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Integration of DNA methylation and RNA sequencing elucidates differential gene regulation associated with alcohol use disorder in the human brain

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Alcohol use disorder (AUD) has many genomic loci contributing to risk, however our understanding of the neurobiological regulation of AUD-related genes is limited. Here, we integrate findings from epigenome- and transcriptome-wide association studies of AUD in the dorsolateral prefrontal cortex (DLPFC) and nucleus accumbens (NAc) from 122 decedents (61 cases and controls) of European ancestry. EPIC methylation data were analyzed using robust multivariable linear regression, with *bacon*-adjusted results to minimize inflation. At false discovery rate (FDR) <0.05, we identified 128 differentially methylated CpGs (DMCs) associated with AUD status across brain regions. Bulk RNAseq data from the same decedents yielded 20,666 and 20,324 genes from DLPFC and NAc for analysis, respectively. AUD-associated differential expression was tested using covariate-adjusted negative binomial regression models. At FDR<0.05, 124 and 105 differentially expressed genes (DEGs) were identified for DLPFC and NAc, respectively. DMCs and DEGs were considered to be intersecting if within 250 kb and on the same genomic strand. We identified seven methylation-expression intersections, with one pair shared across DLPFC and NAc (cg19310307-*HMGB2*). These include: potential transcription factor *ZNF124*; transferrin receptor *TFRC*, responsible for maintaining brain iron homeostasis; two members of the *HMG* chromatin remodeling family (*HMGB2* and *HMGN1*); *OGA*, implicated in synaptic plasticity; *UBE2Q2*, associated with urate concentration; and *LARGE1*, a glycosyltransferase important for neurodevelopment. We additionally identified enrichment of JASPAR transcription factor binding sites overlapping with significant DMCs and DEGs. Overall, these results suggest complex gene regulatory mechanisms associated with AUD that more often differ than intersect across omics and brain regions.