17th World Congress in Fetal Medicine

High resolution chromosomal microarray analysis across all indications in prenatal diagnosis: is more better?

Pangalos C, Hagnefelt B, Karapanou S, Konialis C

1 InterGenetics SA, Center for Medical Genetics and Genomics, Athens, Greece, 2 Genomis Ltd, London, UK, 3 ClinGenics Ltd, London, UK, ATHENS, Greece

Objective

Chromosomal microarray analysis (CMA) has been the recommended test for the pediatric and adult population with developmental disabilities and birth defects since 2008. Since 2010 CMA was gradually introduced in prenatal diagnosis, being the recommended first-line genetic test when a prenatal diagnostic procedure is performed for sonographically detected fetal structural anomalies and has now been extended as a routine test in prenatal chromosomal diagnosis (PCD) across all indications. Within this framework, in 2011 we initiated routine prenatal CMA testing utilizing a relatively low resolution aCGH platform resulting in the overall detection of pathogenic chromosomal imbalances in ~3. 3% of cases, with negligible genetic counseling issues (Konialis & Pangalos, 2015). Due to industry-driven developments, in 2017 we were faced with the problematical issue of replacing this platform with one affording higher resolution CMA. Based on our previous experience, taking also into account the findings from the large multicenter NIH study (Wapner RJ et al, 2012) as well as the findings from several other published studies utilizing high-resolution CMA in PCD for the detection of CNV's <50-100Kb, we deliberately adjusted the CMA resolution in order to avoid the detection and assessment of uncertain findings, which becomes more frequent and more complex with high-resolution prenatal CMA resulting in serious genetic counseling issues in the course of pregnancy. We present our overall experience derived from ~9, 500 prenatal CMA cases and we discuss the findings in terms of diagnostic yield and most importantly in terms of clinical significance versus data and findings derived from studies employing high-resolution prenatal CMA.

Methods

Routinely, DNA was extracted directly from uncultured cells derived from ~10ml of amniotic fluid or an adequate CVS sample, quantified, and processed according to the manufacturer’s protocol using a sex-matched reference. Initially, in 7842 cases during the period 2011-2016, prenatal CMA was performed with a targeted BAC array and analyzed with the BlueFuse Multi software, affording a genomic coverage of 1Mb resolution across the genome backbone and a targeted 150 Kb resolution in 139 regions associated with constitutional disorders. Since February 2017 and in 1556 cases, prenatal CMA was performed with a custom 2x105K oligo array and analyzed with the CytoSure Interpret software, adjusted for the detection of genomic imbalances ≥350-500Kb across the genome backbone and ≥100-150Kb at ~600 targeted regions associated with known constitutional disorders.

Results

Utilizing the initial targeted BAC aCGH platform as a first-tier test, 7842 consecutive PCD cases were analyzed with an overall success rate of 99. 6%. Results were typically available within 4-5 working days. A total of 258 clinically relevant abnormalities (diagnostic yield 3. 3%) were reported across all indications, sub-microscopic CNV’s representing 0. 7% - 1 in 140 of all cases (55 out of 7810 cases) and 21% of all pathogenic results. We did not detect and report any variants of uncertain clinical significance (VOUS), although we did encounter 12 cases with CNV’s of clinical significance but with variable penetrance (0. 15%). Utilizing the custom 2x105K oligo aCGH platform, 1556 consecutive PCD cases were analyzed with an overall success rate of 100%. Results were typically available within 5-7 working days. A total of 69 clinically relevant abnormalities were reported across all indications (diagnostic yield 4. 4%), sub-microscopic CNV’s representing 1. 8% - 1 in 55 of all cases (28 out of 1556 cases) and 45% of all pathogenic results. We did not detect and report any VOUS, although we encountered 10 cases with CNV’s of clinical significance but with variable penetrance and expressivity (0. 65%), a 4x increase compared to the previous aCGH platform.

Conclusion

Utilizing an intermediate prenatal CMA resolution we observed an ~1% increase in overall diagnostic yield (4. 4% vs. 3. 3%), although applying stringent pathogenicity criteria and discarding inherited CNV's with highly variable penetrance and expressivity, the increase is marginally significant (3. 7% vs. 3. 1%). Taking into consideration the findings from the large multicenter NIH study, as well as the findings from several other published studies utilizing high-resolution aCGH platforms for the detection of imbalances <50-100Kb in PCD, our data and extensive experience suggests that our current prenatal CMA parameters for the reporting of CNV's ≥100-150Kb at ~600 targeted regions associated with known constitutional disorders and ≥350-500Kb across the genome backbone provide an optimum balance, between diagnostic yield versus the serious issues of assessing and reporting findings of uncertain clinical significance as a result of the unacceptable application of high resolution CMA in the course of pregnancy.