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Studies in humans and animals show link between GALNT2 gene and levels of HDL cholesterol

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Researchers have uncovered how genes identified from genome-wide association studies (GWAS) affect high-density lipoprotein cholesterol (HDL-C), a biomarker of cardiovascular disease, after comparing several animal models with human patient data. A large team from the Perelman School of Medicine at the University of Pennsylvania, the University of Copenhagen, Bristol-Myers Squibb and several others institutions detail their findings in a paper published today in *Cell Metabolism*.

They report identification of the first known humans with genetic loss-of-function of GALNT2, a novel gene associated with HDL-C and triglyceride levels through GWAS, and then compared the effect of GALNT2 loss-of-function in humans, mice, rats, and nonhuman primates to understand how this gene influences HDL metabolism.

"GWAS has identified many new areas of the genome as novel and potentially important contributors to disease-related traits like lipid levels, but finding the specific genes in these regions and how they affect these traits has been very challenging," said the study's lead author, Daniel J. Rader, MD, chair of Penn's department of Genetics, and lead author on the study. "This study provides one blueprint for how to relate a GWAS-implicated gene to a clinically relevant phenotype across species."

Rader and colleagues identified two humans carrying variants in GALNT2 in two independent families that both completely blocked gene's enzymatic function. They compared the HDL-C levels of the carriers of these variants to mouse, rat, and monkey models of deficiency or inhibition of GALNT2 and found that all the models and the human subjects had low HDL levels compared to models with GALNT2. Researchers also sought to understand how GALNT2 maintains HDL-C levels, as the gene encodes enzyme modifying proteins through carbohydrate additions. The investigators compared all the proteins in the blood and liver - a tissue critical to regulating HDL levels - in the humans, mice and rats with GALNT2 deficiency to pinpoint any proteins with reduced modifications that may impact HDL levels.

The collaborative team concluded that humans, mice, and rats lacking GALNT2 had reduced activity of phospholipid transfer protein (PLTP) in the blood, which indicates GALNT2 as a conserved regulator of HDL levels through its effects on PLTP function.

"The role both HDL and PLTP may play in risk of heart disease remains very unclear. These findings add a new wrinkle to the contribution of PLTP to HDL through GALNT2," Rader said. He also noted that the direct contribution of GALNT2 to the development of cardiovascular disease remains an important unanswered question.

GALNT2 was among the first identified novel genes associated with HDL-C and triglycerides in GWAS for blood lipid traits. Despite the early implication of the GALNT2 locus, the specific role of this gene in HDL-C levels remained elusive. In a previous study, Rader and his colleagues identified 95 loci associated with lipid traits in more than 100,000 subjects.

Provided by Perelman School of Medicine at the University of

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