Special Report: How Genes Affect Health

Specific Gene Mutations Responsible For Heart Problems

By studying five generations of a Dallas family, University of Texas researchers have discovered that a mutation in a key gene causes aortic valve disease, a common heart birth defect, and a major contributor to adult heart disease.

In the trial, researchers scanned the DNA of 11 members of a family that was affected with aortic heart disease. The patients ranged from children with severe narrowing of the aortic valve to 50- and 60-year-olds who had calcium buildup on their heart valves severe enough to warrant replacement valves.

The researchers found that all the relatives with some manifestation of aortic valve disease had a mutation in a gene called Notch 1.

A second, smaller family with the heart disorder in San Diego, California, also had members with a second mutation in the same gene, providing convincing evidence that the researchers had found the genetic link to aortic heart disease, said Dr. Vidu Garg, lead author of the study.

"Mutations in Notch 1 cause an early developmental defect in the aortic valve," he explained.

The aortic valve is located between the left ventricle (the lower chamber of the heart) and the largest artery (the aorta). The left ventricle pumps oxygen-rich blood into the aorta, which carries blood to the brain and the rest of the body.

The normal aortic valve is made up of three leaflets, flaps of tissue that open and close to allow blood flow through the valve in only one direction. About 1 to 2 percent of the world's population is born with only two valve leaflets, a defect called bicuspid aortic valve. The condition predisposes individuals to aortic valve stenosis, which severely narrows the passage for blood to exit the heart and, in many cases, requires surgery at birth.

The narrowing of the valve can be so severe while the fetus is still developing that blood cannot get out of the ventricle. In those cases, the valve does not grow, and the child is born with a condition called hypoplastic left-heart syndrome.

"The left ventricle of these children is almost nonexistent, and they are born with one of the most severe types of congenital heart disease, which accounts for a quarter of all children who die from heart disease," said Dr. Deepak Srivastava, senior author.

"We know that aortic valve problems cause those deaths, so we think Notch 1 mutations are likely the cause of some cases of hypoplastic left heart syndrome as well," he said.

Many people born with bicuspid aortic valve go on to develop early calcification, or hardening, of the aortic valves, which is the third most common cause of heart disease in adults. As calcium deposits build up on the valve, the leaflets do not open normally, and the heart's ability to supply blood to the body decreases. Eventually, the valve must be replaced.

"Our work suggests that calcification of the aortic valve may be a manifestation of a mutation in Notch 1 or related genes," Dr. Garg said. "In the long term, we may be able to use that information to screen those at risk, possibly giving patients the opportunity to make a pharmacological or lifestyle intervention to slow down the progression of the calcification. I think that's where the clinical utility of this research will most likely be."

To identify possible therapeutic agents, further study is needed to determine exactly how the gene leads to calcification.

"Because of these families, we found that the Notch 1 protein normally shuts down factors that control bone development, and this may provide clues for understanding why tissues become abnormally calcified in the setting of disease," Dr. Srivastava said.

(Source: Nature, 2005;437:270-274.)

Gene Variant May Predict Diabetes

Researchers at University of Texas Southwestern Medical Center at Dallas have identified a particular gene variant that might serve as a predictor for type 2 (formerly called non-insulin-dependent) diabetes.

They found that a variation in the gene ENPPI was as much as 13 percent more common in people with type 2 diabetes and in those at greater risk for the disease. While further studies are needed, these results suggest that the variant may serve as an important genetic marker in identifying such patients.

"This important study uncovers one of the genes that appears to predispose to type 2 diabetes," said Dr. Scott Grundy, director of the University's Center for Human Nutrition and the study's senior author.

Researchers evaluated a specific gene in three study groups: South Asians, South Asians living in Dallas, and Caucasians living in Dallas. Some study subjects had type 2 diabetes, others had risk factors for the disease, and others showed no signs of diabetes and had no apparent risk factors.

"The implication from our study is that if a person has this gene variant, then — without waiting for the development of insulin resistance— he or she should be encouraged to follow lifestyle changes that could help prevent the onset of diabetes," said Dr. Nicola Abate, associate professor of internal medicine in the Center for Human Nutrition and the study's lead author.

Type 2 diabetes has become a serious health problem, particularly in light of the growing number of overweight and obese individuals in the United States, Dr. Abate said. In type 2 diabetes, cells ignore available insulin (insulin resistance), and not enough insulin is produced to maintain plasma glucose within a normal range. Obesity is one of the major risk factors for type 2 diabetes, but not all obese people develop type 2 diabetes and not all type 2 diabetic patients are overweight.

Some ethnic populations appear to be at higher risk, regardless of whether they are overweight, particularly South Asians or those originating from India, Pakistan, and Bangladesh.

The study focused on 679 South Asians living in Chennai, India (of whom 223 had type 2 diabetes); 1,083 South Asians living in Dallas who were new immigrants or first-generation immigrants from India, Pakistan, or Bangladesh (of whom 121 had type 2 diabetes); and 358 non-immigrant Caucasians living in Dallas (of whom 141 had type 2 diabetes). All study participants with type 2 diabetes were required to have had diabetes onset before age 60.

All subjects were evaluated for diabetes and a family history of diabetes as well as overall general health. Blood tests were conducted for genetic sampling.

Results showed that the ENPPI variant was present in 25 percent of the nondiabetic group and in 34 percent of the diabetic group of South Asians living in India; in 33 percent and 45 percent, respectively, in the nondiabetic and diabetic South Asians in Dallas; and in 26 percent and 39 percent, respectively, in the nondiabetic and diabetic Caucasians.

The gene ENPPI encodes a protein that blocks the action of insulin.

"Bad news—your policy covers your heart itself but not the arteries."
Genes Can Trump Exercise in Elderly Mobility

Genes can keep elderly people from benefiting equally from exercise, no matter how much effort they expend.

Of nearly 3,000 subjects studied, those who exercised stayed healthier than their inactive peers, but subjects born with a certain gene benefited the most from physical activity, said Dr. Marco Pahor, director of the University of Florida’s Institute on Aging.

"To our knowledge, this is the first study to show behavioral and genetic interaction in functioning and aging, and shows people are already pre-selected, that there are genes that interact with behavior to affect mobility," he said.

Decreasing mobility, along with lack of muscle strength and a decline in aerobic ability, are common aspects of aging that can lead to loss in quality of life, he explained. Understanding the mechanisms of how people lose mobility may lead to ways to help people remain independent longer, he added.

Federal health statistics have shown that about 34 percent of people in the United States aged 70 years or older report difficulty walking a quarter of a mile. These individuals have a higher risk for needing a nursing home or dying over a two-year period, compared with their counterparts who do not report trouble walking the distance.

Despite the undisputed benefits of exercise, not everyone responds the same, even when they do lead active lives—for reasons that have not been entirely clear.

In this study, researchers assessed older adults in an effort to understand the relationship between genetic makeup, the intensity of physical activity, and functional decline. Twice a year throughout the four-year study, participants aged 70 to 79 reported their level of activity and their ability to walk a quarter mile or up 10 stairs.

Researchers also tested the subjects’ blood to identify which version of a gene long associated with exercise performance they had. About one third of the population possesses the DD genotype of the gene, named for the angiotensin-converting enzyme (ACE). The rest have the II or ID version of the ACE gene.

The participants were categorized according to their exercise intensity and their genetic makeup. Overall, about 41 percent of study participants became less mobile over the four-year period. Even though the participants who exercised were less likely to develop substantial physical limitations, not all people received the same benefits, even if they exercised with the same intensity.

About a third of those engaged in significant physical exercise, including walking and strenuous exercise, and they preserved their mobility longer than the 70 percent who engaged in little or no physical activity. Researchers also evaluated the 8 percent who reported participating in weight training.

Genetic makeup influenced long-term physical function. Among exercisers, those with the DD and ID genotypes were more likely to remain fit than those with the II genotype. The II group manifested mobility problems at a 45 percent higher rate. No difference was found in mobility according to genotype among the non-exercisers, suggesting that function was influenced by an interaction between exercise intensity and genetic makeup.

In addition, those who performed weight training and had the DD or ID genotype displayed the lowest rate of mobility loss in any exercise category. In contrast, weight trainers with the II genotype developed physical limitations similar to those experienced by the subjects who were relatively inactive.

The differences in body composition created by the genotype may also yield clues as to what causes mobility limitations to develop with age and what people can do to stay active, Dr. Pahor said. Those with the II genotype, for example, tend to have higher total body fat.

"The good news is that regardless of genotype, the physically active people were at lower risk of losing mobility, suggesting that everyone should exercise to preserve mobility," he recommended.

The study’s lead author, Stephen Kritchevsky, from Wake Forest University School of Medicine, said that people respond differently to exercise and that the implications of that response may change as they age.

"In our study, the II genotype is associated with increased fat in the leg muscles," Dr. Kritchevsky said. "Now energy storage near muscles may benefit young athletes engaged in endurance activities, but in older persons, accumulation of leg fat has been linked to poorer muscle function and metabolic diseases like diabetes."

(See Journal of the American Medical Association, April 10, 2005.)

Gene Variant May Predict Diabetes

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The genetic variation increases the action of this protein and blocks insulin action even more.

Dr. Abate said:

"Earlier studies we conducted showed a propensity toward insulin resistance and type 2 diabetes in South Asians, even when they were thin. This study expanded that to include diabetic patients and Caucasians of European descent. It also took into account the possible influence of environmental factors by comparing South Asians in both Dallas and in Chennai. Consistently, we found that this gene variant in all three groups predicted diabetes."

Dr. Grundy said:

"Dr. Abate’s previous studies showed that abnormalities in the gene ENPP1 contributed to insulin resistance. Now, Dr. Abate and his associates have demonstrated that this gene’s effects on insulin resistance have biological significance in that its abnormalities make it more likely that people will develop diabetes. This study is particularly revealing because of the past difficulty in identifying diabetes-causing genes on the part of geneticists working in the diabetes field."

(Source: Diabetes, April 2005.)