OBSTETRICS

Expanding the scope of noninvasive prenatal testing: detection of fetal microdeletion syndromes

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OBJECTIVE: The purpose of this study was to estimate the performance of a single-nucleotide polymorphism (SNP)—based noninvasive prenatal test for 5 microdeletion syndromes.

STUDY DESIGN: Four hundred sixty-nine samples (358 plasma samples from pregnant women, 111 artificial plasma mixtures) were amplified with the use of a massively multiplexed polymerase chain reaction, sequenced, and analyzed with the use of the Next-generation Aneuploidy Test Using SNPs algorithm for the presence or absence of deletions of 22q11.2, 1p36, distal 5p, and the Prader-Willi/Angelman region.

RESULTS: Detection rates were 97.8% for a 22q11.2 deletion (45/46) and 100% for Prader-Willi (15/15), Angelman (21/21), 1p36 deletion (1/1), and cri-du-chat syndromes (24/24). False-positive rates were 0.76% for 22q11.2 deletion syndrome (3/397) and 0.24% for cri-du-chat syndrome (1/419). No false positives occurred for Prader-Willi (0/428), Angelman (0/442), or 1p36 deletion syndromes (0/422).

CONCLUSION: SNP-based noninvasive prenatal microdeletion screening is highly accurate. Because clinically relevant microdeletions and duplications occur in >1% of pregnancies, regardless of maternal age, noninvasive screening for the general pregnant population should be considered.

Key words: microdeletion, noninvasive prenatal testing, single-nucleotide polymorphism

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The discovery in the maternal circulation of cell-free DNA (cfDNA) of fetal/placental origin has led to a revolution in prenatal screening.[1-3] Common whole-chromosome fetal aneuploidies can now be detected with high sensitivity and specificity[4] and have facilitated a significant reduction in the number of invasive diagnostic procedures that have been performed. In the United States, 2 noninvasive prenatal testing (NIPT) approaches have been commercialized: quantitative "counting" that uses massive or targeted parallel sequencing[5-7] and a single-nucleotide polymorphism (SNP)—based approach that relies on the identification of maternal and fetal allele distributions.[8-13] Both methods can detect pregnancies at high risk for trisomy 21 (Down syndrome), trisomy 18, trisomy 13, and sex

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chromosome abnormalities. The SNP-based approach is also able to detect triploidy.[9,11]

Subchromosomal abnormalities (microdeletions and duplications) may result in physical and/or intellectual impairments that can be more severe than whole chromosome abnormalities. Unlike the risks of aneuploidy that is associated with nondisjunction, the incidence of subchromosomal copy number variations (CNVs) is independent of maternal age. Clinically relevant microdeletions and duplications occur in 1-1.7% of all structurally normal pregnancies.[14] In younger women, the risk for a clinically significant deletion exceeds the risk for Down syndrome. Because some infants with subchromosomal abnormalities may benefit from early therapeutic intervention,[15-17] prenatal detection is important for optimal management. In support of this, it is recommended that chromosome microarray analysis be offered to all women who undergo invasive diagnostic testing.[18] However, with the introduction of NIPT for aneuploidy screening, many women who previously would have had invasive testing are choosing to avoid these procedures because of the small risk of pregnancy loss.[3,19]

Submicroscopic genomic alterations are harder to detect noninvasively because of their small size. A small proportion may be identified incidentally through traditional serum and ultrasound screening, but these tests were not designed to screen for these anomalies. The introduction of a highly accurate noninvasive prenatal screening test that would identify women who are at high risk for microdeletions or duplications therefore would be useful. Recently, proof-of-principle studies that used shotgun or whole-genome sequencing reported the detection of subchromosomal microdeletions and microduplications.[20-23] However, these approaches were limited by the requirement for exceptionally high sequence reads, and interpretation was complicated by the identification of variants of unknown clinical significance. Here, we used a targeted SNP-based approach[9-13] to detect the larger deletions that underlie 5 microdeletion syndromes with clinically severe phenotypes.

TABLE 1
Samples used in the main cohort along with the sample deletion sizes

Samples	Sample deletion size	n
Pregnancy samples		
DiGeorge deletion	arr[hg18] 22q11.21(17,010,000-20,130,000)x1	1
DiGeorge deletion	arr[hg18] 22q11.21(17,020,000-20,130,000)x1	1
DiGeorge deletion	46,XX.nuc ish(HIRAx1)	1
Cri-du-chat deletion	46,XX,del(5)(p15.1p15.3)	1
Cri-du-chat deletion	46,XY,del(5)(p14.2)	1
1p36 deletion	46,XY,del(1)(p36.1)	1
46,XX and 46,XY		352
PlasmArt samples: born triads		
DiGeorge deletion	arr[hg18] 22q11.2(17,270,000- 19,810,000)x1	22
DiGeorge deletion	arr[hg18] 22q11.2(16,950,000-20,250,000)x1	22
Cri-du-chat deletion	arr[hg18] 5p15.33p14.1(91,100-29,500,000)x1	22
46,XX and 46,XY		7
PlasmArt samples: cell lines		
Prader-Willi deletion	arr[hg18] 15q11.2q13.1(20,310,000-27,130,000)x1	16
Angelman deletion	arr[hg18] 15q11.2q13.1(20,310,000-27,220,000)x1	22

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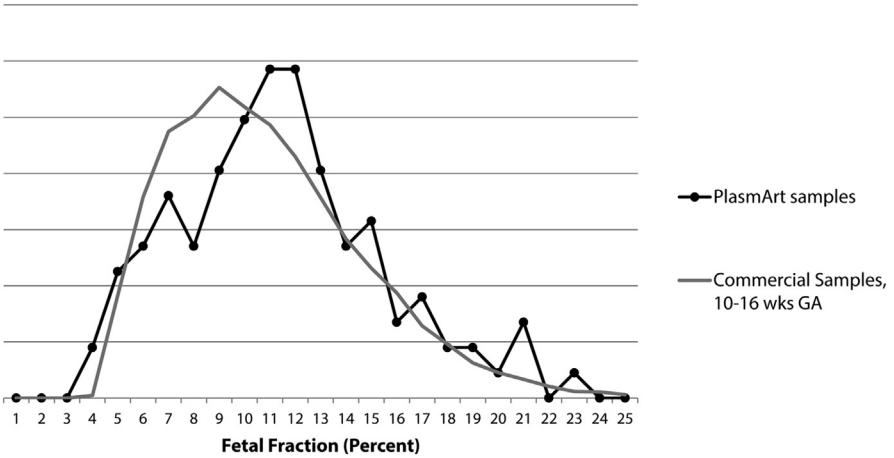
Materials and Methods

Initial validation studies were performed with genomic DNA that had been isolated from 40 characterized cell lines to demonstrate that the SNP-targeted assay

FIGURE 1
Fetal fraction distribution



Distribution of the 111 PlasmArt samples and of 19,910 consecutive commercial samples from 10-16 weeks' gestation.

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