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A GWAS of Opioid Withdrawal Symptom Clusters

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Genome-wide association studies (GWAS) of opioid dependence have identified a very limited number of genome-wide significant (GWS) SNPs. Using data from European ancestry participants with a history of daily IV heroin use (N=1080) in the Comorbidity and Trauma Study (CATS), a case-control study of opioid dependence, we previously examined an alternative phenotype, opioid withdrawal symptom count, observing GWS association of *OPCML* SNPs. For the current analyses, we initially assigned individual opioid withdrawal symptoms to clusters based on relevant literature and correlational relationships and then performed factor analysis to further refine these assignments. We identified five opioid withdrawal symptom clusters and calculated symptom counts for each. Linear regression was then performed to examine SNP association for each cluster with sex, age, and principal components as covariates. Genome-wide significant (GWS) association was found for two of the five withdrawal symptom cluster phenotypes: (1) piloerection/sweating [most highly associated SNP rs144712697 (*OPCML*) beta 1.70 (1.18-2.22); p=2.18E-10] and (2) craving/depression/insomnia [most highly associated SNP rs145353597 (3' to *COL11A1)* beta 1.10 (0.72-1.49); p=2.93E-8]. *OPCML* encodes a cell adhesion molecule that has been reported to impact binding of opioid receptors to G proteins. Chronic morphine treatment significantly alters *OPCML* expression in mice and primates. *OPCML* has been reported to be significantly associated with behavioral phenotypes including ever smoker, alcohol dependence, response to amphetamines, and schizophrenia. A PheWAS examination of rs145353597 finds nominal associations with major depressive disorder diagnosis, alcohol intake, and sleep duration. These preliminary results support the potential utility of GWAS focusing on alternative opioid-related phenotypes.