Practical sharing of experience and clinical cases related to NIPT for aneuploidy screening

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Confined placental mosaicism as a risk factor among newborns with fetal growth restriction

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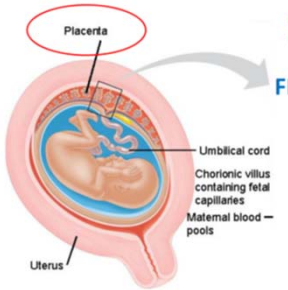
Confined placental mosaicism

1 – 2% CVS
1 – 2% NIPT!



The presence of aneuploid cells in the cytotrophoblast or mesenchymal stroma, during gestation, may interrupt normal placental development and function. These pregnancies therefore show an increased incidence of perinatal complications such as IUGR, intrauterine fetal death (IUFD) and pre-term labour (Henderson et al. 1996). Lestou and Kalousek (1998) subdivided CPM into three types according to the specific abnormal placental cell lineage and this determines clinical outcomes:

- Type 1: abnormal cells confined to the trophoblast cell lineage. More frequently associated with trisomies 3,7,13,18,20,21. Trisomies 8,9,15 are less common and it is not found in others. Clinically reported to result in spontaneous abortion, IUGR, IUFD and perinatal morbidity in 22% of affected pregnancies.
- Type 2: abnormal cells confined to the chorionic stromal cell lineage. Frequently associated with trisomies 2,7,18, while trisomies 5,8,9,10,12,13,21,22 are less common. This is clinically associated with normal outcome and rarely with IUGR or IUFD.
- Type 3: abnormal cells involving both cell lineages. Frequently associated with trisomies 15,16,18; rarely 7,13,20,22. Type 3 is not found with other chromosomes. Clinically IUFD and IUGR are common and most cases of fetal deaths are associated with CPM 16.

Kapaya et al *Obs Case Reports* 2012

PRENATAL DIAGNOSIS, VOL. 17:5: 443–450 (1997)

MATERNAL UNIPARENTAL DISOMY OF CHROMOSOME 2 AND CONFINED PLACENTAL MOSAICISM FOR TRISOMY 2 IN A FETUS WITH INTRAUTERINE GROWTH RESTRICTION, HYPOSPADIAS, AND OLIGOHYDRAMNIOS

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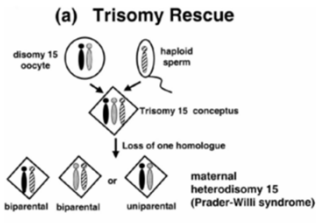

Maternal UPD	Chr 7, 14, 15
Paternal UPD	Chr 6, 11, 14, 15
Less certain	Mat Chr 2, 16 20 & Pat Chr 20

Shaffer et al *Genet in Med* 2001

Rare autosomal trisomies, revealed by maternal plasma DNA sequencing, suggest increased risk of feto-placental disease

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Whole-genome sequencing (WGS) of maternal plasma cell-free DNA (cfDNA) can potentially evaluate all 24 chromosomes to identify abnormalities of the placenta, fetus, or pregnant woman. Current bioinformatics algorithms typically only report on chromosomes 21, 18, 13, X, and Y; sequencing results from other chromosomes may be masked. We hypothesized that by systematically analyzing WGS data from all chromosomes, we could identify rare autosomal trisomies (RATs) to improve understanding of feto-placental biology. We analyzed two independent cohorts from clinical laboratories, both of which used a similar quality control parameter, normalized chromosome denominator quality. The entire data set included 89,817 samples. Samples flagged for analysis and classified as abnormal were 328 of 72,932 (0.45%) and 71 of 16,885 (0.42%) in cohorts 1 and 2, respectively. Clinical outcome data were available for 57 of 71 (80%) of abnormal cases in cohort 2. Visual analysis of WGS data demonstrated RATs, copy number variants, and extensive genome-wide imbalances. Trisomies 7, 15, 16, and 22 were the most frequently observed RATs in both cohorts. Cytogenetic or pregnancy outcome data were available in 52 of 60 (87%) of cases with RATs in cohort 2. Cases with RATs detected were associated with miscarriage, true fetal mosaicism, and confirmed or suspected uniparental disomy. Comparing the trisomic fraction with the fetal fraction allowed estimation of possible mosaicism. Analysis and reporting of aneuploidies in all chromosomes can clarify cases in which cfDNA findings on selected "target" chromosomes (21, 18, and 13) are discordant with the fetal karyotype and may identify pregnancies at risk of miscarriage and other complications.

Pertile et al *Sci Transl Med* 2017

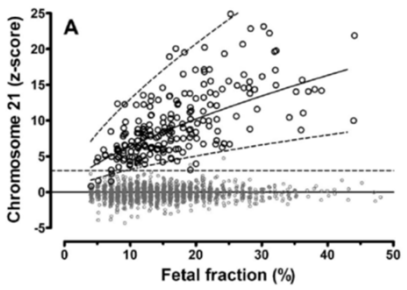
Clinical Chemistry 60:1
251–259 (2014)

Molecular Diagnostics and Genetics

Maternal Mosaicism Is a Significant Contributor to Discordant Sex Chromosomal Aneuploidies Associated with Noninvasive Prenatal Testing

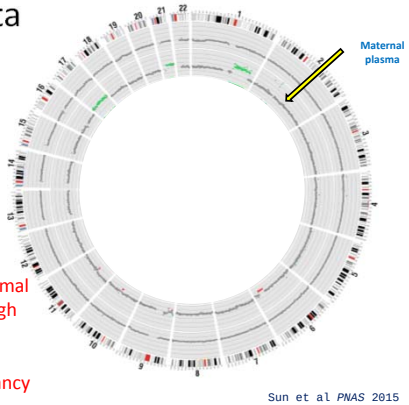
Yanlin Wang,[1,2†] Yan Chen,[2†] Feng Tian,[3] Jianguang Zhang,[3] Zhuo Song,[3] Yi Wu,[2] Xu Han,[2] Wenjing Hu,[2] Duan Ma,[1] David Cram,[1*] and Weiwei Cheng[2*]

RESULTS: Sequencing karyotyping detected chromosome X (ChrX) mosaicism as low as 5%, allowing an accurate assignment of the maternal X karyotype. In a prospective NIPT study, we showed that 16 (8.6%) of 181 positive SCAs were due to an abnormal maternal ChrX karyotype that masked the true contribution of the fetal ChrX DNA fraction.



Palomaki et al *Genet Med* 2011

NIPT data

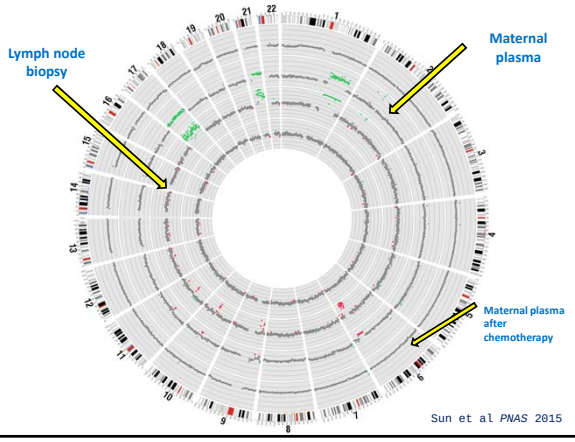


Legend:
Green – chromosomal regions with copy number gain
Red – chromosomal regions with copy number loss

Interpretation:
Multiple chromosomal abnormalities at high concentrations

? Maternal malignancy

Sun et al *PNAS* 2015



Sun et al *PNAS* 2015

Noninvasive Prenatal Testing and Incidental Detection of Occult Maternal Malignancies

Bianchi et al.

JAMA 2015; 314: 162-9

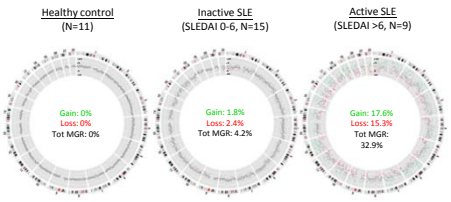
Presymptomatic Identification of Cancers in Pregnant Women During Noninvasive Prenatal Testing

Amant et al.

JAMA Oncol 2015

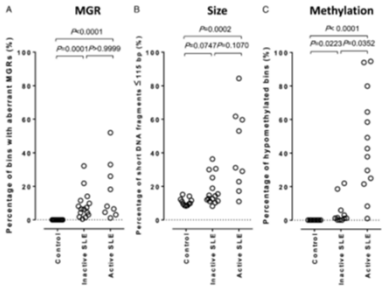
Plasma DNA aberrations in systemic lupus erythematosus revealed by genomic and methylomic sequencing

Rebecca W. Y. Chan[a,b], Peiyong Jiang[a,b], Xianlu Peng[a,b], Lai-Shan Tam[c], Gary J. W. Liao[a,b], Edmund K. M. Li[c], Priscilla C. H. Wong[c], Hao Sun[a,b], K. C. Allen Chan[a,b,d], Rossa W. K. Chiu[a,b], and Y. M. Dennis Lo[a,b,d,1]



MGR: Measurable genomic representation

Chan et al *PNAS* 2014



Chan et al *PNAS* 2014

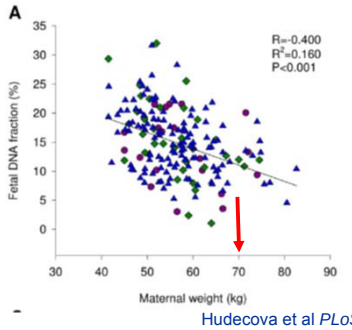
Fetal DNA %

- A minimum requirement

Effect of maternal weight

Reduced fetal fraction

Not solvable with later GA

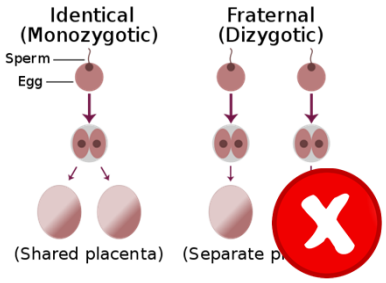


Hudecova et al *PLoS One* 2014

Mosaicism

- Reduce the effective fetal DNA %
- E.g. 10% fetal DNA
- But 1/5th cells affected
- Effective % abnormal DNA is 2%

Vanished Twins



Persistent release of placental DNA