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Research asks why genetic mutation leads to decreased triglycerides in blood

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Common knowledge says that genetic mutations are bad. This is true for most mutations of lipoprotein lipase (LPL), the enzyme in the blood responsible for the breakdown of lipoproteins, which allows tissue to utilize energy from fat. People with these mutations are unable to break down fat in the blood, causing very high levels of lipids in the blood and putting them at risk of heart disease. However, one specific mutation

actually leads to better processing of lipids, leading to improved heart health.

This mutation was first discovered in the early 1990s, and since then scientists have understood the mutation's positive result. It's even used in a gene therapy treatment approved in Europe. But even though the result of the mutation was understood, the mechanism that caused it was not.

"Mutations most commonly result in loss of function," said Saskia Neher, PhD, assistant professor of biochemistry and biophysics at the UNC School of Medicine. "In this case, there's a mutation and the function is actually better. We wanted to know why."

Research published in the journal *Biochemistry* this month helps to finally answer the question. The first author on the study is Cassandra Hayne, a doctoral candidate in UNC's department of biochemistry and biophysics. The discovery comes as the result of great persistence on Hayne's part.

Hayne and Neher used highly purified LPL and the truncated protein, LPL^{S447X}, to compare the ability of each to breakdown lipoproteins. They found no difference in the proteins' ability to process lipoproteins.

"When we didn't find a clear answer, I had to begin thinking about secondary functions of LPL," Hayne said. "I knew that one of those secondary functions was that LPL serves as a bridge to three different cell receptors in the liver."

Hayne found that the increased function of LPL^{S447X} can be attributed to the fact that it more effectively binds to the receptors in the liver, leading to increased uptake of lipoproteins in the liver. The increased liver function explained what is seen in patients' blood: a decrease in triglycerides.

"This finding is really a testament to Cassandra's persistence," said Neher, also a member of the McAllister Heart Institute. "We kept trying this and that, thinking we'd find something different. LPL^{S447X} has been studied for years without a satisfying answer. I feel like we have that now."

More information: Cassandra K. Hayne et al. Biochemical Analysis of the Lipoprotein Lipase Truncation Variant, LPL^{S447X}, Reveals Increased Lipoprotein Uptake, *Biochemistry* (2017). DOI: 10.1021/acs.biochem.6b00945

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