

RETROSPECTIVE ANALYSIS OF PRENATAL SAMPLES WITH SONOGRAPHIC ANOMALITIES USING GENOME-WIDE BAC ARRAY-CGH

Simona De Toffol¹, Livia Marcato¹, Francesca Malvestiti, Sara Chinetti¹, Beatrice Grimi¹, Federico Maggi¹, Giuseppe Simoni¹, Francesca Romana Grati¹

¹Research and Development, Cytogenetics and Molecular Biology, TOMA Advanced Biomedical Assays S.p.A., Busto Arsizio, Varese (ITALIA)

Objective

The introduction of array-CGH (aCGH) into prenatal diagnosis (PD) presents controversy to the clinical cytogenetic community. Some authors pointed out the possible negative implications related to the detection of CNVs of uncertain significance in prenatal diagnosis. However, the application of aCGH analysis to fetuses with sonographic anomalies may improve the diagnosis of genetic abnormalities compared to metaphase karyotype alone. The aims of this study are to retrospectively explore the potentiality of array CGH to the prenatal evaluation of fetal structural anomalies, to determine the detection rate of cryptic chromosomal unbalances in prenatal samples with an indication of sonographic abnormalities and to assess the frequency of variants of uncertain clinical significance.

Methods

Microarray analysis using whole-genome bacterial artificial chromosome (BAC)-based platform with a final average resolution of 0.6Mb (Constitutional Chip 4.0, PerkinElmer) was retrospectively performed on 40 prenatal samples (chorionic villi, amniocytes and abortive tissues) with a sonographic abnormality and a normal karyotype or a *de novo* apparently balanced rearrangement or with a known chromosome partial unbalance.

Results

In all cases with partial cytogenetic unbalances microarray analysis readily detected them and refined their boundaries allowing, in some cases, the replacement of the cytogenetically detected breakpoints. Array CGH analysis identified a cryptic clinically significant chromosome alteration in about 10% prenatal specimens with a normal or with an apparently balanced *de novo* rearrangement. Results of unclear significance were found in about 3% of cases, a value higher than that reported in previous studies because in the majority of cases the retrospective collection didn't enable us to have parental or additional aliquots of fetal samples for confirmatory investigations.

Conclusions

In addition to the conventional karyotyping, the application of genome-wide BAC array CGH for the evaluation of fetuses with sonographic anomalies and normal or apparently balanced *de novo* rearrangement could yield additional diagnoses. Also cases with partial cytogenetic unbalances may take advantage from this application for their fast and precise characterization of breakpoints allowing a more accurate and specific prenatal genetic counselling

KEY WORDS: genome-wide array CGH; prenatal diagnosis; chromosome abnormality; fetal ultrasound; copy number variant