Gene variant may help explain why Black individuals are prone to severe strokes

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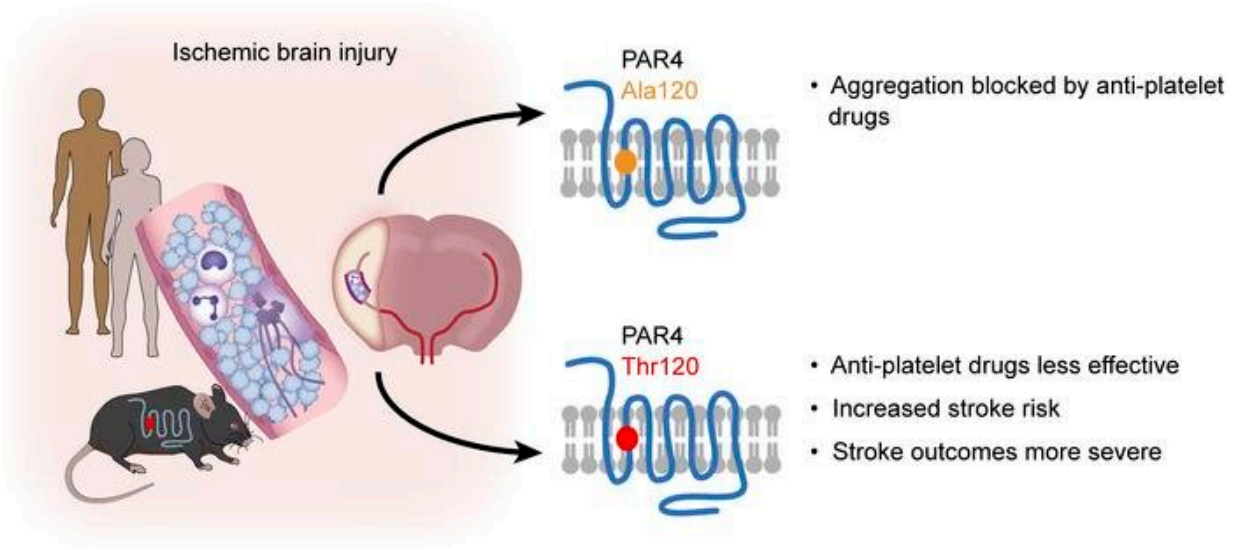

Credit: *Journal of Clinical Investigation* (2023). DOI: 10.1172/JCI169608

In a new study, University of Utah Health researchers have shown that a particular version of a gene may contribute to the higher severity of stroke seen among Black Americans. The findings could help scientists develop more effective stroke medications for people who carry the gene.

The research, which was published in the *Journal of Clinical Investigation*, demonstrated that mice carrying the gene had a higher

level of disability after a stroke. These mice were also less responsive to drugs commonly used to prevent stroke. The results are the first direct evidence linking the gene to medical outcomes.

"This suggests one novel reason for racial disparities in stroke outcomes is that standard anti-platelet therapies may not be appropriate for patients carrying this gene, which includes around 60% of Black patients," says Robert Campbell, Ph.D., the senior author on the paper and an investigator at U of U Health. "One novel reason for racial disparities in stroke outcomes is that standard anti-platelet therapies may not be appropriate for patients carrying this gene."

A gene that turbo-charges blood clotting

Black Americans have a higher risk of stroke than other ethnic groups and a higher rate of death and disability after a stroke. Lifestyle factors and other comorbid medical conditions contribute to this disparity, but previous research has also shown that genetics play a role.

In particular, a version of a gene involved in blood clotting, called PAR4, is common in Black individuals. It's estimated that around 60% of Black individuals and 20% of white individuals have the A allele version of this gene.

PAR4 works by helping blood cells, called platelets, form clots. These clumps of cells are important to help stop bleeding after injury but can cause stroke if they obstruct the flow of blood in the brain. PAR4 sits on the surface of platelets and detects chemical signals released into the blood to activate clot formation.

Other studies had shown that platelets from Black individuals often recruited many more platelets when exposed to the clotting signal compared with platelets from white donors. This led researchers to

suspect that the A allele could be "turbo-charging" the platelets, leading to larger clots and worse stroke outcomes.

To investigate this idea, the researchers looked at data from a large-scale observational study of stroke risk factors in humans. When they tested 7,620 Black participants for PAR4, they found that individuals carrying two copies of the A allele had a higher incidence of stroke and higher levels of disability afterward.

In order to dig deeper, the scientists turned to mice. Working with the pre-clinical model allowed them to control for other genetic and environmental factors, something that's not possible in humans. This meant they could isolate the effects of just one genetic change.

"It's all association until you can prove it from a molecular biology perspective," says Campbell, who is an assistant professor of internal medicine in the Spencer Fox Eccles School of Medicine at University of Utah.

The researchers found that, as they had predicted, platelets from mice carrying the PAR4 A allele had heightened reactivity. Clots formed larger clusters compared with platelets from mice who were completely identical except for that one gene. Mice with the A allele also had greater disability after a stroke.

A need for personalized medicine

From there, the scientists tested stroke-preventing medications on the mice with the two "humanized" versions of the PAR4 gene. "That's where I think it becomes really interesting," says Frederik Denorme, Ph.D., the first author on the study and a researcher at U of U Health.

FDA-approved medications commonly prescribed to prevent stroke,

such as aspirin and ticagrelor, protected mice with the PAR4 variant that is common in whites. But the drugs did not protect mice carrying the PAR4 variant common in Black individuals.

It's too soon for the new findings to change clinical practice, but Denorme says he hopes the study impacts how clinical research is carried out. Clinical trials often enroll mostly white patients, meaning genes that are more common in other populations are not well represented. Boosting racial diversity in trials can reveal when a drug's activity varies among groups, he says.

Denorme believes that the mouse model could be useful for testing possible new medications to improve stroke outcomes in people. "These mice will allow us to address questions like why one drug is not good for all stroke patients," he says. "I think our project hints at the need for personalized medicine based on genetics."

More information: Frederik Denorme et al, The predominant PAR4 variant in individuals of African ancestry worsens murine and human stroke outcomes, *Journal of Clinical Investigation* (2023). DOI: 10.1172/JCI169608

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