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*Brief Communication*

# cfDNA from maternal plasma for noninvasive screening of fetal exomes

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**Abstract:** In recent years, a shift in prenatal screening methods has been observed, moving away from traditional approaches such as ultrasound and maternal serologic markers towards the utilization of noninvasive prenatal testing (NIPT) based on cfDNA extracted from peripheral blood. This cutting-edge technology has established itself as the primary screening method, attributed to its superior detection rate and reduced false-positive rate. Although NIPT predominantly focuses on screening for chromosomal abnormalities, it currently does not encompass the identification of single-gene disorders. Considering that single-gene disorders contribute significantly to birth defects, accounting for 7.5% to 12% of cases, it becomes imperative to integrate screening for single-gene disorders into the birth defect prevention and control system. This study aims to provide a succinct overview of the recent advancements in NIPT specifically tailored for monogenic disorders.

**Keywords:** cfDNA, monogenic disorders, NIPT

Over the past decade, non-invasive prenatal testing (NIPT) has emerged as the most effective screening tool for common fetal chromosomal aneuploidies [1, 2]. Recently, an extension of NIPT has incorporated screening for fetal chromosomal microdeletion and microduplication syndromes (MMS) [3]. Due to the predominant origin of most cfDNA in maternal plasma from the mother (~90%), the high maternal background poses a challenge to detecting fetal-specific variants like monogenic disorders. There exists an urgent need for the development of a comprehensive next-generation NIPT assay capable of simultaneously screening chromosomal disorders and monogenic disorders.

A novel liquid-phase hybridization capture probe design was employed by Xu et al. [4] to homogeneously enrich wild-type and mutant allele-fragmented DNA at single-nucleotide polymorphisms (SNPs) loci in a target chromosomal region. This approach generated high signal-to-noise cfDNA sequencing data. Novel genomic algorithms were utilized to analyze the depth of sequencing in the target region, allele scores, and interlocking SNPs, enabling the accurate isolation of the fetal genome from the maternal background. In a retrospective analysis of 1,129 samples, the study successfully detected 54 fetal aneuploidies, 8 microdeletions/microduplications, and 8 single-gene variants with 100% sensitivity and 99.3% specificity. Additionally, this study, for the first time in cfDNA, identified the presence of meiotic recombination abnormalities in 60.3% of the aneuploid samples, providing crucial insights for further studies on the mechanism of meiotic nondisjunction [4].

Brand et al. [5] identified and elucidated the capability of detecting fetal exome variants from DNA circulating in the mother's blood, a method termed noninvasive fetal sequencing. This method eliminates the necessity for separate genetic testing of either the mother or the father. The study also demonstrated the sensitivity of the method to detect single-base DNA changes and small insertions and deletions in the fetal genome, irrespective of the amount of fetal DNA detected, which are not present in the maternal genome.

Single-gene disorders lacking gross structural abnormalities during fetal development may go unnoticed during early pregnancy ultrasound screening. Next-generation NIPT, however, offers a more comprehensive genetic screening approach, complementing current imaging-based screening methods. This inclusion allows sufficient time for prenatal diagnosis and clinical decision-making. The incorporation of single-gene disorders into the existing NIPT screening system holds significant clinical value and represents the developmental direction for next-generation NIPT.

## Disclosure of conflict of interest

None.

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