Name: Danielle Sambo
Email: danielle.sambo@nih.gov
PI Name: David Goldman
PI email: davidgoldman@mail.nih.gov

Differential effects of prenatal alcohol exposure on brain growth in a mouse model for fetal alcohol spectrum disorder

Danielle Sambo, Ethan Kinstler, David Goldman

Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism

Prenatal alcohol exposure (PAE) results several deleterious effects in the offspring, collectively described as Fetal Alcohol Spectrum Disorder (FASD), including developmental delay, cognitive impairments, and behavioral issues. A number of factors contribute to the susceptibility and severity of FASD, especially the dose, timing, and duration of PAE. Additionally, maternal factors such as age and nutrition as well as genetic influences are known to impact FASD. Current estimates suggest that only 10-15% of children with PAE develop FASD, thus understanding the mechanisms which drive differential susceptibility to FASD is important in understanding its etiology. In this study, we examined the differential effects of PAE on mouse brain development. We measured brain weight in C57BL/6J embryonic day 14 (E14) embryos exposed to saline or 2.9 g/kg alcohol from E7 to E13. Cortices were then isolated and processed for RNA sequencing (RNAseq) to determine the effects of PAE on gene expression in relation to brain weight. We found an average 11.3% decrease in brain weight in alcohol treated embryos, with considerable variation in weights. Alcohol treated brains were characterized as highly affected (weights less than 1.5 standard deviation (SD) of the saline mean) or unaffected (weight within 0.5 SD of the saline mean). We found that across 12 different litters, 24.7% of alcohol treated embryos were highly affected, and 31.5% were unaffected, suggesting that even within an inbred strain of mice, embryos subject to the same PAE are differentially affected by alcohol. RNAseq in saline, alcohol affected, and alcohol unaffected embryos revealed significantly more differentially expressed genes (DEGs) when comparing highly affected versus saline compared to unaffected versus saline. These results suggest that both affected and unaffected embryos had significant changes in gene expression, with greater transcriptomic changes in the affected embryos. Developmental genes and pathways altered by PAE in the affected versus unaffected embryos suggest specific changes related to brain growth and implicate mechanisms for PAE-induced microcephaly.