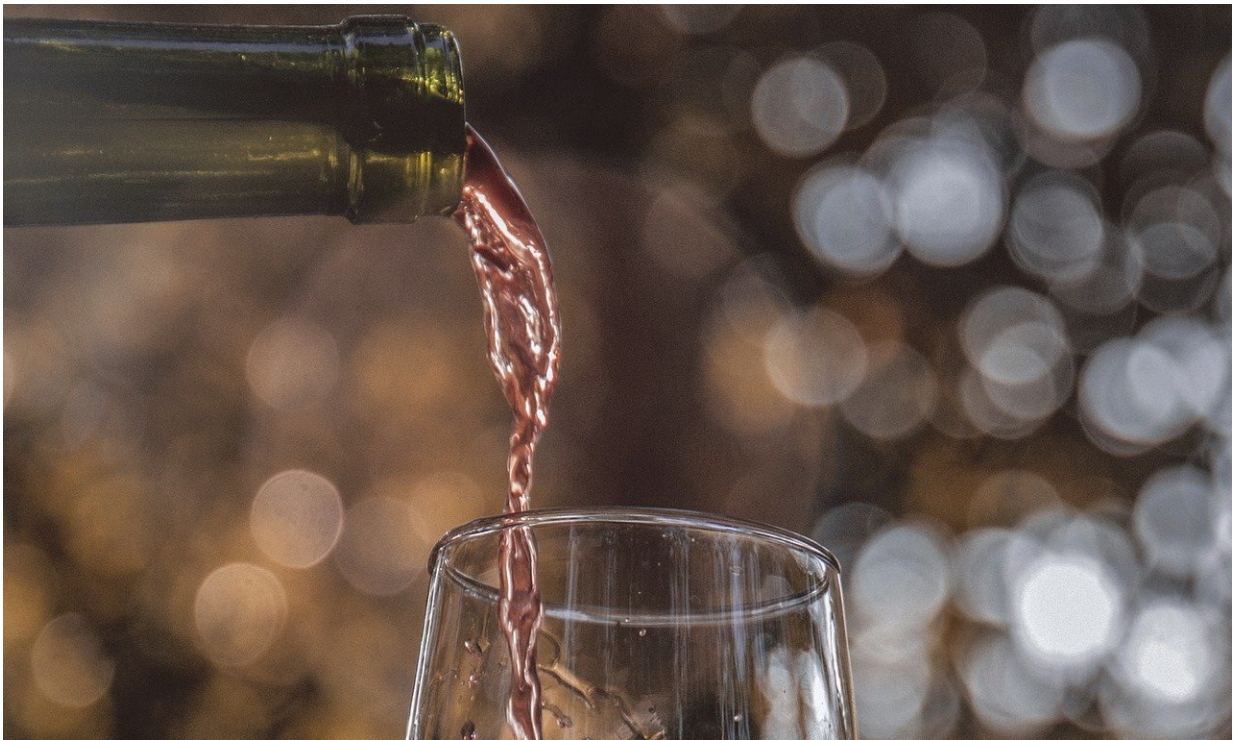


Multi-ancestry study uncovers shared genetics of problematic drinking

December 22 2023, by Christopher Gardner



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A study led by VA Connecticut Healthcare Center/Yale researchers reveals ancestries around the world possess a shared genetic architecture for problematic alcohol use (PAU)—habitual heavy drinking, accompanied by harmful consequences.

The findings, [published](#) in *Nature Medicine*, could help scientists understand the genetic basis of PAU, a major cause of health problems in many age groups. It is a leading cause of death in those it afflicts.

This study is the largest to date for PAU—it identified many new risk genes and uncovered a large amount of new biology. With a better understanding of PAU biology, scientists will have new possibilities in developing treatments.

Hang Zhou, Ph.D., assistant professor of psychiatry and of [biomedical informatics](#) & [data science](#) at Yale School of Medicine and VA Connecticut, and first author of the study, said, "Research with the primary focus on understanding the [molecular mechanism](#) underlying PAU and identification of gene targets for potential pharmacological studies is extremely important for future treatments and could help mitigate the consequences of excessive alcohol use."

Researchers studied more than 1 million people with PAU and included as many genetic ancestral groups as possible, including people with European, African, Latin American, East Asian, and South Asian ancestries.

The Million Veteran Program (MVP) was a major source of data for this study—MVP data were combined with data from many other sources to create the analyses.

Compared to previous research, this work broadened the findings and demonstrated that the genetic architecture of PAU is substantially shared across these populations. There are genetic differences in different populations for PAU, but the similarities are greater. Cross-ancestry information allowed the researchers to improve the power of gene discovery.

"By leveraging the multi-ancestry information, we identified 110 gene regions and had an improved fine-mapping of the potential causal variants in each region," Zhou said.

The researchers also used various methods to prioritize multiple genes with convergent evidence linking association to PAU with brain biology through [gene expression](#) (transcriptional-wide association study in 13 brain tissues) and chromatin interaction analyses in the brain. This work will provide valuable resources and targets for future functional analyses and [drug development](#).

Joel Gelernter, MD, Foundations Fund Professor of Psychiatry, and professor of genetics and of neuroscience at Yale School of Medicine and VA Connecticut, was the study's senior author.

"One of the most important products of this research is the information provided about PAU risk across the entire genome," Gelernter said. "The resulting data allowed us to understand the biology of PAU better, suggesting some already-approved drugs that might become tools for treating PAU in the future, with additional research. The data we produced will be shared with the research community, and this will aid greatly in future research by other scientists."

The drug-repurposing analyses identified several existing medications as potential treatments for PAU, which are described in the published article.

One of the outputs from this study is genome-wide association data, and this kind of information can be used to compute "polygenic risk scores," or PRS, that can be used to estimate an individual's genetic risk for PAU.

The researchers stressed that the PRS they computed is not yet ready for

use in the clinic, but they also tested the association of the PRS for PAU with hundreds of medical traits in multiple biobanks including Vanderbilt University Medical Center's Biobank, Mount Sinai's BioMe, the Mass General Brigham Biobank, and Penn Medicine Biobank. This analysis identified genetic correlations between PAU and many other mental and neurological disorders.

More information: Hang Zhou et al, Multi-ancestry study of the genetics of problematic alcohol use in over 1 million individuals, *Nature Medicine* (2023). [DOI: 10.1038/s41591-023-02653-5](https://doi.org/10.1038/s41591-023-02653-5)

Provided by Yale University

Citation: Multi-ancestry study uncovers shared genetics of problematic drinking (2023, December 22) retrieved 27 April 2024 from <https://medicalxpress.com/news/2023-12-multi-ancestry-uncovers-genetics-problematic.html>

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