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NIDA Genetics Consortium Genome-wide Association Study of Opioid Addiction – The Endgame for Wave 1.

*NIDA Genetics Consortium GWAS of OA Investigators**

Prevalence of addiction to opioids is growing dramatically, as are the public health consequences. Heritability of opioid addiction (OA) is substantial (~60%). However, after more than 30 years of research, including eight genome-wide association studies (GWASs), independently replicable associations have been found only for variants in the opioid receptor genes *OPRM1* and *OPRD1*. Collectively, the GWAS findings have included additional genome-wide significant loci that await independent replication. In an effort to maximize sample size, the NIDA Genetics Consortium GWAS of OA was initiated as a collaborative meta-analysis project, allowing for varying case (e.g., frequency of use [FOU], medication treatment, & diagnoses) and control (e.g., assessed and unassessed for opioid use and OA) criteria. Here, we report on cross-ancestry and ancestry-specific meta-analyses of OA vs. all controls [OAall] (case N=11,943; control N=309,641), OA vs. exposed controls [OAexp] (case N=3,546; control N=4,378), and FOU (N=11,259). Two genome-wide significant loci for OAall were identified in the European American analyses (rs28386916, $P=7.90\times10^{-9}$; rs79935720, $P=3.92\times10^{-8}$); only rs28386916 replicated in an independent sample (P=0.039). Rs28386916 alters the regulatory motif HDAC2_disc6, is near the gene *GPRIN3*, which is highly expressed in brain, and is in linkage disequilibrium with eQTLs for *GPRIN3* in brain. No variants reached genome-wide significance in the OAexp or FOU meta-analysis. In addition to reviewing these GWAS findings, we report on gene-based analyses, genetic correlation among phenotypes, and testing to extend associations reported in the Psychiatric Genetics Consortium and Million Veteran Program opioid dependence preprint GWAS. Plans for Wave 2 will be discussed.

* corporate authorship representing all contributing cohorts and investigator affiliations.
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