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Genome wide association study reveals multiple loci associated with heroin motivation and taking behavior in heterogeneous stock rats

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The behavioral and diagnostic heterogeneity within human opioid use disorder (OUD) diagnosis is not readily captured in current animal models, limiting translational relevance of the mechanistic research that is conducted in experimental animals. In the current study, over 900 male and female heterogeneous stock rats were assessed across several measures of heroin taking, refraining and seeking behaviors. Using a non-linear Bayesian stochastic block model network-based clustering approach, rats were categorized as OUD vulnerable, resilient, or intermediate. Using this model, we have demonstrated phenotypic differences in OUD-like behaviors, cue-induced neuronal patterns of circuit activation, and nucleus accumbens markers of neuroplasticity, all with striking sex differences present. To assess genetic factors that may be contributing toward OUD propensity, a genome-wide association study (GWAS) was performed and genetic variants associated with heroin consumption, escalation of intake and motivation to obtain heroin were identified. Phenotype wide association study analysis showed relationships between OUD vulnerability versus resiliency for the genes Ets2, a regulator of microglial functional plasticity, for total heroin consumption and Phb1l2, a mitochondrial scaffolding protein associated with substance abuse, for motivation to obtain heroin. Furthermore, eQTL analysis revealed a relationship in gene expression between Phb1l2 and MMP15, a gene involved in regulating drug-induced synaptic plasticity. Together, these findings identify novel genetic markers related to individual differences in the susceptibility to OUD-relevant behaviors.