Scientists identify genes associated with peripheral artery disease

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Researchers from the RIKEN Center for Integrative Medical Sciences have worked with a number of universities and hospitals in Japan to use gene maps in the Japanese population to identify three genes associated with peripheral artery disease, a common but debilitating disease that makes walking painful and that can, in serious cases, lead to limb loss. The work, published in *PLOS ONE*, is the first to identify specific genetic factors with the condition.

PAD, though not as well-known as heart attacks and strokes, is also a condition caused by atherosclerosis—deposits of plaque on the inner lining of blood vessels. In addition to limb pain and difficulty walking, it can lead to major cardiovascular and cerebrovascular events, and is estimated to be the third leading cause of death associated with atherosclerosis.

The researchers began by collecting genetic information on 735 people who suffered from PAD from the BioBank Japan project and compared their genomes with 3,383 people without the condition taken from the general population. They looked for simple genetic variations—called single nucleotide polymorphisms, or SNPs—that were more common in the patients than in controls. There were a large number of SNPs that were more common in patients, but the number of patients was not sufficient to allow them to identify which were really significant. They next took the 500 most likely candidate gene variations and analyzed the genes of a further 1,150 cases and 16,752 controls to look for SNPs that were significantly more common in the PAD patients. They found 13

that were statistically significant. They added a further 1,229 cases, and based on this analysis identified three gene loci that were clearly associated with the disease. "It seems," says Kouichi Ozaki of the IMS Laboratory for Cardiovascular Disease, one of the first authors of the study, "that people with these three gene polymorphisms are particularly vulnerable to this disease."

"The three gene polymorphisms were all found to be in the region flanking two different genes," continues Ozaki, "so we needed to find out which gene they were affecting and how." The first polymorphism, on chromosome 13, was found to be associated with the expression of IPO5, encoding a protein that is involved in ridding peripheral arteries of lipoprotein A—which forms part of LDL, or bad, cholesterol. A second was found to be associated with a gene that encodes a receptor of endothelin-1, a peptide that promotes the constriction of blood vessels and inflammation—two processes known to be associated with PAD. And the third was associated with a gene that encodes a protein called histone deacetylase-9, that can regulates cell growth and may be responsible for the thick blood vessel walls typical of PAD.

"What is important," says Ozaki, "is that although this study does help to identify people who might be at risk for PAD, the findings could also be used to elucidate the mechanism through which PAD arises, and hence could help to identify therapeutic targets for future treatments. It is important to remember, however, that the study was done in a Japanese population, so that there could be different patterns in other populations, and further studies should be done in other groups."

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