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Rare Genetic Mutations Protect Against Hypertension

Howard Hughes Medical Institute (HHMI) researchers have found that rare mutations in three genes contribute to blood pressure variation in the general population.

The scientists had previously shown that mutations in the three salt handling genes cause several rare diseases that are characterized by low blood pressure. By sequencing DNA samples obtained from 3,125 people who are participating in the Framingham Heart Study, the researchers identified new functional mutations in these three genes that are likely to be carried by an estimated 100 million people worldwide.

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— **Richard P. Lifton**

The Framingham Heart Study was begun in 1948 in an effort to identify common factors or characteristics that contribute to cardiovascular disease by following its development over a long period of time in a large group of participants who had not yet developed overt symptoms of cardiovascular disease or suffered a heart attack or stroke.

We find that about two percent of the population has mutations in at least one of these three genes - although all of the identified mutations are individually very rare, said senior author Richard P. Lifton, a Howard Hughes Medical Institute researcher at Yale University School of Medicine. Mutation carriers have reduced blood pressure, with a 60 percent reduction in the risk of hypertension at age 60.

The findings, reported in the April 6, 2008, edition of the journal *Nature Genetics*, are important because they yield tantalizing new evidence about why some people seem to be less susceptible to developing high blood pressure, a condition that affects a billion people worldwide and contributes significantly to heart and kidney disease, and stroke.

“This study is an important milestone in the understanding of the genetic causes of hypertension,” said Elizabeth G. Nabel, M.D., director of the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health. “The discovery of a substantial blood pressure lowering effect of many rare mutations in genes involved in sodium handling – and the promise of future discoveries of other genetic mutations – has enormous potential public health impact.”

What's more, by identifying the role played by rare genetic mutations in governing how the kidney regulates salt, the researchers have devised a general approach that may be broadly applicable to uncovering the genetic architecture of common conditions such as hypertension.

This new study, for the first time, extends the findings from patients with rare Mendelian traits to the general population. The findings suggest that independently rare mutations that alter salt handling by the kidneys collectively account for a substantial fraction of the general population's variability in disease susceptibility, said Lifton.

Lifton noted that there are probably about 100 million people worldwide who carry the mutations and are thus protected from hypertension. The mutations we have identified have clinically meaningful effects to individual patients and suggest that independently rare mutations will collectively account for a substantial fraction of the population's variability in disease susceptibility, he said.

The researchers started by examining variations in three genes known to cause rare recessive diseases characterized by large reductions in blood pressure. The analysis was conducted on salt handling genes isolated from people involved in the Framingham Heart Study (FHS), which is directed by Daniel Levy of NHLBI. Levy is a co-author of the *Nature Genetics* report. Co-first authors Weizhen Ji and Jia Ni Foo are at Yale University School of Medicine.

Lifton's team zeroed in on the three salt-regulating genes — NCCT, NKCC2 and ROMK — which his group had previously linked to rare but serious human diseases, including Gitelman and Bartter syndromes. Both are conditions characterized by inherited low blood pressure caused by recessive mutations, where two defective copies of a gene are at play.

Salt handling is an essential function of the kidneys. Our kidneys process more than three pounds of salt per day, and genetic mutations that raise or lower the ability of the organ to absorb and process salt can manifest themselves in higher or lower blood pressure.

Lifton's group has searched worldwide for patients with very high or very low blood pressure due to mutations in single genes. Such patients are often identified through family histories of extreme blood pressure. To date, his group has found a score of gene mutations that lower or raise blood pressure, including those that cause the extreme low blood pressure found in patients with Gitelman and Bartter syndromes.

We used knowledge of the spectrum of mutations that cause Gitelman and Bartter syndromes to sort among the hundreds of sequence changes we observed to identify those that are either known or highly likely to alter the function of the (gene) encoded proteins, Lifton explained.

By sequencing each of the three genes obtained from DNA samples from 3,125 participants in the Framingham Heart Study, and doing additional biochemical, genetic and genomic analysis, the HHMI team found functional mutations in one of the genes in at least 1 of every 64 of the study's participants sampled.

The results show that nearly 2 percent of the FHS cohort has a defective copy of one of these three genes, Lifton said. Unlike patients with Gitelman and Bartter syndromes, these subjects have only one defective copy, not two.

Lifton's group then tracked the influence of the mutation on blood pressure in FHS subjects aged 40-60, a time of life when hypertension manifests itself and can pose serious health risks.

We found that these mutation carriers have a 60 percent reduction in their risk of developing hypertension and have significantly lower blood pressure than those who do not have mutations, Lifton said. The influence of the mutation, he added, approximates effects achieved with drugs used to lower blood pressure.

The practical upshot of the new work, according to Lifton, could be potential new drugs to mimic the effects of the mutation by selectively inhibiting a single gene or several genes.

In addition, the study more broadly underscores the value of genetic analysis — resequencing of genes and genomes to ferret out functional mutations — for understanding individual risk of disease.

A major question about the genetic underpinnings of hypertension and other common diseases has been whether these are accounted for by common or rare DNA variations, said Lifton. Our study demonstrates the role of rare variation, showing that effects of rare mutations in these three genes cause relatively large effects, with clinically significant effects in individual patients. These findings suggest that much of the variation in common disease risk for hypertension and other diseases will be accounted for by rare (genetic) variants.