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A GWAS of Opioid Withdrawal Symptom Count

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The current investigation is a genome-wide association study (GWAS) of opioid withdrawal symptom count, an opioid-related phenotype for which heritability has been less well-characterized. Analyses were performed using data from European ancestry participants of the Comorbidity and Trauma Study (CATS), a case-control genetic association study of opioid dependence. Given that opioid withdrawal symptoms vary with frequency and severity of use, we opted to focus our analyses on opioid dependent cases with a history of daily IV heroin use (the most common endpoint for this sample's opioid users; N=1080) with the rationale that genetic factors likely explain a substantial component of the variance in opioid withdrawal severity in these severely dependent individuals. Linear regression was performed with covariates including sex, age, and three principal components. Genome-wide significant (GWS) association (lowest $p=3.47 \times 10^{-8}$) was found for three intronic SNPs in the *OPCML* gene which encodes a cell adhesion molecule. These SNPs are in high linkage disequilibrium and likely represent a single association signal. Other strongly associated SNPs not reaching GWS are located in the *KCNK12*, *MED27,* and *RASGRF2* genes. While our results are preliminary and will require replication, the observed effects are large (betas ranging from 3.47- 4.43) with some SNPs located in genes for which some potentially supporting data has been previously published. Chronic morphine treatment has been reported to result in significant alteration of *OPCML* expression in mice and primates. A recent publication found evidence that Human Endogenous Retrovirus-K HML-2 integration within *RASGRF2* is associated with IV drug abuse.