Chromosome microarray as first tier approach in low risk pregnancies: detection rate should not be the only criteria for its application

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Chromosome microarray as first tier approach in low risk pregnancies: detection rate should not be the only criteria for its application

Short title: Chromosome microarray in low risk pregnancies: are we ready, already?

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We read with interest the paper by Hillman et al. [1] concerning the use of chromosome microarray (CMA) in prenatal diagnosis. Presented data-sets included: a prospective cohort of pregnant women with ultrasound abnormalities (UA) and a systematic review and meta-analysis of studies on prenatal cases referred for any indication, fetal UA included.

The authors corroborated the CMA usefulness in pregnancies with UA, and reported an additional CMA detection rate in respect to karyotyping of 4.1% in their cohort and of 10% in the whole meta-analysis. These different figures were likely due to the different analytical sensitivity of the used microarray platforms (i.e. BAC vs. oligo-array). A BAC platform comparable to that utilized in the Hillman's study was tested by other groups [2,3], who claimed higher detection rates, by incorporating in their results also large imbalances detectable by means of good quality chromosome preparations. Accordingly, Hillman et al. emphasize the relevance of high-quality laboratory practices to compare CMA and karyotype results in order to avoid a significant bias to any conclusion. Furthermore, CNVs such as the *PMP22* deletion listed among the "positive" results, should be regarded as incidental findings and not be considered in the detection rate estimation of CMA over karyotyping [1,2]. Moreover, such results did not likely answer to the actual questions addressing the couple to the prenatal diagnosis.

However, these results agree with published guidelines and statements indicating that pregnancies with UA would benefit from CMA.

The pregnancies investigated under the heading "any indication" disclosed highly heterogeneous results, with an additional detection by CMA ranging from 0.4 to 50%, while VOUS (Variants Of Uncertain Significance) rate was 1.4%. Therefore, given the heterogeneity and increasing resolution over the years of microarray platforms and the merging of low- and high-risk populations, it is difficult to draw any final conclusion, particularly in respect of CMA use in low risk pregnancies. A recent report has indeed shown that when advanced maternal age or anxiety were the only or main indications for referral, the detection gain by CMA was ranging from 1.0% and 0.6%, respectively [4]. These figures are evidently lower compared to VOUS detection rate.

In our opinion, the higher diagnostic capacity should not be the only criterion to update the health policy committees statements, whose decisions should be planned after a careful assessment of the eventual CMA large-scale application in unselected populations. In this perspective, several crucial issues await to be solved, including the appropriate array design, the assessment of the clinical relevance of a CNV with variable penetrance and expressivity, a consensus on reporting VOUS and the related emotional burden of such findings.

In order to comprehensively assess large-scale application of CMA in low risk pregnancies, we reiterate the advocacy for a model such as ACCE [5], which is formulated on the main criteria to evaluate a genetic test (analytic validity, clinical validity and clinical utility) and also takes into consideration its ethical, legal and social implications, the latter topics being of crucial importance, especially when proposing genetic testing in a prenatal setting. We think that to better balance cost-benefits a team-work between geneticists, obstetricians and public health methodologists should be established with the partnership of non-scientific stakeholders (e.g. pregnant couples/family and associations of patients).

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