Research links gene to stroke risk, finds clues to genetics of many diseases

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(Medical Xpress)—Researchers at the University of Virginia School of Medicine have identified a key gene variation linked to an increased risk of stroke. The discovery comes as part of a breakthrough in the understanding of what causes some people to produce too much homocysteine, an amino acid associated with stroke, cancer, dementia, hardening of the arteries and other diseases.

As part of their work, the researchers have developed a genetic test that can predict which people are at risk for producing too much homocysteine, and their discovery could lead to new treatments for the associated diseases.

The findings also show that the conversion of the enzyme methionine into homocysteine – the primary focus of the researchers' investigation – plays an important role in controlling the activity of genes. That discovery could have significant implications for understanding stroke, cardiovascular disease and other conditions.

While high homocysteine levels have long been suspected as a culprit in diseases, efforts to lower homocysteine in scientific trials have not produced health benefits. The new U.Va. research explains what may be happening to produce the elevated levels, suggesting that one gene in particular, GNMT, is being stimulated to work too hard. The researchers found four other genes that appear to play a role as well, though to a lesser degree.

"What we found was a really striking result for a genome association study," said Stephen R. Williams, a postdoctoral fellow at U.Va.'s Cardiovascular Research Center and U.Va.'s Center for Public Health Genomics. "It's hard to find something that's significant, and it's hard to find something biologically relevant, and we did that five times over."

The researchers set out to determine why certain people metabolize methionine into homocysteine differently than do others. To do so, they reviewed the genomes of nearly 5,000 participants in two studies: the Vitamin Intervention for Stroke Prevention, a trial that aimed to prevent people from suffering a second ischemic stroke; and the Framingham Heart Study, which has followed participants' cardiovascular health for decades. It was through that review that the researchers were able to identify the five critical genes, including one form of the ALDH1L1 gene associated with ischemic stroke in the Framingham study.

The researchers then determined that differences in the regulation of the GNMT gene are the main reasons for the variations in methionine metabolism in people. To reach that conclusion, they created a test based on the DNA from a person who was a high methionine metabolizer and DNA from a low metabolizer, to see how the DNA reacted when treated with methionine.

"What turned out was that the individuals who had higher post-methionine load homocysteine had higher gene-promoter activity," Williams said. "That was really interesting, because it gave us a functional cause that partially explains why this may be happening and the genetics of why people may metabolize methionine differently."

The researchers were able to devise a "risk score" evaluating the risk for developing excess homocysteine based on which gene variations people have. "If you had all of them, you are in the highest risk category," U.Va. researcher Michèle Sale said.

"The risk score actually predicts how an overall population would perform in the post-methionine load test," Williams said. "That's genetic relevance that's actually leading to clinical prediction. So that's really cool."

U.Va.'s discovery came about, in part, because Williams and his fellow researchers were looking where others had not, exploring an unknown portion of the pathway that converts methionine to homocysteine. They believe that it may be possible to reduce stroke risk by targeting this process with drugs before the methionine is converted.

U.Va. researcher Dr. Brad Worrall said the discovery could have far-reaching implications.

"We think this is a very important finding in the realm of epigenetics," he said. "Stephen's work shows that a genetic variant in the DNA coding for this enzyme may alter the promoter for the gene itself. This could potentially be the key to understanding how the gene for this enzyme and this enzyme regulate gene expression much more broadly. This might not only be important for the pathogenesis of stroke and cardiovascular diseases, but potentially other diseases as well."

The findings have been published online by the journal *PLoS Genetics*.

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