Targeted Sequencing of Maternal Plasma for Haplotype-based Noninvasive Prenatal Testing of Spinal Muscular Atrophy

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Objective

• To investigate the feasibility study of haplotype-based noninvasive prenatal testing (NIPT) of Spinal Muscular Atrophy (SMA).

Conclusions

• NIPT strategy for SMA through targeted sequencing of maternal plasma DNA is accurate and the haplotype-based method should be evaluated systematically in a larger population and may serve as a robust and accurate NIPT for SMA.

Methods

• Five families with pregnancy and a child affected by spinal muscular atrophy (SMA) were recruited between November 2014 and March 2015. Deletions of exons 7 and/or 8 in the SMN1 gene were identified by multiplex ligation dependent probe amplification (MLPA). Clinical information for the five couples and their proband child are shown in Table 1. For target capture sequencing of genomic and maternal plasma DNA, a custom-designed 221.43-kilobase (kb) NimbleGen EZ array was used, containing a 28-kb coding region of the SMN1 gene and 2011 SNPs from 3 megabases (Mb) upstream to 3 Mb downstream of the SMN1 gene.

Results

• Parental haplotypes across the SMN1 gene and flanking region were constructed based on the genotyping information from the mother, father, and proband child (Figure 1). The number of informative SNPs on the 221.43-kb target region used for fetal haplotype construction in each family ranged from 95 to 1186. According to parental haplotypes and maternal plasma DNA sequencing data, the PAHP-assisted method identified two normal fetuses (Cases 1 and 5), two carriers (Cases 2 and 3), and one affected fetus (Case 4) (Table 1 and Figure S1). The results were consistent with the standard prenatal diagnosis method using MLPA of AF or CV samples, with no false-positive or negative result.

• Table S1 may be found in the online version of this article.

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