Single genetic defect causes early heart disease

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A team of researchers from the United States and Iran has identified a genetic mutation that causes early onset coronary artery disease in members of a large Iranian family. The genetic mutation leads to heart disease by causing high blood pressure, high blood levels of "bad cholesterol" and diabetes, all risk factors for heart disease. Coronary artery disease is the leading cause of death worldwide.

"Unfortunately, most of the individuals in this family who carried the mutation died in their early fifties from coronary artery disease that resulted in heart attacks and heart failure," said the research team leader, Richard P. Lifton, a Howard Hughes Medical Institute investigator at Yale University School of Medicine. "Our studies identify a single mutation that has quite a large effect on many of the metabolic risk factors for coronary artery disease."

Lifton and his colleagues published their research article in the March 2, 2007, issue of the journal *Science*. Arya Mani, a cardiologist and member of Lifton's laboratory at Yale, was first author of the article. The Yale group collaborated on the studies with researchers at Amir Kabir University of Technology, Azad University and The Social Welfare and Rehabilitation Sciences University, all of which are in Tehran, Iran.

The genetic defect is rare, so the discovery by itself will not provide an explanation for the more common forms of coronary artery disease, which are caused by a constellation of factors, said Lifton. However, he

said, understanding the molecular nature of this single genetic defect, which is at the root of a familial form of such a complex disease, offers invaluable clues. Researchers may be able to apply that knowledge to improve understanding of what causes the body's metabolic machinery to malfunction in the more "garden variety" forms of heart disease.

According to Lifton, physicians in Tehran had long been aware of the family's tragic struggle with early coronary artery disease. In fact, 23 of 28 blood relatives of the first patient identified with this genetic mutation died from coronary artery disease by an average age of 52. The research team obtained medical records and blood samples from all surviving members of the family. The medical records showed that the family members had a characteristic cluster of symptoms called metabolic syndrome. People with this syndrome have hypertension, high blood lipid levels and diabetes, and they are at much higher risk of developing heart disease.

"Dr. Mani identified this family as an example of an extreme outlier of a common disease," said Lifton. "Studying extreme forms of common disease has been a longtime theme in our laboratory." Lifton's strategy is to pinpoint and analyze the rare genetic traits that cause complex disorders. By understanding the causes of those familial forms of complex diseases such as hypertension, Lifton and others have laid the foundation for identifying the mechanisms that underlie more common forms of the disease.

One of the important features of the Iranian family, Lifton noted, was that affected family members exhibited metabolic syndrome and early coronary artery disease, but unaffected family members were normal. "So this told us that the coronary disease was traveling with this cluster of metabolic risk factors," he said. "Those risk factors were behaving as though they were being transmitted through the family as a single factor."

When the researchers performed a detailed genetic comparison of affected and disease-free family members, they found that a specific segment of chromosome 12 was the most likely genomic hiding place for this unknown factor. In mapping the six genes present on this small chunk of chromosome 12, they found that the gene for LDL receptor-related protein 6 (LRP6) was present in that region of the chromosome.

They immediately focused on LRP6, tipped off in part by an earlier discovery by HHMI investigator Matthew Warman at Children's Hospital Boston. In 2001, Warman had shown that members of the LRP gene family were important in bone development. "What caught our attention was that multiple people in the Iranian family we were studying had coronary artery disease and unexplained hip fractures at young ages. We had not made much of the hip fractures at the outset, but once we knew that LRP6 was in this small genomic interval that contained the coronary-artery-disease-causing gene, we immediately thought of LRP6 as the likely culprit," said Lifton.

By sequencing the LRP6 gene in affected family members, the scientists found that the mutation caused the substitution of a single amino acid in the protein the gene produced. In contrast, the researchers did not find the mutation when they analyzed large comparison populations of Iranians and Americans. However, the researchers' statistical analysis of the family members revealed a high correlation between the presence of the mutation, metabolic syndrome, and osteoporosis. In cell culture studies, Dan Wu, a Yale biochemist, found that the mutation compromised how the LRP6 protein functions in the Wnt signaling pathway. Wnt is at the heart of a key metabolic signaling pathway that is important in embryonic development and contributes to an array of normal physiological processes in adults. Lifton emphasized that the compromised Wnt pathway is intriguing and the pathway will likely become an important research target for understanding coronary artery disease.

"For example, now that we know that altered Wnt signaling can lead to multiple components of the metabolic syndrome, this raises the question of whether other mutations in the Wnt signaling pathway—or acquired defects that cause alteration of Wnt pathway activity—might commonly contribute to metabolic syndrome and coronary artery disease," he said.

Basic understanding of how the Wnt pathway malfunctions could lead to new treatments for coronary artery disease. "Although it's a long way off, we might ultimately develop ways to either disrupt or increase the activity of particular components of the pathway, to prevent development of metabolic syndrome and coronary artery disease," he said.

The discovery that the LRP6 mutation also causes osteoporosis raises the possibility of a linkage with coronary artery disease, said Lifton. "There is emerging recognition that osteoporosis and coronary artery disease occur together more often than expected by chance," he said. "We have now implicated altered activity of the Wnt pathway in development of both coronary artery disease and osteoporosis. So, one can imagine identifying patients with osteoporosis and coronary artery disease as a way of selecting those who might be particularly interesting to investigate for altered Wnt signaling."

Source: Howard Hughes Medical Institute