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With mutation, you can have your cream and eat it, too

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People who carry a malfunctioning copy of a particular gene are especially good at clearing fat from their systems. The report in the December *Cell Metabolism*, a Cell Press publication, shows how the mutant gene influences metabolism in this way.

"It looks like this might be something good to have," says Jan Albert Kuivenhoven of the University Medical Center Groningen in The Netherlands, but not so fast. It remains to be seen whether the people he studied will enjoy a lower incidence of heart disease or other health benefits.

The new findings are also a win for genome-wide association studies, which have been under fire recently for their failure to explain many human diseases and traits. "It shows these studies can help us identify new biological roots," Kuivenhoven says.

Epidemiological studies have led to the notion that triglycerides and LDL cholesterol are bad for us while HDL cholesterol is good, he explained. Drugs designed to lower "bad" LDL cholesterol are effective in treating heart disease, and, following on that same logic, efforts are underway to raise HDL cholesterol.

Yet, Kuivenhoven says, "the biology is more complex than everyone wants us to believe." His goal is to work out those details.

In the current study, Kuivenhoven and his colleague G. Kees Hovingh

studied two families with unusually high HDL cholesterol and low triglycerides. They also put together a list of all the genes they suspected might play a role in their distinctive lipid profiles and sequenced them. On that list was GALNT2, a gene that had turned up before in genome-wide association studies (GWAS) as a candidate lipid metabolism gene.

The new sequencing effort identified a mutation in GALNT2. When GALNT2 mutation carriers drank pure cream, they were better able to clear those triglycerides than noncarriers were, the report shows.

It appears that comes from a change in the interaction between the mutant enzyme and another factor known as apolipoprotein C-III. Apo C-III inhibits an enzyme that breaks triglycerides down, and it does that especially well when modified by GALNT2. When GALNT2 loses its function, Apo C-III doesn't do its job as well, either, and triglycerides are cleared more rapidly as a result.

The findings reveal an unexpected and exciting link between lipid metabolism and the sugar modification of proteins (a process known as glycosylation).

"Thirty to fifty percent of proteins are glycosylated," he says. "Nature puts a lot of effort into this, and its physiological relevance is hardly known."

Provided by Cell Press