New study reveals shared genetic markers underlying substance use disorders

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By combing through genomic data of over 1 million people, scientists have identified genes commonly inherited across addiction disorders, regardless of the substance being used. This dataset—one of the largest of its kind—may help reveal new treatment targets across multiple substance use disorders, including for people diagnosed with more than one.

The findings also reinforce the role of the dopamine system in addiction, by showing that the combination of genes underlying addiction disorders was also associated with regulation of dopamine signaling.

Published today in *Nature Mental Health*, the study was led by researchers at the Washington University in St. Louis, along with more than 150 co-authors from around the world.

There has been limited knowledge of the molecular genetic underpinnings of addiction until now. Further, most clinical trials and behavioral studies have focused on individual substances, rather than addiction more broadly.

"Genetics play a key role in determining health throughout our lives, but they are not destiny. Our hope with genomic studies is to further illuminate factors that may protect or predispose a person to substance use disorders—knowledge that can be used to expand preventative services and empower individuals to make informed decisions about drug use," said NIDA Director, Nora Volkow, M.D.

"A better understanding of genetics also brings us one step closer to developing personalized interventions that are tailored to an individual's

unique biology, environment, and lived experience in order to provide the most benefits."

In 2021, more than 46 million people in the United States aged 12 or older had at least one substance use disorder, and only 6.3% had received treatment. Moreover, people who use drugs are facing an increasingly dangerous drug supply, now often tainted with fentanyl.

Approximately 107,000 people died of drug overdoses in 2021, and 37% of these deaths involved simultaneous exposure to both opioids and stimulant drugs. Drug use and addiction represent a public health crisis, characterized by high social, emotional, and financial costs to families, communities, and society.

Substance use disorders are heritable and influenced by complex interactions among multiple genes and environmental factors. In recent decades, a data-rich method, called genome-wide association, has emerged to try to identify specific genes involved in certain disorders. This method involves searching entire genomes for regions of genetic variation, called single-nucleotide polymorphisms (SNPs), that associate with the same disease, disorder, condition, or behavior among multiple people.

In this study, researchers used this method to pinpoint areas in the genome associated with general addiction risk, as well as the risk of specific substance use disorders—namely, alcohol, nicotine, cannabis, and opioid use disorders—in a sample of 1,025,550 individuals with genes indicating European ancestry and 92,630 individuals with genes indicating African ancestry.

"Using genomics, we can create a data-driven pipeline to prioritize existing medications for further study and improve chances of discovering new treatments. To do this accurately, it's critical that the

genetic evidence we gather includes globally representative populations and that we have members of communities historically underrepresented in biomedical research leading and contributing to these kinds of studies," said Alexander Hatoum, Ph.D., a research assistant professor at Washington University in St. Louis and lead author of the study.

Hatoum and the research team discovered various molecular patterns underlying addiction, including 19 independent SNPs significantly associated with general addiction risk and 47 SNPs for specific substance disorders among the European ancestry sample. The strongest gene signals consistent across the various disorders mapped to areas in the genome known to control regulation of dopamine signaling, suggesting that genetic variation in dopamine signaling regulation, rather than in dopamine signaling itself, is central to addiction risk.

Compared to other genetic predictors, the genomic pattern identified here was also a more sensitive predictor of having two or more substance use disorders at once. The genomic pattern also predicted higher risk of mental and physical illness, including psychiatric disorders, suicidal behavior, respiratory disease, heart disease, and chronic pain conditions. In children aged 9 or 10 years without any experience of substance use, these genes correlated with parental substance use and externalizing behavior.

"Substance use disorders and mental disorders often co-occur, and we know that the most effective treatments help people address both issues at the same time. The shared genetic mechanisms between substance use and mental disorders revealed in this study underscore the importance of thinking about these disorders in tandem," said NIMH Director Joshua A. Gordon, M.D., Ph.D.

Genomic analysis in the African ancestry sample revealed one SNP associated with general addiction risk and one substance-specific SNP

for risk of alcohol use disorder. The dearth of findings here underscores ongoing disparities in data inclusion of globally representative populations that must be addressed to ensure data robustness and accuracy, Hatoum and co-authors note.

The inclusion of data from different ancestral groups in this study cannot and should not be used to assign or categorize variable genetic risk for substance use disorder to specific populations.

As genetic information is used to better understand human health and health inequities, expansive and inclusive data collection is essential. NIDA and other Institutes at NIH supported a recently released report on responsible use and interpretation of population-level genomic data by the National Academies of Sciences, Engineering, and Medicine. See also a corresponding statement from the NIH.

While Hatoum and colleagues have identified a genetic pattern indicating broad addiction risk, they note that substance use-specific diagnoses still have meaning.

"The current study validates previous findings of alcohol-specific risk variants, and, importantly, makes this finding in a very large and more diverse study population," said NIAAA Director George F. Koob, Ph.D.

"The finding of shared genetic risk variants across different substance use disorders provides insight into some of the mechanisms that underlie these disorders and the relationships with other mental health conditions. Together the findings of alcohol-specific risk variants and common addiction-related variants provide powerful support for individualized prevention and treatment."

More information: Nora Volkow et al, Multivariate genome-wide association meta-analysis of over 1 million subjects identifies loci

underlying multiple substance use disorders, *Nature Mental Health* (2023). DOI: 10.1038/s44220-023-00034-y

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