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Analytical Validation of Whole-Genome Single-End Sequencing–Based Noninvasive Prenatal Testing for Detecting Submicroscopic Telomeric and Pericentromeric Fetal Copy Number Variants: Insights From Two Rare Cases.

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Objective:

The discovery of fetal cell-free DNA (cfDNA) in maternal plasma, together with advances in next-generation sequencing (NGS), has transformed prenatal screening through noninvasive prenatal testing (NIPT). While NIPT demonstrates high accuracy for detecting common fetal aneuploidies, the detection of chromosomal copy number variations (CNVs), particularly microdeletions and microduplications, remains challenging due to the relatively small size of these genomic alterations. Therefore, this study aimed to validate the ability of whole-genome single-end sequencing–based NIPT to detect submicroscopic fetal CNVs.

Methods:

Single-end sequencing–based NIPT was performed on maternal plasma samples with cytogenetically confirmed CNVs. Cell-free DNA was extracted using the GenoScout EM Dx system, libraries were prepared on the MrLH-96 Dx platform, sequenced on the GenoLab M system, and analysed using GeneMind Fetal Chromosome Aneuploidy Analysis Software V.4 (FCAA).

Results:

Two rare fetal cases with submicroscopic CNVs involving telomeric and pericentromeric regions were retrospectively evaluated using whole-genome single-end sequencing–based noninvasive prenatal testing (NIPT). A 1.7 Mb pathogenic telomeric deletion (1p36.33–p36.32) was successfully detected, demonstrating complete concordance with the confirmatory diagnostic result. In contrast, a 7.6 Mb pathogenic pericentromeric deletion (8p12–p11.21), although confirmed by diagnostic testing, was not reported by the NIPT algorithm because it failed the predefined analytical quality criteria despite the presence of an abnormal CNV signal.

Conclusions:

Whole-genome single-end sequencing–based noninvasive prenatal testing (NIPT) has the potential to detect rare submicroscopic fetal copy number variants (CNVs), including those in clinically significant genomic regions. However, detection performance remains limited in low-mappability pericentromeric regions, emphasizing the need for continued refinement of analytical algorithms. Further validation in larger clinical cohorts is required to establish the robustness and clinical utility of this approach.

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Analytical Validation of Whole-Genome Single-End Sequencing–Based Noninvasive Prenatal Testing for Detecting Submicroscopic Telomeric and Pericentromeric Fetal Copy Number Variants: Insights from Two Rare Cases.

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BACKGROUND & OBJECTIVES

Fetal cell-free DNA (cfDNA) in maternal plasma combined with next-generation sequencing has transformed prenatal screening through NIPT.

NIPT is highly accurate for common aneuploidies, but detecting **microdeletions and microduplications** remains challenging because of their small size.

Aim: to validate whole-genome single-end sequencing–based NIPT for detecting submicroscopic fetal CNVs.

METHODS

1. **Maternal plasma** CNVs confirmed by cytogenetic diagnosis.
2. **cfDNA extraction** CF-DNA isolation Pre-package kit, GeneMind.
3. **Library preparation** NIPT Standard Dx Package, GeneMind.
4. **Single-end WGS** GenoLab M sequencer, GeneMind.
5. **CNV analysis** GeneMind FCAA Software V.4, GeneMind.

RESULTS

Two rare fetal cases with diagnostically confirmed submicroscopic CNVs were evaluated retrospectively.

Table 1 Genomic characteristics, diagnostic confirmation, and NIPT reporting outcomes of two fetal pathogenic deletions.

Case	Chromosome	Region	Location	Size	Classification	CNV (Z-score) (>5.00)	NIPT result
1	chr1	Telomeric	1p36.33–p36.32	1.7 Mb	Pathogenic	**5.31**	**Detected (concordant)**
2	chr8	Pericentromeric	8p12–p11.21	7.6 Mb	Pathogenic	4.78	**Not reported (failed QC)**

CASE 1 (A)
1.7 Mb
Telomeric deletion
chr1 · 1p36.33–p36.32

✓ DETECTED
concordant with diagnosis

CASE 2 (B)
7.6 Mb
Pericentromeric deletion
chr8 · 8p12–p11.21

! NOT REPORTED
signal seen, failed QC

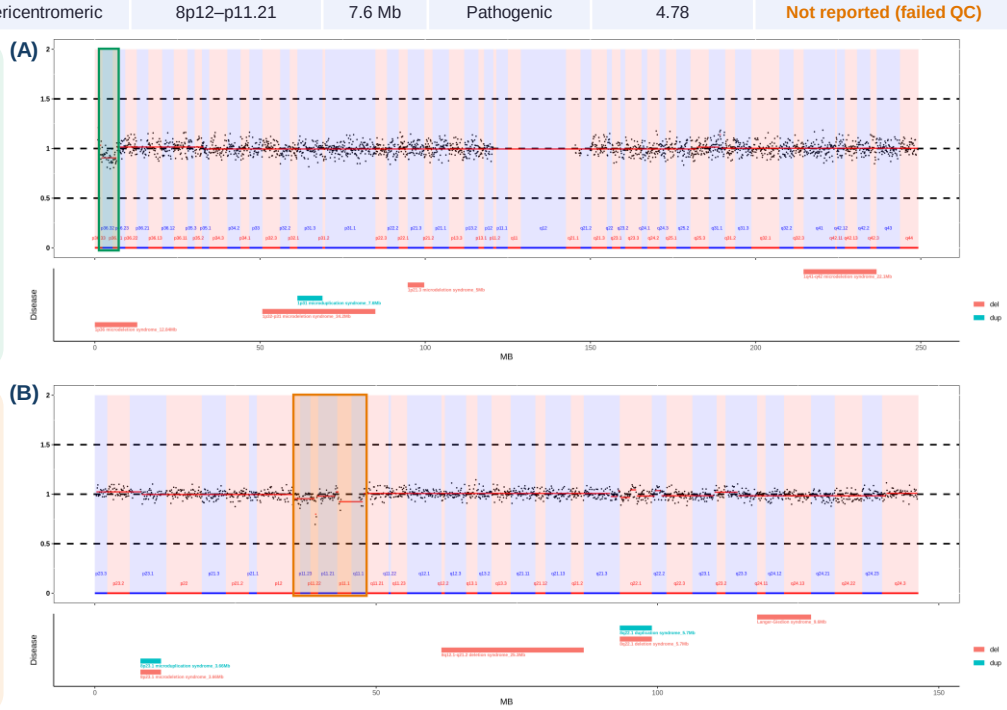


Figure 1: **(A)** A 1.7 Mb telomeric deletion at 1p36.33–p36.32 was detected, concordant with the confirmatory diagnosis. **(B)** A 7.6 Mb pericentromeric deletion at 8p12–p11.21 produced an abnormal CNV signal but was not reported because predefined analytical quality criteria were not met. **Highlighted boxes indicate the deleted regions**

CONCLUSIONS

✓ Detection potential
Whole-genome single-end sequencing–based NIPT can detect rare submicroscopic fetal CNVs, including those in clinically significant regions.

! Current limitation
Detection remains limited in low-mappability pericentromeric regions, as shown in Case 2, where the abnormal signal failed QC criteria.

→ Next steps
Continued refinement of analytical algorithms and validation in larger clinical cohorts to establish robustness and clinical utility.