Name: Tianzhou Ma Email: tma0929@umd.edu

Integration of Multiple QTL Data to Reveal the Causal Relationship Between DNA Methylation and Nicotine Addiction

Zhenyao Ye, Rong Pan, Shuo Chen and Tianzhou Ma

University of Maryland College Park, University of Maryland School of Medicine

Background/Significance:
Nicotine exposure in tobacco smoking leads to DNA methylation changes critical for addiction. On the other hand, the methylation changes can reinforce addiction behaviors and increase susceptibility to dependence. Understanding how DNA methylation and smoking interact with each other will help develop predictive biomarkers and therapeutic and preventative strategies targeting smoking cessation.

Hypothesis/Methods:
In this study, we integrated brain expression and methylation Quantitative Trait Locus (eQTL and mQTL) data from BrainMeta with genome-wide association studies (GWAS) data on smoking. We hypothesized that smoking can causally lead to alterations in DNA methylation while pre-existing methylation patterns might also predispose individuals to be more addicted to smoking. We used cigarettes per day (CPD) as an indicator of nicotine dependence and focused the analysis on genomic regions most associated with CPD. Following a gene-centric approach, we first performed colocalization analysis between GWAS and eQTL as well as between eQTL and mQTL to identify potentially pleiotropic variants of CPD, CpG sites where DNA methylation occur and targeted genes. We then ran bidirectional MR-IVW method and other summary-level MR methods to identify the CpG sites being affected by smoking and those that reinforce nicotine addiction.

Results and Discussion:
Using UK Biobank data, we identified 22 critical CpG sites being targeted by CPD but no CpG sites that potentially impact CPD. We also validated the results using the GSCAN cohort. Findings from our study highlighted potential DNA methylation markers of nicotine addiction and helped understand potential epigenetic mechanism of nicotine addiction useful for preventative strategy of smoking cessation.