

Researchers discover gene mutation that helps prevent heart disease

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Researchers at the University of Maryland School of Medicine in Baltimore have discovered a novel gene mutation among the Old Order Amish population that significantly reduces the level of triglycerides in the blood and appears to help prevent cardiovascular disease. The results of the study will be published in the Dec. 12, 2008, issue of the journal *Science*.

"We found that about 5 percent of the Amish have a gene mutation that speeds up the breakdown of triglycerides, which are fat particles in the blood associated with an increased risk of coronary artery disease," says the lead investigator, Toni I. Pollin, Ph.D., an assistant professor of medicine at the University of Maryland School of Medicine. Carriers of the mutation have half the amount of apoC-III, a protein linked to triglycerides, than people without the gene variant.

Dr. Pollin says that those with this mutation of the APOC3 gene have higher levels of HDL-cholesterol, the so-called "good" cholesterol, and lower levels of LDL-cholesterol, the "bad" cholesterol. In addition, they have less arteriosclerosis (hardening of the arteries) – as measured by the amount of calcium in their coronary arteries. "Our findings suggest that having a lifelong deficiency of apoC-III helps to protect people from developing cardiovascular disease," she says.

Triglycerides and cholesterol are lipids, or fats that circulate in the blood. ApoC-III is a protein that is bound to circulating lipids. It inhibits the breakdown of triglycerides so they stay in the blood longer. Elevated

levels of apoC-III are associated with higher triglyceride levels.

"The discovery of this mutation may eventually help us to develop new therapies to lower triglycerides and prevent cardiovascular disease," Dr. Pollin says. This is the first reported mutation within the human APOC3 gene that specifically blocks the production of apoC-III, causing individuals who carry a copy of the mutation to produce half the typical amount of the protein.

More than 800 members of the Old Order Amish community in Lancaster County, Pa., participated in the study, which was funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health. Researchers used a new approach called a genome-wide association study, or GWAS, to rapidly scan 500,000 markers in the DNA of the participants to find variations, or single nucleotide polymorphisms called SNPs, that are associated with triglyceride levels in the blood. This was followed by direct gene sequencing. The GWAS technique is being used widely by scientists around the world to track down genes associated with many diseases.

As part of the study, participants drank a high-fat milkshake and then were closely monitored for the next six hours with blood tests as well as ultrasound tests of their brachial artery to determine how well their arteries were coping with the fatty meal. Some also were tested to determine if there were calcium deposits in their coronary arteries, which is a clear sign of cardiovascular disease. "What we found is that people who have the mutation are much less likely to have any calcification," Dr. Pollin said.

Researchers believe the mutation was first introduced into the Amish community in Lancaster County by a person who was born in the mid-1700s. This mutation appears to be rare or absent in the general population.

Alan R. Shuldiner, M.D., the study's senior author, says, "The Old Order Amish are ideal for genetic research because they are a genetically homogenous people who trace their ancestry back 14 generations to a small group that came to Pennsylvania from Europe in the mid-1700s." Dr. Shuldiner is a professor of medicine; head of the Division of Endocrinology, Diabetes and Nutrition; and director of the Program in Genetics and Genomic Medicine at the University of Maryland School of Medicine.

The study is part of a larger University of Maryland research project, the Heredity and Phenotype Intervention (HAPI) Heart Study, which examined how genes and lifestyle factors influence the risk of developing cardiovascular disease.

Since 1993, Maryland researchers, led by Dr. Shuldiner, have conducted more than a dozen studies of the Amish, searching for genes that cause a variety of medical problems, such as type 2 diabetes, obesity, osteoporosis and high blood pressure. "We have uncovered a wealth of information in our studies of the Amish over the years, and much of what we have found is not only applicable to this unique population, but the general public as well," Dr. Shuldiner says.

Source: University of Maryland Medical Center

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