P-75

Detection of Emanuel syndrome by genome-wide cell-free DNA screening

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1. Introduction

Emanuel syndrome (ES) is an inherited chromosomal abnormality of a derivative chromosome ¬22. It is characterized by an unbalanced translocation resulting in a pair of duplications, often subsequent to 3:1 segregation of a parental balanced translocation t(11;22). The distinct phenotype of ES includes microcephaly, growth restriction, congenital heart defects, developmental delay, renal anomalies, genital anomalies in males and dysmorphic facial features including micrognathia and cleft palate. Despite many of these findings being detectable with prenatal ultrasound, one study[1] has shown that only 16% of ES cases are detected prenatally by ultrasound. Here we report cases at risk for ES detected by genome-wide cell-free (cf) DNA screening during pregnancy,

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. A retrospective review of data and outcomes for samples that were reported positive for duplications in the regions associated with ES.

3. Results

Suspected ES was identified on cfDNA screening in 10 cases between December 2015 and December 2021. Half of the samples were screened in the first trimester. The most common indication for screening was known parental translocation or history of a previous child with ES. All samples were reported to have a gain of chromosome 11 suggestive of a duplication in the region 11q23, average predicted size 18.45 Mb. Additionally, 9 out of 10 samples included additional comment reporting a gain of chromosome 22 suggestive of a duplication in the region 22q11, average predicted size 3.35 Mb. These findings raise the possibility of an unbalanced translocation in the fetus. For all cases identified with a positive cfDNA screen, diagnostic testing confirmed ES in the fetus or child and/or a parental balanced translocation t(11;22) was confirmed. ES was confirmed in six cases, four via prenatal diagnostic testing and two on postnatal analysis. In all other cases where fetal diagnostic outcome was not available, parental balanced translocation t(11;22) was identified.

4. Conclusions

Genome-wide cfDNA is a valuable tool for prenatal identification of pregnancies at risk for ES, particularly when there is an increased risk for inheritance of an unbalanced translocation. While diagnostic testing is recommended, cfDNA may offer earlier insights.

References

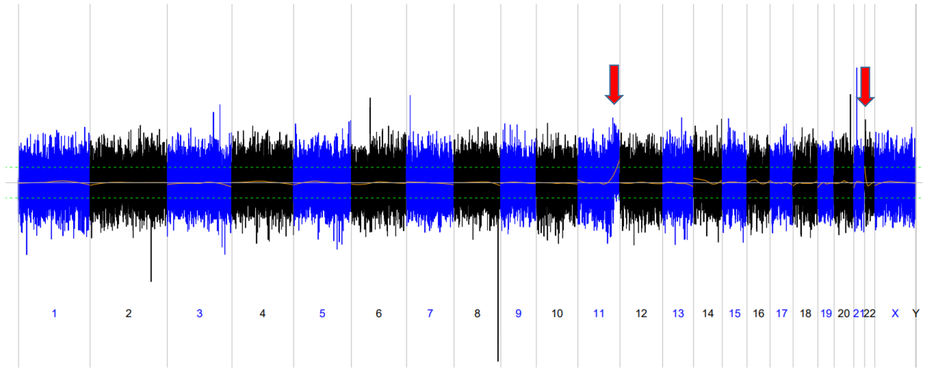
1. Carter MT, St Pierre SA, Zackai EH, Emanuel BS, Boycott KM. Phenotypic delineation of Emanuel syndrome (supernumerary derivative 22 syndrome): Clinical features of 63 individuals. *Am J Med Genet A.* 2009 Aug;149A(8):1712-21. doi: 10.1002/ajmg.a.32957. PMID: 19606488; PMCID: PMC2733334.

Tables + Figures

Table 1. Summary of case details

Case	Indication for screening	Gestational age	cfDNA result: duplications identified (size)		Fetal diagnostic testing	Parental translocation identified?	Fetal ultrasound findings reported
1	Known maternal translocation	12 weeks 1 day	11q23.2-q25 (20.6 Mb)		No follow up information available	Known maternal translocation	
2	Abnormal ultrasound findings	18 weeks 6 days	11q23.3-q25 (18.25 Mb)	22q11.1-q11.21 (3.55 Mb)	Amnio karyotype: 47,XX,der(22)t(11;22)(q23;q11.2)	Confirmed maternal translocation	micrognathia, Dandy Walker malformation, diaphragmatic hernia and two vessel cord
3	Family history of t(11;22); abnormal ultrasound findings	13 weeks 4 days	11q23.3-q25 (18.4 Mb)	22q11.1-q11.21 (3 Mb)	Amnio karyotype: 47,XX+22,der(22)t(11;22)(q23;q11.2)mat	Confirmed maternal translocation	thick nuchal translucency
4	Known maternal translocation and previously affected child	12 weeks 1 day	11q23.3-q25 (18.05 Mb)	22q11.1-q11.21 (3 Mb)	Declined	Known maternal translocation	micrognathia and mild growth restriction
5	Known maternal translocation; advanced maternal age	23 weeks 1 day	11q23.3-q25 (18.3 Mb)	22q11.1-q11.21 (3.65 Mb)	Postnatal karyotype: Each metaphase had an unbalanced 11;22 translocation consistent with Emanuel syndrome.	Known maternal translocation	central nervous system anomalies
6	Advanced maternal age	10 weeks	11q23.3-q25 (18.25 Mb)	22q11.1-q11.21 (3 Mb)	Declined	Confirmed maternal translocation	multiple anomalies
7	Known maternal t(11;22)	12 weeks 2 days	11q23.3-q25 (18.5 Mb)	22q11.1-q11.21 (2.8 Mb)	CVS karyotype: 47, XX,+der(22)t(11;22)(q23.3;q11.2)	Known maternal translocation	
8	Advanced maternal age	19 weeks 6 days	11q23.3-q25 (18.3 Mb)	22q11.1-q11.21 (3.55 Mb)	Amnio microarray: 18.3 Mb duplication at 11q23.3-q25 and 3.42 Mb duplication at 22q11.1-q11.21		diaphragmatic hernia and ventriculomegaly
9	Abnormal ultrasound; family history of previous infant death for unknown cause	22 weeks	11q23.3-q25 (18.1 Mb)	22q11.1-q11.21 (2.85 Mb)	Postnatal Microarray: 18.2 Mb duplication at 11q23.3-q25 and 3.4 Mb duplication at 22q11.1-q11.21		diaphragmatic hernia
10	Known maternal t(11;22); previously affected	9 weeks 2 days	11q23.3-q25 (17.75 Mb)	22q11.1-q11.21 (4.75 Mb)	Declined	Known maternal translocation	micrognathia, growth restriction and possible heart defect

Figure 1. cfDNA sequencing trace (case 9) showing over representation for both chromosomes 11 and 22



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