Genetics of cholesterol point to possible drug targets for heart disease, diabetes

1 October 2018

Credit: CC0 Public Domain

From the DNA of nearly 300,000 veterans, scientists have singled out a handful of genetic mutations that not only govern levels of cholesterol, but may also inform the development and use of drugs for cardiovascular disease and diabetes, according to researchers at the Stanford University School of Medicine and the Palo Alto Veteran Affairs Health Care System.

Scientists zeroed in on three mutations that disrupt the function of their respective genes. That might sound bad, but in this case, it's actually beneficial, as veterans who carried one of these mutations showed improved cholesterol profiles in their blood and a decreased risk of either heart disease, abdominal aortic aneurysms or diabetes, depending on the gene mutation.

"The idea is to use genetic data linked to electronic health records from a very large number of individuals to find genetic variants that simultaneously improve lipid profiles and protect against cardiovascular disease," said Tim Assimes, MD, Ph.D., associate professor of cardiovascular medicine. "From there, you can figure out what the best potential drug targets are."

All three of the main genes pinpointed in the study—PDE3B, PCSK9 and ANGPTL4—could one day be targets for the treatment of either heart disease, abdominal aortic aneurysm or diabetes, respectively. The mutation in PDE3B, however, is the most intriguing, Assimes said, because there's already a drug on the market, called cilostazol, that mimics the beneficial mutation in that gene. Assimes said cilostazol may now also be a strong candidate for treating heart disease.

The study will be published online Oct. 1 in *Nature Genetics*. Assimes is the senior author. Derek Klarin, MD, clinical fellow in surgery at Harvard, and Scott Damrauer, MD, assistant professor of surgery at the University of Pennsylvania and the Corporal Michael Crescenz VA Medical Center in Philadelphia, share lead authorship.

The power of many

To reliably identify the molecular factors that influence cholesterol levels in blood, Klarin, Damrauer and Assimes turned to the power of numbers. Through the Million Veteran Program, a national research initiative based at the Veterans Health Administration that aims to identify the genetic determinants of health and disease among U.S. veterans, the scientists pooled genetic information with cholesterol readouts from 297,626 veterans and looked for variants that play a role in cholesterol levels. The study confirmed 188 previously known genetic markers of cholesterol and identified 118 new ones.

The scientists subsequently chose to home in on a narrow sliver of rare genetic anomalies for further analysis through a technique called phenomewide screen, or PheWAS. They already knew these gene mutations affected cholesterol but wondered whether the mutations likewise could affect the risk of other diseases. The PheWAS technique gleans disease risk information from immense databases of genetic information linked to electronic health

records.

Drugs as mutation copycats

Three gene mutations found through the screen piqued the investigators' curiosity. Each mutation swayed the veterans' cholesterol levels favorably, but differed in how it affected their risk for other diseases: the PDE3B mutation protected against heart disease; the mutation in PCSK9 not only decreased the risk for heart disease, something that was already known, but also the risk of abdominal aortic aneurysm; and ANGPTL4's mutation dampened the risk for Type 2 diabetes.

"All of these mutations are loss-of-function variants, meaning they either substantially diminish or stop the function of the gene altogether," Klarin said. That makes a good case for developing a drug that copies what the mutation does; if a faulty PDE3B gene decreases risk for heart disease, it could be promising pharmaceutical inspiration. In this study, the PDE3B mutation was associated with lower triglycerides, higher HDLs and a 20 percent lower risk of heart disease.

"Amazingly, there's a cheap, generic drug that I already use to treat my patients for vascular disease which also mimics the effects of the mutation in PDE3B on cholesterol levels, but no one has paid attention to these 'side effects,'" Damrauer said. The drug is typically only used to treat the symptoms of blockages in leg arteries to improve how far people with vascular disease can walk without pain. The next step is to investigate whether that same drug could wear multiple therapeutic hats.

'Misled before'

Although this work may help identify new targets to curb heart disease, Assimes cautions against requesting a prescription for cilostazol for solely that purpose.

"The genetics help suggest that this drug can decrease the risk of heart disease by lowering triglycerides, but it's not proof," he said. "I would not prescribe it until a large randomized trial is completed with cilostazol or a related drug looking specifically at heart disease outcomes.

"We've been misled before by drugs that had effects on cholesterol, but they turned out to be cosmetic," he added. "Better cholesterol profiles can look great, but if the drug doesn't affect the outcome you're aiming for, which is heart attack in this case, then it's useless."

Assimes is hoping that won't be the case with cilostazol.

As for the other two genes, PCSK9 and ANGPTL4, Assimes said that further investigation of those are also needed. Several inhibitor drugs that mimic the effects of the PCSK9 mutation are already on the market to reduce the risk of heart attacks. The question is whether their use will also lead to fewer aneurysms. Drugs that mimic the effects of the ANGPTL4 mutation are still under development, and large-scale testing in humans has not yet begun.

More information: Genetics of blood lipids among ~300,000 multiethnic participants of the Million Veteran Program , *Nature Genetics* (2018). DOI: 10.1038/s41588-018-0222-9 , https://www.nature.com/articles/s41588-018-0222-9

Provided by Stanford University Medical Center