Pre-conception Maternal and Paternal Binge Alcohol Exposure Lead to Distinct DNA Methylation Patterns in Alcohol-Naive Male Offspring

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Binge alcohol consumption among adolescents is a major health concern in the United States, with 21% of teenagers reporting binge-pattern drinking behavior in the last 30 days. Binge drinking is defined as raising the blood alcohol concentration above 0.08% within 2 hours. This pattern of alcohol abuse is associated with an increased risk for anxiety and mood disorders in adulthood. Our lab has used a rodent model to demonstrate that pre-conception binge alcohol abuse during adolescence impacts gene expression profiles in the hypothalamus of alcohol-naïve offspring, a region of the brain involved in stress regulation. However, the mechanism for the transmission of this phenotype to offspring remains unknown. DNA methylation is a stable and heritable epigenetic mark that can be influenced by environmental factors and, therefore, presents a strong putative mechanism. Aberrant DNA methylation is implicated in several cognitive disorders that are also associated with alcohol use such as schizophrenia, depression, and addiction. We employed Enhanced Reduced Representation Bisulfite Sequencing (ERRBS) as an unbiased approach to test the hypothesis that parental exposure to binge-pattern alcohol abuse during adolescence alters DNA methylation in the hypothalamus of alcohol-naïve offspring. Wistar rats were administered a repeated binge-EtOH exposure paradigm where they received 3g/kg of 20% (v/v) EtOH via oral gavage once daily for 3 days, then 2 days vehicle and another 3 days EtOH at both early and late puberty (PND37, 67). Animals were paired for mating 24h after the last EtOH dose, with pairs consisting of all combinations of EtOH- and vehicle-treated males and females. The hypothalamus was extracted from male pups at PND7 and genomic DNA was isolated. We found that male offspring of alcohol-exposed parents exhibited differential DNA methylation patterns and that these patterns varied between maternal and paternal exposure. Differentially methylated cytosines (DMCs) were distinct between offspring of maternal EtOH exposure, paternal EtOH exposure, and dual parent EtOH exposure. There were only nine differentially methylated genes common to all treatment groups, which may represent binge-alcohol sensitive regions of the genome. Genes associated with DMCs also displayed alterations in expression, but methylation was not the only predictor of expression levels. Overall, we have shown discrete, yet wide-spread differential DNA methylation in the hypothalamus of alcohol-naïve offspring following parental adolescent binge alcohol abuse. Our study identifies intergenerational transmission of adolescent binge alcohol abuse and suggests phenotypic differences in alcohol-naïve offspring.