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Researchers Identify Genetic Variants Linked to Risk of Nonalcoholic Fatty Liver Disease, Type 2 Diabetes

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(PhysOrg.com) -- For the first time, Yale researchers have identified common genetic variants that predispose lean individuals to nonalcoholic fatty liver disease (NAFLD) and insulin resistance. NAFLD is now the most common chronic liver disease in the U.S. and insulin resistance is the major factor that leads to type 2 diabetes. Their study also explains the mechanism by which individuals develop these conditions, despite maintaining normal body weight. The research appears in the March 25, 2010 issue of the *New England Journal of Medicine*.

The Yale team studied 95 young, lean, healthy Asian-Indian men, a cohort which they have previously found to have a high prevalence of NAFLD, to investigate whether there is a genetic cause for their increased liver fat content and insulin resistance. More specifically, they investigated the possible relationship between two variants in the apolipoprotein C3 (Apo C3) gene with liver fat content and insulin resistance. The team was led by Gerald I. Shulman, M.D., Ph.D., F.A.C.P., a Howard Hughes Medical Institute Investigator and the George R. Cowgill Professor of Physiological Chemistry, Medicine and Cellular & Molecular Physiology at Yale.

They found that individuals with these Apo C3 gene variants had significantly higher plasma Apo C3 concentrations associated with increased plasma triglyceride concentrations, a factor in the development of NAFLD. Furthermore they found that these individuals had much

lower ability to clear plasma triglyceride from the blood stream. More importantly, approximately 40% of the men with these ApoC3 gene variants had NAFLD, whereas none of the men without the gene variants had NAFLD. In addition, those with NAFLD were markedly insulin resistant, a condition that is known to cause type 2 diabetes. Shulman's team then went on to validate these findings in another group of 163 men of mixed ethnicity.

"Nonalcoholic fatty liver disease, insulin resistance, type 2 diabetes, and all of their associated conditions — such as cardiovascular disease, blindness, and kidney failure — are reaching epidemic proportions in this country, yet the genetic and molecular basis for these diseases remains poorly understood. In fact, type 2 diabetes has often been referred to as the 'geneticist's nightmare,'" Shulman says. "These studies demonstrate that the candidate gene approach for insulin resistance can work if it is approached from the underlying mechanism of lipid-induced causes."

Interestingly, when the men with the ApoC3 gene variants underwent a modest weight loss, both NAFLD and insulin resistance improved, which Shulman says demonstrates important gene-environment interactions. "Taken together, I believe these Apo C3 gene variants lower the weight threshold for the development of NAFLD, insulin resistance and type 2 diabetes. Virtually everyone will develop NAFLD and insulin resistance if they become obese. But even at normal weight, individuals carrying these Apo C3 gene variants may develop NAFLD, insulin resistance and type 2 diabetes."

Given the key role that NAFLD and insulin resistance play in the development of type 2 diabetes, Shulman and his team of researchers hope their finding of a genetic component for an increased susceptibility for NAFLD and insulin resistance will lead to new diagnostic tools to identify, and novel therapies to treat, individuals prone to develop these

conditions.

Provided by Yale University