Rare mutations may help explain aneurysm in high-risk families

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An innovative approach to genome screening has provided clues about rare mutations that may make people susceptible to brain aneurysms, predisposing them to brain bleeds, according to preliminary late-breaking research presented at the American Stroke Association's International Stroke Conference 2012.

For the first time, scientists applied a process called whole exome sequencing to seek gene mutations in families in which multiple relatives have intracranial aneurysms, a condition in which weakened, ballooned-out areas in arteries of the brain can rupture and cause a stroke.

Instead of sequencing the entire genome, whole exome screening focuses on the small portion of the genetic blueprint that provides instructions for making proteins. This approach allows researchers to look for rare variations in the genetic code.

"For families with many people affected, it may be likely that a rare mutation leads to a problem in blood vessel structure or function that puts them at much higher risk," said Joseph P. Broderick, M.D., lead author and professor and chairman of the Department of Neurology at the University of Cincinnati Neuroscience Institute in Ohio.

Studying 32 affected people from seven families, the researchers found more than 100,000 genetic variants compared to the reference alleles in the general population who had been previously sequenced.

"It goes to show that we all carry rarer variants, so in such a study we need to narrow them down to the disease in question," Broderick said.

Focusing on categories of genes relevant to blood vessel structure and function, and insuring that at least three affected family members in a family shared a given variant, the researchers narrowed the initial findings to 27 variants in 19 genes.

In a close analysis of one family, researchers found variations in genes for producing collagen, a connective tissue abundant in blood vessels and other tissues. One gene, collagen 5-A2, has been previously linked to Ehlers-Danlos syndrome – a group of inherited connective tissue disorders marked by extremely loose joints with musculoskeletal damage, hyperelastic skin, and easily damaged blood vessels. However, collagen 5-A2 has not been previously linked to the type of Ehlers-Danlos associated with fragile blood vessels or aneurysms.

"Exome sequencing is an exciting new tool for studying how genes are related to various diseases. Using this technique, we may be able to find the relevant genetic variants in a particular family and screen unaffected people in the family for their aneurysm risk," Broderick said.

"It's an example of personalized medicine, but it's currently not easy or simple and our learning curve is currently very steep since we need to determine if these variants are truly causal."

A person's risk, such as in this family, may involve several variants in several genes, plus environmental exposures such as smoking, he said.

Provided by American Heart Association

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