# Multi-omics approach identifies large list of candidate genes associated with alcohol use disorder

August 20 2021

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Researchers from the Icahn School of Medicine at Mount Sinai have published the first study of its kind in the field of addiction genetics

using a multi-omics approach to provide a large list of causal candidate genes associated with alcohol consumption and alcohol use disorder (AUD). The study also shows a potential link between alcoholism, Alzheimer's disease, and other neurodegenerative disorders. The findings were published August 20 in *Nature Communications*.

Alcohol use disorders are complex, moderately heritable, psychiatric disorders associated with heightened morbidity and mortality. While previous studies have identified loci (genetic regions) associated with alcohol consumption, this study aimed to identify the variants and genes themselves. "Identification of causal variants and genes underlying genome-wide association study (GWAS) loci is essential to understand the biology of alcohol use disorder and to improve its treatment," said first and co-corresponding author, Manav Kapoor. Ph.D., an Assistant Professor of Neuroscience and Genetics and Genomics at Mount Sinai at the time of the study.

To identify genes relevant to AUD and drinks per week (DPW), a measure used to evaluate alcohol consumption, the research team integrated multi-omics data, using Mendelian Randomization-based methods on the largest available transcriptomic and epigenomic data from brain tissues and myeloid cells. Using data derived from these tissues, the team fine mapped complex loci and identified likely variants and candidate genes, including *SPI1* and *MAPT* genes, associated with alcoholism. *SPI1* and *MAPT* have also been found to be associated with susceptibility for other psychiatric and neurodegenerative disorders including depression and Alzheimer's disease.

*SPI1* (Spi-1 Proto-Oncogene) encodes an ETS-domain transcription factor (PU.1) that regulates gene expression during myeloid and B-lymphoid cell development and homeostasis. Given *SPI1's* control over expression of several downstream genes, this gene may be a major reason for enrichment of immune pathways in drinking behaviors, as

observed in past transcriptomic analysis of human and animal brains.

The *MAPT* gene analyzed in the study encodes the tau protein, which is known for its role in central nervous system disorders such as Alzheimer's disease, frontotemporal dementia, Parkinson's disease, and other neurodegenerative disorders known as tauopathies.

"This work could lead to novel therapeutics for the treatment for alcohol use disorders," said senior author, Alison Goate, D.Phil., Professor of Genetics and Genomic Sciences and Neuroscience at Mount Sinai. "A number of anti-tau therapeutics are being developed for treatment of tauopathies including Alzheimer's disease, these should also be tested in AUD models." Dr. Goate's lab also has funding to develop inhibitors of *SPI1* for Alzheimer's Disease. The current study suggests these inhibitors may also be useful for treating alcoholism.

**More information:** Manav Kapoor et al, Multi-omics integration analysis identifies novel genes for alcoholism with potential overlap with neurodegenerative diseases, *Nature Communications* (2021). DOI: 10.1038/s41467-021-25392-y

Provided by The Mount Sinai Hospital