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 x 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.