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## **Identification of genetic variants that contribute to compulsive cocaine intake in rats**

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Twin studies suggest that approximately 50% of the vulnerability to cocaine use disorder is determined by genetic factors, but genome-wide association studies (GWAS) in humans have only begun to identify specific genes that confer this risk. The identification of a set of single nucleotide polymorphisms (SNPs) associated with increased vulnerability to develop compulsive cocaine use represents a major goal for understanding of the genetic risk factors to cocaine use disorder and facilitating the identification of novel druggable targets. Here we characterized addiction-like behaviors in heterogeneous stock (HS) rats, a unique outbred strain of rats characterized by high genetic variability that has been developed to mimic genetic variability in humans. HS rats were allowed to self-administer cocaine 6h/daily for 14 days. Animals were also screened for compulsive cocaine use, using progressive-ratio (PR) and responding despite adverse consequences (contingent foot shocks). To minimize cohort-specific effects, we used large cohorts ( $n = 60$ ) and normalized the level of responding within cohorts using a Z-score. To take advantage of the three behaviors related to compulsive intake and further identify subjects that are consistently vulnerable vs. resistant to compulsive cocaine use we computed an Addiction index by averaging normalized responding (Z-scores) for the three behavioral tests. Results showed high individual variability between vulnerable and resistant rats that is likely to facilitate detection of gene variants associated with vulnerable vs. resistant individuals. Such data will have considerable translational value for designing pharmacogenetic studies in humans