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International study identifies new gene targets for hypertension treatment

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A new international report from scientists around the world finds that common variants in 28 regions of DNA are associated with blood pressure in human patients. Of the identified regions, most were completely unsuspected, although some harbor genes suspected of influencing blood pressure based on animal studies. In the study receiving advance online publication in *Nature*, members of the International Consortium for Blood Pressure Genome-Wide Association Studies (ICBP-GWAS) analyzed genetic data from over 275,000 individuals from around the world. They also identified for the first time the involvement of an important physiologic pathway in blood pressure control, potentially leading to a totally new class of hypertension drugs.

"Identifying these novel pathways expands our current understanding of the determinants of blood pressure and highlights potential targets for new drugs to treat and prevent cardiovascular complications," says Christopher Newton-Cheh, MD, MPH, of the MGH Center for Human Genetic Research and the Cardiovascular Research Center, co-chair of the ICBP-GWAS Steering Committee and a senior and corresponding author on the *Nature* paper.

It is well known that hypertension can run in families and that some rare genetic syndromes raise blood pressure, but identifying genes associated with the common form of hypertension has been challenging. To get a study sample large enough to detect variants with modest effects, ICBP-GWAS researchers conducted a meta-analysis of 30 genome-wide association studies that included measurements of participants' blood

pressures. Analysis of 2.5 million DNA sequence variants in more than 69,000 individuals of European ancestry identified several chromosomal regions where genes influencing blood pressure appeared to be located. To confirm the results of the first-stage analysis, the researchers genotyped the strongest variants in more than 133,000 additional individuals of European descent. Combining the results identified 28 gene regions associated with both systolic and diastolic blood pressure, of which 16 were novel. A second paper from the consortium also receiving online publication today in Nature Genetics, identified six additional novel variants..

Some of the new variants were already known to cause other diseases. "We were quite astonished to see that two common variants known for decades to cause hemochromatosis – an iron overload condition that affects as many as 1 in 300 Americans – were also associated with higher blood pressure," says Newton-Cheh. "The hemochromatosis genes are part of a physiologic pathway that is also involved in pulmonary hypertension, but this finding opens our eyes to its potential involvement in systemic hypertension."

To test whether the blood pressure variants identified in Europeans were associated with blood pressure in other ethnicities, the consortium genotyped almost 74,000 individuals of either East Asian, South Asian or African ancestries. Genetic risk scores incorporating all identified variants were strongly associated with blood pressure levels in each of those groups and also with the risk of stroke and coronary heart disease. "Seeing that the blood pressure variants in aggregate lead to stroke and heart attack was perhaps not surprising, given the evidence that blood pressure treatment lowers these risks," said Newton-Cheh.

But the most important finding may be identification of a new pathway central to blood pressure regulation. Three of the 28 blood-pressure-associated regions include genes that are part of a pathway called the

cyclic guanosine monophosphate (cGMP) system, which is involved in the relaxation of blood vessels and excretion of sodium by the kidneys, two fundamental mechanisms of hypertension treatment. Animal studies have suggested a role for this pathway in blood pressure control, and the current findings strongly support its relevance in human patients.

"We have previously shown that variants in natriuretic peptide genes, part of the cGMP system, influence blood pressure. We were therefore pleased but not surprised to see other genes that influence the cGMP system in this recent crop of discoveries," said Newton-Cheh, an assistant professor of Medicine at Harvard Medical School. "The greatest attention in blood pressure research has been focused on another pathway called the renin-angiotensin-aldosterone system (RAAS), which is targeted by several hypertension therapies. But only one common gene variant has been associated with genes in the RAAS pathway.

"Finding several independent associations that converge on cGMP points to its central importance in blood pressure control," he adds. "In fact, there are several drugs that target these systems in development to treat pulmonary hypertension and heart failure, but our findings suggest that they could have a much larger role in hypertension treatment in general. The next phase of our research will focus on finding additional genes and variants that influence blood pressure and on establishing how some of the cGMP-involved genes affect blood pressure in humans and respond to existing drugs and to those in development."

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