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Molecular Brain Signatures of Chronic Alcohol Use Across Species

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Background: Molecular genetic studies of human alcohol use disorder (AUD) indicate that the behavioral is highly polygenic and limited by the heterogeneous nature of human phenotyping and bioassays. Transcriptomic, epigenetic, and chromatic interaction studies of brain structures implicated in alcohol behaviors have shed some light on the underlying biology, but additional information is needed to overcome the lack of tissue specific data.

Rationale: Consilience of alcohol biology across experimental systems may help to prioritize genes and biological processes, in so much as response to ethanol is mediated by perturbations in conserved pathways. We hypothesized greater consilience among primate models, particularly in limbic regions, when using binge-intoxication models to localize gene networks.

Methods: We utilized postmortem brain samples in humans, primates, and mice via publicly available RNA-sequencing (RNA-seq) data. Differential gene expression analyses of human, monkey, and mouse RNA-seq samples varied across model systems and differed by tissues and behavior outcome.

Results: We identified 30 highly conserved co-expression networks across specifies, of which 80% were highly preserved in primates and 47% in mice. Notably, the top 2.5% of these gene networks revealed 57 unique hub genes, several of which are involved in substance use traits, as well as impulsivity, stress, motivation, etc.

Discussion: We provide implications for these findings and how they can inform future GWAS and risk prediction models of AUD.