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Meta-analyses of gene expression differences associated with alcohol use disorder in human brain

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Excessive alcohol consumption is a leading cause of preventable death worldwide. Neurobiological mechanisms associated with alcohol use disorder (AUD) remain poorly understood. We compared differential gene expression from deceased individuals with and without AUD across two human brain regions, nucleus accumbens (NAc) and prefrontal cortex (PFC), in two datasets from independent brain repositories. Bulk RNA-seq data from 155 (79 AUD, 76 non-AUD) NAc samples and 239 (116 AUD, 123 non-AUD) PFC samples across the two datasets were uniformly processed and analyzed separately for differential gene expression using negative binomial regression adjusting for technical and biological covariates. The results from each dataset were then meta-analyzed for each brain region. Using these results, we tested for heritability enrichment of AUD-related phenotypes and used a systematic framework (Stratford et al.) to prioritize known drugs that target AUD-associated genes. We identified 476 significant (FDR<0.05) differentially expressed genes (DEGs) (25 in both regions, 29 only in NAc, 422 only in PFC). Of these DEGs, 17 were also implicated in GWAS of problematic alcohol use or drinks per week. We also identified 29 and 436 drug compounds that target DEGs from our NAc and PFC meta-analysis, respectively. The prioritized list contains drugs already used to treat AUD, such acamprosate, and many other drugs with potential for repurposing. Our meta-analyses identified robust AUD-associated DEGs, providing novel neurobiological insights into AUD, highlighting genes targeted by known drug compounds, and generating opportunity for drug repurposing to improve AUD treatment.