Common gene variants increase risk of hypertension, may lead to new therapies

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A new study has identified the first common gene variants associated with an increased incidence of hypertension - a significant risk factor for heart attack, stroke and kidney failure. The report receiving early online release in the journal *Nature Genetics* identifies variants in genes for proteins involved with cardiovascular response to stress that also appear to influence blood pressure levels, an association previously seen in animals but not demonstrated in humans.

"It's well known that hypertension can run in families, and a few rare genetic syndromes that raise blood pressure have been identified. But the common genetic basis for the type of hypertension that affects a billion individuals around the world has been very difficult to establish," says Christopher Newton-Cheh, MD, MPH of the Massachusetts General Hospital (MGH) Center for Human Genetic Research and Cardiovascular Research Center, first author of the *Nature Genetics* report.

To search for hypertension-associated variants, the investigators focused on two genes called NPPA and NPPB that are involved in the production of atrial and B-type natriuretic peptides (ANP and BNP) - proteins known to relax blood vessels and to be involved in the excretion of dietary sodium. Animals in which both copies of NPPA have been knocked out are hypertensive, and even those with a single functional copy will develop hypertension on a high-sodium diet.

The overall study involved analyzing genetic data from almost 30,000 individuals. The researchers first screened 1,700 participants in the Framingham Heart Study for 13 common variations - called single-nucleotide polymorphisms (SNPs) - in the NPPA and NPPB genes, looking for any correlation with levels of ANP and BNP. SNPs identified in that first stage were validated in three other study groups, including participants from Sweden and Finland; and variants associated with changes in natriuretic peptide levels were then tested in the same individuals for any association with blood pressure levels.

Results of that third stage - which suggested two hypertension-associated SNPs - were validated in another study group. One identified variant, found in almost 90 percent of the population, was associated with a 20 percent reduction of ANP levels and an 18 percent greater incidence of hypertension. The other variant had a similar although less pronounced effect on ANP levels and blood pressure.

"Natriuretic peptides are known to be produced by the heart when it is stressed, and screening for peptide levels is widely used to diagnose heart failure, a condition in which they are sharply elevated," says senior author Thomas Wang, MD, of the MGH Cardiology Division. "It's currently premature to advocate screening natriuretic peptide levels or gene variants to diagnose hypertension risk, but someday it may be possible to treat natriuretic-peptide-deficient individuals with therapies that restore normal levels and reduce risk."

Newton-Cheh adds, "It's likely that many more genes will be found to contribute to changes in blood pressure, and the real challenge will be understanding the mechanism behind their effects. An advantage of these variants is that we know they act by influencing a well-studied pathway that may be modified with therapies that are currently being developed." He and Wang are both assistant professors of Medicine at Harvard Medical School and were co-corresponding authors on the paper.

Source: Massachusetts General Hospital