

Preclinical study links gene to brain aneurysm formation

University of Cincinnati (UC) neurovascular researchers have identified a gene that—when suppressed or completely absent—may predispose a person to brain aneurysms.

Todd Abruzzo, MD, and his colleagues demonstrated that “knocking out” a gene known as endothelial nitric oxide synthase (NOS-3) in an animal model led to intracranial aneurysm formation in 33 percent of study subjects.

Scientists say this suggests that the gene may play an important role in the development of intracranial aneurysms.

An aneurysm occurs when a blood vessel weakens and stretches, forming a bulge in the vessel wall that can rupture and hemorrhage. Intracranial arterial aneurysms are bulges that develop in the arteries that carry blood to the brain.

Previous studies have shown that variants of the NOS-3 gene are markers for vascular disease. The gene also plays an important role in remodeling of blood vessels in response to changes in blood flow.

“When a vessel experiences increased blood flow, it attempts to reduce the shear stress to even levels by enlarging its luminal caliber through a process known as remodeling. This involves reabsorbing the inner layers of the vessel wall and forming new outer layers to replace them,” explains Abruzzo.

“Although we don’t fully understand the genetic determinants that control an individual’s susceptibility to aneurysm formation,” he adds, “this study is an important clue because it links a known gene with a known function to an increased risk for intracranial aneurysm formation.”

Abruzzo says this study supports the idea that the NOS-3 gene is just one step in a complex molecular pathway that links flow-dependent vascular remodeling to intracranial aneurysm formation.

“Our findings suggest that if something goes wrong in the vascular remodeling process, it could trigger formation of an aneurysm,” he adds.

Abruzzo reports these findings in the August 2007 issue of *Current Neurovascular Research*.

The UC-led team analyzed 30 female mice bred to suppress (knock out) one of three genes and molecular pathways associated with vascular disease: inducible nitric oxide synthase (NOS-2), endothelial nitric oxide synthase (NOS-3) or the plasminogen activator inhibitor (PAI-1).

To determine whether absence of the genes resulted in an increased rate of aneurysm formation, researchers blocked one of the two carotid arteries that carry blood to the brain. They then examined brain artery samples for signs of aneurysm formation.

The researchers found no indications of aneurysm formation in the PAI-1, NOS-2 or wild type control groups. Mice with the NOS-3 knock out, however, formed intracranial aneurysms.

Source: University of Cincinnati

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