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Genome-wide association study of problematic opioid prescription use in 132,113 23andMe research participants of European ancestry

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BACKGROUND AND SIGNIFICANCE. The growing prevalence of opioid use disorder (**OUD**) constitutes an urgent health crisis. Ample evidence indicates that risk for OUD is heritable. As a surrogate (or proxy) for OUD, we explored the genetic basis of using prescription opioids 'not as prescribed'.

HYPOTHESIS. We hypothesized that misuse of opiates might be a heritable risk factor for OUD.

RESULTS. We performed a genome-wide association study (**GWAS**) of problematic opioid use (**POU**) in 23andMe research participants of European ancestry (N=132,113; 21% cases). We identified two genome-wide significant loci (rs3791033, an intronic variant of *KDM4A*; rs640561, an intergenic variant near *LRRIQ3*). POU showed a positive genetic correlation with the largest available GWAS of opioid dependence and OUD (rg=0.64-0.80). We also identified numerous additional genetic correlations with POU, including alcohol dependence (rg=0.74), smoking initiation (rg=0.63), pain relief medication intake (rg=0.49), major depressive disorder (rg=0.44), chronic pain (rg=0.42), insomnia (rg=0.39), and loneliness (rg=0.28). Although POU was positively genetically correlated with risk-taking (rg=0.38), conditioning POU on risk-taking did not substantially alter the magnitude or direction of these genetic correlations, suggesting that POU does not simply reflect a genetic tendency towards risky behavior. Lastly, we performed phenome- and lab-wide association analyses, which uncovered additional phenotypes that were associated with POU, including respiratory failure, insomnia, ischemic heart disease, and metabolic and blood-related biomarkers.

DISCUSSION. We conclude that opioid misuse can be measured in population-based cohorts and provides a cost-effective complementary strategy for understanding the genetic basis of OUD.