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Discovery of gene co-expression networks associated with cocaine-related behaviors in Collaborative Cross mice

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The emergence of cocaine use disorder given repeated intake of cocaine varies across individuals and is under strong genetic influence. Genetic differences in cocaine-related behaviors across mouse strains can be used to detect biological correlates which may serve as mechanisms of variable addiction vulnerability. We correlated gene expression profiles in the striatum of thirty-four Collaborative Cross (CC) mouse strains with addiction-related behaviors in these strains including behaviors related to impulsivity and reversal learning, cocaine sensitization, and cocaine intravenous self-administration (IVSA). We used weighted gene co-expression network analysis (WGCNA) to identify co-expression networks in the striatum across cocaine-exposed CC strains, and evaluated their correlation with behaviors. We performed expression quantitative trait loci analyses (eQTL) in drug-naïve Diversity Outbred mice to identify cis eQTL in the striatum that regulated behaviorally-relevant co-expression network members, and compared these networks to previous cocaine-related studies in GeneWeaver. The genes *Krit1*, *Atf6b*, *Sult1a1, Pim1*, and *Entpd3* are correlated to addiction-related behaviors, found in co-expression networks in the cocaine-exposed striatum, and regulated by Cis eQTLs in the striatum of drug-naïve Diversity Outbred mice*. Krit1* and *Atf6b* were correlated to the acquisition of cocaine in these strains, sensitization, and reversal acquisition*. Sult1a1* was correlated to extinction and reinstatement while *Pim1* and *Entpd3* were correlated to extinction, reversal acquisition, and sensitization. As more behavioral traits are characterized in the Collaborative Cross population by ourselves and others, additional relations among genes and behavior can be found. This work was supported in part by NIH P50 DA039841.