New gene sites affecting nonalcoholic fatty liver disease discovered

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NAFLD is a condition where fat accumulates in the liver (steatosis) and can lead to liver inflammation (nonalcoholic steatohepatitis or NASH) and permanent liver damage (fibrosis/cirrhosis). NAFLD affects anywhere from 11% to 45% of some populations and is associated with obesity, hypertension, and problems regulating serum lipids or glucose.

"These findings will help us to better diagnose, manage, and treat NAFLD in the future and help explain why some but not all people with obesity develop particular complications of obesity; some carry genetic variants that predispose them to some but not other metabolic diseases." says lead author Elizabeth K. Speliotes, M.D., Ph.D., M.P.H., an Assistant Professor of Gastroenterology, Internal Medicine, and Computational Medicine and Bioinformatics at the University of Michigan.

Investigators from The Old Order Amish, Age Gene-Environment Susceptibility - Reykjavik Study , Family Heart Study, and Framingham Heart Study, collectively called the GOLD (Genetics of Obesity-related Liver Disease) Consortium meta-analyzed genome wide association data for liver steatosis from 7,126 individuals and then followed up top associating variants in cases of NASH/fibrosis from the NASH-Clinical Research Network that were genetically matched to controls from the MIGen study to find the five variants that reproducibly associate with NAFLD. All the genetic variants found increased fat deposition in the liver. However, only some affected development of inflammation/permanent damage of the liver or development of serum

lipid/glucose abnormalities.

Ingrid Borecki, Ph.D., M.S., Associate Professor of Biostatistics and Genetics, co-director of the Division of Statistical Genomics at Washington University School of Medicine in Saint Louis, and senior author on the paper says "We found that approximately one quarter of the variation in NAFLD is influenced by genetic factors, and the loci we identified in the study account for about 20 percent of that genetic component. Thus the effects of these variants on NAFLD are substantial and possibly could be incorporated into clinical algorithms in the future to better classify people into risk categories. This work comes at a time when the number of people affected by these liver abnormalities is increasing, along with the prevalence of obesity in our population. Thus it is a growing problem."

Interestingly, the pattern of effects on multiple metabolic traits at two associated loci were identical and the genes closest to the best association signal at these loci are predicted to play a role in subsequent steps in triglyceride breakdown. Triglycerides are the major form of fat stored in the liver in NAFLD. This suggests that defects in triglyceride breakdown may contribute to development of NAFLD.

"Through the approaches we undertook in this study we show that we can classify genes into groups, implicating new pathways, not just genes, that affect this disease. This approach can be used to identify pathways that affect other traits as well" Speliotes says.

Speliotes notes that identifying variants and ultimately genes that affect NAFLD opens up new avenues for developing novel therapeutics for this condition. Currently, only weight loss and possibly increased physical activity can decrease hepatic steatosis. Getting people to lose weight and increase their physical activity however is a challenge worldwide, which is why obesity has become a global epidemic. This study provides

possible new drug targets for therapeutic intervention of NAFLD. Further, our comprehensive examination of the effects of these genetic variants on multiple traits can help guide development of therapeutics against the gene targets of these variants so that we can chose targets that have specific effects on a desired disease while minimizing unwanted side effects.

More information: www.plosgenetics.org/article/i … journal.pgen.1001324

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