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Noninvasive Prenatal Diagnosis of a Fetal Microdeletion Syndrome

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To the Editor: The definitive diagnosis of fetal aneuploidy and genomic imbalances requires invasive collection of fetal cells through amniocentesis or chorionic villus sampling. These methods are associated with fetal loss and parental anxiety. Analyses of DNA in maternal plasma have shown the potential for noninvasive diagnosis of common aneuploidies.[1]

A couple presented for prenatal genetic counseling at the Magee–Womens Hospital of the University of Pittsburgh Medical Center. They had previously had a child with developmental delay and dysmorphic features in whom a paternally inherited 4.2-Mb deletion on chromosome 12 between bands 12p11.22 and 12p12.1 had been diagnosed (Fig. 1A). Amniocentesis was performed at 21 weeks of gestation, and micro-array-based comparative genomic hybridization identified the same heterozygous deletion in the male fetus (Fig. 1B).

A maternal blood sample was drawn at 35 weeks of gestation, and plasma DNA was extracted without further enrichment. Real-time polymerase-chain-reaction assay revealed that the relative prevalence of fetal DNA was 5.7%. The maternal plasma DNA was then used as a substrate for Illumina HiSeq2000 DNA sequencing, generating 243,340,714 single-end reads, of which 75% mapped uniquely and perfectly to the Genome Reference Consortium human genome (build 37), GRCh37. Seven maternal plasma samples in which both the mother and fetus were known to be diploid for chromosomes 12 and 14 were also sequenced as reference libraries. Using our previously described method,[2] we determined whether the maternal sample (PL565) was diploid in each of 22 nonoverlap-ping 4-Mb regions on chromosomes 12 and 14 through a pairwise comparison with each of the reference libraries. We detected a 4-Mb depletion in DNA copy number on chromosome 12p in PL565 in all seven pairwise comparisons with a normal sample (adjusted $P \leq 0.05$ for all comparisons) (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM .org). Tests for all other 21 regions resulted in nonsignificant adjusted P values for all seven pairwise comparisons (Table S1 in the Supplementary Appendix).

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

In summary, we have shown proof of concept that a fetal chromosomal microdeletion can be identified by means of noninvasive analysis of DNA in maternal plasma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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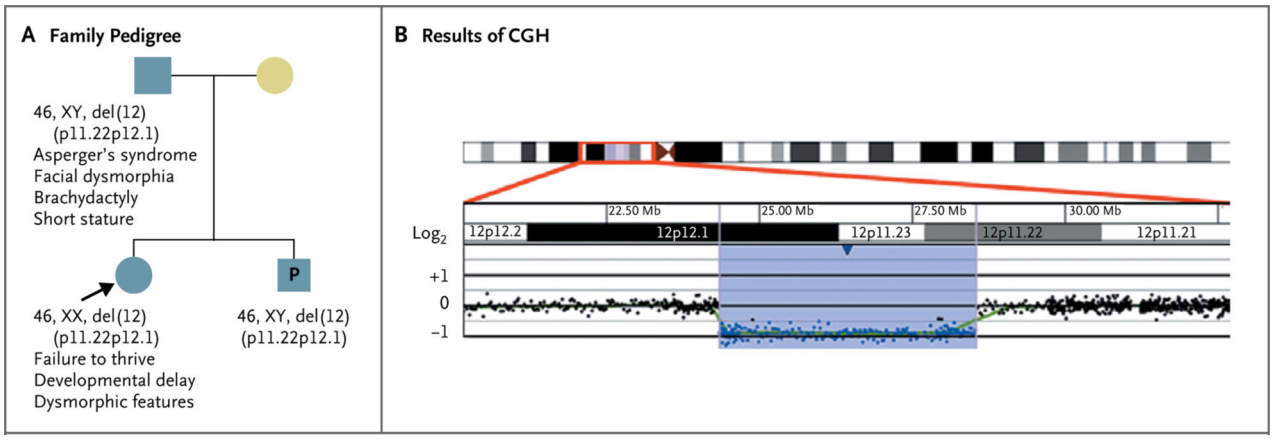

Figure 1. Pedigree of the Affected Family and Results of Comparative Genomic Hybridization (CGH) Showing Deletion on Chromosome 12

In Panel A, the arrow points to the affected proband. Male and female family members are indicated by squares and circles, respectively. P denotes the fetus being evaluated for a possible deletion on chromosome 12. In Panel B, the CGH profile of a sample obtained on amniocentesis shows a heterozygous deletion in the short arm of chromosome 12 between bands 12p11.22 and 12p12.1. A loss in DNA copy number (deletion) was detected by oligonucleotide probes, as represented by dots showing a $\log_2$ ratio of test-versus-reference value of −1. Dots with a $\log_2$ ratio of 0 represent probes with no change in copy number.