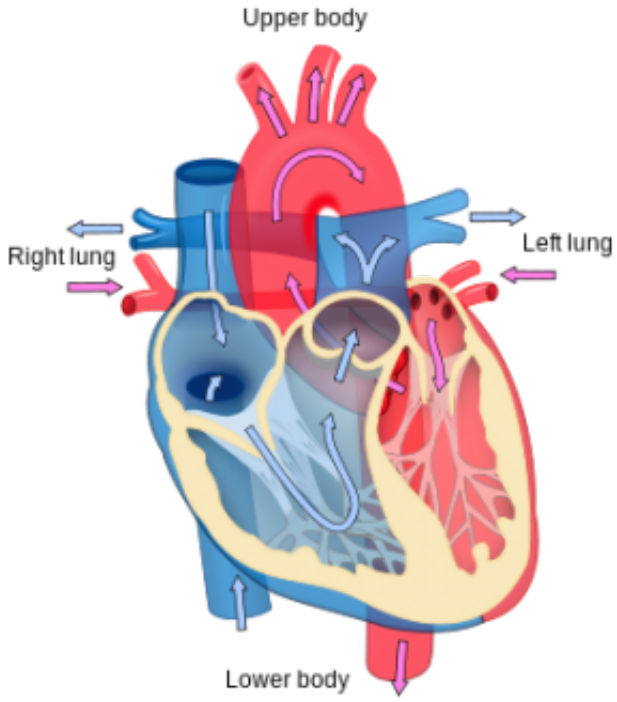
Errors in single gene may protect against heart disease

November 12 2014



Heart diagram. Credit: Wikipedia

Rare mutations that shut down a single gene are linked to lower cholesterol levels and a 50 percent reduction in the risk of heart attack, according to new research from Washington University School of Medicine in St. Louis, the Broad Institute at Massachusetts Institute of Technology and Harvard, and other institutions.

The gene, called NPC1L1, is of interest because it is the target of the drug ezetimibe, often prescribed to lower cholesterol.

The study appears Nov. 12 in *The New England Journal of Medicine*.

Everyone inherits two copies of most genes—one copy from each parent. In the study, the researchers found that people with one inactive copy of NPC1L1 appeared to be protected against high LDL cholesterol —the so-called "bad" cholesterol—and coronary heart disease, a narrowing of the heart's arteries that can lead to heart attacks.

"This analysis demonstrates that human genetics can guide us in terms of thinking about appropriate genes to target for clinical therapy," said first author Nathan O. Stitziel, MD, PhD, a cardiologist at Washington University School of Medicine. "When people have one copy of a gene not working, it's a little like taking a drug their entire lives that is inhibiting this gene."

The investigators mined genetic data from large clinical trials to find individuals with naturally occurring mutations in the NPC1L1 gene that completely shut it down. They analyzed multiple existing studies, pooling data from about 113,000 people. Of these trial participants, only 82 were found to have a mutation that shut off one copy of the NPC1L1 gene. No one had two inactive copies of NPC1L1. Based on a subset of data in the analysis, the researchers estimate roughly 1 in 650 people carry one inactive version of the gene.

The investigators found that people with only one working copy of the gene had LDL cholesterol levels an average of 12 milligrams per deciliter lower than the wider population of people with two working copies of the gene. This approximately 10 percent reduction in LDL cholesterol is comparable to that seen in patients taking ezetimibe. But beyond simply lowering cholesterol, the 82 people with inactive copies

also had about half the risk of coronary heart disease as people with two functional copies of the gene.

The individuals with the rare gene mutations did not appear to differ from the larger population in any other ways, including in measures of blood pressure, body mass index and rates of diabetes.

"Protective mutations like the one we've just identified for heart disease are a treasure trove for understanding human biology," said senior author Sekar Kathiresan, MD, of the Broad Institute, and director of preventive cardiology at Massachusetts General Hospital. "They can teach us about the underlying causes of disease and point to important drug targets."

Among medications that lower cholesterol, ezetimibe is not in the widely prescribed class of drugs called statins, which stop the body from manufacturing its own cholesterol. Instead, ezetimibe blocks dietary cholesterol absorption in the gut by inhibiting the NPC1L1 protein, perhaps approximating the effect of having only one working copy of the NPC1L1 gene.

While ezetimibe is known for its cholesterol-lowering effect, there is debate over whether it also reduces risk of heart disease.

"It's not possible to draw a direct conclusion about ezetimibe from this study," Stitziel said. "But we can say this genetic analysis gives us some confidence that targeting this gene should reduce the risk of heart attack. Whether ezetimibe specifically is the best way to target NPC1L1 remains an open question."

Stitziel and his colleagues pointed out that this question will be addressed later this month with the reporting of results from a large clinical trial called IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT).

The trial was designed to compare outcomes—such as cardiovascular-related death and heart attack—in patients taking a statin plus ezetimibe versus patients taking a statin plus placebo. Together, ezetimibe plus statins have been shown to lower LDL cholesterol more than statins alone. IMPROVE-IT is expected to determine whether the combination therapy also lowers the risk of coronary heart disease beyond the benefit provided by statins alone.

More information: Stitziel NO, et al. for the Myocardial Infarction Genetics Consortium. Inactivating mutations in NPC1L1 and protection from coronary heart disease. The *New England Journal of Medicine*. Nov. 12, 2014.

Provided by Washington University School of Medicine