

APRIL 06, 2006

## Genetically Weakened Blood Vessels Contribute to Some Strokes

Researchers have identified a gene mutation in mice that weakens small blood vessels, making them more susceptible to stress. The mutation appears to increase the danger of a type of stroke that often occurs in humans in the absence of any known risk factors, scientists report.

The mutant gene is known to afflict at least six human families--four Dutch, one Italian, and one French--and perhaps many more, the researchers said. Their discovery, published in the April 6, 2006, issue of *The New England Journal of Medicine*, opens a door toward understanding the very large number of "cerebral accidents" that lead to disability and death among humans.

"Stroke is a leading cause of death and serious long-term disability," the research team led by Simon W. M. John, a Howard Hughes Medical Institute investigator at the Jackson Laboratory, in Bar Harbor, Maine., explained in their research article. The cause of many strokes has remained mysterious, but researchers have suspected that unidentified predisposing factors are present in many patients.

---

"There is nothing small about the consequences  
of small-vessel disease."

- Steven M. Greenberg

---

Approximately two-thirds of symptomatic strokes are caused by disease of the large arteries that supply the brain with blood. Clinicians are often able to identify signs of disease in these blood vessels and prevent or lessen the severity of a stroke through surgery or medication. The remaining third of strokes--most often due to disease of small, inaccessible blood vessels within the brain--are far more difficult to prevent.

According to Steven M. Greenberg, associate professor of neurology at the Harvard Medical School, who wrote an accompanying perspective piece in the same issue of the *New England Journal of Medicine*, "There is nothing

small about the consequences of small-vessel disease. Intra-cerebral hemorrhage, in particular, represents the most catastrophic form of stroke.” Even in the absence of overt symptoms, small-vessel disease can contribute to cognitive impairment in the elderly, he added.

The new work in mice “provides better knowledge of the disorder so these patients and their physicians can identify modifiable risk factors to improve the patients' quality of life,” said Douglas B. Gould, the first author of the research report.

John added that the discovery “is a nice example of using an animal model to learn about the basic mechanism of a disease that is directly relevant to a human condition.” Evidence shows that the mutation in mice occurs in “exactly the same gene” that causes blood vessel weakening in the few known human families, John said.

The mutation alters a normal blood vessel protein known as collagen IV  $\alpha 1$ , a part of the basement membrane, which provides support for the walls of blood vessels. The abnormality seems to make blood vessel cells less resistant to stress, so small blood vessels are more fragile than usual. Thus they tend to break under stressful conditions, such as high blood pressure or the trauma of being born.

The discovery was made as John and his colleagues were trying to develop a mouse model of the eye disorder known as glaucoma. The animals they identified are born with eye problems, but the researchers also noticed a greater-than-usual number were born with other symptoms, including cerebral hemorrhages. This is what led them to the mutant gene that weakens blood vessel structure and to collaboration with French and Dutch researchers.

For this study, John and his colleagues focused on a French family with small-vessel disease, and found them to have the same collagen IV  $\alpha 1$  mutation, along with cerebrovascular problems similar to those that they had seen in their mice. It is not yet known how many other families carry the cell-damaging mutation. The researchers expect that mutations in genes that make other important blood vessel proteins may have similar effects, so there is potentially a whole spectrum of causes that may underlie what seems like a single disorder.

Even for the collagen IV  $\alpha 1$  mutation, the picture is complicated by the interplay of numerous genes. The researchers found that the severity of the eye disorders varied in different strains of mice, indicating that an animal's genetic background determines how the mutation affects it. The scientists expect that this is probably the case in humans, too.

Although many questions remain to be answered, the mutation does stand as a clear risk factor for small-vessel disease that can now be assessed--perhaps

someday through gene-screening programs--and used to recommend preventive measures.

“Our findings suggest that prevention of birth trauma (by using caesarean delivery), and adult trauma, and the avoidance of risk factors for bleeding, may decrease the risk of hemorrhagic stroke in patients with mutated collagen IV  $\alpha 1$ ,”the team wrote. Already, John and his colleagues have found that caesarean delivery of baby mice with the mutation reduced the hemorrhaging associated with birth, suggesting that stress-reduction can be effective.