Novel genetic study sheds new light on risk of heart attack

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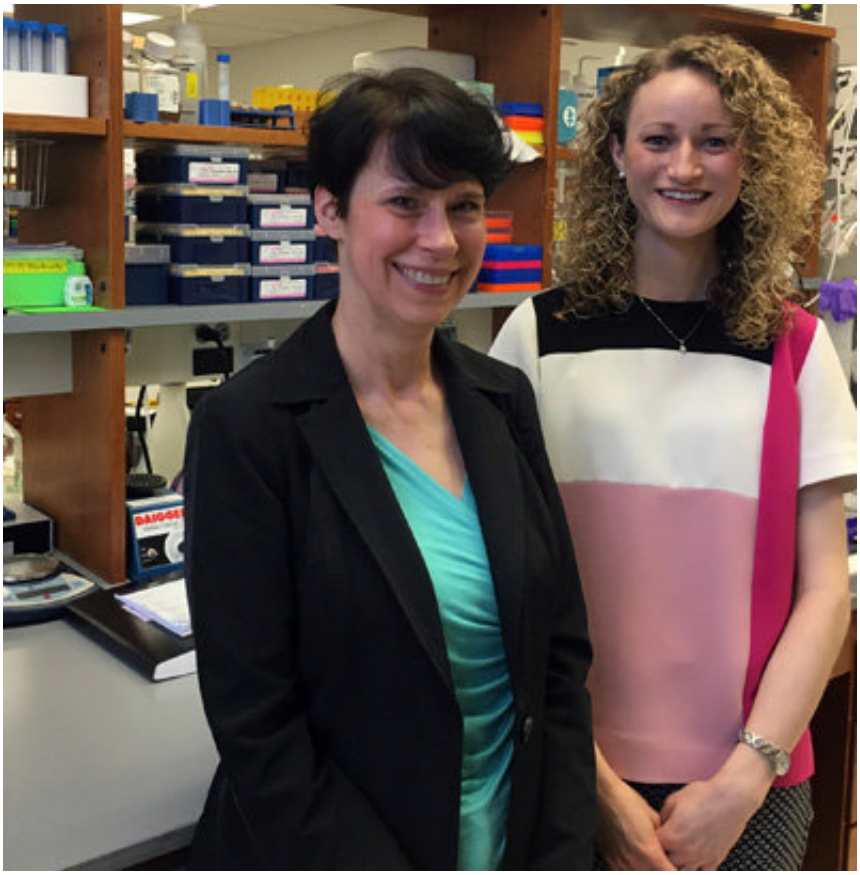

Sandra Zinkel, MD, PhD, left, Christi Salisbury-Ruf and colleagues are studying a protein's role in regulating mitochondrial function that may increase risk of heart attack. Credit: Vanderbilt University

Loss of a protein that regulates mitochondrial function can greatly increase the risk of myocardial infarction (heart attack), Vanderbilt

scientists reported Oct. 3 in the journal *eLife*.

The study illustrates how "integrative genomics," a combination of basic research, a human biobank linked to electronic health records and novel computational genetic approaches can identify genetically determined changes in gene expression that contribute to complex diseases.

"It's that end-to-end type of study, looking at findings in the lab and translating them into something that has important clinical implications," said Eric Gamazon, PhD, the study's co-corresponding author with Sandra Zinkel, MD, PhD.

Gamazon is a computational geneticist and research instructor in Medicine in the Vanderbilt University School of Medicine. Zinkel is associate professor of Medicine and of Cell and Developmental Biology.

Mitochondria are the energy-producing "power plants" of the cell. When they are not working properly, the tissues can become starved for energy. In the heart, mitochondrial dysfunction can lead to susceptibility to heart attack or heart failure.

Mitochondria also play an important role in preventing cancer. They amplify and execute apoptosis, or programmed cell death, which is a way of preventing the growth of abnormal cells.

'Bid' is a protein that can trigger mitochondrial-induced apoptosis and thus is a potential target in the development of new anti-cancer drugs. But what does it do when it's not killing cells?

To find out, Zinkel and colleagues led by graduate student Christi Salisbury-Ruf knocked out the gene for Bid in mice and studied what happens to their mitochondria.

"We found that these mice … in the absence of Bid had mitochondrial defects," Salisbury-Ruf said. "No one had shown that before."

When stressed, their hearts also showed evidence of damage and loss of function similar to what happens to humans who have had a heart attack. Detailed studies showed a loss of structures inside the mitochondria called cristae that are critical for normal mitochondrial function.

This intrigued Gamazon, who wondered if a loss of Bid in humans also was associated with increased predisposition to heart attack.

While at the University of Chicago, Gamazon and Nancy Cox, PhD, who currently directs the Vanderbilt Genetics Institute, developed a method for predicting whether the expression or activity level of certain genes may contribute to diseases as diverse as type 1 diabetes, rheumatoid arthritis and bipolar disorder.

Their technique, called PrediXcan, focuses on gene expression that is turned up or down like a light switch by genetic variations. It was developed with the help of GTEx (Genotype-Tissue Expression), a National Institutes of Health reference data set of genetic variations and gene activity in multiple healthy tissues.

The researchers applied a PrediXcan model for predicting the expression of the BID gene to BioVU, Vanderbilt's DNA databank, and to available GWAS (genome-wide association studies) of myocardial infarction.

BioVU consists of nearly 250,000 samples of DNA that have been extracted from discarded blood samples donated by Vanderbilt patients and linked to their "de-identified" electronic health records, which have been scrubbed of personal identifying information.

The researchers determined the level of BID expression in DNA samples

from more than 29,000 patients, of whom more than 5,000 had experienced a heart attack.

Those with the lowest level of BID expression, in the bottom 5 percent, had a better-than fourfold increased risk of myocardial infarction. Lower BID expression was also associated with greater risk of heart attack in additional (non-BioVU) GWAS samples.

The finding suggests genotyping may be a way to identify patients with low BID expression who are at increased risk of having a heart attack. "If you know someone's at risk then you might tell them, 'You should be more careful about your cholesterol and blood pressure,'" Zinkel said.

More information: Christi T Salisbury-Ruf et al. Bid maintains mitochondrial cristae structure and protects against cardiac disease in an integrative genomics study, *eLife* (2018). DOI: 10.7554/eLife.40907

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