Medical Xpress

Hundreds of new blood pressure gene variations discovered

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Scientists who led the study on blood pressure genetics included (back row, from left) Adriana Hung, MD, MPH, Todd Edwards, PhD, (front row, from left) Jacklyn Hellwege, PhD, Ayush Giri, PhD, and Jacob Keaton, PhD. Credit: Steve Green

In one of the largest studies of its kind, an international research team led by 20 Vanderbilt University scientists has discovered more than 200 new genetic variations associated with high blood pressure.

The study, published December 21 by the journal *Nature Genetics*, also identified specific tissues where blood pressure genes exert their effects

as well as a long list of drugs that act upon those genes.

"We're redrawing the map of blood pressure genetics," said Todd Edwards, Ph.D., associate professor of Medicine in the Vanderbilt University School of Medicine and one of two senior corresponding authors with Adriana Hung, MD, MPH.

While large swaths of the map remain to be filled in, the researchers said they are closer than ever to being able to improve the treatment of high blood pressure based on the patient's genetic make-up.

"The door is wide open," said Vanderbilt research fellow Jacob Keaton, Ph.D., whose identification of gene-drug interactions was a key part of the study. "We're bringing findings to the table that we can do something with to have an impact on precision medicine."

Keaton was the third of three lead authors of the manuscript. Ayush Giri, Ph.D., assistant professor of Obstetrics and Gynecology and of Medicine, was the first lead author, and Jacklyn Hellwege, Ph.D., research fellow in Epidemiology and the Vanderbilt Genetics Institute, was the second.

The study analyzed the relationship between genetic variants and blood pressure traits utilizing the electronic health records of more than 300,000 participants in the Million Veteran Program (MVP) and more than 140,000 participants in the UK (United Kingdom) BioBank study.

The researchers then replicated their findings by analyzing 17,000 samples from the Vanderbilt University biobank, BioVU, and 300,000 from large genetic consortia of blood pressure studies.

MVP is a national effort by the U.S. Department of Veterans Affairs (VA) to collect blood samples and health information from one million

veteran volunteers.

Thirty percent of the participants in the MVP portion of the study were African-Americans, Hispanics, Asians and Native Americans—making this one of the most racially diverse genetic inquiries of its kind, said Hung, associate professor of Medicine in the Division of Nephrology and Hypertension.

Hung is principal investigator (PI) of the MVP "beta" data-only studies grant covering chronic kidney disease and hypertension, and she is the local PI of the MVP at the Nashville VA Medical Center, part of the Tennessee Valley Healthcare System.

The kidney disease/hypertension beta grant was one of the four first grants awarded to use the MVP "mega" biobank, she said. Since MVP was launched in 2011, the biobank has collected samples from more than 700,000 veteran volunteers recruited through 63 VA medical centers across the country.

Locally, Hung and her colleagues have signed up 20,000 veterans, making her "one of the most successful (MVP) recruiters in the United States," Edwards said.

Another unique aspect of the Vanderbilt-led study is that it analyzed not only the impact that genetic variation has on blood pressure but also how genetically-predicted changes in the expression or activity level of other genes can influence, in subtle ways, the physiology of tissues throughout the body.

Using GTEx (Genotype-Tissue Expression), a reference data set of genetic variations and gene activity in multiple healthy tissues developed by the National Institutes of Health (NIH), researchers at the University of Chicago developed a method for predicting how changes in gene

expression may contribute to disease.

The researchers, Nancy Cox, Ph.D., Eric Gamazon, Ph.D., and their colleagues have since moved to Vanderbilt. Their technique, called PrediXcan, has become a powerful tool for discovering the genetic underpinnings of diseases as diverse as type 1 diabetes, rheumatoid arthritis and bipolar disorder.

In the current study, the researchers used S-PrediXcan, a modified version of the PrediXcan method, to detect associations between genetically-predicted gene expression of 840 unique genes in 45 tissues and observed blood pressures (those recorded in veterans' electronic health records).

"Blood pressure is incredibly complicated," Edwards said. "It may be that as we increase the sample size of these kinds of studies … we'll discover that no place in the genome has a zero effect on a trait like blood pressure. It's just that some of the effects are incredibly subtle."

Not only did the researchers identify genes that are potential targets for the development of new drugs, but using genes identified from S-PrediXcan together with bioinformatics-related approaches, they also identify drugs currently on the market for other uses that potentially could be "re-purposed" as anti-hypertensive medications.

"As one of our co-authors said, this was a real 'Tour de France,'" Giri said. "It just kept going."

Currently, "we can't really accurately say what your blood pressure's going to be at age 65 by looking at your genotype," Edwards said, "but we might be able to tailor your treatment a little more accurately with some of the results we have from this study."

More information: Trans-ethnic association study of blood pressure determinants in over 750,000 individuals, *Nature Genetics* (2018). DOI: 10.1038/s41588-018-0303-9

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