Researchers identify two genetic mutations that interact to lower heart attack risk

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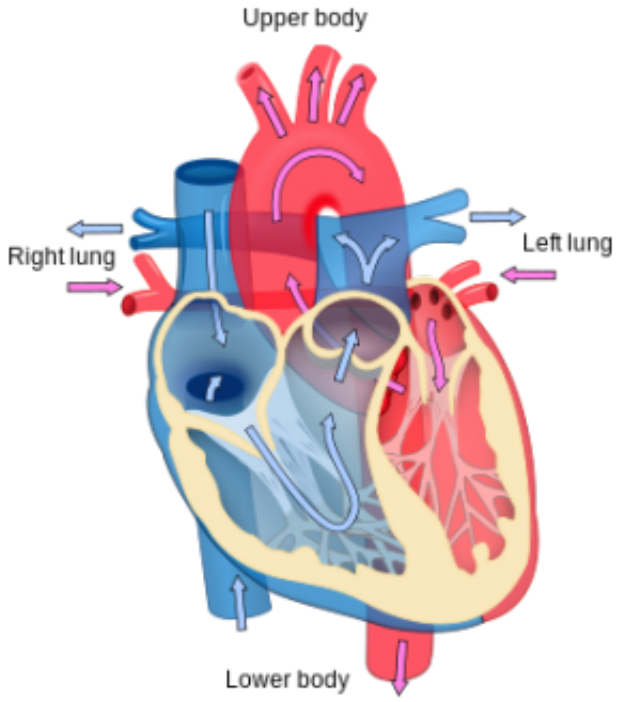

Heart diagram. Credit: Wikipedia

Researchers have determined that two mutations on a single gene can interact in a way that lowers the carrier's risk for a heart attack.

The variants are found in a gene called DBH, which regulates an enzyme involved in the conversion of dopamine to norepinephrine - both of which are important chemical messengers and hormones.

When considered alone, each variant had either an undetectable or minimal effect on the gene's effect on disease risk. But their interaction substantially reduced expression of the DBH gene, creating conditions in the body that protect against a heart attack.

The scientists compared the genetic variants causing reduction in gene expression to data from the clinical records of three groups of patients. In all groups, patients with the two variants had a two- to five-fold lower risk of having a heart attack. About 20 percent of the population carries both variants.

"Our goal is to find genetic variants in key genes that are important medically and important for designing more efficient drug therapies. We want to predict whether there is an increased risk for disease because a class of drugs is less likely to work under conditions that are genetically determined," said Wolfgang Sadee, professor of pharmacology and director of the Center for Pharmacogenomics at The Ohio State University and senior author of the study.

The hormone norepinephrine can over-stimulate the heart when it circulates in the bloodstream or is released within the heart. The interaction that lowers gene expression in turn lowers norepinephrine production. Controlling norepinephrine is important in heart failure treatment: Beta-blockers prevent activation of the norepinephrine target gene in the heart.

"The really important outcome is the suggestion that clinicians need to test people who already have reduced activity of DBH and reduced norepinephrine," Sadee said. "Do they benefit from beta blockers? Maybe not."

The research is published in a recent issue of the journal *Circulation Research*.

Dopamine and norepinephrine are neurotransmitters vital to the regular function of the central nervous system, and dopamine's influence in the brain is well understood. In this case, however, the strong effects of the genetic mutations were seen in liver and lung tissue - and not in the brain.

Lead author Elizabeth Barrie, a pharmacology postdoctoral researcher at Ohio State who completed this work as a graduate student, began her investigation of the DBH gene in the brain. Effects on gene expression associated with the variants were too small to have robust clinical significance.

"I decided to look in liver tissue and saw these really large genetic effects, which we then thought were representative of the effects in the periphery as a whole," Barrie said. "The best thing about this study is we were able to use human tissue samples and do molecular genetic studies to identify which specific variants were important, and then we used other existing databases to validate the results clinically."

The mutations are single-nucleotide polymorphisms, or SNPs (pronounced "snips"). Each gene contains two alternative forms - called alleles - that are functionally identical in most people. However, in some cases, the activity level, or expression, of an allele can differ from its partner allele in a single gene.

The variants identified exist in deep and often overlooked regions of genes. Sadee's lab has designed a technique to predict and determine their functions based on measurements of how much messenger RNA, a carrier of genetic information, each specific allele expresses.

Until now, DBH-related production of norepinephrine was linked to three areas of the body: the brain, the adrenal glands and at nerve terminals in the sympathetic nervous system, which controls the body's

"fight or flight" response. The presence of DBH and norepinephrine in the bloodstream has always been thought to represent a hormone-like response coming from the adrenal glands, Sadee said.

Detecting messenger RNA (mRNA) for the gene in the liver, however, "was the antithesis of everything we've known because DBH is supposed to be made only in neurons," he said. "There was no effect of these variants in the brain and the adrenals. That flies in the face of what was known before.

"It turned out that the message for making DBH protein - the mRNA - is transported in sympathetic neurons to target organs and expressed there at nerve terminals where norepinephrine is needed. Therefore, we can expect a large effect of the genetic DBH variants on these local events."

Because these SNPs influence the local production of norepinephrine in various organs, they might have effects on other disorders and conditions. For example, reduced activation of the DBH gene could represent a risk factor for asthma because lungs need norepinephrine to open constricted airways.

"Norepinephrine has a huge impact on the body on all levels - metabolic effects, a possible association with body mass index, diabetes, you name it," Sadee said. "That's why this is important."

Provided by The Ohio State University