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Large Study Identifies New Genetic Risk Factors for Brain Aneurysm

By sifting through the genomes of more than 10,000 people, researchers have discovered three genetic factors that could help doctors identify people who are at the greatest risk for developing a brain aneurysm.

Howard Hughes Medical Institute investigator Richard P. Lifton and Murat Günel, geneticists at Yale University School of Medicine, led an international team of researchers that identified the risk factors. Any individual may have up to two copies of each of these genetic sequences, which the scientists call risk alleles. Those who carry five or six risk alleles are three times more likely to develop a brain aneurysm than those with one or no risk alleles.

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— **Richard P. Lifton**

The study is the first genome-wide search for common genetic variations that impact the formation of brain aneurysms. The team's findings are reported on November 9, 2008, in an advance online publication in the journal *Nature Genetics*. Researchers in Finland, the Netherlands, and Japan provided patient data for the study, and genetic analyses were conducted at Yale.

Most people with an aneurysm, or bulging blood vessel, in their brain never know it is there until it ruptures, causing a stroke that usually leads to catastrophic neurological damage or death. But if doctors can find an aneurysm before it causes a stroke, it can often be surgically removed to eliminate the threat. Assessing the new genetic information in combination with the other factors known to influence risk of aneurysm - age, gender, smoking, and high blood pressure - could allow doctors to identify which people are at highest risk and would benefit from screening, the researchers say. Screening could be performed by non-invasive imaging of blood vessels in the brain. Further, exploring the biological roles of the genes affected by the three risk alleles could provide clues into what causes aneurysms to form, a process about which Lifton says, we know almost nothing.

About two percent of people alive today are thought to have brain aneurysms, according to the American Heart Association. Many of these never cause any problems. In the subset of aneurysms that eventually rupture, the resulting stroke is usually the first symptom a patient experiences. Some aneurysms, however, can put pressure on surrounding tissue, causing what patients typically describe as 'the worst headache of their life,' Lifton says. Those patients are the lucky ones, he says, since angiograms of the brain can identify clinically important aneurysms that can be surgically corrected before they cause lasting damage.

We do a pretty good job treating these aneurysms before they rupture, says Günel, who is a neurosurgeon. But when a patient suffers a hemorrhage and then comes to the hospital, sometimes despite the best medical care, there's not much you can do. So, he says, there is a big need for tools to help clinicians find treatable aneurysms in more patients.

Equally important, Lifton notes, is figuring out what causes these bulges in blood vessels to form in the first place. We really haven't known anything about the underlying biology of aneurysm, he says. If we can figure that out, it may give us an opportunity to intervene therapeutically - that is, with a drug, instead of surgery.

According to Günel, there have been only limited attempts to sift through the genetic factors that contribute to brain aneurysms so far, and these studies have searched for genes that have strong effects, but occur only rarely within a population. Only recently has the technology become available to do the large, genome-wide association studies needed to search for risk factors that are more common, but whose effects may be too subtle to pick up in small study population.

To mine for these common genetic factors, Lifton, Günel, and their colleagues compared the genomes of more than 10,000 individuals - 2,100 of whom had brain aneurysms (both ruptured and unruptured) and 8,000 who did not. Specifically, they examined more than 300,000 single nucleotide polymorphisms (SNPs). SNPs are found throughout the human genome and represent instances where a single letter of the DNA sequence frequently varies between individuals. The team was looking for SNPs for which one allele was significantly more common among individuals with aneurysms than among those without aneurysms.

To begin the study, collaborators in Europe identified patients with aneurysms and control subjects-1,805 in Finland and 7,205 in the Netherlands. The researchers then determined these individuals' DNA sequence at 300,000 sites of common variation within the genome. These sites are distributed across all of the chromosomes. By comparing the frequency of each variant in individuals with and without aneurysm (cases and controls), the team identified four sites in the genome where a particular sequence variant was significantly more frequent in cases than controls. To confirm these results, the team then studied these 4 chromosome segments in an independent group of 1,171 Japanese subjects. Three of the sites showed

the same association to aneurysm found in the Finnish and Dutch populations, providing strong evidence that the results were not obtained by chance. Lifton points out that, since the risk alleles are present in both the Japanese and the European populations, whose overall genetic backgrounds vary more than groups within Europe, These findings are likely to be relevant for a very large fraction of the world's population.

Each of these three variants has a fairly modest impact on risk, Gunel says — each copy increasing risk by 24 to 36 percent. But when you compare those with the fewest risk alleles to the group with the most risk alleles, the risk of an aneurysm goes up about threefold. In addition, Gunel indicates that there are likely many other alleles that increase risk to a smaller degree - but a larger study will be required to find them.

This information starts to put us on a path toward being able to identify patients who should be screened for brain aneurysms, Lifton says, noting that when the newly identified genetic risk factors are combined with other known risk factors, they will account for a larger difference in risk between individuals. Similarly, Günel adds, patients with the greatest risk can be counseled on lifestyle changes, such as reducing blood pressure and quitting smoking.

The team's findings also have hinted at how some brain aneurysms might develop. One of the risk alleles identified in the study lies near a gene called *SOX17*. Endothelial cells, such as those that line the interior of blood vessels and come in direct contact with the blood, need *SOX17* for their formation. Another of the risk alleles had been previously implicated in other arterial diseases, including heart attack and abdominal aneurysms. That allele lies near a gene that is turned on during aging - which might be the case for genes needed to repair the damage that blood vessels accumulate throughout life, Günel says. We know that most aneurysms occur at branch points in the vessels, possibly due to increased stress on the vessel wall, Lifton says. So it may be that ineffective repair of this damage is responsible for the formation of an aneurysm. Further exploration using animal models will help test this model and determine whether researchers might be able to target the endothelial repair process for potential therapies, he says.