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Genetic Interactions in Alcohol Use Disorder in a High-Risk Population

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While alcohol use disorder (AUD) is known to have a significant genetic basis, there exists a considerable disparity between its heritability and the findings from GWAS. A potential missing piece in this puzzle may lie in genetic interactions, or epistasis, an aspect that has been largely overlooked in addiction research, mostly due to computational and statistical challenges. Our study aimed to explore the role of epistasis in the susceptibility to AUD within an American Indian population, known for its elevated rates of AUD. We took a two-step approach. Initially, we identified a set of 46 core genes associated with AUD through pathway and disease database, large GWAS studies, along with previous analyses of the studied cohort. Expanding this gene set through the propagation of connections from protein-protein interaction (STRING) and regulatory interaction (GeneHancer) databases resulted in 513 genes and 280 regulatory elements. We then conducted an epistasis analysis on an AUD severity phenotype using nearly 100K SNPs associated with the expanded set. The top SNP pairs showing interaction effects were linked to genes enriched in functional networks such as sodium and potassium ion transports, forebrain neuron development, and axion guidance. These genes exhibited significant up-regulation in brain tissues including frontal cortex, anterior cingulate cortex, putamen basal ganglia, and substantia nigra. This study represents the first large-scale epistasis study in AUD, and our preliminary findings suggest that genetic interactions may contribute to susceptibility to AUD.