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Genome-wide Association Study of multiple substance use disorders identifies novel loci related to mental and physical health

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Individual substance use disorders (SUDs) have been categorized diagnostically as discrete clinical entities despite widespread comorbidity within SUDs. Genome-wide association study (GWAS) data have been leveraged to reveal a moderately-largely shared genetic liability across disorders. We have previously shown that a common genetic factor, *a(g)*, accounts for significant genetic covariance across SUDs, above and beyond common substance use behaviors. Here, in subjects of European (N = 82,707-435,563, total N = 1,019,521) and African (N= 9,925- 48,015) ancestries, we identify common allelic effects influencing opioid use disorder, problematic tobacco use, problematic alcohol use, and cannabis use disorder. We find 10 lead pleiotropic SNPs broadly influencing addiction, including significant signals at *PDE4B* and *DRD2* that can be related to brain gene expression, both of which are targets of dopaminergic regulating medications. Phenome-wide latent causal variable analyses and genetic correlations in the UK biobank revealed that disability, pain, and socioeconomic status are plausibly causal risk factors for increasing general predisposition towards SUDs and that earlier sexual initiation and earlier maternal age of first birth share the largest proportion of genetic variance with the GWAS of the *a(g)* factor. Preliminary drug purposing using an imputed transcriptomic profile implicated drugs inhibiting tyrosine kinase and interleukin-related (IL) inflammatory pathways. Combined, these results highlight the role of common genetic variants on multiple SUDs in pathways of both mental health/behavior as well as physical well-being and provide preliminary insights into the role of stress and inflammatory response as mechanisms undergirding SUD.