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Prescription Opioid Genetics Study (POGS): Initial response to opioids predicts opioid use disorder

Background: The U.S. opioid epidemic causes >100,000 deaths/year. Some patients develop OUD after medical use, but risk-stratification tools are limited. Initial drug responses shape addiction risk. For alcohol and other substances, positive effects predict higher risk; negative effects predict lower risk. Positive initial opioid responses may signal OUD risk, but evidence so far is small and unrepresentative.
Method: We surveyed 141,897 23andMe research participants (8,371 OUD+, 133,526 OUD-) on first prescription-opioid experiences and related traits. We tested associations between initial subjective effects and OUD and built machine-learning and decision-tree models to derive a concise screener for OUD risk. We also conducted the first GWAS of subjective opioid effects (N~144,302 participants of European ancestry) and evaluated genetic correlations with OUD.
Results: Initial subjective effects differed strongly between OUD+ and OUD- participants. Predictive models achieved high discrimination (ROC-AUC~0.91; PR-AUC~0.64), and a two-question decision tree separated high- from low-risk individuals with consistent cross-validation performance. GWAS of initial subjective responses identified 7 genome-wide significant loci, including a missense variant in OPRM1, and positive subjective effects showed the strongest genetic correlations with OUD (rg=0.55-0.77).
Conclusion: Initial subjective responses to prescription opioids strongly predict future opioid use disorder; our two-question screener stratifies risk with high accuracy, and the first GWAS of these effects implicates OPRM1, revealing a shared genetic basis with OUD and pointing to scalable tools for early risk identification.

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