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

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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 trisomies, 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 inversion 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.

Tables + Figures

Table 1: Detailed case information

Case	Maternal age	Gestational age at time of cfDNA	Fetal fraction	Predicted deletion on cfDNA (size)	Predicted duplication on cfDNA (size)	Diagnostic testing information as reported to the cfDNA laboratory	Ultrasound findings
1	24y	12 weeks	4.1%	8p23.3p23.2 (5.8 Mb)	8q22.1q24.3 (47.65 Mb)	Microarray and FISH on amniotic fluid: 8.1 Mb deletion of 8p23.3p23.1 and an inverted 47.9 Mb duplication of 8q22.1q24.3 Consistent with recombinant chromosome 8 syndrome and paternal inversion confirmed	Increased nuchal translucency
2	35y	27 weeks	16.5%	8p23.3p21.1 (8.05 Mb)	8p21.1p11.2 (27.5 Mb)	Amniocentesis identified an alteration in chromosome 8 No additional analysis available	Abnormal ultrasound findings not otherwise specified
3	31y	29 weeks	13.1%	8p23.3p23.1 (16.6 Mb)	8p22p12 (17.3 Mb)	Microarray on postnatal blood: 6.69 Mb deletion of 8p23.3p23.1 and an 18.27 Mb duplication of 8p23.1p12 Consistent with inverted dup del (8p) syndrome	Dandy-Walker malformation
4	31y	34 weeks	19.0%	8p23.3p23.1 (6.6 Mb)	8p23.1p22 (1.85 Mb)	Microarray on amniotic fluid: Deletion of 8p23.3p23.1 and duplication of 8p23.1p22 Consistent with inverted dup del (8p) syndrome	Tetrology of Fallot

Figure 1a. cfDNA sequencing traces for Case 1

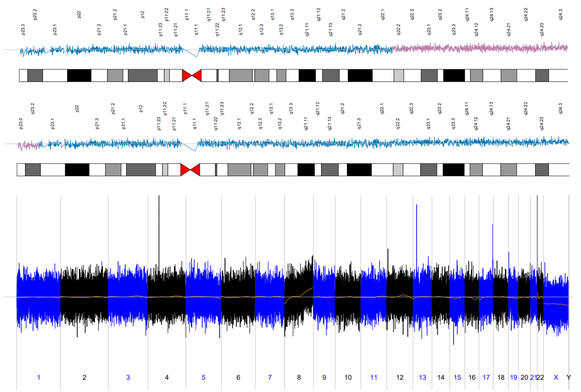


Figure 1b. cfDNA sequencing traces for Case 2

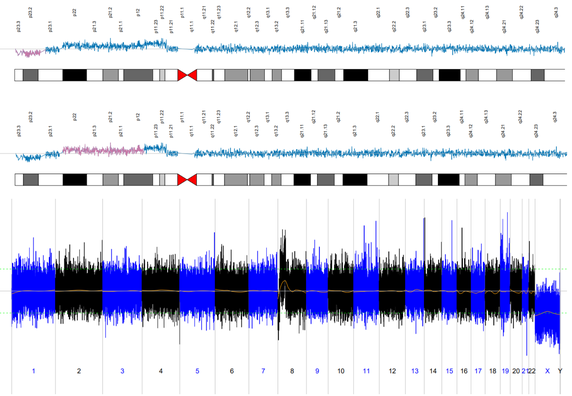


Figure 1c. cfDNA sequencing traces for Case 3

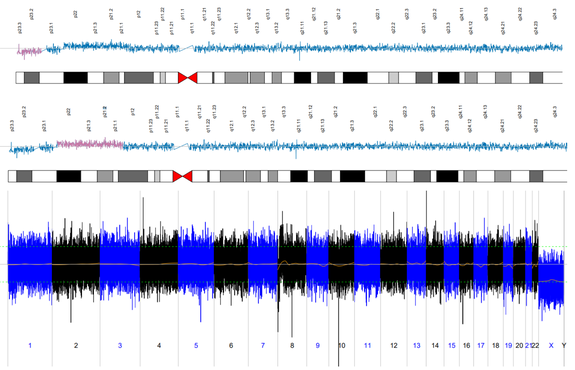
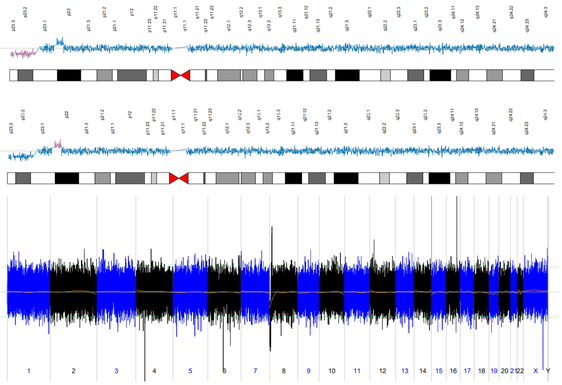


Figure 1d. cfDNA sequencing traces for Case 4



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