

Now you can! Reality & Future Applications of array CGH in prenatal diagnosis

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Array comparative genomic hybridization (aCGH), also called molecular karyotyping, is a recently introduced technique that was developed for high resolution, genome-wide screening of segmental genomic copy number variations (CNVs). Initially, this technique has been employed for the analysis of copy number changes in tumours and tumour cell lines to identify genes involved in the development and pathogenesis of cancers (Rickman et al., 2005). Recently, aCGH has been employed in clinical cytogenetics as an important clinical diagnostic tool to integrate and improve "classical" cytogenetic analysis. aCGH is at present routinely used in post-natal molecular diagnosis for the detection of chromosomal imbalances associated with mental retardation and multiple congenital anomalies (Edelmann L et al., 2009). This tool is also showing promising data in prenatal diagnosis. In fact, currently, prenatal diagnosis is dependent on cell culture which results in an average reporting time for the results of a full karyotype analysis of approximately 14 days. This interval between the collection of a prenatal biological sample and the reporting of results represents a time of great anxiety for parents during a pregnancy. aCGH analysis has been shown to be highly accurate for rapid detection of chromosomal aneuploidies and submicroscopic deletions or duplications on fetal DNA samples. This technique, detects copy-number changes with a high level of sensitivity thus having the potential to enhance or replace current approaches to prenatal diagnosis by providing a me-

thod which is both comprehensive and amenable to automation. aCGH can be performed directly on uncultured amniotic fluid cells, amniotic fluid supernatant cell-free fetal (AFcf) DNA or chorionic villi samples. The enhanced resolution provided by aCGH will enable the simultaneous detection of common aneuploidies, known microdeletion and microduplication syndromes and telomere deletions which could be considered of great benefit in prenatal diagnosis (Rickman et al., 2005). However, the use of aCGH in prenatal diagnosis raises some questions in terms of clinical practice. These include mostly, the cost of procedure and the generation of apprehension when a *de novo* CNV involving a chromosome region not previously associated to a phenotypic effect, is detected (<http://projects.tcag.ca/variation/>). Appropriate genetic counselling before and after the test could reduce many of these inconveniences (Darilek et al., 2008). In fact, genetic counselling issues that are especially pertinent to the use of this testing platform include how to incorporate adequate pretest counselling and consent and how to interpret and convey results to patients, especially those results of uncertain significance (Darilek et al., 2008). However, extensive studies are required to determine if aCGH will become the first-line test to detect chromosomal abnormalities in fetal samples and to establish whether the improve overall detection rates of clinically significant chromosomal abnormalities will justify offering aCGH more universally to all pregnant women (Van den Veyver et al., 2009). For exclusive and focused diagnostic applications, aCGH should be approached from a different perspective. Diagnostic arrays should be constructed in a manner that maximizes diagnostic capabilities while minimizing false positive results to provide clinicians with identified chromosome abnormalities (Bejjani et al., 2006). An example is provided by the platform "GOLD-Chip" recently produced by an Italian pharmaceutical company which is able to identify in just three days prenatally, chromosomal anomalies associated to a large number of genetic syndromes. GOLDChip (Gain or Loss Detection Chip) enables the identification of chromosomal abnormalities and prenatal fetal genomic imbalances associated with clinical conditions such as major trisomy, aneuploidy of the sex chromosomes, microdeletion syndromes and more than 80 genomic disorders including Cri du Chat syndrome, Williams syndrome, Prader Willi/Angelman syndromes, Smith-Magenis syndrome, DiGeorge syndrome, and Miller-Diecker syndrome.

Although, future studies and experience will further elucidate the role that this highly sensitive tool in detecting genomic disorders, it is premature considering this technique as a complete replacement of standard karyotyping. We are confident that aCGH, will likely represents the first approach to cytogenetic testing and will replace

FISH analyses in the clinical laboratory in the near future (Bejjani et al., 2006).

The extension of a CGH to noninvasive prenatal diagnosis using cell-free fetal DNA isolated from maternal plasma (Bischoff et al., 2005) or fetal DNA extracted from AFcfl or from trophoblast cells in cervical mucus (Katz-Jaffe et al., 2005) will revolutionize the practice of prenatal diagnosis.

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