SOUTHWESTERN NEWS

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UT SOUTHWESTERN RESEARCHERS FIND GENE FOR INHERITED FORM OF HIGH CHOLESTEROL

DALLAS – April 27, 2001 – Researchers at UT Southwestern Medical Center at Dallas have located the gene that, when mutated, is responsible for autosomal recessive hypercholesterolemia (ARH), an inherited form of high cholesterol characterized by low-density lipoprotein levels of 350 to 600 milligrams per deciliter.

This disorder, which results in the development of premature coronary artery disease and accumulation of cholesterol in skin and tendons, is rare, but understanding its genesis may lead to the development of new treatments for high blood levels of cholesterol.

Scientists at UT Southwestern located the *ARH* gene on chromosome 1p35 and found six mutations in the gene. The gene encodes a new adaptor protein, which the scientists named ARH. The results of the study are published in the May issue of *Science*.

"This gene is a new key player in the clearance mechanism of LDL from the body. We know it's important because when it is mutated, people have very high plasma cholesterol levels," said Dr. Helen Hobbs, chief of clinical genetics, director of the Eugene McDermott Center for Human Growth and Development, and senior investigator of the study.

Under normal conditions, low-density lipoprotein receptors (LDLR), which are found in the liver, remove LDL cholesterol from the blood. More than 70 percent of LDL cholesterol is removed from the blood by these receptors. Mutations in the *LDLR* gene cause the autosomal dominant disorder familial hypercholesterolemia, a discovery made by UT Southwestern Nobel laureates Drs. Michael Brown and Joseph Goldstein.

Researchers have known that ARH was not caused by mutations in the *LDLR*, but until now had not identified the defective gene that is responsible for the disorder. Hobbs and her colleagues found that defects in *ARH* impair the function of the LDLR and arrest the body's normal ability to clear LDL cholesterol.

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The researchers analyzed the DNA samples of four families with ARH. Two of the families were from Sardinia, where the disease is prevalent, and two families were from Lebanon. The study participants had extremely high LDL-cholesterol levels, ranging from 350 to 600 mg/dL. Optimal LDL-cholesterol levels range between 60 and 130 mg/dL.

After mapping the gene in these families, the researchers identified the defective gene. The researchers found different mutations in each of the four original families. They then examined additional study participants with the same disorder and found that they also had mutations in the same gene.

Two mutations in the gene account for the high frequency of the disease in Sardinia. Mutations were also found in an Iranian, American and two Lebanese study participants.

"We're confident that this is the gene responsible for ARH," said Hobbs.

Dr. Jonathan Cohen, associate professor of internal medicine, co-author of the study and a nutrition scholar in the Center for Human Nutrition, said, "These findings give us insight about how cells move cholesterol around and how the body gets rid of it. Once it's understood, we can manipulate the system more efficiently."

Hobbs and her collaborators recently identified the defective genes responsible for the rare genetic disorder, sitosterolemia, an important finding that may lead to the development of new drugs to treat high cholesterol. Hobbs was also part of the research team that, for the first time, identified a receptor for high-density lipoprotein (HDL) called SR-B1. It is the mechanism by which HDL, the "good cholesterol," is delivered to some cells.

UT Southwestern researchers have discovered the defective genes in all four major inherited forms of hypercholesterolmeia. Brown and Goldstein, director of the Erik Jonsson Center for Research in Molecular Genetics and Human Disease and chairman of molecular genetics, respectively, discovered the defective gene in familial hypercholesterolemia (FH). Dr. Scott Grundy, director of the Center for Human Nutrition, discovered that some patients who appeared to have FH actually had a mutation in a protein found on the LDL called apolipoprotein B.

Other researchers involved in the most recent *Science* study include Dr. Christine Kim

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Garcia, an internal medicine resident and former M.D./Ph.D. student in molecular genetics; Dr. Nick Grishin, assistant professor in biochemistry and assistant investigator in the Howard Hughes Medical Institute; Dr. Kenneth Wilund, research fellow in internal medicine; and Robert Barnes, a program analyst in the Eugene McDermott Center for Human Growth and Development. Other researchers, two of whom had worked previously with Hobbs as postdoctoral fellows, included scientists from the University of Rome; the University of Ferrara, Italy; the University of Sassari, Italy; the University of Modena and Reggioemilia, Italy; and the Bone Marrow Transplant Unit, Ospedale Microcitemico, Cagliari, Italy.

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