Placental studies elucidate discrepancies between NIPT showing a structural chromosome aberration and a differently abnormal fetal karyotype

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The main conclusions are:

1. the use of targeted cytogenetic investigations for confirmatory diagnostic testing of NIPT showing a structural chromosome aberration, should be avoided since another chromosome aberration, even involving another chromosome, may be present in the fetus.

2. the use of karyotyping should be discouraged and replaced by preferably SNP array since a submicroscopic structural aberration or segmental UPD may be present in the fetus even though the NIPT predicts a microscopically visible chromosome aberration.

Objective: Placental cytogenetic studies may reveal the origin of discordant NIPT. We performed placental studies to elucidate discordances between NIPT showing a structural chromosome aberration and the fetus having a different chromosome aberration in three cases.

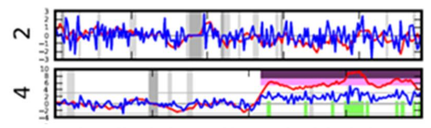
Table 1 Abnormal NIPT showing a structural chromosome aberration, pre-and postnatal follow-up cytogenetic studies and clinical outcome
CTB- cytotrophoblast, MK- mesenchymal core, FTS- first trimester screening, DS- Down syndrome

	Indication for prenatal testing and clinical outcome	NIPT result	Fetal results (summary)	Results of placental studies
1	aFTS DS 1:167 NT 1.9 TOP at 19 6/7 wks Boy, 290 g	dup(4)	del(2)(q37.1) 10 Mb	CTB of 4 biopsies: #4: 100% gain 4q in CTB of biopsies 1 and 2 #2: mos different length del(2) (3, 4 and 56 Mb) MC of 4 biopsies: #4: normal #2: mos different length del(2)(2, 3 and 10 Mb del(2))
2	aFTS DS 1:18, NT 1.9 mm Healthy girl, born at 38+1 wks, 3120g, No congenital malformations. Normal development at 2 yrs	del(13)	Segmental matUPiD 13q31.3q34	CTB of 4 biopsies: mosaic different length del(13) in each biopsy (61.1 Mb, 57.2 Mb, 27.6 Mb, 30 Mb in biopsy 1, 2, 3 and 4 resp) MC of 4 biopsies: ~25Mb ROH on 13q31.3q34
3	aFTS DS 1:63, NT 1.7 mm Male new-born at 38+5 wks, birth weight 3338g, induced labour due to mild preeclampsia. Normal development at the age of 2 yrs	del(15)	mos gain 15q22.31q26.3 and gain 13q33.2q34 (~5% in uncult and 10% in cult cells)	CTB of 4 biopsies: #15: mos 17Mb del(15)(q25.3q26.3)/62.5Mb dup (15)(q11.2q25.3) #13: normal MC of 4 biopsies: #15: mos ~36Mb gain of 15q22.31q26.3 #13: mos ~10Mb gain of 13q33.2q34

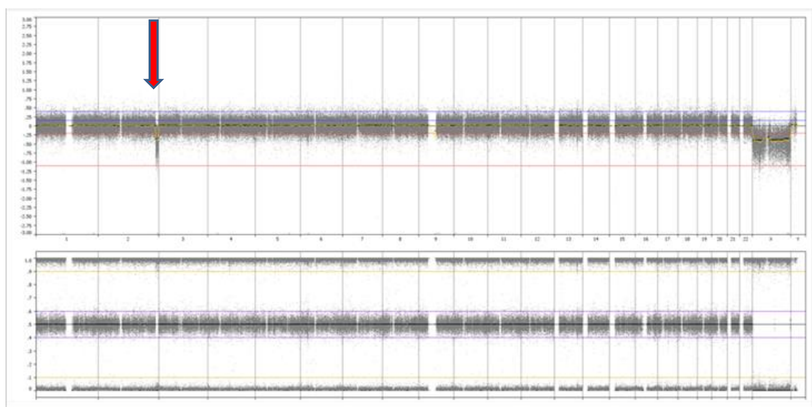
Material and methods: NIPT was performed as part of the Dutch Trident 1 study (Trident=Trial by Dutch laboratories for Evaluation of Non-Invasive Prenatal Testing). The method that was used shortly involved genome-wide shallow massively parallel shotgun sequencing and genome-wide analysis with WISECONDOR, that has a resolution of ~15 Mb at a sequencing depth of about 10-12 million reads per sample. Sex chromosomes were not analysed. Diagnostic testing with genomic SNP microarray (Illumina Infinium_CytoSNP_850K) was performed in cases with NIPT showing a duplication on 4q (case 1), a terminal deletion of 13q (case 2) and a terminal deletion of 15q (case 3). Placental studies involved SNP array analysis of cytotrophoblast and mesenchymal core of chorionic villi of four placental quadrants.

Prenatal results – case 1

1. NIPT: duplication 4q

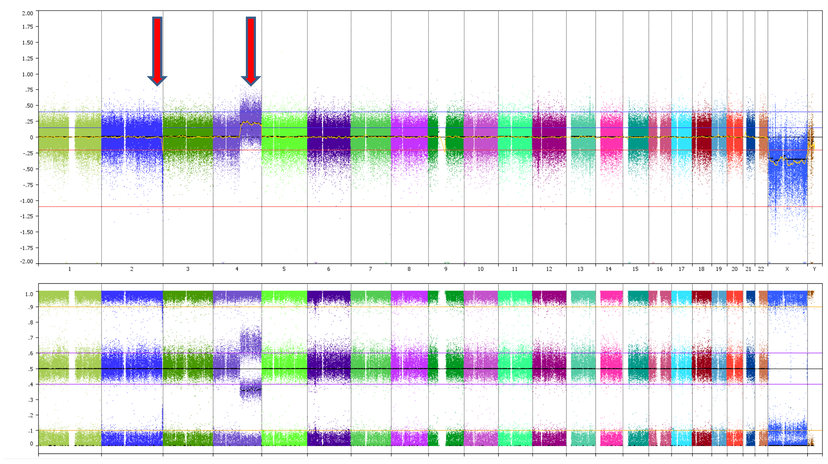


2. SNP array on uncultured amniotic fluid cells: del(2)(q37)



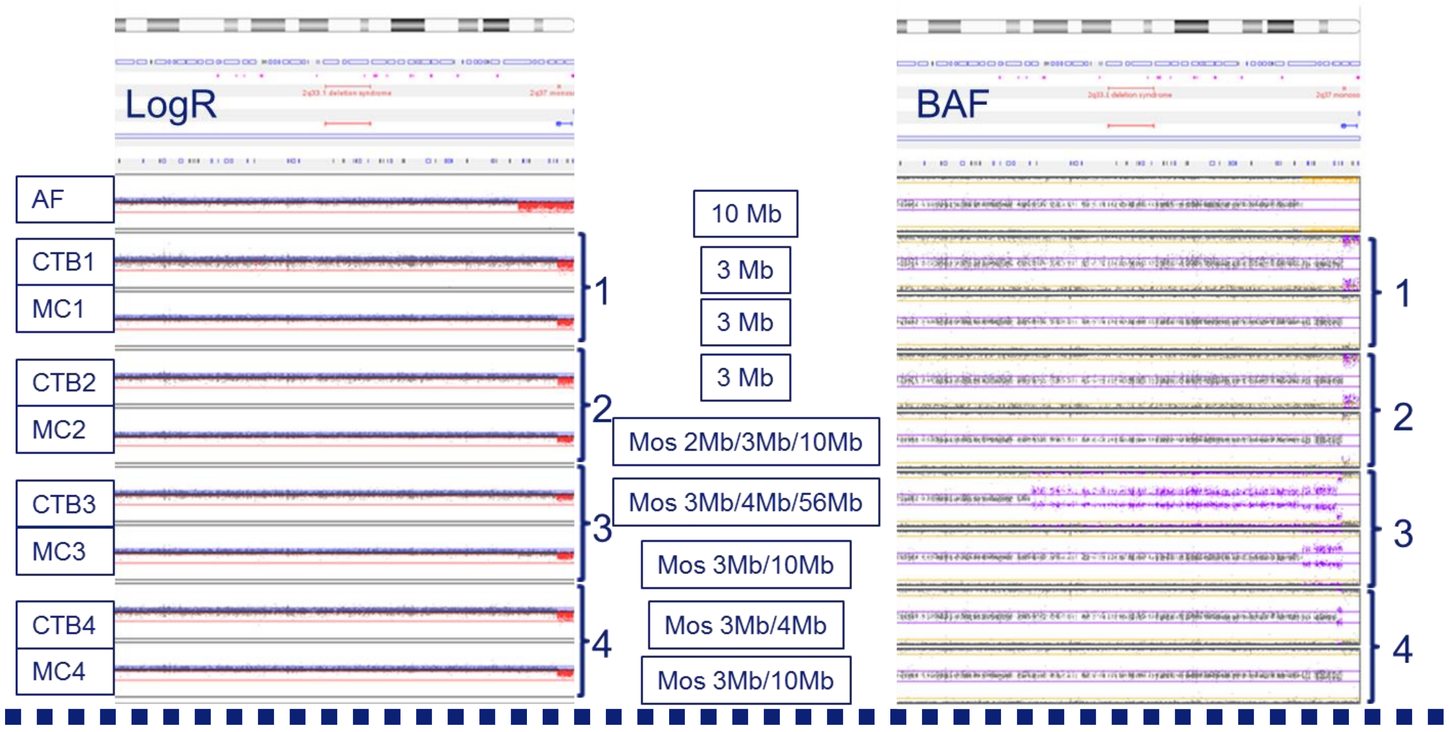
Postnatal confirmatory studies in the placenta – case 1

1. Cytotrophoblast of one placental biopsy, showing a dup(4q) and del(2q)



←MCC

2. del(2) in cytotrophoblast and mesenchymal core of 4 placental biopsies



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