

BREAKING RESEARCH NEWS

Yale Researchers Unravel Mystery of Brain Aneurysms

Yale researchers have taken the first critical steps in unraveling the mysteries of brain aneurysms, the often fatal rupturing of blood vessels that afflicts 500,000 people worldwide each year and nearly killed Vice President-elect Joseph Biden two decades ago.

An international team — led by Murat Gunel, professor of neurosurgery and neurobiology, and Richard Lifton, Sterling Professor and chair of genetics, and a Howard Hughes Medical Institute investigator — scanned the genomes of more than 2,000 individuals suffering from intracranial aneurysms along with 8,000 healthy subjects. They discovered three chromosome segments, or loci, where common genetic variations can create significant risk for ruptured aneurysms, which in turn cause strokes. The subjects came from hospitals in Finland, the Netherlands and Japan, and the results were similar in all groups, indicating that these variations increase risk among diverse human populations.

The findings, reported online in the journal *Nature Genetics*, could lead to new screening tests to identify hundreds of thousands of people at risk for strokes caused by bleeding and point to new therapies that might be able to strengthen blood vessels in the brain before they burst.

“Even though we have made significant strides in treating unruptured aneurysms, until now we have not had an effective means of identifying the majority of individuals at risk of developing this deadly problem. These genetic findings provide a starting point for changing that equation,” Gunel said.

The median age when hemorrhagic stroke occurs is 50 years old, and usually there are no warning signs. In the majority of cases, the resulting strokes cause death or severe brain damage. Without an understanding of the cause of these events, physicians have been left to respond after the fact, once the damage has largely been done. Biden was one of the lucky individuals who survived a ruptured aneurysm with minimal damage — although at the time he was stricken, his condition was thought to be grave enough that a priest was summoned to confer last rites.

The Yale study showed that the risk of harboring an aneurysm increased with the number of risk variants, or alleles. Individuals with the highest number of risk alleles tripled their risk of an aneurysm, researchers found.

Based on this large collaborative study, a screening test may one day be able to identify those who are at higher risk of forming brain aneurysms or suffering a bleeding stroke as a result.

“These findings provide fundamental insights into the genetic and biochemical changes

that cause this devastating brain disease, providing hope that we may also be able to provide preventive therapy before rupture occurs,” Lifton said.

For instance, the new findings implicate variations in the gene SOX17, which is known to play a crucial role in the early development and repair of endothelial cells that make up the arterial walls of blood vessels. “These variations may interfere with the ability to produce cells that repair damage to the blood vessels, suggesting a path forward for developing new approaches to prevention,” Gunel said.

Kaya Bilguvar of Yale was first author of the paper. Other Yale researchers included Shrikant Mane, Christopher E. Mason, Murim Choi, Emilia Gaal, Yasar Bayri, Luis Kolb, Zulfikar Arlier, Sudhakar Ravuri, and Matthew W. State.

The work was funded by the National Institutes of Health, the Yale Center for Human Genetics and Genomics, the Yale Program on Neurogenetics and the Howard Hughes Medical Institute.

Citation: Nature Genetics, Nov. 9, 2008

Links:

Murat Gunel

<http://www.med.yale.edu/neurosurg/faculty/gunel.html>

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<http://www.med.yale.edu/genetics/fac/RichardLifton.php>

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Embargoed for release: 1 PM Nov. 9, 2008 Yale News Releases are available at

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