Association of the OPRM1 Variant rs1799971 (A118G) with Non-Specific Liability to Substance Dependence in a Collaborative de novo Meta-Analysis of European-Ancestry Cohorts

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The mu1 opioid receptor gene, OPRM1, has long been a high-priority candidate for human genetic studies of addiction. Because of its potential functional significance, the non-synonymous variant rs1799971 (A118G, Asn40Asp) in OPRM1 has been extensively studied, yet its role in addiction has remained unclear, with conflicting association findings. To resolve the question of what effect, if any, rs1799971 has on substance dependence risk, we conducted collaborative meta-analyses of 25 datasets with over 28,000 European-ancestry subjects. We investigated non-specific risk for ”general” substance depen-

dence, comparing cases dependent on any substance to controls who were non-dependent on all assessed substances. We also examined five specific substance dependence diagnoses: DSM-IV alcohol, opioid, cannabis, and cocaine dependence, and nicotine dependence defined by the proxy of heavy/light smoking (cigarettes-per-day <20 vs. >/= 10). The G allele showed a modest protective effect on general substance dependence (OR = 0.90, 95% C.I. [0.83-0.97], p value = 0.0095, N = 16,908). We observed similar effects for each individual substance, although these were not statistically significant, likely because of reduced sample sizes. We conclude that rs1799971 contributes to mechanisms of addiction liability that are shared across different addictive substances. This project highlights the benefits of examining addictive behaviors collectively and the power of collaborative data sharing and meta-analyses.
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