Symposium Title: Environmental Risk Factors Associated with Chromosome 21 Nondisjunction

Chair: Jessica Ezzell Hunter

Discussant: Deborah Fidler

Overview: Down syndrome is an intellectual and developmental disability syndrome with a prevalence of approximately 1 in 700 live births in the US. (Parker, et al. 2010) Down syndrome is due, in most cases, to the presence of an extra copy of chromosome 21 (trisomy 21). Most cases of trisomy 21 are maternal in origin, typically due to nondisjunction errors during meiosis I that occurs during fetal development or meiosis II that occurs later in life. The most characterized risk factors for maternal chromosome 21 nondisjunction are advanced maternal age at conception (Allen et al., 2009, Yoon et al. 2000) and recombination errors (Oliver et al., 2008; Oliver, et al. 2012). Environmental risk factors and their association with chromosome 21 nondisjunction have also been reported, though these risk factors are less well understood. (Sherman, et al., 2013; Coppede 2016) Additional studies are needed regarding environmental exposures and their role as independent risk factors, contributors to the effects of maternal age and recombination, or both. This symposium will explore recent studies focused on environmental risk factors for nondisjunction errors. The first presentation uses occupational information among mothers with and without a child with DS to investigate the role that occupational exposure prior to conception may have on nondisjunction risk. The second presentation compared metabolomic profiles of amniotic fluid and maternal serum from pregnancies with and without trisomy 21 to identify perturbed metabolic pathways associated with both presence and absence of trisomy 21 and variable outcomes associated with trisomy 21. Finally, the third presentation explores the association between maternal folic acid supplementation and congenital heart defects in infants with Down syndrome, and how this association may be moderated by genetic variation in genes involved in the folate pathway. These presentations highlight recent studies using innovative approaches to elucidate the molecular etiology of trisomy 21 risk and outcomes.

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Paper Title: The Association between Maternal Occupation and Down Syndrome: A Report from the National Down Syndrome Project

Authors: Colleen Keen¹, Jessica Ezzell Hunter², Emily Graves Allen³, Carissa Rocheleau⁴, Martha Waters⁵, Stephanie L. Sherman⁶

Introduction: Previous reports have shown an association between low maternal socioeconomic status (SES), particularly low household income, and maternal meiosis II chromosome 21 nondisjunction errors (Hunter et al., 2013; Torfs and Christianson, 2003). Recently, there has been an interest in accumulation of toxic elements from the environment as a potential risk factor for maternal meiotic errors. Maternal occupation could provide an avenue in which exposure to environmental toxins, as well as psychosocial stress, may be measured.

Methods: Occupation information was assessed from mothers of 714 Down syndrome (DS) cases (532 MI cases, 182 MII cases) and 973 controls who identified as having employment for at least a period of 6 months or longer at 3 months prior to conception. Using data collected on job title, industry, and general duties, women were assigned standard occupation classifications (SOCs) using NIOSH’s Industry and Occupation Computerized Coding System (NIOCCS). Women who did not indicate having a job were grouped together as “unemployed”. Multivariate logistic regressions were completed on each stratified occupation group, including the unemployed, to examine four outcomes: (1) case vs. control, (2) control vs. MI case, (3) control vs. MII case, (4) MI vs. MII case. All models were adjusted for maternal age, parity, income, and smoking during pregnancy.

Results: Women who worked in the life, physical and social sciences had an increased risk of having an infant with DS (OR = 4.6; 95% CI: 1.4, 14.5), with a specific risk for cases due to MI errors (OR = 5.7; 95% CI: 1.8, 18.2). Women employed in food preparation and serving related occupations had an increased likelihood of having a child with DS also specific to MI errors (OR = 1.9; 95% CI: 1.1, 3.3). Women in production occupations were times more likely to have a child with DS specific to MII errors (OR=3.2; 95% CI: 1.6, 6.6). Low income was a significant predictor among all occupation groups for MII errors and among the food preparation and serving related occupations for MI errors.

Discussion: There is a paucity of information on the etiology and risk factors of maternal meiotic chromosome 21 nondisjunction. Understanding the role maternal occupation plays in accumulated exposure to environmental toxins would contribute to this gap of research. The kinds of exposures that women in the occupational categories associated with meiotic errors are likely vastly different. It would be of significant interest to gain some specificity on the compounds of exposure that have biologic plausibility for mitigating meiotic processes by conducting further research. Polyaromatic hydrocarbons, solvents, and cleaners could be examined by means of an exposure analysis to determine if there is an association.

References/Citations:

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Paper Title: Metabolomic Patterns in Second-Trimester Amniotic Fluid and Maternal Serum Associated with Fetal Trisomy 21

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Introduction: Trisomy 21 is associated with a vast array of medical conditions and birth defects including cognitive impairment and congenital heart defects, yet the biological mechanisms driving the variable presentation of associated phenotypes remain largely unknown. Metabolomic analysis of a large set of paired second-trimester maternal serum and amniotic fluid samples was performed with the objective to 1) further elucidate the fetal metabolic fingerprint associated with trisomy 21 at mid-pregnancy and 2) investigate whether metabolic pathways dysregulated in trisomy 21 fetuses offer potential mechanisms of associated disorders.

Methods: We used untargeted high-resolution metabolomic analysis based on a dual liquid chromatography setup. Data were obtained from 39 pairs of maternal serum and amniotic fluid samples from trisomy 21 pregnancies and from 80 karyotypically normal pregnancy control sample pairs. Discriminatory features were identified in both biofluids using partial least squares discriminant analysis and variable importance in projection scores after adjusting for significant covariates. These features were then used as input for metabolic pathway enrichment analysis using the program Mummichog. Feature selection based on results from the amniotic fluid samples and subsequent pathway analysis showed a complex and extensive set of perturbations associated with trisomy 21.

Results: Results indicated dysregulation of multiple pathways. The top ranked among these (p<0.001) were related to steroid metabolism, lipid metabolism, nucleotide metabolism, and amino acid metabolism. Parallel analyses are currently being conducted on the maternal serum samples to detect possible environmental exposures associated with trisomy 21 pregnancies.

Discussion: Overall, results revealed a broad array of metabolic perturbations in second-trimester trisomy 21 amniotic fluid. These offer novel insight into possible fetal origins of the cognitive impairment, age-related neurodegeneration, and associated birth defects. This untargeted analytical platform will lay a foundation for follow-up targeted studies to confirm metabolic associations of interest and their role in phenotypic outcome pathogenesis.

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Paper Title: Maternal Folic Acid Supplementation and Congenital Heart Defects in Down Syndrome

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Introduction: Maternal folic acid supplementation may be associated with a decreased risk for some congenital heart defects. Individuals with Down syndrome have an increased risk for congenital heart defects and preliminary epidemiologic evidence suggests that maternal folic acid supplementation around the time of heart development may reduce that risk. As well, genetic variation in the folate pathway in the mother or the infant with Down syndrome may interact with the effect of folic acid supplementation. We investigated this potential gene x environment interaction.

Methods: Mothers of a child with Down syndrome (proband) participating in the National Down Syndrome Project and Emory Down Syndrome Study reported periconceptual exposures, including use of prenatal vitamin and supplements containing folic acid. Genotypes of common SNPs in four genes in the folate pathway (MTR, MTHFR, MTRR and SLC19A1/RFC1) were obtained on mothers and the probands. Logistic regression was used on this data to assess the relationship between maternal folic acid exposure and its interaction with folate genotypes and specific congenital heart defects while controlling for maternal race/ethnicity, proband sex, maternal use of alcohol and cigarettes, gestational diabetes, and maternal age at birth of proband.

Results: Folic acid supplementation was less frequent among probands with complete atrioventricular septal defects (AVSD=425; OR = 0.68; p = 0.02), atrial septal defects (ASD=142; OR = 0.64; p = 0.04) and compared to probands with no heart defect (controls=816). There was no statistically significant association with folic acid and partial atrioventricular septal defects (pAVSD=95; OR = 0.89; p = 0.37) or ventricular septal defects (VSD=169; OR = 0.69; p = 0.07), although ORs were in the similarly reduced. We obtained genotype results for 6 SNPs with the 4 genes in the folate pathway on a subset on children with AVSD (n=173) and controls (n=186). We found a significant interaction with rs2330183 in the SLC19A1/RFC1 maternal gene and her use of folic acid (interaction term, p=0.007) and the risk for AVSD. No SNP genotypes in the proband significantly associated the risk of AVSD.

Discussion: Our findings suggest an association of periconceptual maternal folic acid use and the risk for certain congenital heart defects in infants with Down syndrome. We also have preliminary evidence of an interaction between SLC19A1/RFC1 genetic variation and folic acid use on risk for AVSD. Additional genetic studies will be conducted and presented.

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