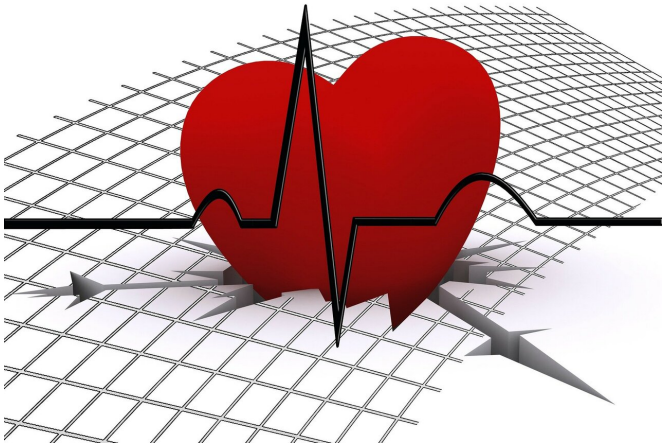
Researchers link gene variant in Amish population to lower risk of heart disease

2 December 2021



Credit: CC0 Public Domain

University of Maryland School of Medicine (UMSOM) researchers, working with scientists from the Regeneron Genetics Center (RGC), discovered a new gene variant associated with lower levels of heart-damaging LDL cholesterol and a blood clotting protein called fibrinogen that appears to significantly lower a person's risk of heart disease. While the gene variant is extremely rare in the general population (less than 1 in 10,000), it is found in about 12 percent of those living in the Lancaster county, Pennsylvania Amish community, according to the study published today in the journal *Science*.

Researchers have long known about gene mutations linked to cholesterol levels. This is the first time, however, they have found a gene variant that can significantly reduce the level of two heart disease risk factors and subsequently reduce a person's risk of heart disease. The finding could potentially lead to novel treatments that may help prevent clogged arteries, blood clots, and cardiovascular disease.

"Leveraging data from more than 500,000 from the general population, it was found that those who carried this variant had a 35 percent lower risk of heart disease compared to those who did not," said study leader May Montasser, Ph.D., Assistant Professor of Medicine at UMSOM and a member of UMSOM's Program for Personalized and Genomic Medicine. "The genetic variant appears to either control the synthesis of cholesterol and fibrinogen or accelerate their clearance from the blood, which protects the heart. This finding could lead to targeted drugs that mimic the action of this variant to keep arteries free of plaque and clots."

Genetic sequencing of samples from nearly 7,000 Amish study participants who have been participating in genetic research with UMSOM since 1995 was performed at the RGC. The researchers found a genetic variant in the gene B4GALT1 was associated with a nearly 14 mg/dL lower LDL cholesterol and nearly 30 mg/dL lower fibrinogen. After the variant was identified, they tested its effects in mice that were genetically modified to express the variant.

"The mouse model, encoding for this gene mutation, also showed decreased levels of LDL cholesterol and fibrinogen, confirming the effect of this variant," said Giusy Della Gatta, Ph.D., study leader and RGC senior staff scientist. "This model represents an invaluable tool to unravel the molecular mechanisms that help protect against cardiovascular disease."

The Amish community is ideal for genetic studies due to its common lineage and homogeneous lifestyle that makes finding novel links between genes and health easier for scientists. Study co-author Alan Shuldiner, MD, John L. Whitehurst Professor of Medicine and Associate Dean for Personalized & Genomic Medicine at UMSOM, founded the Amish Research Clinic in Lancaster, PA. The clinic's research has discovered genes playing a role in type 2 diabetes and heart disease,

as well as a gene that plays a role in determining why some people don't respond to the anticlotting medicine Plavix.

"This is a ground-breaking finding and would not have been possible without the participation and partnership of the Amish community," said E. Albert Reece, MD, Ph.D., MBA, Executive Vice President for Medical Affairs, UM Baltimore, and the John Z. and Akiko K. Bowers Distinguished Professor and Dean, University of Maryland School of Medicine. "We are so grateful for their continuing commitment to research and advancement of precision medicine."

More information: May E. Montasser et al, Genetic and functional evidence links a missense variant in B4GALT1 to lower LDL and fibrinogen, *Science* (2021). DOI: 10.1126/science.abe0348

Provided by University of Maryland School of Medicine