New genetic clues point to new treatments for 'silent' stroke

March 25 2021

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Scientists have identified new genetic clues in people who've had small and often apparently 'silent' strokes that are difficult to treat and a major cause of vascular dementia, according to research funded by the British Heart Foundation (BHF) and published in *The Lancet Neurology*.

Researchers discovered changes to 12 genetic regions in the DNA of people who have had a lacunar stroke—a type of stroke caused by weakening of the small blood vessels deep within the brain. Over time, damage to the blood vessels and subsequent interruption to blood flow can lead to long-term disability, causing difficulty with thinking, memory, walking and ultimately dementia.

There are few proven drugs to prevent or treat lacunar strokes. The blood vessels affected are less than a millimetre wide and a lacunar stroke can strike without the person knowing. It's not usually until someone has had a number of these strokes and starts to see signs of dementia that they realise something is wrong.

To date, only one genetic fault has been associated with lacunar strokes. However, after over a decade of research, Professor Hugh Markus and his team at the University of Cambridge working with researchers from around the world now believe their genetic breakthrough holds the key to finding much-needed treatments for lacunar stroke and vascular dementia.

Researchers scanned and compared the genetic code of 7,338 patients who had a lacunar stroke with 254,798 people who had not. Participants were recruited from across Europe, United States, South America and Australia after they attended hospital and had an MRI or CT brain scan.

They discovered that many of the 12 genetic regions linked to lacunar strokes were involved in maintaining the neurovascular unit—the part of the brain that separates the blood vessels from the brain and ensures that nerves function normally. These genetic changes are thought to make the small blood vessels 'leakier', causing toxic substances to enter the brain, and meaning that messages travelling around the brain slow down or don't arrive at all.

The team now plan to test whether new treatments can correct these abnormalities on brain cells in the lab. They hope to begin human clinical trials in the next ten years.

The study also highlighted that high blood pressure, type 2 diabetes and a history of smoking are causally associated with an increased risk of lacunar stroke, identifying things that we can immediately tackle.

Professor Hugh Markus, BHF-funded researcher, leader of the study and neurologist at the University of Cambridge, said:

"These small and often silent lacunar strokes have gone under the radar for a long time, and so we haven't been able treat patients as well as we'd like to. Although small, their consequences for patients can be enormous. They cause a quarter of all strokes and they are the type of stroke which is most likely to lead to vascular dementia.

"We now plan to use this new genetic blueprint as a springboard to develop much needed treatments to prevent lacunar strokes from occurring in the first place and to help stave off dementia."

Dr. Matthew Traylor, first author of the study at Queen Mary University of London, said:

"Genetics offers one of the few ways we can discover completely new

insights into what causes a disease such as lacunar stroke. It is only by better understanding of what causes the disease that we will be able to develop better treatments."

Professor Sir Nilesh Samani, Medical Director at the British Heart Foundation and cardiologist, said:

"This is the most extensive genetic search to date which truly gets to grips with what cause lacunar strokes. These findings are a significant leap forward and we now have a much greater understanding of the genetics and biology behind what causes the small blood vessels deep in the brain to become diseased.

"Lacunar strokes affect around 35,000 people in the UK each year. This research provides real hope that we can prevent and treat this devastating type of stroke much better in the future."

More information: *The Lancet Neurology* (2021). DOI: 10.1016/S1474-4422(21)00031-4

Provided by British Heart Foundation