A Single NIPT for Aneuploidies, Microdeletions and Point Mutations

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INTRODUCTION: We hereby present the development of a NIPT of major aneuploidies, microdeletions and 50 monogenic diseases by leveraging parental carrier status information. All monogenic diseases under investigation are associated with moderate or severe phenotype, including Hematological, Kidney, Opthalmological, Neurological, Inherited Metabolic Diseases, such as Thalassaemia, Cystic Fibrosis, Phenylketonuria and Tay-Sachs.

MATERIALS AND METHODS: The carrier status of maternal cfDNA referred for NIPT and paternal DNA was investigated for 496 causative mutations in 49 disease associated genes. An enriched sequencing library was prepared using custom TArget Capture Sequences (TACS) as previously described. TACS were designed based on genomic locations of known causative mutations for the 50 monogenetic diseases, in addition to select regions on chromosomes 13, 18, 21, X, Y and critical regions of 22.q11, 1p36, Wolf-Hirschhorn and Smith-Magenis microdeletion syndromes. Enriched products were sequenced using NGS and the data was processed using a custom bioinformatics pipeline.

RESULTS: A total of 325 mutations were identified in 266 samples, 78 of which were unique pathogenic mutations. All unique point mutations were confirmed by Sanger sequencing. All aneuploidies and microdeletions were correctly classified with 100% specificity and sensitivity.

CONCLUSIONS: The fetal risk for the 50 monogenic diseases can be determined by identifying the carrier status of the parents using our targeted capture enrichment assay. This is the first time that NIPT is made available for a high number of single gene diseases together with aneuploidies and microdeletions, opening a new chapter in prenatal screening. This novel NIPT is expandable to hundreds of single gene diseases and can be taken potentially by all pregnant women as early as the 10^{th} week of gestation.