Obesity amplifies genetic risk of nonalcoholic fatty liver disease

April 26 2017

Dr. Jonathan Cohen and Dr. Helen Hobbs are pictured. Credit: UT Southwestern Medical Center

An international study based at UT Southwestern Medical Center revealed a striking genetic-environmental interaction: Obesity

significantly amplifies the effects of three gene variants that increase risk of nonalcoholic fatty liver disease (NAFLD) by different metabolic pathways.

NAFLD, which in its most serious form can lead to chronic liver disease (cirrhosis) and liver cancer, is a growing problem associated with the obesity epidemic. Despite intense study, the relationship between obesity and NAFLD had remained unresolved.

Of the three gene variants, or alleles, examined in this study, the strongest genetic-environmental interactions were found in the PNPLA3 gene variant, the first genetic cause of NAFLD ever identified. That variant was identified in The Dallas Heart Study, a longitudinal, multiethnic, population-based study directed by Dr. Helen Hobbs, co-senior author of the *Nature Genetics* study published online this week. Her scientific partner, Dr. Jonathan Cohen, a Professor of Internal Medicine, also is a senior author. The study's first author is Dr. Stefan Stender, a postdoctoral researcher from Copenhagen University Hospital working in the Department of Molecular Genetics and the Eugene McDermott Center for Human Growth and Development.

"While all obese individuals who have fatty liver disease would benefit from weight loss, our data suggest that those who have the risk allele in PNPLA3 are likely to benefit more," said Dr. Hobbs, Director of the McDermott Center, a Howard Hughes Medical Institute (HHMI) Investigator, and a Professor of Internal Medicine and Molecular Genetics.

The National Institutes of Health (NIH) describes NAFLD as one of the most common causes of liver disease in the United States. It estimates that 30 to 40 percent of U.S. adults have simple fatty liver, a buildup of fat in the liver without significant inflammation or cell damage. An estimated 3 to 12 percent of adults in the U.S. have a more serious form

of NAFLD, called nonalcoholic steatohepatitis (NASH), a buildup of liver fat with inflammation and cell damage that can lead to cirrhosis and is associated with liver cancer.

Looking first at the accumulation of fat in the liver, the researchers found that the prevalence of fat buildup ranged from 9 percent in lean individuals who did not have a PNPLA3 risk allele to 84 percent in obese individuals with two copies of the risk allele - one from each parent. In lean individuals, the risk alleles had a detectable but modest effect on liver fat accumulation.

"If you are thin, then you are unlikely to have excess fat in your liver even if you have the PNPLA3 risk alleles," said Dr. Cohen, who has appointments in the Center for Human Nutrition and the McDermott Center and who holds the C. Vincent Prothro Distinguished Chair in Human Nutrition Research. "On the other hand, if you are obese and lack the variant, then there is a good chance that you won't have excess fat in your liver.

"But if you are obese and do have the variant - particularly if you have two copies of the variant - you are very likely to have excess fat in your liver," he said, adding that these findings may help resolve some puzzling aspects of the relationship between obesity and fatty liver disease.

"It was very clear from our initial studies that these genetic variations did not affect body fat content, so at first it appeared that the gene's effect was independent of obesity," Dr. Cohen said. "The relationship between the PNPLA3 variant, obesity, and fatty liver disease represents a classic example of a gene-environment interaction."

This gene-environment interaction also results in those individuals who have the PNPLA3 risk allele and are obese developing inflammation and fibrosis, two later stages of NAFLD, the researchers report.

The Dallas Heart Study and the Dallas Biobank Study contained too few patients with end-stage liver disease (cirrhosis) to examine gene-environment interactions. Therefore, the researchers turned to data from a large cohort study in Copenhagen that included 384 subjects with cirrhosis. The risk of having cirrhosis among those with two copies of the risk allele who were very obese (defined as body mass index above 35) increased 5.8 times compared with those who were obese but lacked risk alleles.

The findings indicate that the interaction between obesity and genetics appears to promote chronic liver disease (cirrhosis) as well as the accumulation of fat in the liver, the researchers write. Similar effects were reported for the other two genes. The researchers noted that the three gene variants act via three different metabolic pathways.

"The risk alleles of the three strongest NAFLD risk variants confer only moderate risk in lean individuals but are major risk factors in people with higher BMIs, suggesting that genetic screening would be especially valuable in this subgroup," the researchers reported.

More information: Stefan Stender et al, Adiposity amplifies the genetic risk of fatty liver disease conferred by multiple loci, *Nature Genetics* (2017). DOI: 10.1038/ng.3855

Provided by UT Southwestern Medical Center