Investigating rare genetic mutations led scientists to surprising blood pressure discovery

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The kidneys are often the unsung heroes in maintaining healthy blood pressure, filtering 180 liters of fluid and a pound of salt every day to

keep levels in check. But new research by University of Pittsburgh geneticists and nephrologists shows that, surprisingly, a cellular channel outside the kidneys is doing some of the heavy lifting when it comes to keeping blood pressure under control.

The finding, reported today in the American Heart Association journal *Hypertension*, points to a promising new target for clinical trials to test existing medications for their potential to lower blood pressure.

"Our findings were entirely unexpected," said Brandon Michael Blobner, Ph.D., who did the research as part of his doctoral dissertation at Pitt and is now a bioinformatics scientist at BlueSphere Bio in Pittsburgh. "Previously there had been some hints that mutations to salt-processing channels outside the kidneys affected blood pressure, but it would have been impossible to confirm the mechanism without the massive genetics databases that we had access to through cross-disciplinary partnerships."

Nearly half of U.S. adults have high blood pressure, or hypertension, which is associated with chronic kidney disease and stroke, and it disproportionately affects Black individuals. Only 1 in 4 people have their high blood pressure under control, making it one of the nation's biggest public health problems, according to the U.S. Centers for Disease Control and Prevention.

High blood pressure is caused, in part, by the levels of fluid and salt getting out of whack, putting stress on artery walls and damaging blood vessels and organs.

The Pitt study focused on the passages—or channels—that the membranes of certain cells use to regulate fluid volume, based on how much sodium the cells contain. Blobner was curious if mutations in the genes that encode subunits of that channel might affect blood pressure.

With the encouragement of Thomas Kleyman, M.D., the Sheldon Adler Professor of Medicine at Pitt, Blobner worked with Ryan Minster, Ph.D., assistant professor of human genetics at Pitt's School of Public Health, to build a dataset with genomic sequences and blood pressure records on more than 28,000 people who were participating in either the Trans-Omics in Precision Medicine (TOPMed) Whole-Genome Sequencing Project or the Somoan Soifua Manuia Study.

"One of the really exciting things, for me, about this project was that it was so targeted and hypothesis-driven," Minster said. "Often with these big genomics projects, we're more agnostic—casting a wide net—and it can take decades for validation of a discovery. This project made a significant find remarkably quickly."

Scientists have known that rare mutations in the genes encoding the channel's alpha, beta and gamma subunits—all three found in kidney cells—can cause dangerous extremes in blood pressure. But when the scientists looked into more subtle mutations, they discovered that a fourth subunit—delta—influences blood pressure. Importantly, delta is found outside the kidney, in immune cells, as well as those that line the lungs, heart and colon.

"I'm a nephrologist—my entire career has been dedicated to understanding the kidney and its role in maintaining sodium levels to moderate blood pressure," said Kleyman, who is also chief of the renal-electrolyte division at UPMC and senior author of the research. "But our research in the last several years has expanded my focus. This study cements that we must branch beyond the kidney to better target blood pressure medications."

One of the dangers with some blood pressure medications is that they can cause high potassium levels, which can be deadly. But this problem is associated with poorly functioning kidneys. Theoretically, if a person's

high blood pressure is due to fluid and salt imbalances caused by malfunctioning channels in cells outside the kidneys, then such medications may be an effective treatment, with less risk of high potassium levels.

"One of the things we're particularly interested in at UPMC is targeting therapeutics—you want to give the right drug to the right person at the right time," Kleyman said. "This study may help us someday identify people with specific, subtle genetic mutations that predispose them to a type of hypertension acting outside the kidneys. Knowing that, we can better help that person control their blood pressure."

More information: Rare Variants in Genes Encoding Subunits of the Epithelial Na+ Channel Are Associated With Blood Pressure and Kidney Function, *Hypertension* (2022). www.ahajournals.org/doi/abs/10 … TENSIONAHA.121.18513

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