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Functional Screening of 3'-UTR Variants Combined with Genome-wide Association Identifies Causal Regulatory Mechanisms Impacting Alcohol Consumption and Alcohol Use Disorder

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Genome-wide association studies (GWAS) have identified loci associated with alcohol consumption and alcohol use disorder (AUD), but many are in non-coding regulatory regions, where additional information is needed to evaluate their function. Our objective is to determine how variants and genes at regulatory loci functionally contribute to alcohol consumption and AUD.

We evaluated the activity of variants in 3' untranslated regions (3'-UTRs) of genes in loci associated with neurological disorders using a massively parallel reporter assay (MPRA) in neuroblastoma and microglia cells. Of the 13,515 variants tested, 400 (neuroblastoma) and 657 (microglia) significantly impacted gene expression. Heritability enrichment analysis found that functional variants explained a higher proportion of heritability in GWASs of alcohol phenotypes than all candidate variants.

We identified genes whose 3'-UTR are associated with alcohol consumption by aggregating variant effects from MPRA and GWAS results, using drinks per week from GSCAN as a discovery cohort and alcohol use disorders identification test-consumption (AUDIT-C) from the Million Veteran Program (MVP) as a replication cohort.

Using these identified genes, we stratified brain tissue samples using a 3'-UTR activity score calculated by combining SNP genotypes with MPRA effect values and evaluated differential expression of genes between groups with high and low 3'-UTR activity. A pathway analysis of these differentially expressed genes identified several inflammation response pathways.

By using only genotypes and MPRA effect to stratify the samples, the pathways identified are downstream of the genetic component. This suggests that variation in response to inflammation contributes to the propensity to increase alcohol consumption.