Gene mutation behind protein that helps regulate cholesterol levels identified

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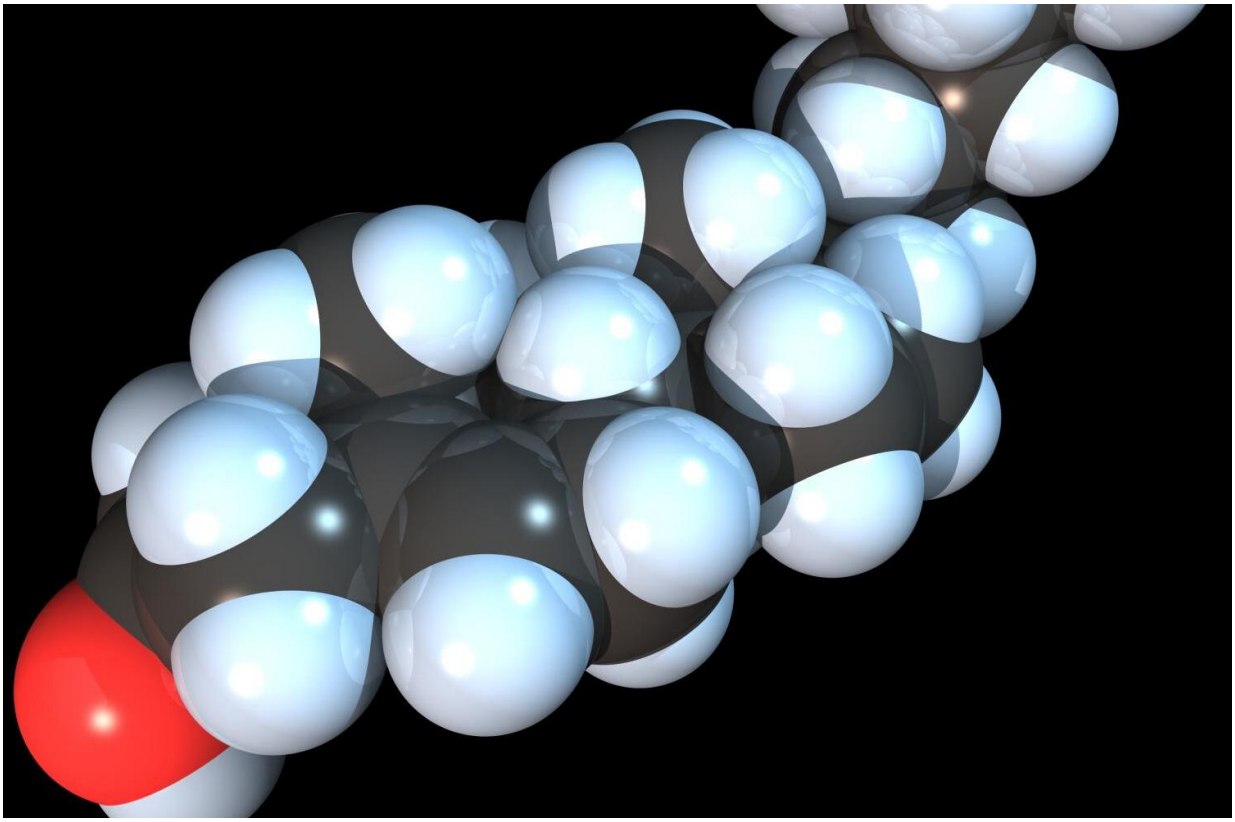

Space-filling model of the Cholesterol molecule. Credit: RedAndr/Wikipedia

A team of researchers affiliated with several institutions in China has identified a gene mutation that is at least partly responsible for regulating cholesterol levels in the bloodstream. In their paper published in the

journal *Science*, the group describes how they tracked down the gene mutation responsible for the creation of a key protein involved in the process.

As the researchers note, low-density lipoprotein cholesterol (LDL-C) can build up in arteries, leading to heart attacks and strokes. For that reason, it would be helpful to know what causes it. Prior research has shown that genetics plays a factor in what happens to food containing LDL-C when it is consumed. But what genetic factors cause more of it to wind up in the arteries in some people and less in others? In this new effort, the researchers sought to learn more about such factors.

The study centered on analyzing the genes of a single family who all, save one, had abnormally low levels of LDL-C in their blood. The researchers were able to isolate a particular gene mutation that differed for the one unique individual—a gene mutation called LIMA1. Pleased with their findings, the group then conducted genetic testing on 509 people from a group called the Chines Kazakh—they are known to have low levels of LDL-C in their blood. The initial family came from this group. Analysis of the data showed that those individuals with low levels of LDL-C in their blood also carried the same gene mutation, and those without it had normal levels. A closer look revealed that the gene mutation was responsible for the production of a protein, which they called LIMA1. That protein, the researchers surmised, was a regulator of LDL-C.

To learn more about LIMA1, the researchers conducted studies with mice and found that the protein appears to be expressed in the small intestine. They also suggest that the protein could be synthesized, possibly leading to new drugs to reduce cholesterol levels in people—and hopefully to reduce the risk of developing cardiovascular disease.

More information: Ying-Yu Zhang et al. ALIMA1variant promotes

low plasma LDL cholesterol and decreases intestinal cholesterol absorption, *Science* (2018). DOI: 10.1126/science.aao6575

Abstract

A high concentration of low-density lipoprotein cholesterol (LDL-C) is a major risk factor for cardiovascular disease. Although LDL-C levels vary among humans and are heritable, the genetic factors affecting LDL-C are not fully characterized. We identified a rare frameshift variant in the LIMA1 (also known as EPLIN or SREBP3) gene from a Chinese family of Kazakh ethnicity with inherited low LDL-C and reduced cholesterol absorption. In a mouse model, LIMA1 was mainly expressed in the small intestine and localized on the brush border membrane. LIMA1 bridged NPC1L1, an essential protein for cholesterol absorption, to a transportation complex containing myosin Vb and facilitated cholesterol uptake. Similar to the human phenotype, Lima1-deficient mice displayed reduced cholesterol absorption and were resistant to diet-induced hypercholesterolemia. Through our study of both mice and humans, we identify LIMA1 as a key protein regulating intestinal cholesterol absorption.