INTRODUCTION

The implementation of chromosomal microarray (CMA) technology in the clinical prenatal setting has achieved consensus for use in cases with fetal defects in ultrasound examinations. The expansion of CMA as a standard examination for all patients undergoing invasive procedures has not achieved the same level of consensus. The main arguments against it include (1) counseling challenges related to the identification of so-called variants of unknown significance (VUS) or with inconclusive genotype and (2) costs involved, especially when weighed against the relatively smaller benefit for “lower risk” indications, where healthcare is mainly funded by the government.

Lower cost technologies, although comprehensive but also less challenging, have thus been proposed as “add-on tests” to women with “lower risk” indication. Prenatal BACs-on-Beads™ (PNBoBs™) is a newly emerging targeted isolation-based technology intended to detect rapid DNA copy number gains and losses. PNBoBs™ is a well-suited alternative for rapid FISH or QF-PCR as, unlike those technologies, it also has the ability to detect common microdeletions aside of the common trisomies. The microdeletion regions reported by PNBoBs™ are recurrently demonstrated and relatively well-characterized and microdeletion syndromes which may be easily missed by prenatal cytogenetics, such as recessively well-known genotype-phenotype correlation and associated with relatively minor challenges in terms of genetic counseling.

AIM OF THE STUDY

Comparison of the diagnostic performance of PNBoBs™ and QF-PCR assays for prenatal detection of chromosome abnormalities.

MATERIALS AND METHODS

- **Study description**: on a retrospective anonymized cohort (May 2015 - December 2018)
- **IRB approval**: Toma laboratory IRB protocol 000006
- **All patients gave consent for the analyses**
- **2748** chromosomal microarrays (CMA) samples were prospectively analyzed with conventional karyotyping and PNBoBs™ (Phenomenex/Wilk, Turin, Italy).
- **DNA extractions and PNBoBs™ analyses** were conducted as previously reported.
- **Classification of samples**:
  1. Classification by indication for prenatal diagnosis.
  2. Classification by indication for preimplantation genetic diagnosis (PGD).
  3. Classification by indication for postnatal diagnosis.

RESULTS

<table>
<thead>
<tr>
<th>Indication</th>
<th>PNBoBs (n=1919)</th>
<th>QF-PCR (n=1590)</th>
<th>p-Value (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1728 (90.61%)</td>
<td>1310 (82.27%)</td>
<td>&lt;0.001 (0.75-1.00%)</td>
</tr>
<tr>
<td>Other</td>
<td>191 (9.39%)</td>
<td>280 (17.73%)</td>
<td>0.001 (1.09-2.22%)</td>
</tr>
</tbody>
</table>

- For the full cohort the detection rate for chromosome abnormalities was reported as 2.96% (95%CI:2.39%-3.66%) for CMA and QF-PCR (Table 1).
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CONCLUSIONS

- Although PNBoBs™ may have the breadth and scope to replace chromosomal microarrays in the prenatal setting, particularly when a fetal anomaly has been detected by US analysis, it is a well-suitable alternative for QF-PCR as PNBoBs™ is superior in terms of sensitivity for a wider set of chromosome abnormalities in all indications, specifically for those pregnancies without any chromosome abnormality that might double as a level of stratification.
- In low risk indication, the approach PNBoBs™/Karyotyping provides a yield of detection higher than stand alone QF-PCR or in combination with karyotyping since no chromosome abnormalities detectable by QF-PCR remain undetected in karyotyped cases will be detected by karyotyping.
- However, it is also important to consider the costs associated with these assay approaches.

REFERENCES

- 5. AMA 46,XY (8)/45,X (20) 46,XY (20) rsa(X)x1 (CVS) mos 45,X[11]/46,XY[42] (n=metaphases)

POSTER LEGEND

Ultrasound findings (US) abnormal maternal age (AMA), increased risk for Down syndrome after maternal serum screening or cfDNA testing (IMSS-DS) or HR-cfDNA; and the location of polymorphic loci, microdeletions, and microduplications of the 22q11.22 microdeletion syndrome. (A) Theoretical number of chromosome abnormalities detected by aneuploidies and microdeletions in all indications.

Table 1: Detection rates of chromosome abnormalities by CMA and QF-PCR

- **Table 1**: Detection rates of chromosome abnormalities by CMA and QF-PCR
- **Table 2**: Description of the abnormal
- **Table 3**: ID

Figure 1 - Case 2 results: A) abnormal cell line carrying a dic(22;22) (p15.32;p22)dn(WHSC1-,WHSC2-); B) aneuploidy of chromosomes 21, 18, and 13; C) CMA arrayCGH results: arr[hg19],D8S2333+(WHSC1,WHSC2) 4p16.3(WHSC1,WHSC2) 20p11.22 (WHSC1-,WHSC2-).dash 22q11.22 microdeletion.

Figure 2 - Case 4 results: A) abnormal cell line carrying a dic(22;22) (p15.32;p22)dn(WHSC1-,WHSC2-); B) aneuploidy of chromosomes 21, 18, and 13; C) CMA arrayCGH results: arr[hg19],D8S2333+(WHSC1,WHSC2) 4p16.3(WHSC1,WHSC2) 20p11.22 (WHSC1-,WHSC2-) dash 22q11.22 microdeletion.

Figure 3 - Case 1 results: A) abnormal cell line carrying a dic(22;22) (p15.32;p22)dn(WHSC1-,WHSC2-); B) aneuploidy of chromosomes 21, 18, and 13; C) CMA arrayCGH results: arr[hg19],D8S2333+(WHSC1,WHSC2) 4p16.3(WHSC1,WHSC2) 20p11.22 (WHSC1-,WHSC2-) dash 22q11.22 microdeletion.

Figure 4 - Case 2 results: A) abnormal cell line carrying a dic(22;22) (p15.32;p22)dn(WHSC1-,WHSC2-); B) aneuploidy of chromosomes 21, 18, and 13; C) CMA arrayCGH results: arr[hg19],D8S2333+(WHSC1,WHSC2) 4p16.3(WHSC1,WHSC2) 20p11.22 (WHSC1-,WHSC2-) dash 22q11.22 microdeletion.

Figure 5 - Case 4 results: A) abnormal cell line carrying a dic(22;22) (p15.32;p22)dn(WHSC1-,WHSC2-); B) aneuploidy of chromosomes 21, 18, and 13; C) CMA arrayCGH results: arr[hg19],D8S2333+(WHSC1,WHSC2) 4p16.3(WHSC1,WHSC2) 20p11.22 (WHSC1-,WHSC2-) dash 22q11.22 microdeletion.