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From Genes to Treatments: Leveraging Rat Genetic Diversity to Unlock Novel Therapeutic Targets in Alcohol Use Disorder

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Alcohol use disorder (AUD) affects approximately 15% of adults who consume alcohol, with only 10% of treated individuals responding to currently FDA-approved medications. Given the role of genetics in AUD development and the heterogeneous nature of the disorder, we investigated individual differences in alcohol addiction-like behaviors and ran a genome wide association study in genetically diverse heterogeneous stock (HS) rats. We used over 600 male and female HS rats that self-administered oral ethanol and measured multiple AUD-related behaviors. Dependence was induced using chronic intermittent ethanol vapor exposure, and behavioral experiments were conducted during acute withdrawal. We assessed withdrawal behaviors, sensitivity, tolerance, and the ability of pharmacotherapies to reduce alcohol drinking in dependent rats. We identified individual differences in response to alcohol during withdrawal, development of tolerance, and sex differences. Cluster analyses indicate variation in addiction phenotypes that can be helpful for identifying successful therapeutic targets for populations with varying symptomology. Preliminary GWAS results found multiple significant quantitative trait loci (QTLs). Early proof-of-concept studies tested repurposed, FDA-approved compounds that work on downstream targets of genes of interest. Our study highlights the importance of understanding individual differences in AUD-related behaviors and can identify novel targets to treat AUD. These data, combined with observed cellular and transcriptomic variations, can provide valuable insights into potential therapeutic targets to improve treatment outcomes for AUD patients.