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Clinical management of pregnancies with positive screening results for rare autosomal aneuploidies at a single center

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Abstract

Objective: To review our experiences on clinical management of pregnancies with positive noninvasive prenatal testing (NIPT) results for rare autosomal aneuploidies (RAAs) at a single center.

Methods: We performed a retrospective study and reviewed data from 18,016 pregnancies undergoing NIPT at a single center in China from March 2017 to February 2020. Depending on the patient's choice, women with positive screening results for RAAs underwent chromosomal microarray analysis for invasive prenatal diagnosis.

Results: Thirty-three positive cases for RAAs were identified, with a positive screening rate of 0.18%. The most common RAA was trisomy 7 (33.3%), while trisomies for other chromosomes were less frequent. Monosomies involving chromosomes 16, 14, and 22 were observed.

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Twenty-eight cases of RAAs underwent invasive diagnosis. Abnormal pregnancy outcomes were observed in four cases, including true fetal mosaicism (n=1), partial uniparental disomy (n=1), miscarriage (n=1), and structural anomalies on ultrasound (n=1).

Conclusions: RAAs at NIPT might be associated with fetal uniparental disomy, mosaic aneuploidy, and poor pregnancy outcomes, but most positive cases have normal pregnancy outcomes. For RAAs, genetic counseling on the potential risks of abnormal NIPT results, as well as on benefits and limitations of invasive prenatal diagnosis, might help guide clinical management.

Keywords

Rare autosomal aneuploidy, non-invasive prenatal test, chromosomal microarray analysis, uniparental disomy, trisomy, pregnancy outcome

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Introduction

Noninvasive prenatal testing (NIPT) is a technology for determining fetal aneuploidy using massively parallel sequencing analysis of maternal cell-free fetal DNA (cffDNA).[1] Currently, NIPT is recommended as a first-tier or second-tier prenatal screening test for common fetal aneuploidies (e.g., trisomies 21, 18, and 13) in routine clinical practice.[2,3] Moreover, growing evidence has shown that NIPT has high sensitivity and specificity in detecting fetal sex chromosomal aneuplodies.[3–5] Karyotyping and chromosomal microarray analysis (CMA) are often offered as the prenatal diagnostic testing method for pregnancy with a high-risk NIPT result. Indeed, most published reports focused on the clinical utility of NIPT on prenatal screening of fetal common aneuploidies and sex chromosomal aneuploidies.

In clinical practice, rare autosomal aneuploidies (RAAs) involve all autosomal chromosomes other than 21, 18, or 13 and are often reported as additional findings of NIPT. The most common RAAs detected in cffDNA involve aneuploidies 7, 16, 15, and 22, while aneuploidies involving other chromosomes are relatively rare. Notably, the frequency of RAAs and the proportion of abnormal pregnancy outcomes in these cases largely vary.[6–10] Therefore, more clinical information on the incidence and pregnancy outcome are urgently required to facilitate genetic counseling and relieve the anxiety of affected couples. Positive NIPT results for RAAs increase the risk of pregnancy complications, including miscarriage, intrauterine growth restriction, fetal mosaicism, confined placental mosaicism (CPM), and uniparental disomy (UPD).[6–10] Furthermore, invasive diagnostic procedures, such as amniocentesis and chorionic villus sampling, are associated with an additional risk of fetal loss.[11] Therefore, the balance between the risk of invasive diagnostic procedures and the potential risk of suspected RAAs on pregnancy should be fully evaluated before opting for invasive diagnostic testing.

In the current study, we reviewed NIPT results for RAAs that were detected at a single center during the past 2 years. Information on confirmatory invasive diagnostic testing results and pregnant outcomes are also summarized during and after pregnancy.

Materials and methods

Patients

This was a retrospective analysis of data of a cohort of 18,016 pregnancies of women who underwent NIPT. These women were tested at the Center for Genetic Medicine of Maternity and Child Health Care Hospital Affiliated to Xuzhou Medical University between March 2017 and February 2020. Pregnant women of 12 to 23 weeks' gestation underwent NIPT after pretest counseling and signing of informed consent. A total of 5 mL of peripheral blood from the pregnant women was collected into an ethylenediaminetetraacetic acid tube for further processing. All of the patients' details were de-identified. The study was approved by the Ethics Committee of the Maternity and Child Health Care Hospital Affiliated to Xuzhou Medical University (no. 2019-05).

NIPT

Whole-genome sequencing of cffDNA from maternal blood was performed on an ion proton platform. Maternal blood samples were spun at 1600 $\times$g for 10 minutes at 4°C, followed by re-centrifugation at 16,000 $\times$g for 10 minutes at 4°C to remove residual cells. Plasma cffDNA was extracted using a kit according to the manufacturer's instructions (Darui Biotechonology Co., Ltd., Guangzhou, China). Subsequently, library preparation, quality control, and pooling were loaded on an ion proton semiconductor sequencer (Life Technologies, Carlsbad, CA, USA). Briefly, the cffDNA was end-repaired using T4 DNA polymerase and T4 polynucleotide kinase, and it was then ligated to a barcode adapter using T4 DNA ligase. After amplification of the library by polymerase chain reaction (PCR), double-size selection was performed to remove the residual adaptors and primers with Agencourt AMPure XP beads (Darui Biotechonology Co., Ltd., Guangzhou, China), followed by quantification using the Ion Library Quantitation Kit (Thermo Fisher, Eugene, OR, USA). The libraries were loaded on an ion semiconductor chip for sequencing. Combined GC-bias correction and Z-score calculation were used to determine the risk of fetal chromosomal aneuploidies. Fetal chromosomal aneuploidies were identified using the criteria of a Z-score >3 or <-3. For RAA-positive cases, confirmatory diagnostic testing was performed depending on individualized desire after genetic counseling.

Confirmatory invasive prenatal testing

Depending on the patient's choice, women with NIPT-positive RAAs underwent confirmatory diagnostic testing by amniocentesis, karyotyping, and CMA. Chromosomal karyotype analysis of cultured amniotic fluid cells at 320 to 400 band resolution was performed by following a previously described method.[4] For CMA analysis, genomic DNA was extracted from fetal cells in fresh amniotic fluid using the QIAamp DNA Blood Mini Kit (Qiagen GmbH Inc., Hilden, Germany) according to the manufacturer's instructions. DNA was then digested, followed by PCR, a PCR product check, purification, quantification, fragmentation, QC gel labeling, hybridization, washing, staining, and scanning according to the manufacturer's instructions. Finally, the data were visualized and analyzed on Affymetrix Chromosome Analysis Suite (ChAS) Software (Affymetrix, Santa Clara, CA, USA) with reference to the human assembly GRCh37/hg19. The reporting threshold for the size of copy number variants was set at 500 kb with a marker count of $\geq$50 for gains and 200 kb with a marker count of $\geq$50 for losses.

Genetic counseling and clinical follow-up

For pregnant women with suspected RAAs, test characteristics and possible explanations, including the fetus not being affected, fetal growth restriction, fetal mosaicism, CPM, and UPD, were discussed with the women and their partners. Moreover, counseling regarding the potential risks, benefits, and limitations of the invasive diagnostic testing was offered to the patients. Depending on the patient's choice, chromosomal karyotype analysis and amniocentesis were offered for prenatal cytogenetic analysis for fetal RAAs. Fetal UPD was tested by CMA analysis of amniotic fluid. Chromosomal mosaicism was examined according to the technical standards of prenatal screening and diagnosis for fetal common chromosomal abnormalities and open neural tube defects.[12] In most cases, serial prenatal ultrasound screening was performed in the second and third trimesters for a fetal anatomy scan to monitor fetal growth. Additionally, clinical information on pregnancy outcomes, such as birth weight, congenital malformation, preterm birth, miscarriage, stillbirth, and neonatal death, was collected through telephone follow-up. A normal pregnancy outcome was defined as that without fetal growth restriction, congenital malformation, preterm birth, miscarriage, stillbirth, or neonatal death.

Results

Positive results for RAAs were reported in 33 women, with a screening positive rate of 0.18% (33/18016). Of the entire cohort undergoing NIPT, the average maternal age was 30.0 years and the average gestational age at the time of NIPT sampling was 21.1 weeks. For the 33 RAA-positive cases, the average maternal age was 30.0 years. Among the positive cases, 45.5% (15/33) of women received NIPT as a second tier following intermediate-risk serum screening results. A total of 12.1% (4/33) of the women with RAAs underwent NIPT owing to high-risk serum screening results, and 24.2% (8/33) underwent NIPT because of an advanced maternal age (Table 1).

Of the women who underwent NIPT, 11 (33.3%, 11/33) had positive results for trisomy 7. The second most common rare aneuploidy detected was trisomy 22 (12.1, 4/33), followed by aneuploidies involving trisomies of chromosomes 8 (9.1%, 3/33), 9 (6.1%, 2/33) and 2 (6.1%, 2/33). Moreover, trisomies 20, 16, 15, 10, 6, and 3 were found in one case each (Figure 1a). Moreover, monosomies for chromosomes 16 (9.1%, 3/33), 14 (3.0%, 1/33), and 22 (3.0%, 1/34) were observed in one case each (Figure 1b). The proportion of positive cases with an increased number of chromosomes was 84.8%, which is higher than that of cases with decreased copy chromosomes.

Twenty-eight (84.8%, 28/33) pregnant women who consented to amniocentesis underwent confirmatory diagnostic testing by karyotype analysis and CMA. In one case of trisomy 15 (Z-score: 12.366), the fetal karyotype was found to be 46,XN (53)/47,XN,+15(47) mosaicism on amniocentesis, and this woman chose to end the pregnancy. Partial UPD (2p25.1-p22.3, 24.36 Mb) of chromosome 2 was found in one case of trisomy 2 (Z-score: 12.92), and clinical follow-up showed fetal loss attributed to vaginal bleeding. Moreover, miscarriage occurred at 15 weeks in a pregnancy with suspected trisomy 22 at NIPT. Additionally, pregnancy was terminated owing to structural anomalies found by ultrasound in a case of false fetal monosomy 16 (Table 2). In this study, four of the women who were positive for RAAs had adverse pregnancy outcomes, except for three women who were lost to follow-up.

Table 1. Distribution of maternal age and gestational age of pregnant women who underwent noninvasive prenatal testing.

	Maternal age (years)			Gestational age (weeks)		
Variable	Median	Average	Min–Max	Median	Average	Min–Max
Total women	29	30.0	17–46	18	21.1	12–26
Women with fetal RAAs	31	30.0	20–42	19	18.2	13–22

RAAs, rare autosomal aneuploidies; Min–Max, minimum-maximum.

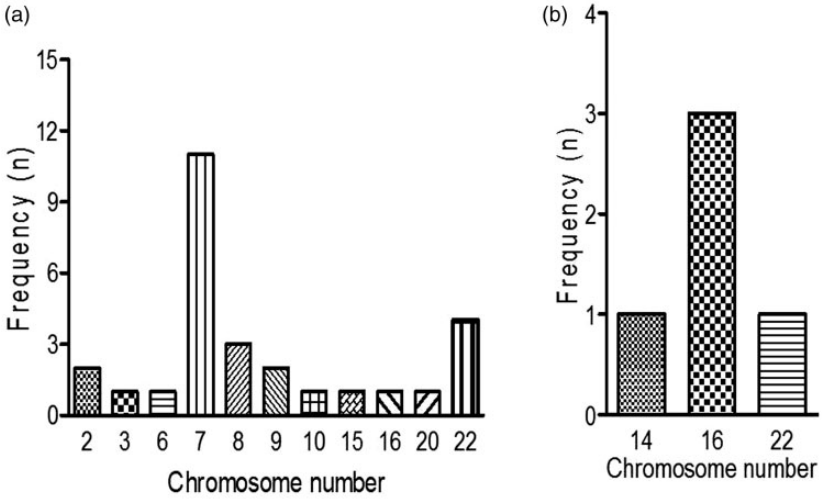

Figure 1. Frequency of rare autosomal trisomy cases and rare autosomal monosomy cases at noninvasive prenatal testing. (a) Frequency of rare autosomal trisomy cases. (b) Frequency of rare autosomal monosomy cases.

Discussion

NIPT is a technology based on whole-genome sequencing and analysis of cffDNA in maternal blood. During recent years, this technology has been widely used a first-tier or second-tier method in the screening of fetal trisomies of chromosomes 21, 18, and 13.[1–5] RAAs are often reported as the additional findings of NIPT in clinical practice. However, limited clinical information on the incidence and pregnancy outcomes of suspected RAAs makes genetic counseling difficult. The current study retrospectively reviewed the clinical experiences of NIPT for screening of chromosomal aneuploidies other than common trisomies at a single hospital in China. Overall, 33 RAAs were detected by NIPT from 18,016 samples, with a screening rate of 0.18%. The screening rate of these aneuploidies in this cohort is lower than that of previous reports.[6] Clinical follow-up further showed that most of these positive cases had normal pregnancy outcomes.

In the present study, 28 women with fetal RAAs received invasive diagnostic testing following abnormal prenatal screening results. Most of the RAAs in this cohort

Table 2. Noninvasive prenatal testing results for rare autosomal aneuploidies validated by karyotyping and CMA of amniocytes.

				NIPT results			
Sample ID	MA (years)	GA (weeks)	Serum screening	Suspected aneuploidies	Z-score	CMA/karyotyping	Pregnancy outcome
Case 1	33	17	High risk	Trisomy 10	9.41	Normal	Normal liveborn
Case 2	31	19	Intermediate risk	Trisomy 15	12.366	46,XN(53)/47,XN,+15(47)	TOP
Case 3	24	22	Intermediate risk	Monosomy 16	−7.331	Normal	TOP, fetal structural abnormalities
Case 4	25	15	NA	Trisomy 16	15.02	Normal	Normal liveborn
Case 5	30	20	Intermediate risk	Trisomy 22	8.254	Normal	Normal liveborn
Case 6	36	13	NA	Trisomy 22	9.489	ND	Miscarriage at the gestational age of 15 weeks
Case 7	25	22	High risk	Trisomy 2	12.92	arr 2p25.1p22.3 × 2 hmz, 24.36 Mb, uncertain	Fetal loss, vaginal bleeding
Case 8	34	14	NA	Trisomy 2	11.35	arr 15q14q23 × 2 hmz, 31.20 Mb, uncertain	Normal liveborn
Case 9	30	19	Intermediate risk	Trisomy 6	6.77	Normal	Normal liveborn
Case 10	42	19	NA	Trisomy 7	38.53	ND	Normal liveborn
Case 11	26	20	Intermediate risk	Trisomy 7	7.79	Normal	Normal liveborn
Case 12	35	19	NA	Trisomy 7	11.09	ND	Normal liveborn
Case 13	24	18	High risk	Trisomy 7	6.36	Normal	Normal liveborn
Case 14	31	18	Intermediate risk	Trisomy 7	10.78	Normal	Normal liveborn
Case 15	32	16	NA	Trisomy 7	13.31	Normal	Normal liveborn
Case 16	31	21	Intermediate risk	Trisomy 7	9.74	arr 15q14q23 × 1, 267 kb, benign	Normal liveborn
Case 17	28	20	Intermediate risk	Trisomy 7	7.03	Normal	Normal liveborn
Case 18	38	17	NA	Trisomy 8	11.18	Normal	Normal liveborn
Case 19	38	16	NA	Trisomy 8	5.08	Normal	Normal liveborn
Case 20	36	18	NA	Trisomy 9	8.91	Normal	Normal liveborn
Case 21	22	19	Intermediate risk	Trisomy 7	5.07	Normal	Normal liveborn
Case 22	27	20	NA	Trisomy 22	NA	arr16p11.2 × 3, 1.9 Mb, benign	Normal liveborn
Case 23	25	17	Intermediate risk	Trisomy 7	7.79	arr Yq11.223q11.23 × 3, 3.76 Mb, likely benign	Normal liveborn
Case 24	23	18	NA	Trisomy 9	NA	arr 20p12.1 × 1, 420 kb, uncertain	Normal liveborn
Case 25	36	17	NA	Trisomy 8	NA	Normal	Normal liveborn
Case 26	31	20	Intermediate risk	Monosomy 14	−5.13	ND	Normal liveborn
Case 27	39	17	NA	Trisomy 7	7.58	ND	Normal liveborn
Case 28	28	16	High risk	Monosomy 22	−6.07	Normal	Normal liveborn
Case 29	26	19	NA	Trisomy 22	6.77	Normal	Normal liveborn
Case 30	20	17	Intermediate risk	Monosomy 16	−6.57	CMA: arr 16p11.2 × 1, 1.18 Mb, benign	Normal liveborn
Case 31	29	19	Intermediate risk	Trisomy 3	11.72	Normal	NA
Case 32	23	19	Intermediate risk	Monosomy 16	−6.10	Normal	NA
Case 33	31	19	Intermediate risk	Trisomy 20	6.42	Normal	NA

MA, maternal age; GA, gestational age; NIPT, noninvasive prenatal testing; CMA, chromosomal microarray analysis; TOP, termination of pregnancy; NA, not available; ND, not detected.

were false positive. Previous reports have shown that suspected RAAs at NIPT can be associated with an increased risk of CPM.[7,10,13,14] In this study, fetal demise occurred in a case with undiagnosed trisomy 22. Moreover, another woman with false positive results for fetal monosomy 16 ended the pregnancy owing to fetal structural anomalies. CPM is associated with a broad spectrum of complications in pregnancy, ranging from no clinical phenotype to intrauterine fetal growth restriction, or even intrauterine fetal death.[15–17] Clinicians should be aware that CPM might not be proven during pregnancy. Although the underlying etiologies for these two abnormal pregnancies remain unclear, CPM might be expected as a possible explanation for adverse pregnancy outcomes. Other studies have also shown an increased risk of adverse pregnancy outcomes in pregnancies with false positive RAAs detected by NIPT.[6,7] Notably, an abnormal placental karyotype is difficult to be confirmed during the course of pregnancy, thereby causing difficulty in predicting the risk of the fetus's condition. Moreover, suspected RAAs have an increased risk of spontaneous abortion and fetal developmental problems.[10] Therefore, fetal development and growth should be closely monitored for pregnancies with false positive RAAs at NIPT. In such cases, serial prenatal ultrasound screening should be performed in the second and third trimesters for a fetal anatomy scan to monitor fetal growth.

In this cohort, we also found a pregnancy with a true mosaic trisomy involving chromosome 15 that was identified by amniocentesis and CMA. In this case, mosaic trisomy 15 was initially found by cffDNA sequencing, and was subsequently confirmed by amniocentesis. The features of mosaic trisomy 15 have been described previously, and mainly include intrauterine growth retardation, cardiac diseases, craniofacial dysmorphisms, and other organ anomalies.[18,19] In this case, no fetal structural anomaly was detected by ultrasound scans until 24 weeks' gestation. Clinical follow-up showed that this pregnancy was ended by the patient's choice.

Moreover, chromosomal aneuploidies at NIPT might indicate UPD, which can be caused by trisomy or monosomy rescue.[20] Follow-up CMA identified a partial UPD (2)(p25.1–p22.3) in a pregnancy with suspected trisomy 2 in our study. UPD can cause disorders by functional loss of imprinted genes or homozygosity of autosomal recessively inherited mutations.[21] There is no definitive evidence of imprinting disorders related to the region of 2p25.1-p22.3. However, fetal loss due to unexplained vaginal bleeding was present in this pregnancy. As described previously, UPD is associated with multiple imprinting disorders, such as transient neonatal diabetes mellitus,[22] Russell–Silver syndrome,[23] Beckwith–Wiedemann syndrome,[24] maternal and paternal UPD(14) syndromes,[25,26] Angelman syndrome, Prader–Willi syndrome,[27] and UPD(20) maternal and paternal syndrome.[28,29] Other reports have also shown that aneuploidies at NIPT have a high risk of fetal UPD.[7,9] Therefore, genetic counseling on imprinted diseases should be performed if encountering RAAs involving established imprinted disease loci, such as pat6q24, mat7p11.2-p12 and q32.2, pat11p15.5, mat/pat14q32, mat/pat15q11-q13, and UPD(20) mat (several loci involved)/pat20q13.3. Importantly, these patients should be informed of the risk of imprinted disorders that cannot be entirely precluded by an ultrasound scan. Moreover, the possibility of an increased risk for recessively genetic disorders caused by UPD should be mentioned to pregnant women. In cases with rare aneuploidies involving imprinted syndromes, invasive diagnosis by CMA analysis

should be performed to determine potential fetal UPD. By contrast, invasive diagnostic procedures might not be necessary for aneuploidies that do not involve imprinted loci.

In our study, four pregnancies from positive cases of RAAs had abnormal pregnancy outcomes, which is a similar proportion to that found in previous reports.[8,9] However, this value is much lower than that in several other studies in which pregnancy complications, such as miscarriage, fetal mosaicism, and UPD, as well as intrauterine growth restriction, occurred in the majority of positive cases of RAAs by NIPT.[7,10,30] The discrepant results for pregnancy outcomes from these different studies causes difficulty in genetic counseling for these positive cases. Several factors might have contributed to the discrepant results. First, the time of gestation of our cases at NIPT was late. Therefore, some abnormal pregnancies might have been excluded by pre-test ultrasound before performing NIPT. Second, most of our cases came from women with pregnancies and not from high-risk women as in other studies. Third, the particular NIPT platform used might also have been an important factor contributing to the inconsistent results on detecting RAAs by NIPT.

This study has some limitations. The sample size of RAAs was limited in this study. Additionally, this was a retrospective study on a single NIPT platform. Therefore, more samples in large-scale studies are required to derive a conclusive result. Moreover, the family history or obstetric history of adverse pregnancy outcomes, especially for genetic disorders, have been recognized as risk factors for complications of pregnancy.[31,32] Therefore, assessment of the family history or obstetric history of pregnancies with positive NIPT results for RAAs would benefit from determining factors that contribute to distinct pregnancy outcomes in these cases. Consequently, future investigation is warranted to examine the relation between an adverse family history or obstetric history and the outcomes of pregnancy with positive NIPT results for RAAs.

In summary, this study shows that most pregnancies with positive NIPT results for RAAs have a favorable pregnancy outcome. However, positive cases of RAAs may be associated with fetal UPD, which might incur a poor obstetric outcome depending on the chromosome that is affected. Moreover, RAAs at NIPT might also suggest an increased risk of CPM and fetal mosaic aneuploidy, which should also be disclosed to affected women. Current diagnostic procedures, such as CMA analysis, have the capacity for diagnosing fetal mosaic aneuploidies and UPD, while CPM cannot be proven during pregnancy. Therefore, genetic counseling on the potential risks of positive NIPT results for RAAs, as well as the benefits and limitations of invasive diagnostic testing, might help guide clinical management.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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