Genome-wide cfDNA and chromosome 8 recombination events: a case series

Brittany Dyr, MS; LGCG; Vanessa Nitibhon MC, CGC; Kimberly Fanelli, MS, CGC; Karen Compton, MMSc, CGC; Sophie Crowdes, MS, CGC; Erica Soster, MS, LGCG
Labcorp Women’s Health and Genetics, Laboratory Corporation of America® Holdings, San Diego, CA

1. Introduction
In addition to screening for common trisomies and sex chromosome aneuploidies, genome-wide cell-free DNA (cfDNA) is capable of detecting certain fetal (placental) copy number variants (CNVs). Two defined syndromes involving CNVs as a result of recombination on chromosome 8, inverted duplication-deletion 8p syndrome and recombinant chromosome 8 syndrome, may be detectable by genome-wide cfDNA. This case series reviews one laboratory’s experience detecting chromosome 8 CNVs on genome-wide cfDNA.

2. Methods
Maternal blood samples submitted to one commercial lab for genome-wide cfDNA screening were subjected to DNA extraction, library preparation, and genome-wide massively parallel sequencing. Sequencing data were analyzed using a proprietary algorithm to detect trisomy, select microdeletions, and genome-wide CNVs >7Mb, as previously described. Outcomes including diagnostic testing information were elicited from the clinicians as part of routine, ongoing laboratory protocol for positive cases. Selected cases reported a gain and a loss on chromosome 8, raising the possibility of a complex chromosome 8 rearrangement, and for which diagnostic testing information was available.

3. Results
Four cases (Table 1) were identified for review. At the time of cfDNA screening, average maternal age was 30 years and average gestational age > 25 weeks. All cases reported ultrasound findings at the time of screening. Diagnostic testing confirmed chromosome 8 abnormalities in all cases. Case 1 was submitted for screening at 12 weeks with an indication of increased nuchal translucency. Confirmation of cfDNA findings (Figure 1) was performed by microarray and FISH on amniotic fluid and recombinant chromosome 8 syndrome was confirmed. Subsequent parental testing identified a paternal pericentric inversion on chromosome 8. In the remaining cases (Figure 1), diagnostic testing confirmed chromosome 8 abnormalities suspected to be consistent with inverted dup del (8p) syndrome.

4. Conclusions
While microarray is recommended after the detection of fetal structural anomalies, patients may decline prenatal diagnosis. In these cases, genome-wide cfDNA may be offered to patients interested in screening for CNVs. As described here, larger pathogenic CNVs can be identified by genome-wide cfDNA, which may be suggestive of known syndromes such as inverted dup del (8p) or recombinant chromosome 8 syndrome. Early identification of these complex CNVs can help provide important prenatal information, guide diagnostic testing, and help with future family planning.

<table>
<thead>
<tr>
<th>Case</th>
<th>Maternal age</th>
<th>Maternal gestational age</th>
<th>Fetal finding</th>
<th>Predicted copy number</th>
<th>Predicted cfDNA (Mb)</th>
<th>Predicted cfDNA (Mb)</th>
<th>Diagnostic testing</th>
<th>Extraembryonic fluid</th>
<th>Postnatal blood</th>
<th>Recombinant chromosome 8 syndrome confirmed</th>
<th>Chromosome finding</th>
<th>Chromosome finding</th>
<th>Chromosome finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31y</td>
<td>12 weeks</td>
<td></td>
<td>4.1%</td>
<td>5.8 Mb</td>
<td>5.8 Mb</td>
<td>Microarray on amniotic fluid</td>
<td>Duplication of 8p23.3p23.1 and an inverted 8p23.3p23.2</td>
<td>FISH</td>
<td>No additional analysis available</td>
<td>Consistent with inverted dup del (8p) syndrome</td>
<td>5.8 Mb duplication of 8p23.3p23.1</td>
<td>4.78 Mb duplication of 8p23.3p23.1</td>
</tr>
<tr>
<td>2</td>
<td>31y</td>
<td>16.5 weeks</td>
<td></td>
<td>16.8%</td>
<td>16.6 Mb</td>
<td>16.6 Mb</td>
<td>Microarray and FISH on amniotic fluid</td>
<td>Deletion of 8p22p12 and an 18.27 Mb duplication of 8p23.3p23.1</td>
<td>FISH</td>
<td>No additional analysis available</td>
<td>Consistent with recombinant chromosome 8 syndrome</td>
<td>18.27 Mb duplication of 8p23.3p23.1</td>
<td>17.3 Mb duplication of 8p23.3p23.1</td>
</tr>
<tr>
<td>3</td>
<td>35y</td>
<td>27 weeks</td>
<td></td>
<td>15.5%</td>
<td>8.1 Mb</td>
<td>8.1 Mb</td>
<td>Microarray and FISH on amniotic fluid</td>
<td>Deletion of 8p23.3p23.1 and an 27.5 Mb duplication of 8p23.3p23.1</td>
<td>FISH</td>
<td>No additional analysis available</td>
<td>Consistent with recombinant chromosome 8 syndrome</td>
<td>27.5 Mb duplication of 8p23.3p23.1</td>
<td>24.7 Mb duplication of 8p23.3p23.1</td>
</tr>
<tr>
<td>4</td>
<td>24y</td>
<td>29 weeks</td>
<td></td>
<td>4.1%</td>
<td>5.8 Mb</td>
<td>5.8 Mb</td>
<td>Microarray and FISH on amniotic fluid</td>
<td>Duplication of 8p23.3p23.1 and an 47.65 Mb duplication of 8p23.3p23.1</td>
<td>FISH</td>
<td>No additional analysis available</td>
<td>Consistent with inverted dup del (8p) syndrome</td>
<td>47.65 Mb duplication of 8p23.3p23.1</td>
<td>45.9 Mb duplication of 8p23.3p23.1</td>
</tr>
</tbody>
</table>

Table 1: Detailed case information

Figure 1a. cfDNA sequencing traces for Case 1

Figure 1b. cfDNA sequencing traces for Case 2

Figure 1c. cfDNA sequencing traces for Case 3

Figure 1d. cfDNA sequencing traces for Case 4