Genetic variation may lead to early cardiovascular disease

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Researchers from Duke University Medical Center have identified a variation in a particular gene that increases susceptibility to early coronary artery disease. For years, scientists have known that the devastating, early-onset form of the disease was inherited, but they knew little about the gene(s) responsible until now. The results are published January 2 in the open-access journal *PLoS Genetics*.

In a previous study, a region on chromosome 7 was linked to coronary artery disease (CAD). More recently, the researchers focused on identifying the gene in this region that confers risk of early-onset CAD and identified it as the neuropeptide Y (NPY) gene. NPY is one of the most plentiful and important proteins in the body and is a neurotransmitter related to the control of appetite and feeding behavior, among other functions.

The current research, led by Svati Shah and Elizabeth Hauser, found evidence for six related variations in the NPY gene that show evidence of transmission from generation to generation and association across a population of early-onset CAD patients.

The researchers evaluated 1,000 families for CAD or evidence of a true heart attack, as part of the GENECARD study put together by the Duke University Cardiology Consortium. An independent, nonfamilial study used a collection of samples of nearly everyone who had an angiogram at Duke since 2001. Co-authors William Kraus and Christopher Granger founded this repository, called CATHGEN, which is now nearing 10,000

subjects. The nonfamilial work showed a strong relationship between the NPY genetic variants associated with coronary disease.

The genetic results were even stronger in patients with onset of CAD before the age of 37. "We showed a strong age effect," said Hauser. "If one has the NPY gene variants in one of two copies (from mother and father), then you may develop coronary disease earlier."

"These young patients are a vulnerable population on whom CAD has a significant long-term impact, but they are particularly hard to identify and therefore to initiate preventive therapies for," Shah said. "These and other genetic findings may help us in the future to identify these patients prior to development of CAD or their first heart attack."

The group further examined NPY levels in blood and found that, among the six NPY variants, there is a single-nucleotide change of the DNA code on the NPY promoter region of the gene - the part of the gene that turns it on and off. This single-letter change was associated with higher NPY levels, suggesting that this was the functional change that predisposes a person to early onset CAD.

"If you had 1 or 2 copies of this mutant version of the gene, there could be a change in NPY level," Shah said. "The concept is that small changes over time can promote atherosclerosis (hardening of the arteries) at a very young age."

Mouse studies subsequently confirmed that the NPY pathway promotes atherosclerosis. The next step may be to examine the children of the people who were studied. Studying the heterogeneity among individuals with early-onset disease - overweight versus normal weight families, for example - will also be important.

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al. (2009) Neuropeptide Y Gene Polymorphisms Confer Risk of Early-Onset Atherosclerosis. PLoS Genet 5(1): e1000318. doi:10.1371/journal.pgen.1000318
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