The Discovery of Unbalanced Translocations through Genome-Wide cfDNA Testing

I. Background

The MaterniT® GENOME test reports on genome-wide copy number variants ≥7Mb, making it uniquely positioned to identify deletions and duplications, such as those in unbalanced translocations. Since late 2015, more than 28,000 MaterniT® GENOME samples have been ordered. Here we describe cases in which the MaterniT® GENOME results were suggestive of an unbalanced translocation.

II. Methods

Maternal blood samples submitted for genome-wide cfDNA testing were subjected to DNA extraction, library preparation, and whole-genome massively parallel sequencing as described by Jensen et al. Sequencing data was analyzed using a novel algorithm as described by Lefkowitz et al.

III. Results

A total of 28,760 samples were submitted to the clinical laboratory and 1,392 (4.8%) of these resulted positive. Among all positives, 46 were interpreted as possible translocation events between two chromosomes, fetal and/or maternal confirmation by prenatal diagnosis, postnatal and/or prenatal blood chromosomes was reported in 28 cases. Another 16 cases were classified as likely concordant without diagnostic testing given known familial translocation or significant clinical history such as multiple congenital anomalies or poor neonatal outcome. Two cases were lost to follow up and no cases were reported discordant to the laboratory (Figure 1).

Ultrasound findings alone was the predominant indication for testing in 43% of cases and multiple indications were assigned to 35% of cases. Including cases with multiple indications, ultrasound findings were reported in a total of 72% of cases. In 26% of cases there was prior knowledge of parental translocation or family history suggestive of a translocation, and for nearly half of these cases it was the sole indication for testing. Only two cases (4%) were screened due to advanced maternal age alone and three cases (7%) had no indication provided. All four cases referred for abnormal serum screening were also referred with another indication, such as ultrasound finding (3) and advanced maternal age (1).

IV. Conclusions

Identification of complex chromosomal rearrangements via genome-wide cfDNA prenatal screening marks a new era in prenatal testing. In this case series we demonstrate that cfDNA screening may report findings suggestive of unbalanced familial translocations, at early gestational ages, which previously could only be tested for with diagnostic testing. Families with a known history of a translocation may be averse to the small but present risk associated with a diagnostic procedure, especially if they have a history of recurrent abortions. Additionally, cfDNA screening may discover families at risk of carrying a translocation. Patients and providers may not have otherwise had this information until a couple had experienced multiple losses or received abnormal diagnostic testing results from a previous abnormal pregnancy or child. The diagnostic odyssey may take an emotional and financial toll on a couple and knowledge of a familial translocation potentially saves an extensive work up with each loss. This knowledge allows families to fully consider all of their reproductive options in future pregnancies. MaterniT® GENOME is a relevant screening tool for families with a known translocation or suggestive family history.

V. References


Figure 1.

Follow up of Suspected Translocations on MaterniT® GENOME (n=46)

- Confirmed Translocation seen/postnatal diagnosis, and/or parental karyotype
- No diagnostic testing but likely concordant due to significant family or clinical history
- No follow up reported to laboratory

Figure 2.

Indication for Testing

- Ultrasound findings
- Family history
- Advanced maternal age
- Multiple indications
- None provided

Table 1. Parental translocations discovered due to cfDNA results

<table>
<thead>
<tr>
<th>Case</th>
<th>Indication(s) for testing</th>
<th>cfDNA result</th>
<th>Fetal diagnostic test/result</th>
<th>Parental follow up</th>
<th>History of recurrent pregnancy loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Abnormal ultrasound finding</td>
<td>39.10 Mb gain of 3p, loss 1p</td>
<td>Ameicrosomy array 46,XX,der(2),t(2;3)(p22.2,p22)</td>
<td>Confirmed maternal t(23)</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Advanced maternal age, abnormal ultrasound finding</td>
<td>60.4 Mb gain 4q; 35.15 Mb gain 1qy</td>
<td>Ameicrosomy karyotype 47,XY,+t(18;21)(q13,13)</td>
<td>Confirmed maternal t(18) and paternal t(10,17)</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Advanced maternal age, abnormal serum screening</td>
<td>10.50 Mb loss of 3p, 30.85 Mb gain 1qy</td>
<td>Ameicrosomy karyotype and POC array 46,XX,der(57)(10p15,2p12)</td>
<td>Confirmed maternal t(57,10)</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Abnormal ultrasound finding</td>
<td>18.55 Mb loss 1q, 24.60 Mb loss of 1q</td>
<td>Declined Testing</td>
<td>Confirmed maternal t(11,13)</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Abnormal ultrasound finding</td>
<td>18.75 Mb loss of 3p, inclusion of Chr 12 q51</td>
<td>Ameicrosomy karyotype and FISH</td>
<td>Confirmed maternal t(15,14)</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Advanced maternal age</td>
<td>36.25 Mb gain 8p and 33.5 Mb loss 13q</td>
<td>POC karyotype 46,XX,der(13)(13t13.13)</td>
<td>Confirmed maternal t(13,13)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

For cases submitted with a known history of a translocation, the average gestational age was 13.7 weeks. However, in samples with no known history of a translocation (including samples where it was unknown to the laboratory whether or not there was a history of a translocation), the average gestational age was 14.2 weeks, likely related to the increase in the number of cases reported with ultrasound findings in this group.