

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 trisomy¹. Tests using circulating cell-free DNA (ccfDNA), likely derived from cells of the placenta, have demonstrated CPM as a cause for discrepancies between ccfDNA 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^{2,3}.

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 ccfDNA from chromosome 2 – trisomy 2

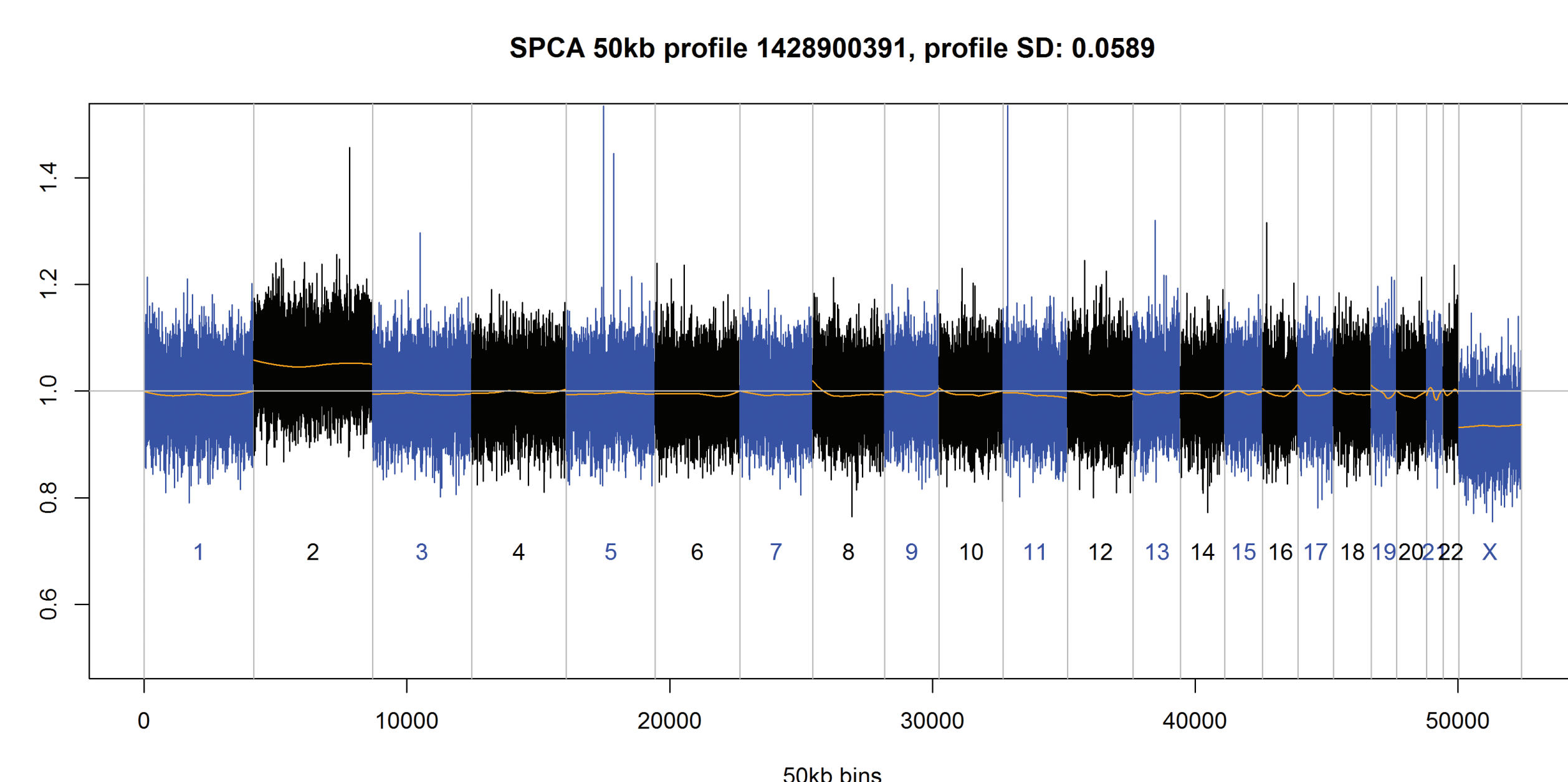


Figure 1a: 50kb traces from ccfDNA sequencing indicating trisomy 2

CASES

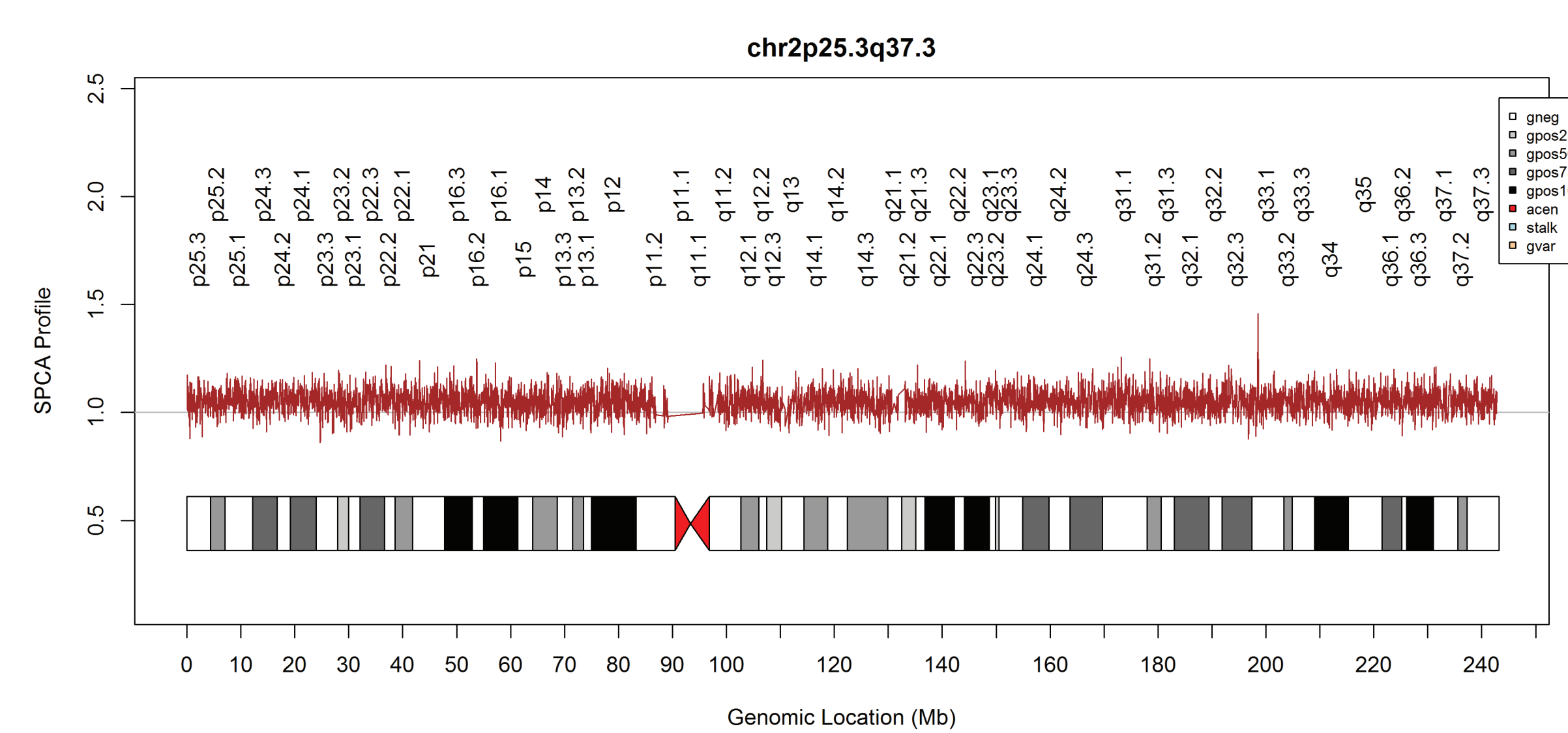


Figure 1b: Ideogram of chromosome 2 from cfDNA sequencing demonstrating trisomy 2

Heterodisomy

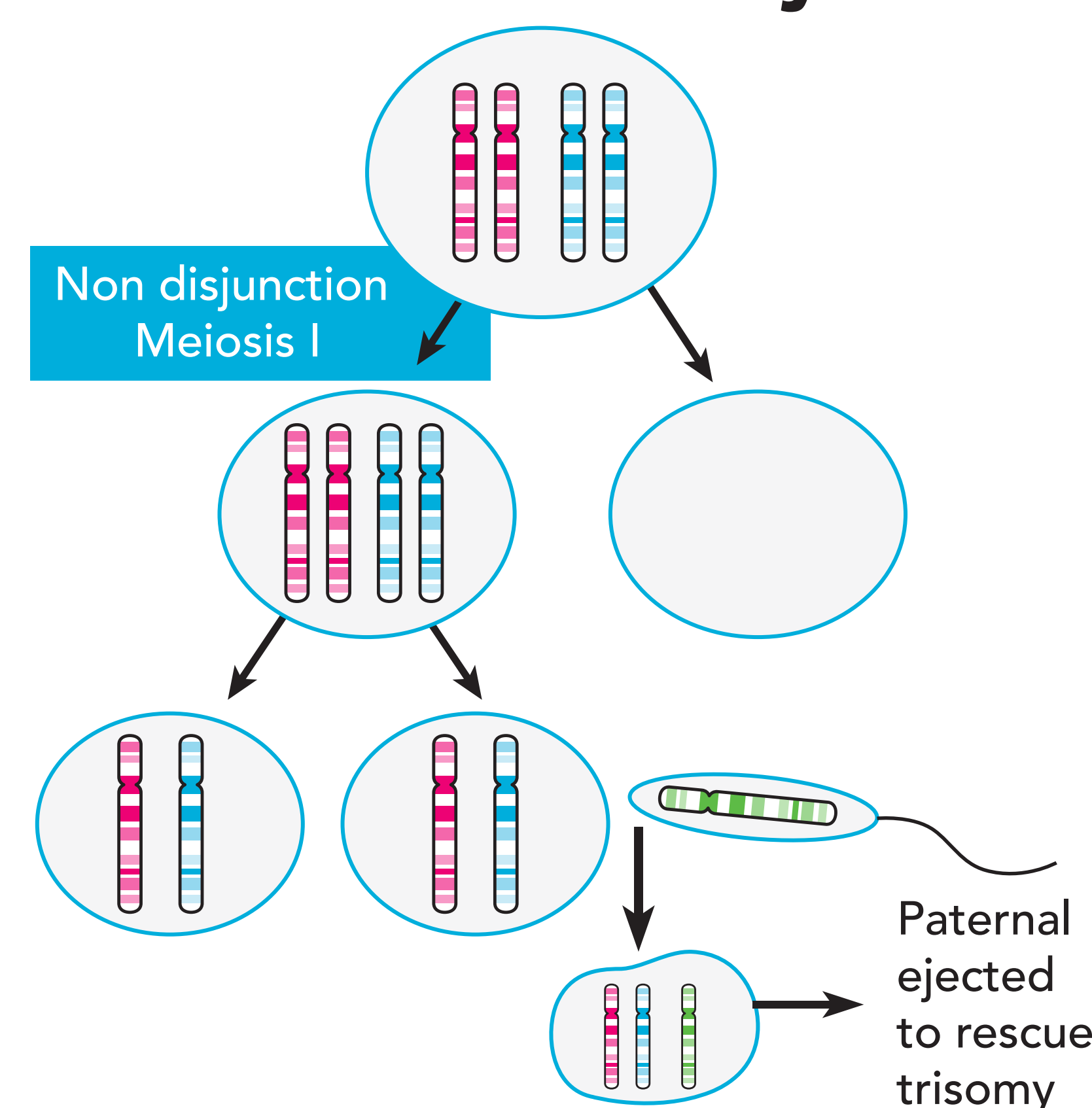


Figure 2: Uniparental heterodisomy caused by non-disjunction event during Meiosis I with subsequent trisomy rescue⁴

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 ccfDNA 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

Patient subsequently had premature rupture of the membranes at 23 weeks GA and eventually delivered a premature female infant with phenotypic features of hemi-facial microsomia, also called Goldenhar syndrome. Placental analysis was desired by the patient, but the placenta was lost to follow-up due to premature delivery of the infant.

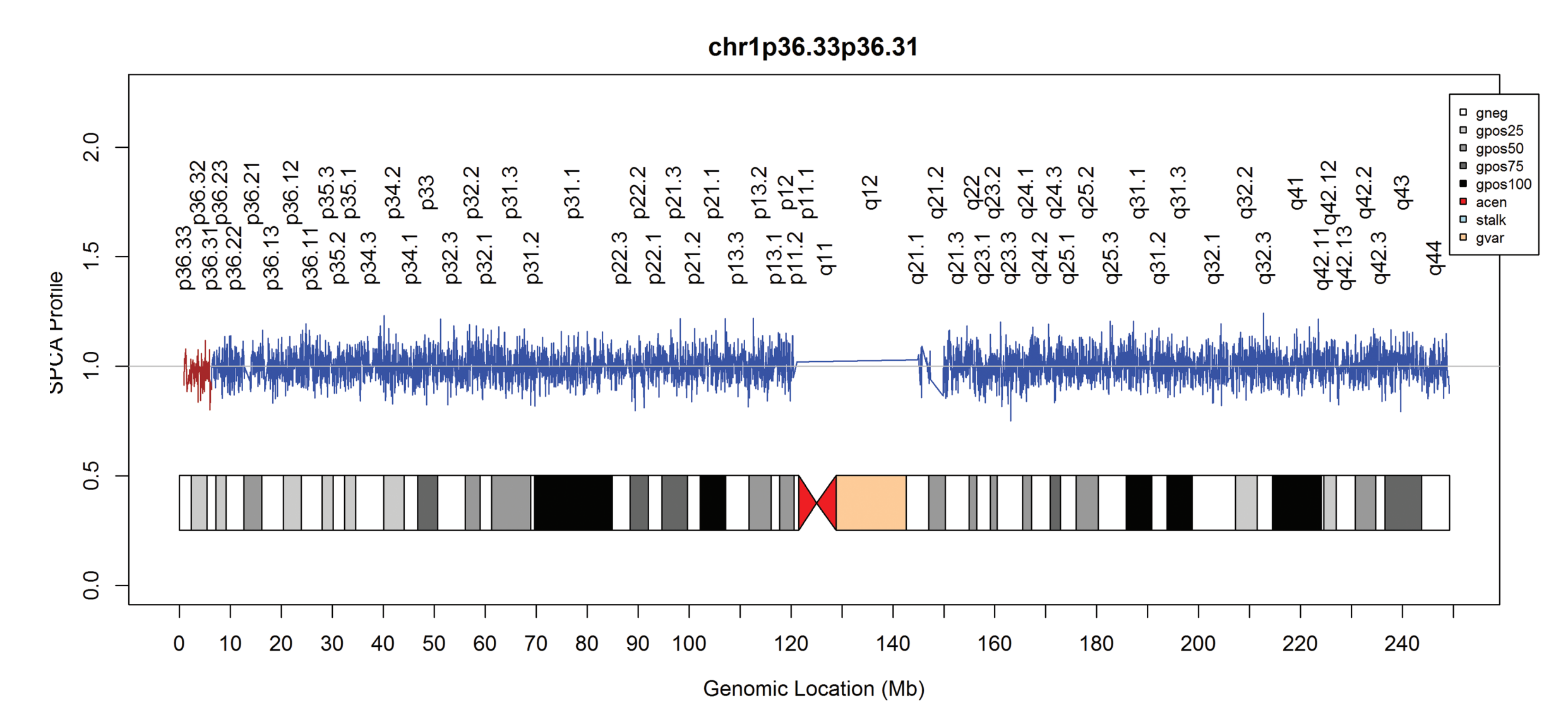


Figure 3: Ideogram of chromosome 1 demonstrating under-representation of 1p36.33-p36.31 by sequencing of ccfDNA

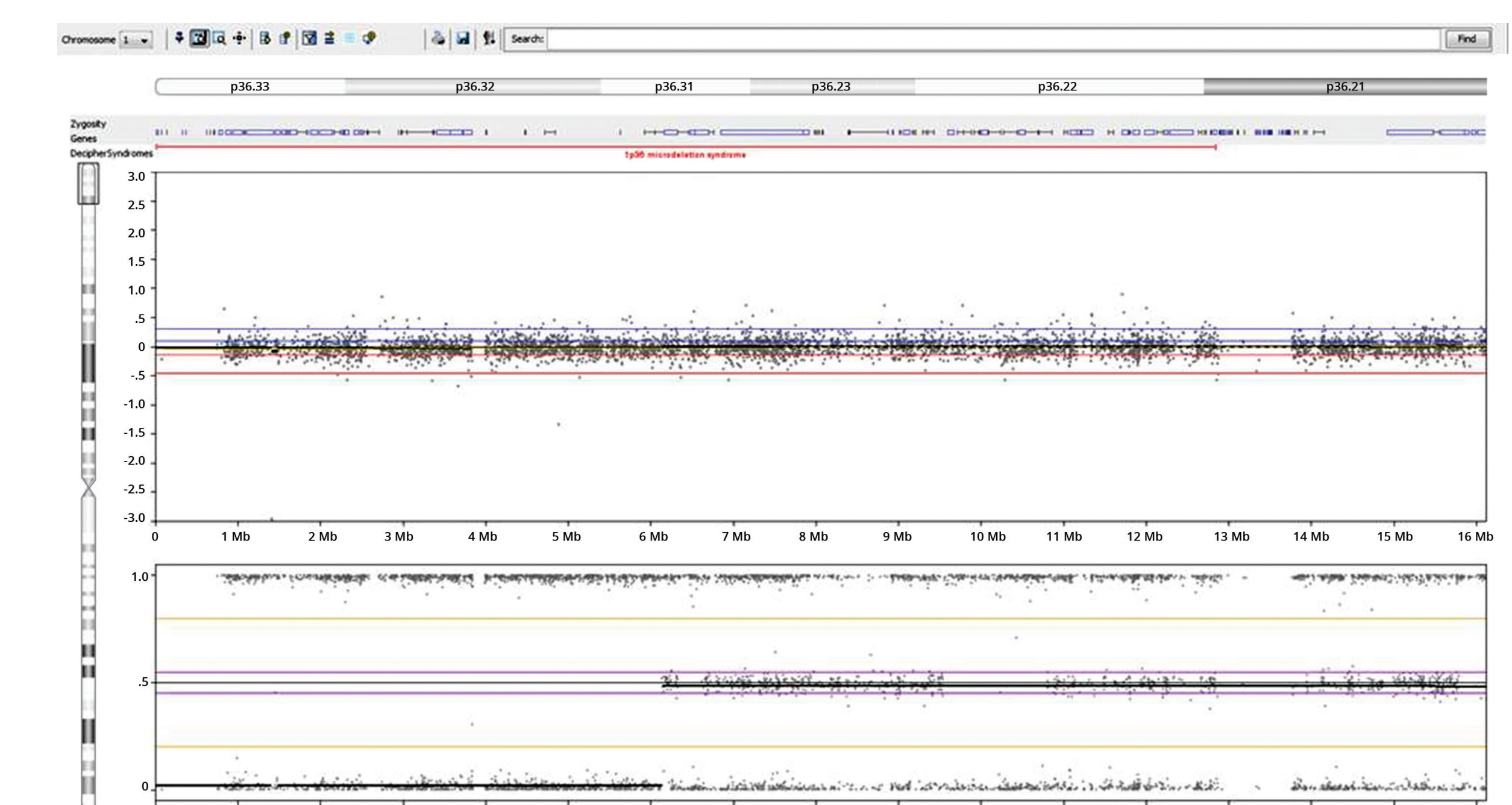


Figure 4: SNP-based aCGH demonstrating disomy of region 1p36 with area of allelic homozygosity

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 ccfDNA is thought to be derived. Segmental monosomy rescue is one possible explanation for the presence of a deletion by ccfDNA 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 ccfDNA. 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

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