IN THIS ISSUE

Amplification of DIP-STRs from cell-free fetal DNA in maternal plasma

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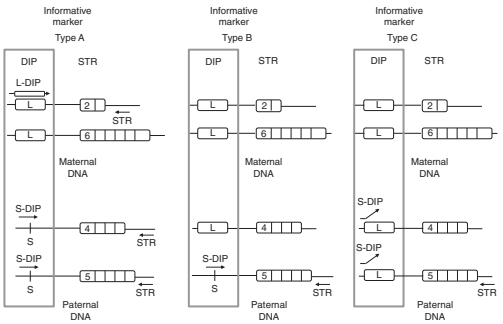

Noninvasive prenatal genetic analysis requires methodologies capable of detecting and analyzing cell-free fetal DNA (cffDNA) amid the overwhelming background of maternal DNA that is circulating in maternal plasma. For noninvasive prenatal paternity testing, analytical methods must be sensitive enough across multiple polymorphic markers to assess the probability of paternity, specific enough to distinguish paternally transmitted alleles from maternal DNA, and targeted enough to avoid the discovery of unwanted secondary findings. Deletion/insertion polymorphism linked to short tandem repeat polymorphism (DIP-STR) markers were originally developed for forensic use, to target and characterize trace DNA evidence in mixed biological specimens. In this issue, Moriot and Hall describe the application of DIP-STRs to the selective amplification of paternally transmitted alleles in cffDNA. The authors used 18 previously reported and 10 newly developed DIP-STR markers to test 95 blood samples collected at varying gestational ages from 48 pregnant women. Buccal swabs were collected from both parents and genotyped, and informative markers were selected for evaluation. False-positive amplification of maternal alleles was not observed. False-negative results occurred in 8/116 polymerase chain reaction (PCR) assays (6.9%). Successful amplification of DIP-STRs was achieved from maternal plasma that was collected as early as 10 weeks gestational age and from samples in which fetal DNA comprised as little as 3.5% of total cell-free plasma DNA. The authors conclude that DIP-STR markers can be used for noninvasive prenatal paternity testing and suggest that this approach might also be useful for noninvasive prenatal diagnosis of some genetic diseases. They caution, however, that further investigation is needed to determine how many informative markers are required for conclusive paternity testing and to develop DIP-STR markers for diagnostic use. —*Raye Alford, News Editor*

High-throughput curation of the Mendeliome by evaluation of autozygosity

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Linking genes to phenotypes is necessary for the accurate interpretation of DNA sequence variations, yet thousands of known genes still lack definitive phenotype associations. The autozygome—the set of ancestral genomic regions in an individual that are identical by descent—has proven to be a powerful tool for the discovery of autosomal recessive disease genes. In this issue, Maddirevula et al. demonstrate the usefulness of the autozygome not for the discovery of disease genes but for the high-throughput validation of candidate gene–disease associations. The authors searched their database of 2549 research and clinical exomes to identify homozygous variants that were expected to be functionally deleterious (i.e., considered appropriate for classification as pathogenic or likely pathogenic) but located in genes that had not been definitively linked to disease. Among 52 patients, the autozygome revealed homozygous variants in 48 previously reported candidate disease genes. For 30 of these genes, the observed patient phenotypes were identical or nearly identical to previously reported phenotypes. For 15 genes, the observed patient phenotypes were considered by the authors to represent expansions of the previously reported phenotypes. For three genes, the observed patient phenotypes were dissimilar to previously reported phenotypes and classified by the authors as allelic disorders. The authors conclude that large-scale analysis of autozygomes can provide evidence in support of alleged gene–disease associations and facilitate high-throughput mapping and curation of the Mendeliome, which will increase the diagnostic yield of clinical genomic sequencing by informing variant interpretation. They assert that, because autozygosity permits assessment of the phenotypic expression of variants in a homozygous state, this approach offers opportunities to identify phenotypic features that might not be readily evident when variants are observed in a compound heterozygous state. The authors also emphasize that the continued sharing of variants is essential to the rapid confirmation of tentative gene–disease associations. —*Raye Alford, News Editor*