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

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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. After divergent selection for high and low propensity to explore a mildly stressful novel environment, the bred High Responders and Low Responders show contrasting heritable behaviors. They 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 functional variants in some genes, initially derived from Sprague-Dawley (SD) founders, account for the current molecular and behavioral divergence of the two lines. We are mapping quantitative trait loci in an F2 cohort and ~1,000 SD animals, aiming to find alleles at multiple genes that may be relevant to the corresponding human phenotypes, e.g., could explain variable opioid responsiveness. Our study also integrates genotyping data with RNAseq results in specific brain regions to relate the genetic, neural, and behavioral facets that contribute to addiction liability. As part of this NIDA-supported study we participate in a multi-site collaboration to create high-quality whole-genome maps for >100 inbred strains representing the majority of the rat models currently in use in research. This effort will provide a complete catalog of DNA variants based on linked-read as well as true long-read sequencing. With this resource, functional and genetic mapping studies using the rat will rely on a more complete reference, with more accurate annotation of genes and regulatory elements.