17th World Congress in Fetal Medicine

Prospective chromosome analysis of 3429 amniocentesis samples in China using copy number variation sequencing

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Objective

To evaluate copy number variation sequencing (CNV-Seq) as a first tier diagnostic method for detection of fetal abnormalities in a general population of pregnant women with high-risk prenatal indications.

Methods

Prospective analysis of 3429 pregnant women referred for amniocentesis and fetal chromosome testing for different risk indications, including advanced maternal age (AMA), high-risk maternal serum screening (HR-MSS), and positivity for an ultrasound soft marker (USM). Amniocentesis was performed by standard procedures. Amniocyte DNA was analyzed by CNV-Seq with a chromosome resolution of 0. 1 Mb. Fetal aneuploidies including whole chromosome and segmental imbalances were confirmed by secondary gold standard cytogenetic and molecular methods and their pathogenicity determined following guidelines of the American College of Medical Genetics for sequence variants.

Results

Clear interpretable CNV-Seq results were obtained for all 3429 amniocentesis samples. CNV-Seq identified 3293 (96%) samples with a normal molecular karyotype and 136 samples (4%) with an altered molecular karyotype. A total of 147 fetal aneuploidies were detected, comprising 46 whole chromosome aneuploidies (pathogenic), 38 submicroscopic microdeletions/microduplications with known or suspected associations with chromosome disease syndromes (pathogenic), 6 other microdeletions/microduplications (likely pathogenic), 6 chromosome X deletions (potentially pathogenic) and 51 variants of unknown clinical significance (VOUS). Overall, the cumulative frequency of pathogenic/likely pathogenic aneuploidies in the patient cohort was 2. 6%. In the three high-risk AMA, HR-MSS and USM groups, the most common whole chromosome aneuploidy detected was trisomy 21, followed by sex chromosome aneuploidies, trisomy 18 and trisomy 13. Across all clinical indications, there was a similar incidence of submicroscopic CNVs, with approximately equal proportions of pathogenic and VOUS aneuploidies. If karyotyping had been used as an alternate cytogenetics detection method, CNV-Seq would have returned a 1. 0% higher yield of pathogenic/likely pathogenic aneuploidies.

Conclusion

In a large prospective clinical study, CNV-Seq delivered high reliability and accuracy for identifying clinically significant fetal abnormalities in prenatal samples. Based on key performance criteria, CNV-Seq appears to be a well-suited methodology for first tier diagnosis of pregnant women in the general population at risk of a fetal chromosome abnormality.