19th World Congress in Fetal Medicine

Prenatal WES for rapid detection of copy number variants and single gene disorders in uncultured samples

Cirigliano V, Lloveras E, Ordoñez E, Castilla I, Lechuga M, de Alemeida M, Perez C, Leon M
Veritas Intercontinental, Barcelona, Spain

Objective

Chromosomal microarrays are currently the standard of care for the detection of segmental imbalances in prenatal diagnosis. However, the large proportion of cases with normal results frequently prompts additional testing for monogenic disorders, mainly performed by sequencing, either targeted to specific indications or to include the whole exome. We aimed to develop a whole exome sequencing (WES) test with an improved capture assay to detect both CNVs and SNVs on the same sample and on the same data. The aim of this study was to assess its performance for genomewide detection of CNVs in uncultured prenatal samples.

Methods

Retrospective analysis of 24 archived DNA extracted from uncultured amniotic fluids (17) and CVSs (8) between 2017 and 2019, with selected CNVs of different sizes reported as pathogenic by aCGH. Samples were sequenced using an improved whole exome capture of 51 Mb designed to allow genomewide CNV detection and optimised to reinforce sequencing coverage of a wide subset of genes related with fetal structural abnormalities and developmental delay. Sequencing was performed at 100X mean depth and data analysed with a dedicated software including exome depth for CNV detection and exomiser for SNVs priorization based on HPO terms.

Results

All samples passed sequencing QC metrics and were included in the analysis. Full concordance between WES and aCGH results was observed with only an expectable slight difference in the locations of CNVs breakpoints. CNVs ranged between 13.8Kb and 52.9Mb in size: 17 cases with a unique event (12 losses, 5 gains), 4 cases with 2 CNVs (gain and loss), two more samples had respectively 2 and 3 losses. One rare case of chromothripsis, with 8 duplications along different regions of the same chromosome, was also correctly identified with high confidence.

Conclusion

WES analysis can be used to identify pathogenic CNVs in uncultured prenatal samples. Testing for CNVs as a first line test on sequencing data has the great advantage of allowing rapid addition of virtual multigene panels to extend the analysis to SNVs/indels in case of normal result. While reducing time and costs for the analyses, this single test approach has the potential to increase the overall diagnostic yield in prenatal diagnosis.