. Morita).

1 noninvasive prenatal testing (NIPT)
After the karyotype was revealed, the detailed NIPT data were confirmed. The fetal fraction rate was 12.76%. The Z-scores of chromosomes 13, 18, and 21 were 0.14792, 11.7663, and 0.07616, respectively. The Z-scores were within the normal range for chromosomes 13 and 21, but higher for chromosome 18 (Z-score > 3 is considered abnormal). The karyotype findings by NIPT showed an increase in the DNA fragments from chromosome 18p, indicating duplication of chromosome 18p (Fig. 2).

3. Discussion

This case report demonstrates two important clinical issues. First, in addition to trisomy 13, 18, and 21, NIPT can detect structural chromosomal anomalies, such as deletions and duplications. Second, an NIPT report “positive for trisomy 18” does not rule out the possibility of tetrasomy 18p and the detailed NIPT data can show subchromosomal copy number variations, to a certain extent, before definitive diagnostic testing.

Regarding the first issue, NIPT is not a confirmatory test but a screening test, and from the amount of cell-free DNA of chromosome 13, 18, and 21 NIPT can detect not only trisomies but also structural chromosomal anomalies and the probability of tetrasomy 18p. There are some case reports of deletions and duplications of chromosome 18 detected by NIPT (Table 1)[5–9]. In two cases, NIPT could not identify a fetus positive for chromosome 18 anomalies, but in the others it could identify the possibility of chromosome aberrations. NIPT using genome-wide massive parallel sequencing could screen for the possibility of deletions and duplications of chromosome 18. Considering this, genetic counseling about deletions and duplications is necessary before NIPT.

Regarding the second issue, an NIPT report “positive for trisomy 18” can indicate not only trisomy 18 but also the possibility of tetrasomy 18p, and the detailed NIPT data can show subchromosomal copy number variations to a certain extent, before definitive diagnostic testing. Tetrasomy 18p has the usual number of copies of chromosome 18, plus an isochromosome 18p. As a result, each cell has four copies of the short arm of chromosome 18. The size of the gene involved in tetrasomy 18p is 15 mega base pairs (Mb). The four copies of the...
short arm of chromosome 18 represent an approximately 40% increase in DNA compared with that in full trisomy 18 [10]. Some commercial laboratories use cell-free DNA screening for genome-wide gains and losses of 7 Mb or more, and so should be able to detect tetrasomy 18p. Improving cell-free DNA screening technology will increase accuracy in the near future.

While NIPT can be used to detect subchromosomal copy number variations, the American College of Obstetricians and Gynecologists does not recommend routine screening for genome-wide gains and losses with cell-free DNA [11], partly because of patient anxiety (the limitations and benefits of NIPT need to be discussed in genetic counseling), incomplete validation of NIPT for detecting copy number variations, clinical use, and cost-effectiveness. Although expanded cell-free DNA screening has been introduced in some clinical practices, research into positive predictive values (PPVs) and effective genetic counseling is still needed.

NIPT is valid for screening for trisomy 13, 18, and 21 with high sensitivity. Miranda J. et al. reported that in fetuses with increased nuchal translucency, NIPT would miss 12-19% of genetic anomalies [12]. NIPT would miss some genetic abnormalities in fetuses that harbored sex-chromosome aneuploidies, clinically relevant atypical chromosomal anomalies (trisomy 22, trisomy 21 mosaicism, and unbalanced translocation), and submicroscopic pathogenic variants. NIPT originally targeted only 3 anomalies, namely trisomies 13, 18, and 21, and not sex-chromosome aneuploidies. Further, when using trophoblast-derived cell-free DNA for NIPT, false positive results could be obtained because of placental mosaicism. Due to this limitation of target diseases and placental mosaicism, invasive testing is important when NIPT produces positive results.

Tetrasomy 18p syndrome is seen in approximately 1 in every 180,000 live births. The clinical phenotypes of this disease include neonatal feeding problems, developmental delays (mild to severe), microcephaly, abnormalities in muscle tone, dysmorphic features, and variants in brain MRI [13]. In the case presented here, prenatal evaluation by ultrasound showed an increased nuchal translucency at 12 weeks of gestation, while at 16 weeks of gestation there were no abnormal findings. Tetrasomy 18p is difficult to detect or diagnose from fetal ultrasound scans. Isochromosome 18p is one of the most commonly observed isochromosomes. In the case presented here, a supernumerary marker in G-banding was thought to originate from chromosome 18 because of the NIPT result. Without the NIPT result, determining the origin of the supernumerary marker would have been more difficult.

Isochromosomes arise as a result of two independent events: nondisjunction and centromeric misdivision. An alternative mechanism for the formation of an isochromosome is a U-shaped exchange, which would typically produce a dicentric isochromosome [14]. Isochromosomes tend to originate from the maternal side, and nondisjunction, which occurs during maternal meiosis, suggests that advanced maternal age is a contributing factor.

In conclusion, in addition to detecting trisomy 13, 18, and 21, NIPT can be used to identify structural chromosomal anomalies. An NIPT result “positive for trisomy 18” does not exclude the possibility of tetrasomy 18p, and detailed NIPT data can show subchromosomal copy number variations and indicate the need for further testing.

Screening for genome-wide gains and losses with cell-free DNA is not recommended, and further research is necessary to improve detection of smaller copy number variations.

Contributors

Yuko Tamaki contributed to conception and design of the study, acquisition of data, analysis and interpretation of data, and drafting the article.

Yukiko Katagiri contributed to critically revising the article for important intellectual content, and supervision.

Nahomi Umemura contributed to acquisition of data, and analysis and interpretation of data.

Naoki Takeshita contributed to critically revising the article for important intellectual content, and supervision.

Mineto Morita contributed to supervision, and final approval of the version to be submitted.
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