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Study of Polynesian participants yields new clues to genetic causes of high cholesterol

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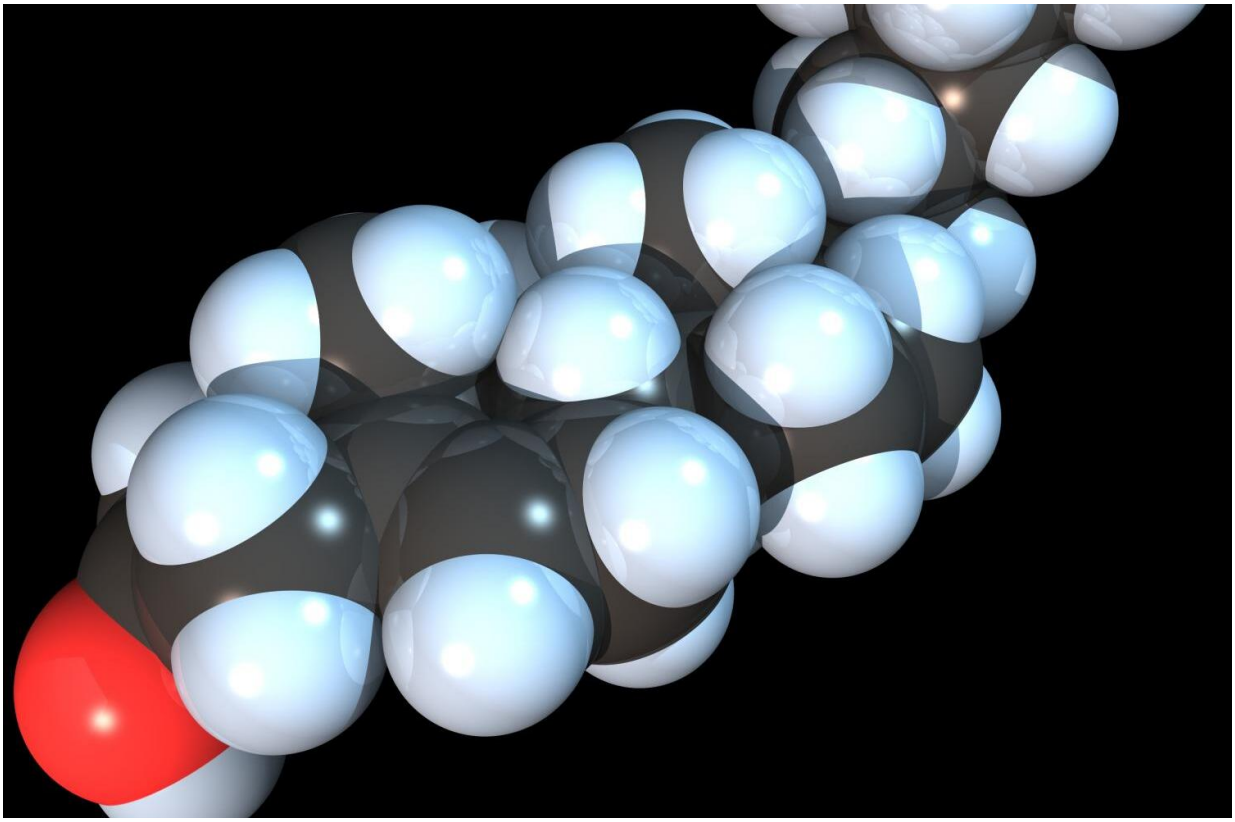

Space-filling model of the Cholesterol molecule. Credit: RedAndr/Wikipedia

The discovery of a genetic variant that is relatively common among people of Polynesian ancestry, but incredibly rare in most other populations, is giving clues to the genetic underpinnings of high

cholesterol in all people, according to new research led by University of Pittsburgh School of Public Health geneticists in partnership with several other groups, including the University of Otago and the Samoan health research community.

The surprising finding, published this week in the journal *Human Genetics and Genomics Advances*, demonstrates the importance of ensuring diversity in genetic databases.

"If we had only been looking in populations with European ancestry, we might have missed this finding entirely," said lead author Jenna Carlson, Ph.D., assistant professor of human genetics and biostatistics at Pitt Public Health. "It was through the generosity of thousands of Polynesian people that we were able to find this variant, which is a smoking gun that will spark new research into the biology underlying cholesterol."

High cholesterol is a major cause of disease burden in countries of all income levels, is a risk factor for heart disease and stroke, and is estimated to cause 2.6 million deaths annually worldwide, according to the World Health Organization.

Carlson and her team built their study to explore a signal that popped up in a large genome-wide survey looking for genes associated with lipids, or fats, in the body. It suggested that a gene variant on chromosome 5 could be associated with cholesterol. The team set out to "fine map" the region using genetic data from 2,851 Samoan adults from the Obesity, Lifestyle, And Genetic Adaptations (OLAGA, which means "life" in Samoan) Study Group, whose members had also provided health information, including lipid panels. To double-check the finding, the team looked for the association in 3,276 other Polynesian people from Samoa, American Samoa and Aotearoa New Zealand, and the same connection between the variant and cholesterol was seen in them.

Using data from the western Polynesian Samoan participants, the team was able to fill in the missing information around the region they were interested in on chromosome 5. This led them to BTNL9—a gene that directs the production of the BTNL9 protein. Proteins typically signal to cells to perform actions, though scientists still haven't characterized the precise role of the BTNL9 protein.

It turned out that Polynesian people with low levels of HDL "good" cholesterol and high levels of triglycerides had a "stop-gain" variant in BTNL9, which means the gene was being directed to stop doing its protein-production job, a strong hint that the BTNL9 protein is involved in helping cells maintain healthy cholesterol levels.

"We don't know a lot about this variant because it's not seen in published genome references, which overrepresent European ancestry individuals—it's virtually nonexistent in European ancestry populations, has very low frequency in South Asians and isn't even particularly common in eastern Polynesian people, such as Māori living in Aotearoa New Zealand," Carlson said.

"But the way it's linked to lipid panels in Samoan people tells us that this gene is important to cholesterol, something we didn't know before. By further exploring BTNL9, we might someday discover new ways to help everyone maintain healthy cholesterol levels."

More information: Jenna C. Carlson et al, A stop-gain variant in BTNL9 is associated with atherogenic lipid profiles, *Human Genetics and Genomics Advances* (2022). DOI: 10.1016/j.xhgg.2022.100155

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