Rare gene mutations raise risk of early heart attack

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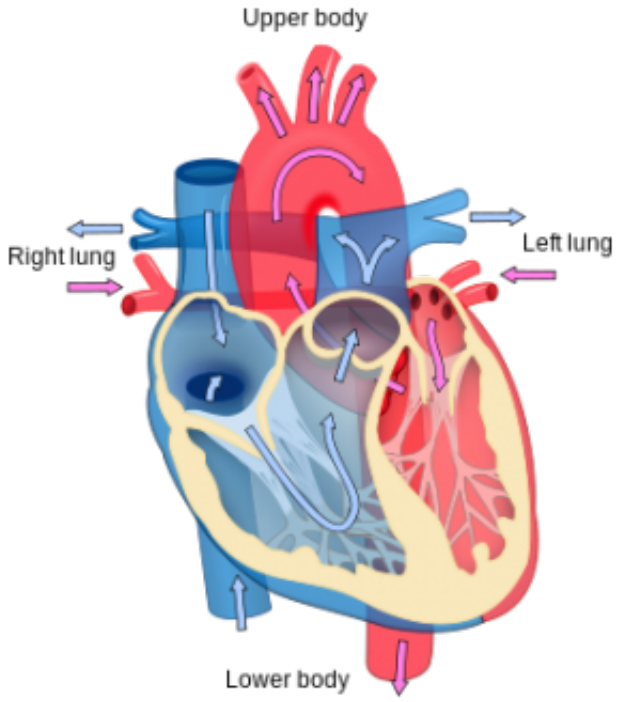

Heart diagram. Credit: Wikipedia

A team of investigators from the Broad Institute, Massachusetts General Hospital and other leading biomedical research institutions has pinpointed rare mutations in a gene called APOA5 that increase a person's risk of having a heart attack early in life. These mutations disable the APOA5 gene and also raise the levels in the blood of triglyceride-rich lipoproteins, a type of fat. The researchers' findings,

together with other recent genetic discoveries—specifically, the identification of protective mutations in the APOC3 gene that lower triglyceride levels and the risk of heart attack—refocus attention on abnormal triglyceride metabolism as an important risk factor for heart attack at any age. The work—the largest exome sequencing study yet published for any disease—appears this week in the journal *Nature*.

"Our APOA5 result tells us that beyond LDL levels, which are well known to contribute to heart attack risk, abnormalities in triglyceride metabolism also play an important role," said Sekar Kathiresan, a senior author of the study, Broad associate member, and director of preventive cardiology at Massachusetts General Hospital. "This gives us an important window into the biology of the disease and also suggests potential new avenues for therapeutic development."

There are some striking parallels between Kathiresan's work and a similar study conducted over 40 years ago and published in 1973. That historic effort, which was led by Joseph Goldstein and his colleagues, examined several hundred people from Seattle, Washington who had suffered a heart attack before age 60. Looking at the levels of lipids in the blood, Goldstein and his team identified high total cholesterol levels as the major abnormality associated with early-onset heart attack. That work spurred decades of research trying to unravel the role of LDL, the major carrier of cholesterol in the bloodstream, in causing atherosclerosis—the progressive accumulation of fatty material in blood vessel walls that can lead to a heart attack. It also led to a Nobel Prize for Goldstein and his colleague Michael Brown. Interestingly, in the seminal work from 1973, the second most common abnormality observed by Goldstein and his colleagues was elevated blood triglycerides.

In addition to underscoring the role of high triglycerides in heart attack risk, Kathiresan and his colleagues also found that harmful LDL receptor mutations are more prevalent than previously believed—roughly twice as

common than had been estimated in the Goldstein study.

"In 1973, Goldstein's work taught us what types of lipids in the blood are most important for early heart attack risk," said Kathiresan. "Now, after sequencing all of the genes in the genome, we can directly point to the specific genes that are most important. There is remarkable consistency between the observations from 40 years ago and today."

Heart attacks are extremely common. In the United States, someone suffers from one roughly every 34 seconds. Even though the condition is widespread, it tends to strike later in life. Only about 5 percent of people who suffer a heart attack do so at a relatively young age—before age 50 for men and before age 60 for women. Tragically, the first sign of illness in this minority is often a devastating heart attack, inflicting significant damage to the heart and resulting in severe disability, even death.

Kathiresan has had a long-standing interest in the genetics of early-onset heart attack. In his current work, he and his colleagues conducted a large-scale, DNA sequencing-based study, focusing exclusively on the protein-coding portion of the genome, called the exome. They analyzed the exomes of roughly 10,000 people—half of whom had suffered from an early heart attack and half who had not.

Using this exome-based approach, the researchers zeroed in on two genes, LDLR and APOA5. Their findings implicating a role for multiple rare mutations in the LDL receptor gene (LDLR) in early heart attack confirms what is already well-known from decades of research: that high levels of LDL, the so-called "bad" cholesterol, is a key risk factor that raises the risk of heart attack. The second major finding—evidence linking rare mutations in the APOA5 gene, encoding an apolipoprotein, and early heart attack—highlights the role of triglyceride levels in heart attack. Kathiresan and his colleagues discovered that people carrying APOA5 mutations have higher levels of blood triglycerides and a

roughly two-fold increased risk of a heart attack.

Although APOA5 had been previously implicated in the condition, it required the resolution of large-scale DNA sequencing to definitively make the connection between APOA5 and heart attack risk.

"We simply wouldn't have made this critical connection without our careful and disciplined approach to whole exome sequencing and subsequent data analysis," said Stacey Gabriel, a co-author of the *Nature* study and director of the Broad Institute's Genomics Platform.

This work points to several features being key to successful sequencing studies focused on finding rare variations (or "variants") in the genome. These include the importance of large sample sizes to help distinguish harmful from benign genetic variants (typically thousands of cases and controls), as well as precise statistical analyses, including so-called "aggregation tests" that enable the combined analysis of multiple distinct rare variants within the same gene.

Together with his recent discovery of another apolipoprotein gene, APOC3, that also influences triglyceride levels and heart disease, Kathiresan's findings point to an important role for triglycerides in influencing heart attack risk—something that had been largely disregarded until recently. In addition to casting new light on disease biology, the work also suggests a potential path for future therapeutic development in heart disease.

More information: Do, R et al. Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. *Nature*. Online First: December 10, 2014. DOI: 10.1038/nature13917

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