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New genetic risk factors for aneurysms identified

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In the largest genome-wide study of brain aneurysms ever conducted, an international team led by researchers at the Yale School of Medicine have identified three new genetic variants that increase a person's risk for developing this deadly disease.

The massive study of intracranial aneurysms involved more than 20,000 subjects and was published in the April 4 online edition of the journal *Nature Genetics*. The new study, the second by Yale researchers published within the last 15 months, brings to five the number of regions of the genome that have been found to contribute to the nearly 500,000 cases of this devastating disorder diagnosed worldwide annually.

"These findings provide important new insights into the causes of intracranial aneurysms and are a critical step forward in the development of a diagnostic test that can identify people at high risk prior to the emergence of symptoms," said Murat Gunel, professor of neurosurgery, genetics and neurobiology at Yale and senior author of the paper. "Given the often-devastating consequences of the bleeding in the brain, early detection can be the difference between life and death."

The ambitious international collaboration was headed by Gunel and Richard Lifton, Sterling Professor and chair of the Department of Genetics at Yale and a Howard Hughes Medical Institute Investigator. Sixty-nine authors from 32 institutions in 10 countries contributed to the findings by analyzing 5,891 aneurysm patients from Japan and Europe and 14,181 unaffected subjects. They searched across the entire genome

for changes in the genetic code that were shared more often by aneurysm patients than by unaffected individuals. The researchers determined that if a person carries all of the risk variants discovered by the Yale-led team, they are five to seven times more likely to suffer an aneurysm than those individuals who carry none.

Gunel and Lifton noted that such huge studies are possible only because of the dramatic improvement in speed and efficiency of genomics technology and the cooperation from nearly 70 international researchers who recruited thousands of subjects and collected DNA samples.

While these findings have transformed the understanding of the genetic risks for intracranial aneurysms, considerable work remains, note the researchers. "These five findings explain about 10 percent of genetic risk of suffering an aneurysm," Gunel said. "This is 10 percent more than we understood just a couple of years ago, but there is a long way to go."

Lifton agrees: "While much remains to be done, this study provides fundamental new clues about the causes of this catastrophic disease that point to new opportunities for early diagnosis and therapeutic intervention."

The median age when aneurismal hemorrhagic stroke occurs is 50 years old, and there are typically no warning signs. In the majority of cases, the resulting strokes cause death or severe brain damage. Without a way to diagnose aneurysms prior to these events, physicians have been mostly left to respond after the fact, once the damage has largely been done, Gunel said.

"Although we face many more challenges, we now achieved the first steps necessary to attain over a decade long goal of early diagnosis and biology-based treatments of aneurysms," he said.

Provided by Yale University