30 METABOLOMIC PROFILING AND THE DEVELOPMENTAL ORIGINS OF DISEASE: A MATERNAL HIGH FAT DIET IS ACCOMPANIED BY ALTERATIONS IN THE FETAL PRIMATE METABOLOME

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OBJECTIVE: Gas chromatography-mass spectrometry (GC-MS) metabolomics is unique from other "omics" in its capacity to efficiently decipher systems biology because of its proximity to phenotype. We established a primate model of *in utero* exposure to a high-fat (HF) maternal diet leading to fetal fatty liver and demonstrated that an altered fetal epigenomic profile accompanies persistent differential reprogrammed gene expression; reversal of the maternal diet partially abrogates these effects. Given these observations, we aimed to characterize the fetal metabolic spectral footprint and identify candidate biomarker(s) associated with the development of obesity.

STUDY DESIGN: Pregnant macaques were fed control (n 22) or HF (n 33) diet for up to 4 years, then reverted from HF to control diet in yr5 (n 7). Serum from neonates (e130) or juvenile (1 yr) offspring generated comprehensive spectral footprints from GC/LC-MS. Multivariate data was analysed with SIMCA-P software (Umetrics) and data were visualized in reduced planar space via principal component analysis with projection onto latent structures with partial least squares-discriminate analysis. Using this reduced data set, significance was derived among candidate metabolites (ANOVA and comparative t-tests).

RESULTS: Of >200 GC-MS identified metabolites, 90 metabolites were chosen for further analysis after meeting QC standards. Observed fetal phenotypic differences were accompanied by an altered spectral footprint of 15 metabolites at a $p<.005$. Despite ongoing obesity, dams resuming a control diet partially reverted their offsprings metabolite profile to a semi-restorative spectrum with a persistent single metabolite (RT_m/z 18.69_217). Analysis of contributing metabolites revealed two of novel characteristic retention time and mass (7.03_103 & 7.07_159 $p<.01$).

CONCLUSION: Collectively, we demonstrate that in utero exposure to a HF diet alters the fetal epigenome to parlay a characteristic metabolic spectral footprint. Application of metabolomics identified putative biomarkers for obesity detectable in neonatal primates.

31 DISCOVERY OF DNA METHYLATION MARKERS FOR PRENATAL ANEUPLOIDY TESTING

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OBJECTIVE: Testing circulating cell free fetal RNA in maternal plasma is currently the most promising approach for noninvasive trisomy 21 detection. The method involves measuring the ratios of heterozygous SNPs on fetal RNA. In this study, 10samples were used to assess an alternative technical strategy using epigenetic (methylation) markers to distinguish and enrich fetal DNA for aneuploidy testing.

STUDY DESIGN: A unique approach for genome wide discovery of epigenetic markers was used to fractionate genomic DNA based on the methylation status. Using 10 paired samples, material from placenta and maternal buffy coat were tested for methylation. Highly methylated DNA fractions were then used in comparative genome hybridization studies to identify differentially methylated loci. Validation of our findings was performed using SEQUENOM™EpiTYPER technology. Results were then compared to a previously a published report that used standard bisulfite sequencing for discovery of T21 methylation markers.

RESULTS: We have identified 25 differentially methylated regions (DMRs) of DNA that distinguish fetal and maternal genes. 14/25 of these genes had previously been reported using a standard bisulfite procedure. 13/14 of the DMRs were concordant with the previously published results showing that these genes exhibit DMRs. Although 11/13 genes were in concordance with the previously published data, 2/ 13 genes exposed sequencing errors reported in the previous publication. In addition to the 13 genes identified, 9 novel hypermethylated and 5 hypomethylated fetal gene targets were identified. The results from genome wide scanning were confirmed by mass spectrometry analysis.

CONCLUSION: We have developed a new method for the rapid discovery of epigenetic markers presenting a viable approach to NIPD testing for fetal aneuploidy.

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32 CYTOKINE GENE SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) AND LENGTH OF GESTATION

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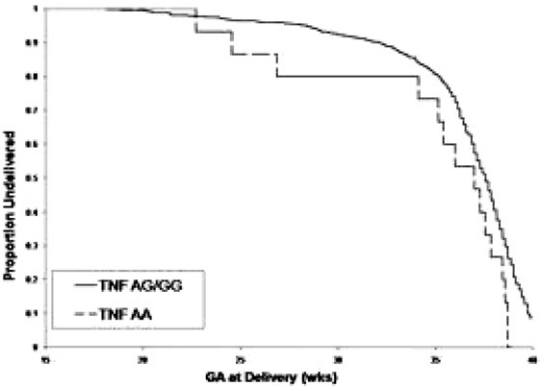
OBJECTIVE: Allelic variants in cytokine genes may modify length of gestation by altering the inflammatory response to environmental stimulants. The objective of this study was to determine if length of gestation varied by genotype for the pro-inflammatory cytokine gene SNPs; tumor necrosis factor (TNF)-α-308, interleukin 1(IL-1)-β+3954, and interleukin-6 (IL-6)-174.

STUDY DESIGN: DNA was extracted from whole blood from 834 women with singleton pregnancies enrolled in a randomized trial of omega-3 supplementation for the prevention of recurrent preterm birth. Genotyping was performed by polymerase chain reaction. For each SNP, gestational age (GA) at delivery censored at 40 weeks was compared between women homozygous for the variant genotype and those with the usual homozygous or heterozygous genotypes using the log-rank test; Kaplan Meier survival curves were generated.

RESULTS: There was a significant difference between the Kaplan Meier curves (Figure 1) such that the variant A-A genotype of TNF-α-308 had shorter duration of pregnancy than AG/GG ($p=0.03$). The curves were not different between genotypes for the other 2 SNPs; IL-1β +3954, $p=0.47$; IL-6-174, $p=0.15$.



CONCLUSION: Allelic variants in TNFα-308 but not IL-1β+3954 or IL-6-174 are associated with shorter length of gestation.

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33 PRESCHOOL NEURODEVELOPMENTAL OUTCOME OF CHILDREN FOLLOWING FETAL MYELOMENINGOCELE CLOSURE

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OBJECTIVE: To investigate the preschool neurodevelopmental outcomes of children following fetal myelomeningocele (fMMC) surgery.

STUDY DESIGN: Prior to the NIHCD-MOMS trial, 54 children underwent fMMC closure at our institution. Thirty (56%) returned at 5 years of age for standardized examination using the Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III) and the Beery-Buktencia Developmental Test of Visual-Motor Inte-gration-IV (VMI-IV), both with an expected mean of 100+15. Scores were grouped as high average, aver-age, mildly delayed and severely delayed by standard deviation intervals (>116, 115-85, 71-84, <70).

RESULTS: Overall shunt rate was 47% (n=14). While mean WPPSI-III-Verbal-IQ (100.8+19 [50-131]) for the entire fMMC cohort was not different from population norms, mean WPPSI-III-Performance-IQ (93.1+15.1 [50-114]) and mean VMI-IV (88.3+19 [50-120]) were lower than general population norms. The majority of fMMC scored within high-average and average range at their WPPSI-III assessment (Table). Mean WPPSI-III-Verbal-IQ and mean VMI-IV of non-shunted fMMC children were significantly higher than shunted fMMC patients ($P=0.04$ and $P=0.02$). Mean WPPSI-III-Performance-IQ tended to be higher in non-shunted fMMC children ($P=0.05$).

CONCLUSION: The majority of fMMC children in this highly selective population have average preschool neuro-developmental scores. Values suggest mainstream schooling with some expectations for additional sup-port. Scores may be influenced by family environmental factors necessitating comparison to siblings if pos-sible. Children who did not require shunt-placement for progressive ventriculomegaly were more likely to have better scores.

Overall percentage of fMMC children with high average, average, mildly delayed and severely delayed IQ.

	High-average	Average	Mild delayed	Severely delayed
WPPSI-III-Verbal-IQ	16%	77%	0%	7%
WPPSI-III-Performance-IQ	0%	90%	0%	10%
VMI-IV	10%	50%	20%	20%

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