Studies identify 44 novel gene sites associated with hypertension risk

September 12 2016

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In papers receiving advance online publication in *Nature Genetics*, two international multi-institutional research teams describe identifying a total of 44 novel gene sites associated with hypertension or high blood

pressure. The studies, co-led by investigators at Massachusetts General Hospital (MGH), point towards potential new treatment strategies for the condition affecting around one-third of U.S. adults.

"High blood pressure or hypertension is a major cause of heart disease and stroke worldwide, but its underlying causes are poorly understood," says Christopher Newton-Cheh, MD, MPH, of the MGH Center for Human Genetic Research and Cardiovascular Research Center, senior author of both papers. "Existing therapies target only a small subset of the pathways that contribute to hypertension, so identifying additional genes that influence blood pressure can point us in new directions, giving us exciting new leads for drug development."

It is well known that hypertension tends to run in families, but while around half the risk of the condition can be attributed to inheritance, the approximately 60 hypertension genes identified in previous studies explain only about 2 percent of that risk. To identify additional risk variants, the two current investigations conducted meta-analyses using novel, custom genotyping arrays, each of which test for more than 200,000 variants, combined with data from the group's previously published studies.

In one study the researchers analyzed data from more than 327,000 individuals genotyped with an array called the Exome Chip, which is designed to identify rare gene variants that change protein structure. That analysis identified 31 novel gene sites associated with hypertension risk, as well as rare gene variants in natriuretic peptide receptor 1, which is the receptor for two proteins called natriuretic peptides that are known to relax blood vessels and control sodium excretion and were shown in previous work led by Newton-Cheh to be associated with hypertension risk.

For the second study, the investigators used the Cardio-Metabochip

array, which focuses on variants associated with cardiovascular and metabolic traits, to analyze data from more than 345,000 individuals participating in 73 studies. That analysis revealed associations with 66 gene sites, 17 of which were new. While that analysis was conducted on studies enrolling individuals of European ancestry, analyzing data from more than 64,000 non-European individuals with a risk score based on those 66 variants showed a similar association with both hypertension and with damage to tissues in the heart and key vascular structures but not to the kidney which has long been considered a major regulator of blood pressure.

Four risk-associated sites were identified by both studies, leaving a total of 44 novel risk-associated genes. Overall these two studies, the largest reported meta-analyses of investigations into the genetics of hypertension, point towards pathways other than that involved with salt excretion by the kidneys—the system previous genetic studies have focused on—as potential treatment targets. Findings of the Cardio-Metabochip study particularly highlighted the role of the endothelial cells that line blood vessels and control how strongly they constrict. Other potential targets, other than the previously identified natriuretic peptides, include an enzyme involved in the synthesis of the hormone noradrenaline, which is well known to influence heart rate and blood pressure.

An assistant professor of Medicine at Harvard Medical School, Newton-Cheh explains, "Even with hundreds of thousands of people studied and over 100 blood pressure genes identified to date, we estimate that there are still hundreds more to find. Only when we can study millions of people—particularly people of non-European ancestry who have been underrepresented in past studies—will we have a chance at finding them all."

More information: Meta-analysis identifies common and rare variants

influencing blood pressure and overlapping with metabolic trait loci, *Nature Genetics*, DOI: 10.1038/ng.3660