

Submitter Email: Olivier George

Submitted Email: olgeorge@health.ucsd.edu

Identification of gene variants that predict cocaine addiction-like behaviors in heterogeneous stock rats

Olivier George

Psychiatry, University of California San Diego

Individual differences in the response to cocaine and the vulnerability to cocaine use disorder are heritable. Family and twin studies demonstrate that about 50% of the vulnerability to cocaine use disorder is determined by genetic factors. Presently, the identities of gene variants that mediate this risk remain largely unknown, hindering efforts to design pharmacological interventions. However, major advances in next-generation sequencing techniques and improvements of animal models of compulsive-like cocaine use provide a unique opportunity to address this knowledge gap. To address this gap, we used whole-genome sequencing in >800 rats that have been behaviorally characterized for addiction-like behaviors in rats using the model of extended access to chronic intravenous cocaine self-administration (6 h/day, 0.5 mg/kg/infusion). We measured escalation of intake, continued responding despite an exponential increase in cost (Progressive ratio responding, PR), responding despite adverse consequences (contingent footshocks), and irritability-like behaviors (bottle brush test) to establish an addiction index. We identified 34 QTLs associated with addiction-like behaviors and identified 9 known genes of interest based on previous human GWAS and preclinical studies and 20+ novel genes of interest with few if any, previous studies in the addiction field. We will highlight the gene variants associated with compulsive-like cocaine seeking and taking using a model of extended access to cocaine self-administration in heterogeneous stock rats and describe how large-scale and behavioral analysis of cocaine self-administration changes our understanding of the transition to addiction-like behaviors.