Combined Application Value of Chromosome Karyotype Analysis and Chromosomal Microarray Analysis (CMA) in Prenatal Diagnosis

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ABSTRACT **Objective:** Chromosome karyotype analysis is the gold standard for prenatal diagnosis yet carries multiple limitations. Chromosomal microarray analysis (CMA) can overcome these drawbacks to a certain extent. This study aims to evaluate the clinical application value of combined chromosome karyotype analysis and CMA in the diagnosis of fetal chromosomal abnormalities in Yancheng.
Methods: Retrospectively analyze amniotic fluid test results collected from January 2020 to December 2023, with combined detection of chromosome karyotype analysis and CMA performed on all specimens.
Results: The positive detection rate of combined karyotype and CMA testing reached 21.70%. Cases included 159 aneuploidies, 27 mosaic aneuploidies, 19 balanced chromosomal abnormalities, 46 pathogenic or likely pathogenic copy number variations (CNVs), and 51 variants of uncertain clinical significance (VUS).
Conclusion: Combined application of CMA and chromosome karyotype analysis is recommended for prenatal diagnosis to elevate positive detection rates, provide scientific and accurate genetic diagnosis, and improve the quality of prenatal genetic counseling.

INDEX TERMS prenatal diagnosis; chromosome karyotype analysis; chromosomal microarray analysis

I. INTRODUCTION

REDUCING birth defects is a core component of China's Healthy China 2030 Initiative Framework [1]. The etiologies of birth defects are complex, and the critical window for their development spans fertilization and fetal intrauterine growth. Genetic factors directly or indirectly contribute to over 80% of birth defects, making them the primary pathogenic category [2]. Among genetic causes, chromosomal numerical abnormalities, large fragment duplications/deletions, and pathogenic copy number variations (pCNVs) constitute major risk factors for birth defects [3].

Amniocentesis is the most common sampling technique in prenatal diagnosis to obtain fetal cells for chromosomal testing. G-banded karyotyping has long served as the gold standard for chromosomal examination, capable of detecting aneuploidies, polyploidies, mosaicism, and structural chromosomal abnormalities. However, it is limited by low resolution and long turnaround time.

Chromosomal microarray analysis (CMA), a high-resolution, high-throughput whole-genome molecular scanning technique, enables identification of microdeletions and microduplications as small as 50–100 Kb [4]. It can detect polyploidies, aneuploidies, copy number variations (CNVs), uniparental disomy, and mosaicism, rendering it a vital tool for prenatal diagnosis and genetic counseling [4]. Nevertheless, single use of karyotyping or CMA in prenatal diagnosis has inherent constraints. Therefore, this study integrates cytogenetic (karyotyping) and molecular genetic (CMA) techniques to analyze prenatal diagnostic specimens [4].

II. MATERIALS AND METHODS

A. STUDY SUBJECTS

This retrospective study enrolled 1,392 amniotic fluid specimens from pregnant women who underwent amniocentesis at the Prenatal Diagnosis Center of Yancheng Maternity and Child Health Hospital between January 2020 and December 2023. Inclusion criteria for invasive testing included: Advanced maternal age ($\geq$35 years old); High-risk or failed non-invasive prenatal testing (NIPT); Nuchal translucency (NT) $\geq$2.5 mm; Abnormal maternal serum screening results; Abnormal ultrasound soft markers (nuchal fold $\geq$6 mm, absent nasal bone, etc.) or structural malformations (congenital heart disease, urinary system anomalies, nervous system defects, craniofacial malformations, and other systemic

disorders); Adverse obstetric history (parental genetic abnormalities, prenatal exposure to medications or toxicants); Other high-risk indicators.

This research was approved by the Medical Ethics Review Committee of Yancheng Maternity and Child Health Hospital (Approval No. 2024-LW-002). All fetal parents signed informed consent forms prior to amniocentesis for simultaneous karyotype and CMA testing.

B. AMNIOTIC FLUID COLLECTION

Under real-time ultrasound guidance, 30 mL amniotic fluid was extracted transabdominally: 20 mL allocated for karyotype analysis, and 10 mL for CMA testing.

C. G-BANDED CHROMOSOME KARYOTYPE ANALYSIS

Amniotic fluid was centrifuged at 1,500 rpm for 10 minutes; 1.5 mL supernatant and cell pellet mixture was inoculated into two separate culture flasks. Cells were incubated in a 37 °C (±0.5 °C) constant-temperature CO_2 incubator for 6–7 days. Medium replacement was performed after initial observation; original medium was transferred to a new flask for continuous culture, while 5 mL fresh amniotic fluid medium was added to the original flask. After an additional 24 hours of incubation, cells were microscopically monitored to determine optimal harvest timing.

Prior to cell harvest, colchicine was added to arrest cell division. Supernatant was discarded, and trypsin digestion solution was applied for 10 minutes to dissociate cells. Harvested cells were analyzed and karyotyped following the International System for Human Cytogenetic Nomenclature (ISCN) 2020.

D. CHROMOSOMAL MICROARRAY ANALYSIS (CMA)

Genomic DNA with a Qubit concentration ≥100 ng/μL was extracted. Whole-genome copy number detection was performed using the Affymetrix Cytoscan™750K array chip, strictly following reagent and instrument manufacturer protocols. Scanned chip data were analyzed via ChAS software.

CNV screening referenced public databases including DGV (Database of Genomic Variants), ClinGen, ClinVar, and Decipher, alongside the hospital's local variant database. Pathogenicity classification and interpretation of CNVs complied with ACMG guidelines and the 2021 consensus statement on prenatal chromosomal variant interpretation.

E. STATISTICAL ANALYSIS

All clinical data were collated and calculated using Microsoft Excel.

III. RESULTS

A. DISTRIBUTION OF INDICATIONS FOR AMNIOCENTESIS

A total of 1,392 amniotic fluid samples underwent combined karyotype and CMA testing. Case breakdown by indication: Advanced maternal age: 200 cases; Abnormal NIPT results: 291 cases; NT thickening (≥2.5 mm): 126 cases; Abnormal maternal serum screening: 128 cases; Adverse obstetric history: 157 cases; Abnormal fetal ultrasound findings: 111 cases; Other indications (failed NIPT, parental chromosomal abnormalities, etc.): 103 cases; Coexistence of two or more high-risk indicators: 276 cases. The overall positive detection rate of chromosomal abnormalities was 21.70% (302/1392). Subgroup breakdown of abnormal results: Aneuploidy: 159 cases (11.42%); Mosaic aneuploidy: 27 cases (1.94%); Balanced chromosomal abnormalities (BCAs): 19 cases (1.36%); Pathogenic/likely pathogenic CNVs (CNV(P)): 46 cases (3.30%); Variants of uncertain significance (CNV(VUS)): 51 cases (3.66%).

Among the 159 aneuploid cases, the distribution of chromosomal disorders was as follows: Trisomy 21: 84 cases (6.03%, 84/1392); Trisomy 18: 13 cases (0.93%, 13/1392); Trisomy 13: 3 cases (0.22%, 3/1392); Sex chromosomal aneuploidy: 59 cases (4.24%, 59/1392); Subgroups with abnormal NIPT results (87/291, 29.90%) and multiple concurrent high-risk indicators (61/276, 22.10%) exhibited significantly higher aneuploid detection rates.

B. DIAGNOSTIC EFFICACY OF NON-INVASIVE PRENATAL TESTING (NIPT)

NIPT screens fetal chromosomal aneuploidies by detecting cell-free fetal DNA in maternal peripheral blood [5]. As a non-invasive and efficient primary prenatal screening tool, it is the preferred assay for autosomal aneuploidy identification. In this cohort, the subgroup with abnormal NIPT results demonstrated the highest true positive rate for fetal chromosomal anomalies.

Samples with abnormal NIPT results were stratified by concurrent risk factors: isolated abnormal NIPT (291 cases) and advanced maternal age combined with abnormal NIPT (108 cases) constituted the two largest subgroups. Isolated abnormal NIPT: 87 aneuploidies (29.90%), 15 mosaic aneuploidies (5.15%); Advanced maternal age + abnormal NIPT: 52 aneuploidies (48.15%), 8 mosaic aneuploidies (7.41%).

TABLE 1. DETECTION OF VARIOUS CHROMOSOMAL ABNORMALITIES IN AMNIOTIC FLUID SAMPLES FROM PREGNANT WOMEN WITH DIFFERENT PRENATAL HIGH-RISK INDICATIONS

Indications	Cases	Aneuploidy		Mosaic aneuploidy		BCAs		CNV(P)		CNV(VUS)	
Advanced maternal age	200	5	2.50%	0	0.00%	2	1.00%	0	0.00%	4	2.00%
NIPT(+)	291	87	29.90%	15	5.15%	1	0.34%	20	6.87%	9	3.09%
NT thickening (≥2.5mm)	126	4	3.17%	0	0.00%	1	0.79%	4	3.17%	3	2.38%
Abnormal maternal serum screening	128	1	0.78%	0	0.00%	2	1.56%	1	0.78%	4	3.13%
Adverse obstetric history	157	0	0.00%	2	1.27%	0	0.00%	3	1.91%	16	10.19%
Abnormal fetal ultrasound	111	1	0.90%	0	0.00%	2	1.80%	6	5.41%	6	5.41%
Other indications	103	0	0.00%	0	0.00%	9	10.34%	4	4.60%	0	0.00%
combined risk indicators	276	61	22.10%	10	3.62%	2	0.72%	8	2.90%	9	3.26%
ALL	1392	159	11.42%	27	1.94%	19	1.36%	46	3.30%	51	3.66%

TABLE 2. DISTRIBUTION OF COMMON ANEUPLOID SUBTYPES DETECTED IN SUBGROUPS WITH DISTINCT HIGH-RISK PRENATAL INDICATIONS

Indications	Cases	Total aneuploidy	Aneuploidy						Sex chromosome aneuploidy	
			Trisomy 21		Trisomy 18		Trisomy 13			
Advanced maternal age	200	5	3	1.50%	0	0.00%	0	0.00%	2	1.00%
NIPT(+)	291	87	35	12.03%	8	2.75%	2	0.69%	42	14.43%
NT thickening (≥2.5mm)	126	4	4	3.17%	0	0.00%	0	0.00%	0	0.00%
Abnormal maternal serum screening	128	1	1	0.78%	0	0.00%	0	0.00%	0	0.00%
Adverse obstetric history	157	0	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Abnormal fetal ultrasound	111	1	1	0.90%	0	0.00%	0	0.00%	0	0.00%
Other indications	103	0	0	0.00%	0	0.00%	0	0.00%	0	0.00%
combined risk indicators	276	61	40	14.49%	5	1.81%	1	0.36%	15	5.43%
ALL	1392	159	84	6.03%	13	0.93%	3	0.22%	59	4.24%

Samples were further categorized by NIPT high-risk subtype: 47 NIPT Trisomy 21 high-risk cases: 39 confirmed abnormal (82.98%); 35 true Trisomy 21 (74.47%), 2 mosaic Trisomy 21, 1 BCA, 1 pathogenic CNV; 16 NIPT Trisomy 18 high-risk cases: 10 confirmed abnormal (62.50%); 8 true Trisomy 18 (50.00%), 1 mosaic Trisomy 18, 1 VUS; 15 NIPT Trisomy 13 high-risk cases: 4 confirmed abnormal (26.67%); 2 true Trisomy 13 (13.33%), 2 pathogenic CNVs; 151 NIPT sex chromosome high-risk cases: 57 confirmed abnormal (37.75%); 42 full sex aneuploidies (27.81%), 7 mosaic sex aneuploidies, 5 pathogenic CNVs, 3 VUS. A total of 64 abnormal diagnoses were identified in the advanced maternal age + abnormal NIPT subgroup (detailed in Table 5). NIPT achieved the highest diagnostic accuracy for Trisomy 21 (>80% in both subgroups). Sensitivity was lower for Trisomy 18, Trisomy 13, sex chromosomal aneuploidies, and other autosomal abnormalities, potentially limited by the study's moderate sample size; larger cohorts are required for further validation.

TABLE 3. CHROMOSOMAL ABNORMALITY DETECTION RESULTS FOR NIPT-POSITIVE SUBGROUPS WITH ADDITIONAL OVERLAPPING

Indications	Cases	Aneuploidy		Mosaic aneuploidy		BCAs		CNV(P)		CNV(VUS)	
NIPT(+)	291	87	29.90%	15	5.15%	1	0.34%	20	6.87%	9	3.09%
NIPT(+)+advanced maternal age	108	52	48.15%	8	7.41%	0	0.00%	3	2.78%	1	0.93%
NIPT(+)+adverse obstetric history	3	1	33.33%	0	0.00%	0	0.00%	1	33.33%	0	0.00%
NIPT(+)+abnormal ultrasound	4	2	50.00%	2	50.00%	0	0.00%	0	0.00%	0	0.00%
NIPT(+)+other indications	2	0	0.00%	0	0.00%	0	0.00%	1	50.00%	0	0.00%

TABLE 4. CONFIRMATORY DIAGNOSTIC RESULTS OF AMNIOTIC FLUID SAMPLES WITH ISOLATED NIPT HIGH-RISK SUBTYPES

NIPT(+)		Cases	Total abnormal		Aneuploidy		Mosaic aneuploidy	BCAs	CNV(P)	CNV(VUS)
Autosomal risk	Trisomy 21	47	39	82.98%	35	74.47%	2	1	1	
	Trisomy 18	16	10	62.50%	8	50.00%	1			1
	Trisomy 13	15	4	26.67%	2	13.33%			2	
Sex chromosome risk		151	57	37.75%	42	27.81%	7		5	3
Other autosomal risk		62	22	35.48%			5		12	5
Total		291	132	45.36%	87	29.90%	15	1	20	9

TABLE 5. CONFIRMATORY DIAGNOSTIC RESULTS OF AMNIOTIC FLUID SAMPLES WITH CONCURRENT ADVANCED MATERNAL AGE AND NIPT HIGH-RISK SUBTYPES

NIPT(+)		Cases	Total abnormal		Aneuploidy		Mosaic aneuploidy	BCAs	CNV(P)	CNV(VUS)
Autosomal risk	Trisomy 21	38	36	94.74%	34	89.47%	1		1	
	Trisomy 18	6	3	50.00%	3	50.00%				
	Trisomy 13	3	1	33.33%	1	33.33%				
Sex chromosome risk		40	19	47.50%	14	35.00%	4		1	
Other autosomal risk		21	5	23.81%			3		1	1
Total		108	64	59.26%	52	48.15%	8	0	3	1

C. DISCREPANCIES BETWEEN KARYOTYPE ANALYSIS AND CMA FOR CHROMOSOMAL ABNORMALITY DETECTION

1,391 specimens completed both karyotyping and CMA; 1 sample failed cell culture due to insufficient amniotic fluid cellularity and only underwent CMA testing. A total of 71 specimens showed inconsistent results between the two platforms. Breakdown of discrepant cases: 17 specimens with normal CMA results but abnormal karyotypes: 15 balanced chromosomal abnormalities (BCAs), 3 mosaic aneuploidies with mosaic ratios $<30\%$, 2 full aneuploidies; 1 case failed karyotyping due to insufficient cells; 1 sex chromosome mosaicism with divergent mosaic ratios between platforms; 17 mosaic cases with inconsistent mosaic percentage quantification between karyotyping and CMA; 35 specimens with isolated pathogenic CNVs detected exclusively by CMA (Table 6). Notably, CMA failed to identify all 15 BCA cases. CMA offers superior sensitivity for CNV detection, while karyotyping only identifies segmental deletions >10 Mb and provides imprecise localization of small structural variants. In contrast, karyotyping outperforms CMA for mosaicism and balanced translocation identification. Therefore, combined interpretation of karyotype and CMA data yields the most accurate fetal chromosomal diagnosis.

TABLE 6. DISTRIBUTION OF ABNORMAL VARIANT TYPES IN SPECIMENS WITH INCONSISTENT KARYOTYPE AND CMA RESULTS

Detection method	Normal result	Aneuploidy	Mosaic aneuploidy	BCAs	CNV(P)	Total cases
CMA	17	2	17	0	35	71
Karyotype analysis	34	0	19	15	3	71

IV. DISCUSSION

Birth defects refer to structural, functional, or metabolic developmental abnormalities in fetuses, representing a leading cause of infant mortality and childhood disability that imposes substantial burdens on families and society. China's overall birth defect incidence is approximately 5.6%, with roughly 900,000 new cases annually, including 250,000 visibly apparent malformations detected at birth [6]. Chromosomal/gene variants and environmental exposures jointly contribute to birth defect pathogenesis [7].

Amniocentesis is an invasive prenatal diagnostic procedure performed under real-time ultrasound guidance, where a fine needle penetrates the maternal abdominal wall and uterine cavity to aspirate amniotic fluid. The procedure carries minor risks of infection and pregnancy loss [8], leading to widespread maternal anxiety. Integrated nursing interventions [9] and targeted psychological counseling [10] effectively alleviate patient fear, improve uptake of amniocentesis, and advance birth defect prevention [11].

In this study, subgroups with abnormal NIPT results or multiple concurrent high-risk indicators demonstrated significantly higher detection rates of aneuploidy and mosaicism, with no meaningful differences in BCA and CNV detection across subgroups. NIPT is widely implemented in early prenatal screening to identify Trisomy 13/18/21 and sex chromosomal anomalies [12], [13]. Among all NIPT-positive subgroups, patients with concurrent advanced maternal age exhibited the highest aneuploid risk.

NIPT achieved an overall Trisomy 21 detection accuracy of 88.24% (75/85). Ten NIPT Trisomy 21 high-risk cases returned normal combined karyotype/CMA results, likely explained by confined placental mosaicism distorting circulating cell-free fetal DNA profiles [14], [15]. Lower diagnostic performance was observed for Trisomy 18, Trisomy 13, sex chromosome disorders, and rare autosomal variants. These findings confirm NIPT as a screening tool only: all NIPT-high-risk patients require invasive prenatal diagnosis to rule out false-positive results. Clinicians should prioritize intensified genetic counseling for women with combined advanced age and abnormal NIPT results.

CMA identifies chromosomal anomalies via detection of genomic dosage imbalance but cannot detect balanced translocations or low-level mosaicism [16]. G-banded karyotyping, the traditional gold standard, is limited by low resolution and cannot resolve CNVs smaller than 10 Mb [17]. Aneuploidies, mosaicism, and pathogenic CNVs are strongly associated with adverse fetal developmental outcomes. While BCAs rarely cause fetal malformations [18], carriers face elevated risks of offspring with unbalanced structural rearrangements, requiring personalized reproductive genetic guidance [3]. Combined karyotype and CMA testing significantly improves overall fetal chromosomal anomaly detection rates [19].

Seventy-one specimens exhibited discordant results between the two platforms. Two cases showed normal karyotyping but abnormal CMA mosaicism, a rare discrepancy attributed to divergent assay workflows: karyotyping analyzes cultured metaphase cells, whereas CMA interrogates uncultured native amniotic cell genomic DNA [20]. Aneuploid cell lines exhibit genetic instability during prolonged cell culture, leading to reduced mosaic proportions in karyotyping preparations [21]. Fluorescence in situ hybridization (FISH) delivers more precise quantification of mosaic aneuploidy ratios than karyotyping or CMA [22], yet most patients in this cohort declined supplementary FISH testing.

Karyotyping demonstrates near-perfect sensitivity for BCAs and moderate-to-high ratio mosaicism, while CMA fails to detect balanced translocations and mosaicism with proportions below 30% [23]. CMA is uniquely capable of identifying pathogenic microdeletions and microduplications. Accordingly, simultaneous karyotype and CMA testing is recommended for all patients undergoing invasive prenatal diagnosis to maximize diagnostic accuracy and standardize high-quality genetic counseling. Supplementary FISH or CNVplex testing is advised for ambiguous mosaic results to refine risk stratification.

V. CONCLUSION

G-banded chromosome karyotype analysis and CMA each possess unique advantages and unavoidable limitations; CMA cannot fully replace karyotyping in prenatal diagnostic workflows. Combined application of the two technologies improves the reliability of fetal chromosomal testing. Supplementary FISH or CNVplex analysis is recommended for definitive characterization of mosaic chromosomal anomalies. This cohort study provides comprehensive insights into clinically significant genomic variants detected in prenatal care.

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