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International study identifies gene variants associated with early heart attack

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The largest study ever completed of genetic factors associated with heart attacks has identified nine genetic regions - three not previously described - that appear to increase the risk for early-onset myocardial infarction. The report from the Myocardial Infarction Genetics Consortium, based on information from a total of 26,000 inviduals in 10 countries, will appear in *Nature Genetics* and is receiving early online release.

"For several decades, it has been known that the risk for heart attack - the leading cause of death and disability in the U.S. - clusters in families and that some of this familial clustering is due to differences in DNA sequence," says Sekar Kathiresan, MD, director of Preventive Cardiology at Massachusetts General Hospital (MGH) and corresponding author of the *Nature Genetics* report. "We set out to find specific, single-letter differences in the genome, what are called single-nucleotide polomorphisms (SNPs), that may be responsible for an increased familial risk for heart attack."

Groundwork for the current study was laid more than 10 years ago when co-author Christopher O'Donnell, MD, now based at the Framingham Heart Study, began to gather data on patients treated at the MGH for early-onset heart attack - men under 50 and women under 60. Kathiresan soon joined the project, and in 2006 they formed the Myocardial Infarction Genetics Consortium along with David Altshuler, MD, PhD, of the MGH Center for Human Genetic Research and the Broad Institute of MIT and Harvard, eventually involving six groups around the world

that had collected samples on a total of about 3,000 early-onset heart attack patients and 3,000 healthy controls.

The current study took advantage of several scientific tools developed over the past decade. These include the International Haplotype Map, a comprehensive map of SNPs across the genome; genotyping arrays that allow screening of hundreds of thousands of SNPs at once; and a gene chip developed by Altshuler's team that can simulaneously screen for SNPs and for copy-number variants - deletions or duplications of gene segments, a type of change associated with several disease categories. After analysis of the consortium's samples identified SNPs that could be associated with heart attack risk, the researchers ran replication screens in three independent groups of samples, resulting in a total of 13,000 heart attack patients and 13,000 controls.

Significant associations with the risk of early-onset heart attacks were found for common SNPs in nine genetic regions. Three of those associations with heart attack risk were identified for the first time; and one of the novel regions also had been found, in a separate study by O'Donnell, to promote the buildup of atherosclerotic plaque in the coronary arteries. To analyze the effect of inheriting several risk-associated SNPs, participants were assigned a genotype score, which revealed that those with the highest number of risk-associated variants had more than twice the risk of an early-onset heart attack as those with the fewest. No risk associations were identified with copy-number variants.

Although the increased risk associated with individual SNPs is small, knowledge gained from the association could prove extremely valuable. "One of the known variants we identified is at a gene called PCSK9, which was originally identified in 2003," explains Kathiresan, an assistant professor of Medicine at Harvard Medical School. "Extensive study of that gene region has led to significant insight into the biology of

atherosclerosis and heart attack and to efforts to develop targeted drugs. We are optimistic that investigating the mechanics of the newly mapped variants could yield similar insights. And since we already have effective ways to reduce heart-attack risk, individuals at higher genetic risk may benefit from earlier intervention, something that needs to be tested in future studies."

Source: Massachusetts General Hospital