

Submitter name: Eric Otto Johnson  
Submitted email: [ejohnson@rti.org](mailto:ejohnson@rti.org)

## **NIDA Genetics Consortium Genome-wide Association Study of Opioid Addiction – An Update.**

NIDA Genetics Consortium GWAS of OA Investigators<sup>1</sup>

<sup>1</sup>Corporate authorship representing all contributing cohorts and investigator affiliations.  
Submitted by Eric Otto Johnson on behalf of the consortium.

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 six genome-wide association studies (GWASs), independently replicable associations have been found only recently for variants in the opioid receptor genes *OPRM1* and *OPRD1*. Three GWAS (largest discovery N=5,697) have reported genome-wide significant loci, but all 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 criteria (e.g., frequency of use, medication treatment, & diagnoses). Here, we focus on cross-ancestry meta-analyses of OA vs. all controls [OAall] (case N=11,140; control N=308,389) and OA vs. exposed controls [OAexp] (case N=3,546; control N=4,378). One genome-wide significant association for OAall was identified (rs189500020,  $P=6.14 \times 10^{-9}$ ). This signal is driven by European ancestry, with MAF of 1%. The variant is monomorphic in African ancestry. Function of the top variant is unknown, however, other variants in this locus (e.g. rs74891029,  $P=7.73 \times 10^{-7}$ ) are associated with differential chromatin states across brain tissues, with the affected gene (*BAZ2A*) being expressed across the brain, most strongly in cerebellum. No variants reached genome-wide significance in the OAexp meta-analysis. The genome-wide significant signal requires replication and/or other confirmatory evidence. Addition of cohorts and analyses are ongoing, with the expectation that true signals will emerge for OA as it has for other complex diseases, with increases in sample size.