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Gene is likely cause of stroke-inducing vascular malformations

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UCSF scientists have discovered that a gene controlling whether blood vessels differentiate into arteries or veins during embryonic development is linked to a vascular disorder in the brain that causes stroke.

The UCSF studies were done in mice, and the new findings are the first to provide information on both the progression and regression of this particular brain disorder, known as BAVM, and to provide molecular clues into the disease, which is not well-understood and chiefly affects young people.

BAVM, for brain arteriovenous malformation, is a vascular disorder causing arteries and veins to be directly connected, rather than through capillaries. This direct connection produces enlarged, tangled masses of vessels that are prone to hemorrhagic rupture, bleeding and stroke. Because they develop most often in growing tissues, BAVMs are responsible for half of the hemorrhagic strokes in children.

Study findings were published in a recent issue (Aug. 5, 2008) of the *Proceedings of the National Academy of Sciences*.

The UCSF team identified the gene, known as Notch, as a potential cause of BAVMs because of its role in directing embryonic blood vessel formation. Using genetic tools, the team "turned on" a constantly active Notch gene in endothelial brain cells, which are the cells lining blood vessels in the brain, and found that BAVMs were induced. When researchers turned the gene off, the mice exhibited full recovery from

the disease's progression.

"This was exciting. The activated Notch gene caused BAVM in all of the mice, making it an unprecedented, potent molecular lesion in the induction of the pathology," said Rong Wang, PhD, senior author on the study, associate professor and director of the Laboratory for Accelerated Vascular Research and Mildred V. Strouss Endowed Chair in Vascular Surgery at UCSF. "Furthermore, we found that repression of the gene in already-ill mice led to their recovery."

Approximately one million people worldwide suffer from BAVMs, though very little is known about the molecular mechanisms that cause them. Results from an ongoing clinical trial funded by the National Institutes of Health on the effectiveness of brain surgery, the only treatment option for the disease, questions whether the risks associated with surgery outweigh the risk of "waiting for a rupture," the UCSF researchers say.

"Our study offers hope for future treatments because even the effects of stroke such as paralysis and ataxia, or loss of muscle coordination, were reversed once we turned off Notch," said Patrick A. Murphy, lead author on the paper and a graduate student from the UCSF Biomedical Science Program, working with Wang. "This pathway has not yet been implicated in human disease, so these findings prompted our ongoing research into Notch signaling and allow us to examine the cellular and molecular mechanisms of BAVM."

Knowledge gained about development of BAVM may also shed light on the process of blood vessel disease in other organs like the lung and liver, according to the UCSF team. "In the future, we may be able to inhibit or even reverse the disease process," said Tyson Kim, co-author on the paper and a bioengineering graduate student from the UCSF MD/PhD combined program, working with Wang.

Based on the study findings, the UCSF team now considers Notch a strong candidate as a key regulator of human BAVM and is undertaking additional research to find the disease's cause. In addition to using the mouse model to study disease progression and regression, Wang and colleagues also are studying the gene's role in human AVMs by examining levels of Notch signaling pathway molecules in surgical tissue samples.

"Although more work needs to be done to determine whether the research can be applied to clinical practice and whether up-regulation of Notch causes BAVM and stroke in humans, identifying the role of this pathway offers hope for developing treatments for this and other related diseases," Wang said.

Source: University of California - San Francisco