PRESS RELEASE

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Increased risk of developing alcohol addiction linked to gene mutation

Researchers at the Yong Loo Lin School of Medicine, National University of Singapore, have discovered how genetic variation in a single gene, chrna3, can alter alcohol sensitivity. These findings provide new insights into factors that may predispose individuals to alcohol use disorders and could inform personalised treatment plans.

Singapore, 27 October 2025 — Researchers from the Yong Loo Lin School of Medicine at the National University of Singapore (NUS Medicine) report that the gene, CHRNA3, acts as a key regulator of alcohol sensitivity. Published in the *Journal of Neuroscience*, the study provides long-sought experimental evidence to back up human genetic studies, linking *CHRNA3* function changes to measurable differences in innate alcohol sensitivity.

The study was led by Associate Professor Ajay S. Mathuru from the Department of Physiology at NUS Medicine with first author, Dr. Joshua Raine, Research Fellow, and Dr. Caroline Kibat, Senior Research Fellow, from the same department. The team found that mutations in the gene *chrna3*, a nicotinic acetylcholine receptor gene expressed in the nervous system, are associated with lowered sensitivity to alcohol in a preclinical laboratory model.

To determine if genetic factors can contribute to developing alcohol use disorders, the researchers utilised a two-choice assay where it is possible to self-administer alcohol voluntarily. They quantified avoidance versus attraction behaviour and analysed brain gene expression for key neurotransmitter receptors.

In normal conditions, brief attraction to alcohol followed by rapid avoidance as the dose rises, was observed. In contrast, preclinical laboratory models with mutations in *chrna3* delay this switch to avoidance, self-administering alcohol for much longer and tolerating higher concentrations.

The mutation was associated with altered brain expression of glutamatergic and GABAergic receptor genes, which regulate excitatory and inhibitory signalling respectively, and reduced alcohol's typical effects on behaviour by weakening the calming effect at low doses. These findings indicate that normal *chrna3* function helped control alcohol exposure and may underlie individual differences in alcohol sensitivity.

By linking the *chrna3* gene to measurable behavioural and brain changes, this study strengthens the biological understanding of addiction risk and offers insights into genetic predisposition to alcohol dependence.

“Our study provides direct experimental evidence that *chrna3* regulates alcohol sensitivity,” said Assoc Prof Mathuru. “Variants altering this gene’s function may increase the risk of developing alcohol use disorders in humans, a possibility that needs further investigation. Finding such risk factors can help develop more effective prevention and treatment strategies.” Assoc Prof Mathuru is a Joint Principal Investigator at Institute of Molecular and Cell Biology, A*STAR. He holds appointments with N.1 Institute for Health at NUS, the Institute of Digital Medicine (WisDM), and the Healthy Longevity Translational Research Programme at NUS Medicine. Collaborators of the study include Professor Antónia Monteiro and Dr Tirtha Das Banerjee from the Department of Biological Sciences at NUS.

The refined self-administration assay used in this study provides a cost-effective technique with faster turn-around times to uncover how specific genes modulate addiction-associated behaviours. It can complement other approaches to improve efficiency and guide future targeted therapies.

Building on this work, the team aims to analyse CHRNA3 variants in humans for similar alcohol sensitivity. They have extended their research to map reward and avoidance circuits and to dissect interactions using single and combined mutations in CHRNA5-CHRNA3-CHRNB4 gene cluster linked to substance addiction. The team’s future work aims to uncover mechanistic links across neurotransmitter systems altered in these mutants, assess impacts on other behaviours, and examine relevance to co-occurring human conditions - informing personalised preventive strategies for individuals with such genetic predispositions.

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Through a dynamic and future-oriented five-year curriculum that is inter-disciplinary and inter-professional in nature, our students undergo a holistic learning experience that exposes them to multiple facets of healthcare and prepares them to become visionary leaders and compassionate doctors and nurses of tomorrow. Since the School's founding in 1905, more than 12,000 graduates have passed through our doors.

In our pursuit of health for all, our strategic research programmes focus on innovative, cutting-edge biomedical research with collaborators around the world to deliver high impact solutions to benefit human lives.

The School is the oldest institution of higher learning in the National University of Singapore and a founding institutional member of the National University Health System. It is one of the leading medical schools in Asia and ranks among the best in the world (Times Higher Education World University Rankings 2025 by subject and the Quacquarelli Symonds (QS) World University Rankings by subject 2025).

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