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

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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=1.51x10^{-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=2.56×10^{-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=1.40×10^{-7}) in cerebellum. Beyond *OPRM1*, gene-based analyses identified *PPP6C* as associated with OA at genome-wide significance (p=2.09×10^{-6}). *PPP6C* variants (e.g., rs864882) were previously associated with smoking and alcohol phenotypes, supporting the locus as pleiotropic for addiction.