# Study shows synergistic association between genetic and behavioral risks for liver disease

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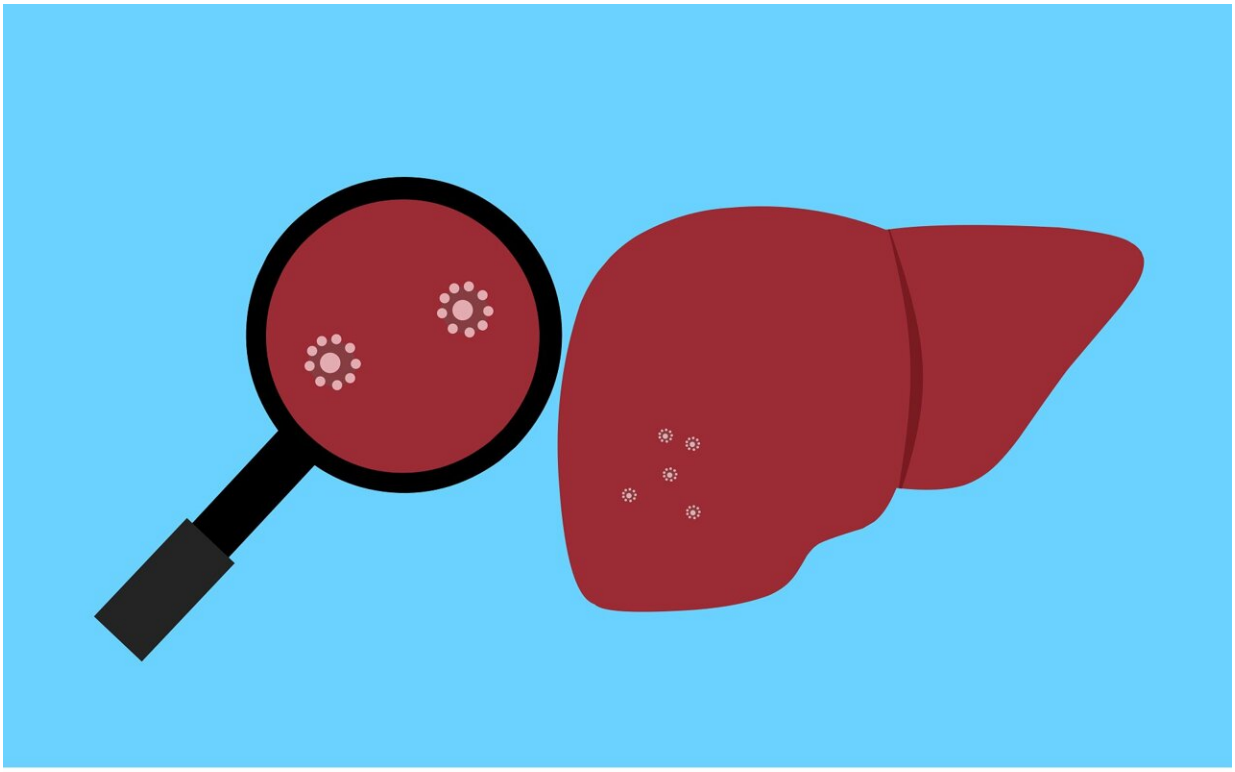

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Excessive alcohol use and obesity are known to increase the risk for developing cirrhosis and liver cancer, but the risk is not the same for everyone with those factors. Researchers at Baylor College of Medicine

found that a key genetic variant risk factor, PNPLA3, plays a synergistic role in increasing the risk for cirrhosis, liver cancer and liver-related death when combined with alcohol use and obesity. The findings were published today in *JAMA Network Open*.

The researchers conducted a prospective study of more than 400,000 people in the United Kingdom Biobank to assess whether PNPLA3 variant status could help stratify risk for heavy alcohol users with obesity. The risk for liver disease increases with any one of those factors, but the findings showed a dramatically increased risk when a person had all three.

The risk for developing cirrhosis was 17.5-fold higher for people with all three risk factors, compared to 1.75-fold higher for PNPLA3 variant alone, 1.76-fold higher for obesity alone and 2.35-fold for excessive drinking alone. The risk for developing liver cancer was 30.1-fold higher and the risk for liver-related mortality was 21.8-fold higher in people with all three risk factors.

"The PNPLA3 variant could be important in improving risk stratification for progression of liver disease," said Dr. Hyunseok Kim, first author of the study and a clinical fellow at Baylor at the time of research. "For example, a person with the PNPLA3 variant could be more proactively counseled about drinking habits and body mass index. The person might also be a candidate for more preventative measures like more frequent screenings or advanced imaging."

"Our study provides a unique opportunity to study the prognostic roles of PNPLA3, obesity and excessive alcohol use in the risk of liver disease," said Dr. Chris Amos, co-corresponding author of the study. Amos is director of the Institute for Clinical and Translational Medicine, professor of medicine and section chief of epidemiology and population sciences and associate director for population and quantitative science at

the Dan L Duncan Comprehensive Cancer Center at Baylor. "We don't see this kind of dramatic finding often, so we are excited by the clinical implications of these results."

"Currently, patients are not routinely screened for this gene variant, but our results show that checking this variant status may be a useful risk-stratification tool in surveillance of liver disease," said Dr. Fasiha Kanwal, co-corresponding author of the study. Kanwal is professor of medicine, section chief of gastroenterology and hepatology and member of the Dan L Duncan Comprehensive Cancer Center at Baylor.

The research team said that further study is needed to validate their results in a different dataset. Their findings used data mostly from people of European descent. The researchers hope to learn whether the results are similar in people of other ethnicities.

**More information:** Hyun-seok Kim et al, Synergistic Associations of PNPLA3 I148M Variant, Alcohol Intake, and Obesity With Risk of Cirrhosis, Hepatocellular Carcinoma, and Mortality, *JAMA Network Open* (2022). DOI: 10.1001/jamanetworkopen.2022.34221

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