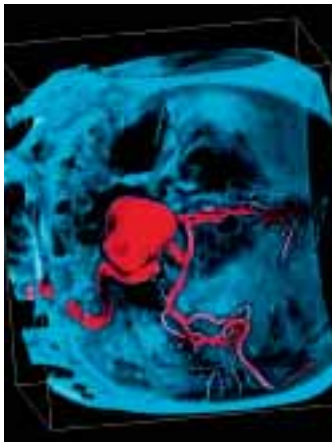


Avoiding Rupture

GENETIC CLUES COULD PROVIDE ADVANCE WARNING OF BRAIN ANEURYSM RUPTURE.

A ruptured brain aneurysm can kill with the speed and surprise of an assassin's bullet: before rupture, most intact brain aneurysms—distended areas in blood vessel walls—do not cause symptoms. A lucky patient will have an intense headache before the aneurysm bursts; this warning can alert doctors to check for an aneurysm using a brain scan so that they can correct the problem surgically.



A three-dimensional CT scan shows a bulging aneurysm (red) in an artery in the brain.

Now, an international study has found three genetic clues to help anticipate and prevent brain aneurysm rupture.

HHMI investigator Richard P. Lifton and Murat Gunel, of the Yale School of Medicine, led an international team in the first genomewide search for common genetic markers for brain aneurysms. They uncovered three genetic variations that together can increase the risk of the condition threefold—by about the

same amount as known nongenetic factors such as high blood pressure, smoking, and age. The results were published in the December 2008 issue of *Nature Genetics*.

The study compared the genomes of more than 10,000 people—2,100 with intact or ruptured brain aneurysms and 8,000 controls. Specifically, the scientists examined over 300,000 single nucleotide polymorphisms (SNPs)—areas in the genome known to vary in the human population. They were looking for any SNPs more commonly found in individuals with aneurysms.

The subjects were Finnish, Dutch, and Japanese. These countries' populations are relatively genetically homogeneous, which helped the researchers distinguish only the relevant genetic patterns.

The three genetic markers the scientists found will increase understanding of the biological causes of brain aneurysms and help doctors to identify people at risk. Two variants lie near genes that function in the formation and maintenance of blood vessels. The third, which had previously been linked to brain aneurysms, lies near a gene associated with arterial diseases.

"We ought to be able to identify more variants that contribute as we study more patients," Lifton says. Both lifestyle and genetic factors would then help doctors identify individuals who should receive regular brain scans. ■ —OLGA KUCHMENT

IN BRIEF

fied 22 genes that, when "knocked down" with RNA interference, allowed tumors to metastasize but had no effect on the growth of the original tumors. Further study showed that one gene, called *Gas1*, keeps melanoma from metastasizing in living mice. The team tested human metastatic melanoma cells and discovered that *Gas1* was often present at substantially reduced levels than normal.

"We can use this approach to find metastasis suppressor genes for virtually any type of cancer," says Green, who is at the University of Massachusetts Medical School. The team published its work on November 1, 2008, in *Genes and Development*.

SHUTTING THE DOOR ON MALARIA

When malaria-causing parasites enter a human body through the bite of an infected mosquito, they must enter liver cells and mature there before enacting full-blown disease. Researchers have found that these parasites, called *Plasmodium*, enter liver cells through a "door" used by cholesterol, which the liver filters from blood. When a cholesterol

receptor called SR-BI is scarce, infection levels drop dramatically.

Malarial liver infection had already been linked to the organ's filtering of lipids. To learn more, a team led by HHMI international research scholar Maria M. Mota studied how removing different lipoprotein receptors from liver cells affects infection. When cells' SR-BI production (or function) was blocked, infection levels fell 50–70 percent. Besides allowing *Plasmodium* in, SR-BI may supply cholesterol for the parasites' membranes.

The results were published in the September 2008 issue of *Cell Host & Microbe*. Now Mota, at the University of Lisbon, Portugal, and collaborators are working to design better SR-BI inhibitors; brief treatment may be able to stop infection without significantly impairing liver cell function. The team is also searching for other *Plasmodium* doorways.

LOST GENE SPELLS NEURODEGENERATION

Losing one working copy of a specific gene causes major symptoms of human

neurodegenerative disease in mice, researchers have found.

The team, including HHMI international research scholar Freda Miller, had previously discovered that the *p73* gene keeps neurons alive in growing mice. But its function in adult mice was unclear, because most animals that lack the *p73* protein die young.

"We had a number of hints that *p73* might be doing something throughout the lifetime of the animal, but we hadn't suspected that it had anything to do with neurodegeneration," Miller says.

Her team found that while mice with one good copy of *p73* develop normally, they lose neurons—and cognitive skills—as they age. Their brains develop tangles of the nervous-system protein tau, as seen in Alzheimer's disease. The researchers reported their results on September 11, 2008, in *Neuron*.

Other studies have found that some Alzheimer's patients have just one functional copy of *p73*. Miller, at the Toronto Hospital for Sick Children, and colleagues are now testing the link between *p73* and neurodegenerative disease in human populations.