

Male hypertension may have genetic link

Although high blood pressure affects up to 50 million people in the United States, it remains a medical mystery. Scientists have noticed that the condition seems to run in families, but they haven't pinpointed the gene or genes responsible. Two studies now suggest that variations on or near a gene called *ACE* may hint at a susceptibility to hypertension in men.

The *ACE* gene encodes angiotensin-converting enzyme, a protein that works with other compounds to regulate blood pressure. Because essential hypertension, or high blood pressure, can lead to heart disease, stroke, and kidney problems, doctors prescribe drugs to impede the interaction of these chemicals.

Scientists in Massachusetts have now found that a slightly unusual version of the *ACE* gene may signal a higher-than-usual risk of hypertension in the 30 percent of people in the United States who carry it. Geneticists had suspected that this version of the *ACE* gene might help them trace the origin of high blood pressure, but they had been disappointed by the conflicting results of earlier studies.

Another new study, assessing blood pressure variations among adolescent siblings, finds that genetic variations in or around the *ACE* gene account for more than one-third of the dissimilarities.

The findings of both studies, which appear in the May 12 *CIRCULATION*, apply almost exclusively to men. The variations seemed to have little effect on women.

In the Framingham (Mass.) Heart Study, researchers analyzed genetic data and blood pressure readings from 3,095 white men and women. After accounting for risk factors such as age and weight, the scientists linked the genetic variation to a 59 percent increase in the incidence of high blood pressure.

The researchers focused on a variation that occurs on a strand of inactive DNA in the *ACE* gene. Men with this variation make *ACE*, but they nonetheless show a propensity for high blood pressure, says study coauthor Christopher J. O'Donnell, a cardiovascular epidemiologist at Framingham. The connection suggests that the variation occurs along with a functional portion of *ACE* or with a nearby gene that predisposes the men to hypertension, O'Donnell says.

Previous research may have failed to establish a link between the *ACE* variation and high blood pressure because too few people were studied, O'Donnell says. Researchers need larger numbers to discern the effects of a single genetic characteristic on a system as complex as the one by which chemicals regulate blood pressure, he says.

In the other study, researchers at the Mayo Clinic in Rochester, Minn., the University of Michigan in Ann Arbor, and the University of Texas at Houston compared the blood pressure and genetic makeup of 1,488 white Minnesota siblings whose average age was 15. They found that having a specific genetic variation in the DNA in and around the *ACE* gene accounted for roughly 38 percent of the differences in blood pressure between brothers, says study coauthor Eric Boerwinkle, a human geneticist at Texas. The greater the divergence in the brothers' blood pressure readings, the more likely they were to differ genetically in the region of the *ACE* gene, he says.

Young participants were studied to eliminate the effects of aging and other factors that increase blood pressure over time.

The two studies indicate that a gene or genes with "major importance for blood pressure regulation" is concealed in the area of the *ACE* gene, writes Florent Soubrier of the St. Louis Hospital in Paris in an accompanying commentary.

Many genes in that region "are very good candidates for blood pressure control," including *ACE* itself, says Myriam Fornage, a geneticist currently at Case Western Reserve University in

Cleveland who coauthored the Minnesota study. Among them are a growth hormone gene and a gene that encodes an enzyme that helps make adrenaline.

"These sorts of studies are valuable," but scientists need to put them in perspective, says Daniel F. Catanzaro, a molecular biologist at Cornell University Medical College in New York City. Doctors already have a biochemical test for renin, one of the key chemicals regulating blood pressure. That test enables them to diagnose hypertension and to assess chemical imbalances, he says. The genetic studies, while potentially worthwhile, "are investigations to determine which rainbows have pots of gold at the end of them," he says.

Nevertheless, finding the genes responsible for heightened risk could help identify potential high blood pressure patients earlier and avoid trial-and-error drug therapy, Boerwinkle says.

—N. Seppa