Evidence of aneuploidy rescue as revealed by circulating cell free DNA screening

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INTRODUCTION
Rescue of an aneuploidy to restore the euploid state in early embryonic development is a well-documented explanation for confined placental mosaicism (CPM). Historically, case reports have focused on the rescue of a complete trisomy or monosomy. Since the advent of prenatal chromosomal microarray, segmental CPM has also been reported, suggestive of the rescue of a partial monosomy or trisomy. Tests using circulating cell-free DNA (cfDNA), likely derived from cells of the placenta, have demonstrated CPM as a cause for discrepancies between cfDNA results and fetal karyotype. Here we report two cases, one complete trisomy and one segmental monosomy, suspected to be rescued to the euploid state in the fetus.

METHODS
Maternal blood samples submitted to Sequenom Laboratories for MaterniT21® Plus testing were subjected to DNA extraction, library preparation, and whole genome massively parallel sequencing as previously described. Sequencing data were analyzed using a novel algorithm to detect trisomies and other subchromosomal events.

CASES

CASE #1
Indication for testing:
Abnormal serum screening – MSAFP 4.02 MoM and 1:42 risk for Down syndrome

MaterniT21 Plus result:
Negative for trisomies 13, 18, and fetal sex consistent with male fetus.
Fetal fraction 11.8%

Follow-up:
Abnormal ultrasound – IUGR, short long bones
Amniocentesis elected with karyotype and aCGH
Karyotype – 46,XY,inv (2)(p11.2q13)
aCGH – maternal uniparental heterodisomy of chromosome 2
Re-evaluation of cfDNA from chromosome 2 – trisomy 2

Interpretation:
This case most likely represents a maternal non-disjunction event at Meiosis I, with subsequent trisomy rescue early in development. Trisomy 2 is evident in cfDNA traces as the “fetal” DNA is likely derived from the trophoblast of the placenta which may be partially rescued or not rescued at all.

CASE #2
Indication for testing:
Advanced Maternal Age – 36 years old at delivery

MaterniT21 Plus result:
Negative for trisomy 13, 18, 21 and fetal sex consistent with female fetus.
Additional finding – under-representation of chromosome 1p36, suggestive of 4.64 Mb deletion
Fetal fraction 9.62%

Follow-up:
Amniocentesis elected with aCGH
aCGH – arr(1-22.X)x2, a region of allelic homozygosity (ROH) spanning 5.4Mb on 1p36.33-p36.31 (734,552-6,143,529) was detected

Interpretation:
Segmental monosomy rescue has been previously described with microarray analysis of direct sampling of chorionic villi, which is largely made up of trophoblasts, the same cell type from which cfDNA is thought to be derived. Segmental monosomy rescue is one possible explanation for the presence of a deletion by cfDNA analysis and disomy of the same region but with allelic homozygosity along the segment predicted to be deleted when aCGH was performed on amniocytes.

DISCUSSION
These cases may represent a complete trisomy rescue as well as a segmental monosomy rescue event detectable by cfDNA. CPM of an aneuploidy can lead to complications in pregnancy, including IUGR and premature delivery. There is not enough data to determine whether a similar effect can be caused by CPM of a segmental rescue. Additionally, aneuploidy rescue and segmental rescue can lead to UPD or partial UPD, in some cases causing an imprinting error in the fetus.

REFERENCES
1. Patel, Anika. Case of 131kb deletion in FMR1 present in chorionic villi, but not amniocytes. Presented at the OB/GYN special interest group forum at the American College of Medical Genetics and Genomics Meeting. March, 2015. Salt Lake City, UT