
With their prospective cohort study on chromosomal microarray analysis (CMA) performed in high-risk pregnancies, Hillman and colleagues contribute another study to this field and also present their data in the context of an up-to-date systematic review and meta-analysis of the literature. They provide overall detection rates of abnormalities by CMA compared with conventional karyotyping for various indications, as well as of variants of unknown clinical significance (VOUS), and report how these have changed over time.

This is a timely publication, as it draws together the significant number of important and large prospective clinical trials on CMA for prenatal testing that have been published recently. The combined data from these studies represent a cohort of over 18,000 prenatal samples. Taken together, their findings clearly indicate that, compared with conventional karyotyping, the use of CMA in prenatal diagnosis improves substantially the detection rate of pathogenic chromosomal abnormalities. The findings provide evidence for the feasibility of introducing CMA into routine prenatal diagnosis practice, indicating that it is acceptable to apply CMA as a first-line diagnostic test, at least concurrently with conventional karyotyping.

Statements issued by the American College of Obstetrics and Gynecology (ACOG), Canadian College of Medical Geneticists (CCMG) and Italian Society of Human Genetics (SIGU) have recommended that CMA should be offered as an adjunctive tool to selected groups of high-risk pregnancies (e.g. those with abnormal ultrasound findings and normal conventional karyotyping results), using the technique as a second-line test only, after standard karyotyping. The main reasoning behind this relates to the fact that CMA performed for indications other than abnormal ultrasound findings would likely be associated with a low positive predictive value, since the vast majority of fetuses tested would be clinically unaffected.

The higher detection rate by CMA compared with conventional karyotyping reported by Hillman et al. is not confined to cases with abnormal ultrasound findings; the results of their meta-analysis demonstrate the improved diagnostic ability of CMA to detect clinically relevant abnormalities and the utility of bringing CMA into routine prenatal practice as a primary diagnostic tool for a number of other indications. Furthermore, the findings clearly indicate that offering CMA only as a second-line test in high-risk pregnancies may substantially limit prenatal diagnostic potential, since a significant proportion of copy number variants (CNVs) that can cause serious disability are not detected by traditional karyotyping.

There is still understandable concern regarding the use of CMA on prenatal samples, related mainly to the potential detection by CMA of mild or unpredictable phenotypes and/or VOUS. In the meta-analysis of Hillman et al., VOUS are reported to occur in ∼1.4% of prenatal samples. However, it is well described that the incidence of VOUS detected is related mainly to the specific array platform used and its resolution.

In fact, the ideal microarray platform and resolution for use in the prenatal setting remain to be determined. High-resolution oligonucleotide or single-nucleotide polymorphism (SNP) microarray platforms offer the theoretical opportunity to find additional sub-microscopic chromosomal abnormalities, compared to bacterial artificial chromosome (BAC) arrays at lower resolution, and are the default array choice for postnatal cytogenetics. The potential benefits of using high-resolution microarrays for prenatal diagnosis are greater, but the probability of finding VOUS may also be greater. In contrast, BAC arrays usually detect substantially fewer VOUS than do high-resolution microarrays, but their potential in detecting small clinically relevant CNVs may also be lower.

In conclusion, the work of Hillman et al. is an important addition to the growing body of evidence on the diagnostic superiority of CMA over conventional karyotyping, with the ultimate goal of improved prenatal diagnosis and a lower risk of giving birth to a chromosomally abnormal neonate.

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