Genomic SEM GWAS of Opioid Addiction: Digging into $OPRM1$ and Beyond

Eric Otto Johnson$^{1,2}$, Nathan Gaddis$^2$, Ravi Mathur$^2$, and the NIDA Genetics Consortium (NGC) Opioid Addiction GWAS Consortium

$^1$Fellows Program, RTI International; $^2$GenOmics, Bioinformatics, and Translational Research Center, RTI International

Opioid addiction (OA) has strong heritability (~60%), yet few genetic variant associations have been identified and independently replicated. Of seven published genome-wide association studies (GWAS), only one has identified a genome-wide significant association with OA ($p=1.51\times10^{-8}$ rs1799971, the A118G variant in $OPRM1$) and independently replicated it ($p<0.05$). We applied genomic Structural Equation Modeling to conduct a GWAS across published studies (PGC, MVP, and Partners Health) and the NGC GWAS: 23,367 cases and total effective sample size of 88,114 individuals of European ancestry (EA). While OA phenotypes varied across cohorts, genetic correlations among phenotypes were uniformly high ($r_g > 0.9$). Model fit for a single latent genetic factor was excellent: $X^2=0.0857$, 2df, $p=0.958$, SRMR=0.0202. We observed the strongest evidence to date for $OPRM1$: 32 genome-wide significant variants associated with OA; lead SNP rs9478500 ($p=2.56\times10^{-9}$). Strong linkage disequilibrium in EA results in 3 main haplotypes: one carrying major alleles across rs1799971 and the genome-wide significant intron 1 variants; one carrying the minor (protective) rs1799971-G and major intron 1 alleles; and one carrying rs1799971-A and minor (risk) intron 1 alleles (e.g., rs9478500-C). The haplotype carrying minor (risk) intron 1 alleles appears to drive the OA association. These variants also showed opposite directions of effect on $OPRM1$ expression: lower expression with rs9478500-C ($p=0.00066$) and higher expression with rs1799971-G ($p=1.40\times10^{-7}$) in cerebellum. Beyond $OPRM1$, gene-based analyses identified $PPP6C$ as associated with OA at genome-wide significance ($p=2.09\times10^{-6}$). $PPP6C$ variants (e.g., rs864882) were previously associated with smoking and alcohol phenotypes, supporting the locus as pleiotropic for addiction.