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Genome-wide association study of 'not as prescribed' prescription opioid use in 132,113 23andMe research participants

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Background: Opioid use disorders (**OUD**), which represent a serious health crisis, are known to be moderately heritable.
Rationale: Rather than studying OUD directly, we sought to explore the genetic basis of using opioids 'not as prescribed' in a population with low rates of OUD.
Hypothesis: We hypothesized that 'not as prescribed' opioid use is heritable and may constitute an endophenotype for OUD.
Results: We performed a genome-wide association study (**GWAS**) of problematic opioid use (**POU**; 'ever taking opioid prescriptions not as prescribed') in 132,113 23andMe research participants of European ancestry (N_{cases}=27,805, $N_{controls}$=104,308). Our GWAS identified two genome-wide significant loci (rs3791033, an intronic variant of *KDM4A*; rs640561, an intergenic variant near *LRRIQ3*). POU showed positive genetic correlations with OUD, as measured by the Million Veterans Program (rg=0.58) and the Psychiatric Genomics Consortium (rg=0.83). We also identified strong genetic correlations between POU and substance use traits, particularly alcohol dependence (rg=0.74) and tobacco use disorders (rg=0.74). In addition, we observed genetic correlations between POU and chronic pain (rg=0.42), pain relief medication intake (rg=0.49), insomnia (rg=0.36), loneliness (rg=0.28), and depression (rg=0.36). Lastly, although POU was positively genetically correlated with risk-taking (rg=0.35), conditioning POU on risk did not substantially altered the magnitude or direction of these genetic associations, suggesting that the signal that we captured is specific to opioids and not merely risk-taking, as previously speculated.
Discussion: Opioid misuse measured in population-based cohorts may provide a cost-effective strategy to augment the power of studies directly examining OUD.