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Transcriptomic Landscape of Compulsive-like Alcohol Drinking

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Alcohol use disorder (AUD) affects nearly 15 million Americans, and effective treatments are scarce. A key characteristic of AUD is continued alcohol use despite negative consequences, often leading to relapse even after persistent efforts to abstain long-term. While genetic factors play a role, they account for only a small portion of AUD variance, with many genetic variations found in non-coding regions. This suggests that epigenetic mechanisms may have a significant impact on AUD risk and the shift from casual to persistent alcohol use. Identifying affected genes and epigenetic processes could lead to new therapeutic targets.

A mouse model of AUD developed by our lab allows us to study epigenetic influences. In this model, isogenic C57BL6/J mice are trained in an operant alcohol self-administration (SA) task, with alcohol consumption measured quantitatively. Mice are categorized into three groups based on their consumption patterns: non-drinkers, low drinkers, and high drinkers. Among high drinkers, two subgroups are identified: punishment-sensitive mice, who decrease consumption when punished, and punishment-resistant mice, who continue despite punishment.

Single-nucleus RNA sequencing in the dorsomedial striatum, a brain region linked to cognitive flexibility and compulsive behaviors, is conducted on samples from punishment-resistant, punishment-sensitive, and water-control mice. This analysis aims to deepen our understanding of epigenetic factors in AUD susceptibility and potentially inspire new treatments.