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PgmNr 2174: The genetics of addiction in a large Northern Nevada cohort of the Healthy Nevada Project.

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Addiction, particularly to opioids, has reached epidemic levels in the U.S. By merging the genetics of a large population with comprehensive Electronic Health Records (EHR), socio-economic, geographic, and environmental data, the Healthy Nevada Project (HNP) aims to identify disease associations specific to local communities. Here we use Helix Exome+ sequencing of 20,000 HNP participants to examine genetic and phenotypic associations of substance addiction. The current control cohort contains 650 participants carefully selected as users of opiates, other illicit drugs, or alcohol, but who do not exhibit dependence or addiction. The case cohort consists of 1,000 participants with at least one addiction diagnosis in the last 12 years. A genome-wide association study (GWAS) was performed across cohorts using 2.5 million high-quality variant calls (GQ>20) obtained after applying additional thresholds (90% SNP call rates, 85% individual call rates, Hardy-Weinberg $p>1x10^{-6}$). PLINK v. 1.9 performed logistic associations with age, gender, and principal components to control for population stratification as covariates, and the standard log-additive genetic model. Two phenome-wide analyses (PheWAS) were performed: the first PheWAS examined associations between significant SNPs identified in the GWAS and EHR phenotypes based on ICD codes; the second identified associations between incidence of addiction and ICD-based diagnoses. Of the 10 strongest associated SNPs ($p<1x10^{-5}$), four are in genes reported in prior genetic studies of addiction. Two genes, *ITPR2* and *GABBR2,* have functional relevance in opioid, cocaine, alcohol and nicotine addiction pathways. A third association in the HNP cohort lies in *ITGA9*, a gene down-regulated in long-term oxycodone use in mice and linked to human drug abuse. A fourth variant identified is in *PARK2*, a gene often linked to Parkinson's Disease, supporting the notion that the molecular mechanisms of neurodegeneration of the two disorders are similar. The strongest association in our cohort is a variant in the geneless region 20q11.2 not yet affiliated to addiction. PheWAS results show strong clinical links with addiction: tobacco use disorder ($p<1x10^{-55}$), mood disorders, depression, and anxiety ($p<1x10^{-10}$). SNPs associated with addiction in the HNP are linked to alcoholism, tobacco use disorder, emphysema, and lupus. This study shows prior identified and possible novel genomic associations with substance addiction in a large HNP cohort.