**Genetics of Novelty Seeking and Propensity for Drug Abuse in Outbred Rats**

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Understanding individual differences in vulnerability to substance abuse and addiction constitute a long-standing challenge for clinicians and researchers. We are studying the genetic and functional basis of novelty-seeking behavior in two rat lines that offer a uniquely powerful model for understanding neural mechanisms of drug seeking, addiction, and relapse. We have selectively bred rats for high and low propensity to explore a mildly stressful novel environment. These bred High Responders (bHRs) and Low Responders (bLRs) show contrasting, heritable behaviors. Compared to bLRs and outbreds, bHRs exhibit higher novelty-seeking and impulsive behaviors, lower anxiety, greater propensity to psychostimulant sensitization, and lower thresholds for drug- and cue-induced relapse. bLRs exhibit anxious and depressive behaviors and are more responsive to psychosocial stress, which triggers drug-seeking behavior. The two lines exemplify extremes of emotional reactivity that map onto human temperamental differences and underlie two paths to drug abuse—novelty seeking and reactivity to psychosocial stress. We hypothesize that DNA variants that were initially derived from outbred Sprague-Dawley (SD) founders account for the molecular and behavioral differences between the two lines. We seek to identify these causal genes by mapping quantitative trait loci using samples from an extant $F_2$ cross between the bHRs and bLRs. We will also examine an independent cohort of SD rats since they represent the founders and will enable higher resolution mapping. Specific genes that have given rise to the divergence between bHR and bLR may be directly relevant to corresponding human phenotypes or provide clues to pathways that could explain or predict the differential vulnerability to addiction and relapse in humans. Integrating genotyping data with RNAseq gene expression results in specific brain regions will enable us to relate the genetic, neural, and behavioral facets contributing to addiction liability and translate this knowledge to more precise and effective treatment for patients.

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