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New genetic link found for alcohol-related liver cirrhosis

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In most people, any liver damage that might occur from drinking alcohol is reversible. However, in 25 to 30 percent of alcoholics what begins as accumulation of fat in the liver progresses to inflammation, fibrosis and ultimately irreversible cirrhosis, for which the only treatment is a liver transplant. A new study indicates that specific gene mutations might predispose some people to irreversible liver cirrhosis.

"It will be a major breakthrough if there are reliable diagnostic markers and a known genetic disposition that puts some alcoholics at increased risk to develop irreversible cirrhosis," said Chandrashekhar R. Gandhi, Ph.D., a professor at the University of Cincinnati and the Cincinnati Children's Hospital Medical Center and leader of the research team.

It has been challenging to study liver cirrhosis, also called end-stage liver disease, because most animals used in experiments do not develop the disease. Gandhi's research team is the first to develop a mouse model with depleted levels of a protein called augmenter of liver regeneration (ALR), which is essential for the survival of liver cells called hepatocytes.

"The mice with lower ALR levels spontaneously developed fatty liver, inflammation and fibrosis," explained Sudhir Kumar, Ph.D., a postdoctoral researcher and member of the research team. "This led us to hypothesize that ALR might be an important protein, whose deficiency or abnormality could be a critical factor in excessive liver injury due to additional stress, such as alcohol."

To test this hypothesis, the researchers gave ALR-deficient and normal mice alcohol for four weeks. The ALR-deficient mice developed excessive liver fibrosis, which is very similar to cirrhosis in people. The normal mice showed fat deposition but not fibrosis. Kumar will present this research at the American Society for Investigative Pathology (ASIP) Annual Meeting during Experimental Biology 2015.

The researchers next investigated whether abnormalities in the ALR gene exist in people. Their preliminary analysis revealed several mutations known as single nucleotide polymorphisms (SNPs) in the ALR gene, many of which haven't been identified before.

"We postulate that some of these SNPs could be responsible for the predisposition to develop cirrhosis," said Gandhi. "If that's true, it may be possible to identify such SNPs or measure ALR levels in blood to help catch liver problems earlier. Then an effective treatment can be provided to slow or reverse the ongoing liver injury." The researchers plan to expand their study by examining how often the ALR SNPs they have identified occur in patients with alcoholic liver disease compared to people without the disease.

Liver transplantation is the only therapy for end-stage liver disease, but is not available to everyone, is expensive, requires long-term immunosuppression, and comes with a risk that the body may reject the organ. With a shortage of donors, a significant number of people do not live long enough to receive a donated liver.

According to the Centers for Disease Control and Prevention, more than 36,000 people in the U.S. died from chronic liver disease and cirrhosis in 2013. Approximately half of those cases were caused by excessive alcohol intake.

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