

Gene variant boosts risk of fatty liver disease, scientists discover

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Researchers at UT Southwestern Medical Center have found that individuals who carry a specific form of the gene PNPLA3 have more fat in their livers and a greater risk of developing liver inflammation. They also found that Hispanics are more likely to carry the gene variant responsible for higher liver-fat content than African-Americans and Caucasians.

The new findings, published online today in the journal *Nature Genetics*, provide a gene-based explanation for the results of a 2004 UT Southwestern-led study that determined that the propensity to develop nonalcoholic fatty liver disease differs among ethnic groups, with a higher percentage of Hispanics developing the disorder than African-Americans or Caucasians.

"A single variation in the PNPLA3 gene was strongly associated with hepatic fat content, even after adjusting for other factors, such as obesity, diabetes status and alcohol intake," said senior study author Dr. Helen Hobbs, director of the Eugene McDermott Center for Human Growth and Development and an investigator for the Howard Hughes Medical Institute at UT Southwestern.

"Sequence variations in this gene explain much of the increased propensity of Hispanics to accumulate excess liver fat," she said.

Nonalcoholic fatty liver disease (NAFLD) is the most common form of liver disease in Western countries, and its incidence is growing. Previous

UT Southwestern research has shown that it may affect as many as one-third of adults in America.

"The gene variations we have identified might provide a way to predict who is most at risk for developing fatty liver disease and liver injury in response to environmental stresses such as obesity or infection," said Dr. Jonathan Cohen, professor of internal medicine in the McDermott Center and one of the authors of the study.

NAFLD results from the accumulation of triglycerides in the liver and is associated with metabolic disorders such as insulin resistance, obesity, diabetes and high cholesterol – many of the conditions that contribute to heart disease. It can also lead to liver inflammation, cirrhosis and liver cancer.

Approximately 10 percent of liver transplants performed in the U.S. are for cirrhosis related to NAFLD, according to the researchers. Treatments for NAFLD include weight loss, exercise, reducing alcohol intake and improved diabetes control.

"Knowing who is at increased risk of developing liver disease could aid physicians in encouraging their patients to make lifestyle changes or take other preventive measures to help mitigate their underlying genetic risk for the disorder," said Dr. Cohen, holder of the C. Vincent Prothro Distinguished Chair in Human Nutrition Research.

The new findings come out of the Dallas Heart Study, an 8-year-old groundbreaking investigation of cardiovascular disease that involves a large multiethnic group of participants. The \$12 million study investigates the links between genetics, lifestyle and the risks for heart disease.

As part of the Dallas Heart Study, more than 3,500 individuals from

Dallas County provided blood samples in 2000 for DNA isolation and other tests. Each participant also underwent multiple body scans with magnetic resonance imaging and computed tomography to examine the heart and other organs. Along with discovering new genetic ties to differences in blood levels of cholesterol and triglycerides, the researchers have used this information to identify new drug targets for the prevention and treatment of heart disease.

Data-gathering for the new study on fatty liver disease took advantage of a unique aspect of the Dallas Heart Study. Researchers with the study were the first to analyze hepatic fat in a large population using a technique called proton magnetic resonance spectroscopy – the most sensitive and quantitative noninvasive imaging technique available to measure the amount of fat in the liver. With this technique, they screened more than 2,100 individuals across multiple ethnicities. They then correlated that data with DNA tests from the same people and found the link to the PNPLA3 gene.

The next step in the research is to investigate how the various forms of the PNPLA3 gene affect lipid metabolism.

Other researchers from the McDermott Center involved with the study were lead author Dr. Stefano Romeo, a postdoctoral research fellow; Dr. Alexander Pertsemlidis, assistant professor; Dr. Chao Xing, assistant professor of clinical sciences; and Julia Kozlitina, a graduate student participating in a joint program between Southern Methodist University and UT Southwestern. Researchers from Perlegen Sciences, Lawrence Berkeley National Laboratory and the UT Health Science Center at Houston also were involved.

Source: UT Southwestern Medical Center

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