Shared Genetic Architecture and Neurobiological Pathways of Problematic Alcohol Use and Anxiety Disorders

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Introduction

Problematic alcohol use (PAU) and anxiety disorders (ANX) frequently co-occur, suggesting shared genetic and neurobiological underpinnings. However, the direction of potential causal effects and specific mechanisms that underlie this overlap are unclear. This study investigates the shared genetic architecture and neurobiological pathways underlying PAU and ANX.

Methods

We utilized summary statistics from large-scale genome-wide association studies (GWAS) of PAU and ANX. Conjunctional false discovery rate (ConjFDR) analysis identified single nucleotide polymorphisms (SNPs) associated with both traits, categorizing them as concordant or discordant based on the direction of their effects. FUMA was used to map these SNPs to independent loci. In FUMA, we also conducted differential gene expression analysis across 30 general and 54 specific tissue types. Mendelian Randomization (MR) assessed causal associations between ANX and PAU.

Results

ConjFDR identified 97 lead SNPs, of which 89 had concordant and 8 had discordant effects on PAU and ANX (Fig1). These loci were mapped to 97 genes including DRD2 and PDE4B, with links to dopaminergic and cAMP signaling pathways. Gene expression was enriched in the brain, nerve, adrenal gland, esophagus, stomach and colon, with notable expression in the prefrontal cortex, anterior cingulate cortex, hippocampus, hypothalamus, substantia nigra and amygdala (Fig2.). MR analyses indicated bidirectional causal associations between ANX and PAU (Fig3).

Fig1 ConjFDR Manhattan Plots of PAU and ANX

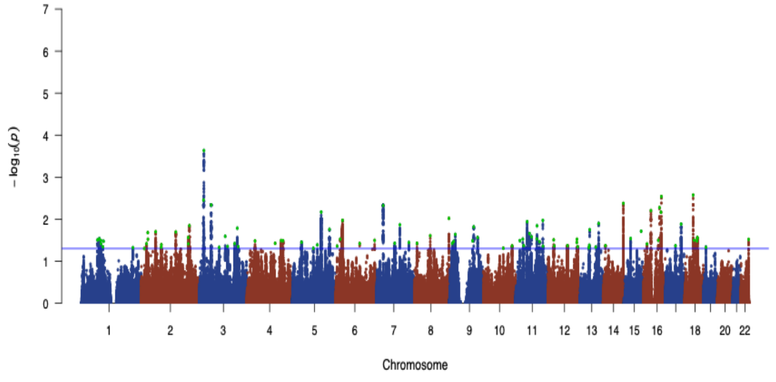


Fig2 Differentially Expressed Genes Across 54 GTEx v8 Tissue Types

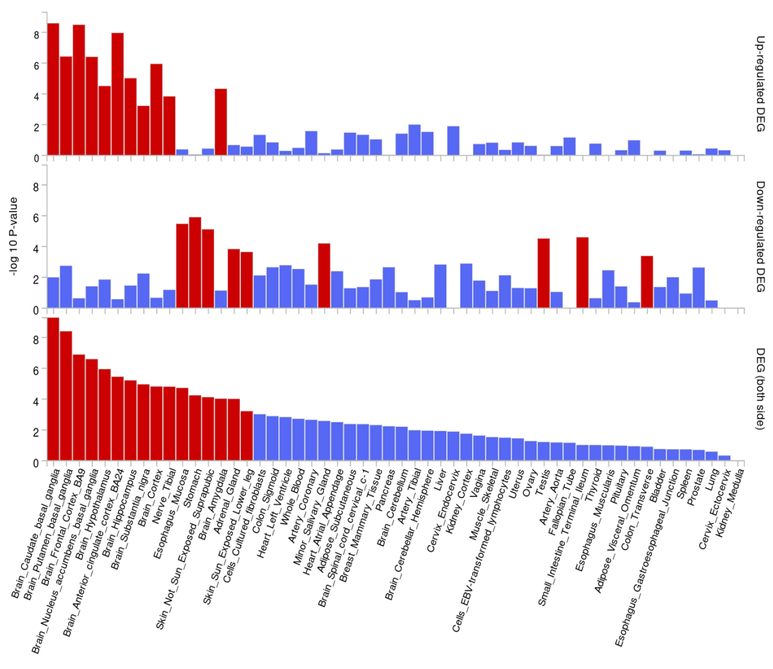
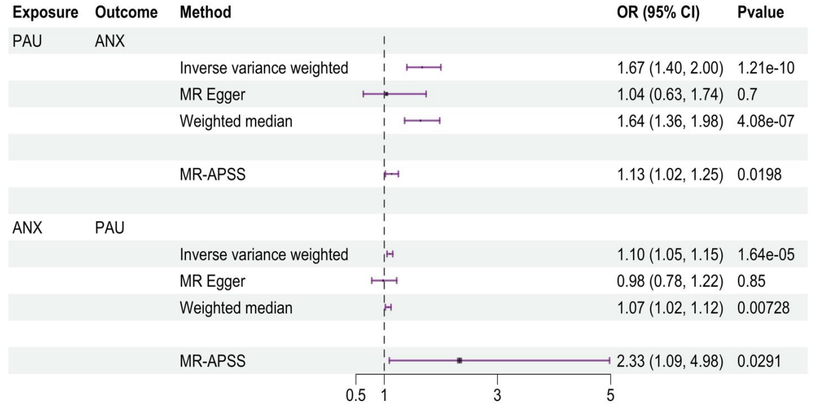


Fig3 Causal Associations Between PAU and ANX: MR Forest Plot



Conclusions

We characterized the genetic and neurobiological overlap of PAU and ANX, identifying differentially expressed genes enriched in addiction and anxiety relevant brain regions. MR analyses highlighted reciprocal, causal relationships between PAU and ANX. These findings advance our understanding of comorbid psychiatric conditions and provide targets for therapeutic development.

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