

PERSPECTIVES & OPINIONS



Helen Hobbs

HEART OF  
THE MATTER

Brian Harkin

Helen Hobbs, who thrives in the fast pace and intensity of medicine, did not settle easily into the more measured world of research. Now chief of human genetics at the University of Texas Southwestern Medical Center at Dallas, her desire for better treatments drives her to pore over susceptibility factors to learn who develops disease and who does not—and why.

*What affects a person's disease susceptibility?*

The expression of a person's genes over time, in the context of environmental factors such as exercise, diet, aging, and stress, produces susceptibility or resistance to certain diseases. The term phenotype is used to capture the physical and biochemical characteristics that result from this interplay of genes and the environment. Phenotype in humans includes not only overt effects, like a heart attack or stroke, but the more subtle changes we uncover through blood tests and imaging studies.

*How are you using phenotype analysis in your research?*

We've used sophisticated imaging together with more conventional medical testing to develop very precise phenotypes in a large study population. In the Dallas Heart Study, we enrolled 3,500 individuals—African American, Hispanic, and Caucasian—between 30 and 65 years of age, and obtained a series of phenotypes for each participant, including imaging studies to visualize the heart, blood vessels, liver, and other tissues and blood tests to measure the levels of many different proteins and lipids.

*What have you found?*

Our work with a gene called PCSK9 is the most significant contribution of the Dallas Heart Study. We discovered that variant forms of PCSK9 are associated with lower levels of low-density lipoproteins (LDL), the “bad” cholesterol. We found that one out of every 50 African Americans has a PCSK9 variant associated with a 28 percent reduction in LDL; Caucasians with a different variant experience a 15 percent reduction in LDL.

We assessed these PCSK9 variations in more than 12,000 samples collected in the Atherosclerosis Risk in Communities Study across 15 years. The findings were unequivocal: low LDL is remarkably cardioprotective. The African Americans with the PCSK9 mutations had an 88 percent decrease in heart disease risk—and this included many individuals with hypertension or diabetes, or those who smoked. The Caucasians with the other PCSK9 sequence variation had a 50 percent disease risk reduction. These are much greater reductions in coronary heart disease than we see when we lower plasma LDL to similar levels with a statin drug in adults.

We published those results in 2006. It now seems reasonable to consider lowering LDL during early adulthood in individuals who have other risk factors. The NIH is considering a trial to test this, and pharmaceutical companies are looking at PCSK9 as a drug target.

*In this case, genotype seems to be especially important?*

These results show how a genotype can provide information that is not captured in phenotype. The PCSK9 genotypes we identified tell us about the level of LDL in the blood over a lifetime rather than at one moment in time. Individuals with mutations in PCSK9 have lower levels of LDL starting at birth so the arteries feeding the heart are exposed to cumulatively fewer LDL particles over time. We have known for years that high levels of LDL are sufficient to cause heart disease, even in the absence of other risk factors. These new data tell us that the reverse is also true; low levels of LDL starting early in life provide protection from heart disease, even in those individuals who have other risk factors.

*How do mutations in PCSK9 cause lower levels of LDL in the blood?*

PCSK9 expression causes degradation of LDL receptors, which are proteins on the surfaces of cells that bind and remove LDL from blood. Mutations that interfere with the synthesis of PCSK9 result in an increase in the number of LDL receptors, which leads to lower levels of LDL in the blood.

*Is there more to come?*

Soon it will be possible to sequence entire genomes of study subjects. A major challenge will be to link the sequence differences identified in genes to traits and diseases. We will need large collections of very carefully phenotyped individuals of different ancestries. The Dallas Heart Study was designed specifically to address this need.

Very few population studies include large numbers of individuals whose ancestors are not from Europe. Genomes differ depending on ancestry. For example, we showed that Hispanics tend to deposit more fat in the liver, which can lead to liver injury and, ultimately, liver failure. In September 2008, we reported that sequence variations in a gene of unknown function called PNPLA3 are responsible for a large fraction of the differences in liver fat between Hispanics and other groups. Now we are exploring whether those sequence variations in PNPLA3 predispose individuals to liver injury after exposure to alcohol, drugs, or infection.

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INTERVIEW BY RICHARD CURREY. HHMI investigator Helen H. Hobbs is director of the Dallas Heart Study.