Researchers Show Surprising Interaction between Genes, Gender, and Hypertension

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In surprising results, a study of more than 1,200 patients with extremely low or high blood pressure by researchers at the University of California, San Diego (UCSD) School of Medicine showed that the influence of genes on blood pressure may vary based on gender.

"Sex is like a prism that refracts the effects of the gene very differently for men and women," said Daniel T. O'Connor, M.D., UCSD professor of Medicine and Pharmacology, whose study is now on-line in advance of publication in the January issue of the journal *Hypertension*.

The research team found that the gene-by-sex interaction was the rule, not the exception in their study of a large, community-based sample of primary care patients in Southern California. They set out to discover whether gender interacts with genes in contributing to extremes of blood pressure, by looking at the medical records of 611 male and 656 female aged-matched, Caucasian patients whose blood pressure (BP) readings fell in the top and bottom five percent among 53,000 patients.

"Our findings show that specific genetic variations – which give rise to receptors that might be targets for ACE inhibitors or beta-blockers and other therapies used to treat hypertension – impact blood pressure differently in men and women. Knowing these genetic mutations may help us better diagnose hypertension and select the appropriate therapy," said O'Connor, adding that these findings support that the most appropriate therapy might well depend on whether the patient is a man or a woman.

Hypertension, or high blood pressure, is a serious disease that can result in heart attacks, strokes or kidney failure. Scientists have known for some time that hypertension is a "heritable" condition that runs in families, though diet and other factors also contribute to high blood pressure. It is also known that there are differences in the occurrence of hypertension between men and women, and varied responses to treatments. For example, men normally have slightly higher BP readings than women.

Accounting for these differences, the researchers set out to test their hypothesis that the influence of genes on blood pressure and hypertension varies with a patient's gender. Ernst

Beutler, M.D., of The Scripps Research Institute Department of Molecular and Experimental Medicine, organized a blood sample collection over a two-year period in order to prepare genomic DNA from the patients' white blood cells. The researchers then focused on the genetic profiles, or genotypes, of more than 1,200 men and women whose systolic (the higher number in a BP reading) and diastolic (lower number) measurements fell at the extreme – highest and lowest – percentiles of distribution.

The study yielded 48 different genetic variations, or polymorphisms, on 35 different genes that encode proteins involved in blood pressure regulation. Thirty-three of the genes were on autosomes (chromosomes found in both sexes), and two were on the "X-linked" or sex chromosomes.

"Of the 35 genes, we found six genes that were quite different in the frequency of variation between people of either sex who had extremely high or low blood pressure," said O'Connor.

Several diseases are caused by a variation on a single gene on the chromosome, called a single nucleotide polymorphism (SNP, pronounced "snip"). Examples of so-called SNP diseases are sickle-cell anemia and Huntington's disease, where a single variant or mutation has a dramatic effect.

In contrast to these single-gene-specific diseases, the UCSD researchers observed more subtle variants on six different genes, indicating that multiple genes can contribute to high blood pressure. "We discovered that there's more than one gene at work in hypertension," said O'Connor, adding that the team was surprised to find that these SNPs appear to affect men and women differently.

Among the gene variants, each was differently associated with blood pressure measurements in men versus women. Of 48 SNPs, two influenced blood pressure only in men, while two other SNPs contributed only in women. All four SNPs demonstrated significant gender-by-gene interaction effects on blood pressure. Two other SNPs also showed significant gene-by-gender interactions, but their effects were not significant in either men or women alone. Furthermore, the scientists documented several examples where particular gene variations were observed to show directionally opposite effects on blood pressure in men and women.

The researchers conclude that "the results suggest that development of genotype-based diagnostic and therapeutic indices for hypertension must take gender into account to provide an accurate assessment of the role of genes in the origin, treatment and consequences of this complex trait."

"Further studies may help scientists understand what genetic variables can predict the likelihood of a patient suffering from hypertension," said O'Connor.

Additional contributors to this paper include Brinda K. Rana, Paul A. Insel, Samuel H. Payne, Kenneth Abel, Michael G. Ziegler and Nicholas J. Schork.

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