

Tiny Clue Reveals New Path Toward Heart Disease

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Geneticists have discovered a new gene that may put individuals at higher risk of developing cardiovascular disease.

The identification of the gene, called kalirin, implicates a biological mechanism never before linked to cardiovascular disease, according to the Duke researchers who led the study. Further study of this new clue could lead to novel ways to treat or even prevent the disease, the researchers said.

"The ultimate goal is to determine who will develop cardiovascular disease," said lead study investigator Liyong Wang, Ph.D., a research associate at the Duke Center for Human Genetics. "Our discovery could lead to a clinical tool for assessing a person's risk of coronary artery disease, so that physicians can try to prevent the disease from progressing."

The team, which includes researchers from several universities in the United States and the United Kingdom, reports its findings in the April 2007 issue of *American Journal of Human Genetics*. The research was sponsored by the National Institutes of Health.

Coronary artery disease affects more than 13 million Americans and is one of the nation's leading causes of death. The disease occurs when the arteries supplying blood to the heart become narrowed or clogged by plaque deposits. Left untreated, the disease can completely block the blood flow to the heart, leading to a heart attack.

While risk factors such as smoking, high blood pressure and high cholesterol are known to contribute to coronary artery disease, little is known about genes that render an individual susceptible to developing the disease, said study co-investigator Elizabeth R. Hauser, Ph.D., an associate professor of medicine at the Duke Center for Human Genetics.

In a previous study, the researchers had scanned the entire genome -- the body's genetic blueprint -- of a group of families in which at least two siblings had early onset coronary artery disease, looking for regions of "linkage" where DNA variations appeared to be inherited along with the disease. They found just such a region: a small section of the long arm of chromosome 3 where just a handful of genes were located. Chromosome 3 is one of the 23 pairs of chromosomes that comprise the human genome.

In the current study, the researchers focused on specific gene variants, called single nucleotide polymorphisms (SNPs), that occur when a single nucleotide building block in the long strand of DNA is altered. The researchers sought SNPs that occurred more or less often in individuals with coronary artery disease than in individuals without it, as such a link would indicate that these gene variants were associated with the disease.

The researchers first obtained DNA from 500 patients who had volunteered to be studied while being examined at the cardiac catheterization laboratories at Duke University Hospital. Using these DNA samples, the researchers scanned the same small section of chromosome 3 for SNPs that differed in sequence between individuals with and without coronary heart disease.

One SNP, in the kalirin gene, varied between individuals with heart disease and those without. The researchers repeated the same experiment in four additional patient populations, scanning the DNA of a total of 4,000 individuals, and turned up the same result.

"This finding opens up a whole new area of study for looking at risks of cardiovascular disease," said senior study investigator Jeffrey M. Vance, M.D., Ph.D., director of the Center for Molecular Genetics and Genomic Medicine, Miami Institute for Human Genomics at the Miller School of Medicine.

The researchers are now studying kalirin in the blood vessels to see how variations in the gene contribute to cardiovascular disease.

So far, they have found that this particular SNP is significantly correlated with the degree of atherosclerosis in human aortas, the large blood vessel that brings blood from the heart to all parts of the body.

Kalirin contains the hereditary information for the production of a protein that is involved in the migration of cells from one spot to another within smooth muscle. According to the researchers, the newly identified SNP may change the level of this protein in blood vessels, causing cells to congregate in one spot and form a plaque in the vessels to the heart.

In addition to identifying the genetic variations in the kalirin gene, the researchers also identified two genes that are involved in the same biological pathway, known as the Rho-GTPase signal transduction pathway.

Source: Duke University Medical Center

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