Variants in the genome interact with each other and with the environment to affect cardiovascular disease risk

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Scientists at deCODE genetics, a subsidiary of Amgen, and collaborators from the Icelandic health care system and Copenhagen University, have published a study in the journal *Cell* titled "Complex effects of sequence variants on lipid levels and coronary artery disease."

The work described in the paper is based on searching for variants in the genome that are associated with variance in quantitative traits and the assumption that those variants must interact either with other variants or components of the environment.

It is well established that "bad" cholesterol (also called non-HDL cholesterol and LDL cholesterol) directly contributes to the development of cardiovascular disease.

The environment and the genome both influence bad cholesterol and consequently cardiovascular health. This influence can be complex and intertwined. For example, drinking alcohol tends to increase bad cholesterol, but the study showed that carriers of a particular sequence variant that is known to slow down the metabolism of alcohol are protected against the negative effects of alcohol consumption on coronary artery disease.

Carriers of particular sequence variants that associate with liver fat are more susceptible to increases in bad cholesterol upon consumption of oily fish than non-carriers.

Similarly, the authors show that variants in the genome interact with each other to affect cholesterol levels. The study demonstrates that homozygotes of the APOE2 allele that protects against the risk of Alzheimer's disease risk are as likely to have high levels of bad cholesterol (non-HDL cholesterol) as non-carriers, but have much fewer particles carrying the cholesterol (ApoB).

These homozygotes are at a similar risk of developing coronary artery disease as non-carriers, demonstrating that is the amount of bad cholesterol and not the number of bad cholesterol-carrying particles that confers the risk of disease. Furthermore, the authors show that blood group secretor status influences cholesterol levels and cardiovascular

disease risk among individuals who are not in the A1 blood group but has no influence among those in the A1 blood group.

These examples highlight the complex and fascinating ways in which the genome and the environment interact to affect health and demonstrate that a broad range of models are required for a comprehensive understanding of the genetics of human diseases.

More information: Daniel F Gudbjartsson, Complex effects of sequence variants on lipid levels and coronary artery disease, *Cell* (2023). DOI: 10.1016/j.cell.2023.08.012.
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