New gene variant that protects against coronary heart disease uncovered

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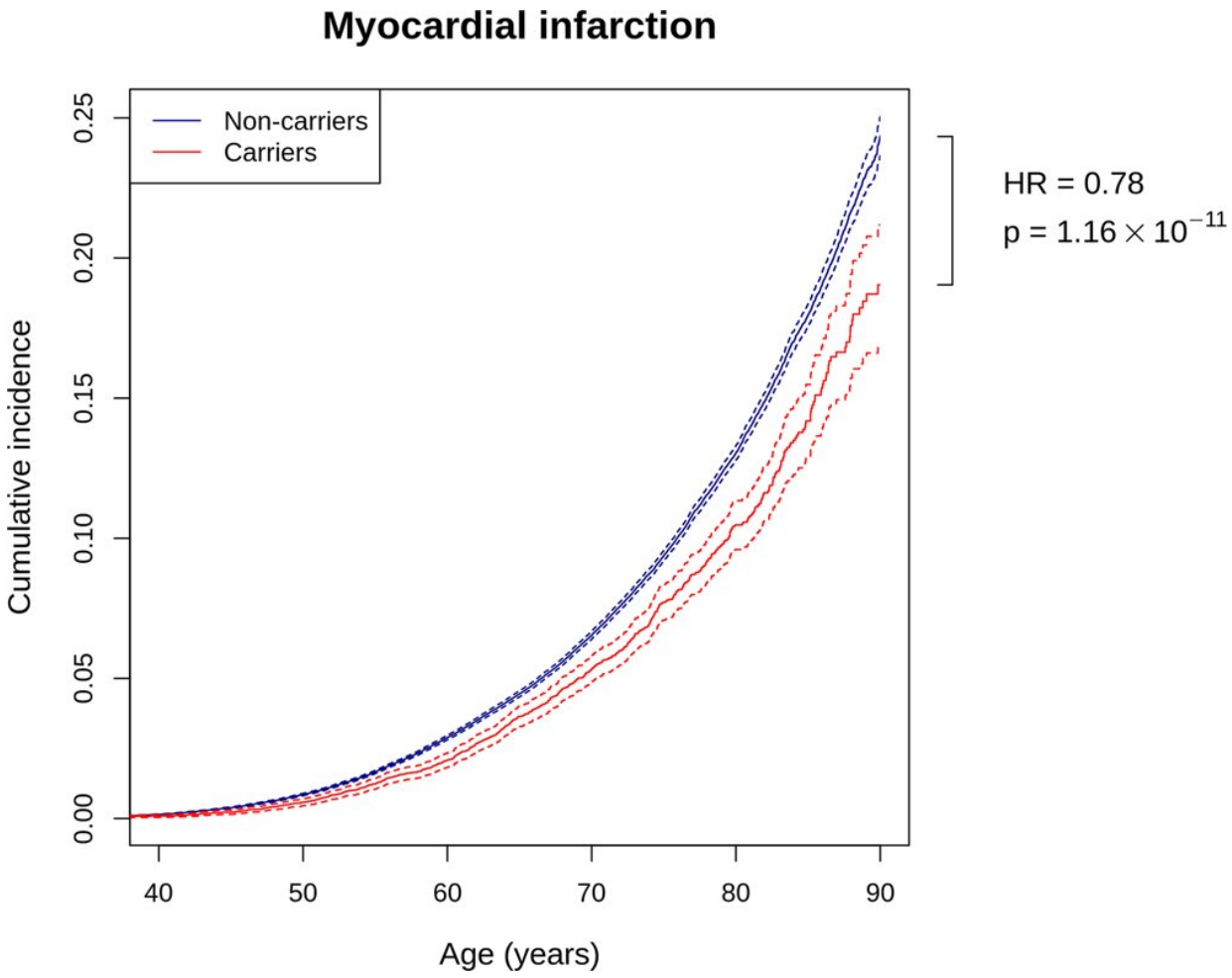

Cumulative incidence plots for first event of myocardial infarction in FinnGenR6. Red line represents carriers (homo- or heterozygous) for either rs534125149 or rs201988637 (n = 17,838), and blue line represent non-carriers (n = 242,567). Hazard ratio and p-value are from cox-proportional hazards model. Dashed lines represent 95% confidence intervals. Credit: *Communications*

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A variant typical of the Finnish population that protects against heart diseases was identified in the FinnGen genomic study coordinated by the University of Helsinki. The risk of developing heart diseases is roughly one-fifth lower in carriers of the variant compared to the population on average.

The protective effect of the newly discovered variant against coronary heart disease is likely to be caused by the below-average arterial stiffness of variant carriers.

The variant in question is located in the MFGE8 gene that produces a protein called lactadherin, which is known to affect the process of arterial stiffening. The results indicate that the variant inhibits the function of the lactadherin protein. However, further studies are needed to ascertain this.

The findings, published in the *Communications Biology* journal on 17 August 2022, are based on a FinnGen dataset comprising more than 260,000 Finnish biobank sample donors.

Discovery made possible by the FinnGen research dataset

Cardiovascular diseases remain the most common cause of death worldwide. In Finland too, one-third of all deaths are caused by cardiovascular diseases.

In the recently published study, genomic variation between individuals with coronary heart disease and other study subjects was compared in

the FinnGen dataset. The results exposed 38 genetic loci associated with a risk of coronary heart disease, of which four, including the MFGE8 gene, were previously unknown.

"Hundreds of genetic factors affecting the risk of developing cardiovascular diseases have already been identified. However, the number of known variants that reduce the risk of disease and directly indicate the active gene, like the MFGE8 variant, is relatively low," says Doctoral Researcher Sanni Ruotsalainen from the University of Helsinki's Institute for Molecular Medicine Finland, who carried out the study.

Identifying the link between MFGE8 and coronary heart disease is a good example of the special benefits the Finnish population offers to genetic research. The variant in question is 70 times more common in Finland than in the overall European population, which is why it has not been observed in previous similar gene studies elsewhere. The variant is found in roughly 5.5% of Finns, with slightly higher frequency in eastern Finland than in western parts of the country.

A protective effect against coronary heart disease opens up perspectives in drug development

The variant was also found to have an effect on the age of onset of coronary heart disease. Carriers of the protective variant suffered a myocardial infarction or were diagnosed with coronary heart disease on average 18 months later than the rest of the population.

"In terms of developing new drug therapies, variants that reduce the risk of developing diseases are particularly interesting," says the study's principal investigator, Professor Samuli Ripatti from the University of Helsinki.

For example, PCSK9 inhibitors, the next-generation cholesterol drugs already in use, have been developed on the basis of a similar observation. This new finding introduces a new mechanism of action alongside cholesterol that protects against cardiovascular diseases.

"Our findings also demonstrated that the MFGE8 variant did not increase the risk of any other disease. Therefore, a drug molecule mimicking the functioning of the gene could make it possible to develop entirely novel therapies for the prevention of cardiovascular diseases," Ripatti notes.

More information: Sanni E. Ruotsalainen et al, Inframe insertion and splice site variants in MFGE8 associate with protection against coronary atherosclerosis, *Communications Biology* (2022). DOI: 10.1038/s42003-022-03552-0

Provided by University of Helsinki