

**Final report summary:**

# Can we identify the genes that cause disease of small blood vessels in the brain?

**What causes leukoaraiosis?**

A genome wide association study.

## Why did we fund this research?

Disease of the small blood vessels in the brain is known as cerebral small vessel disease, or SVD. It is a major cause of stroke, accounting for about 20% of all strokes. In addition, it is the major cause of vascular cognitive impairment and vascular dementia, which is the second most common form of dementia in the UK<sup>1</sup>.

Despite the importance of SVD in the development of stroke and dementia, we have only a limited understanding of what causes it, severely hampering the development of new treatments.

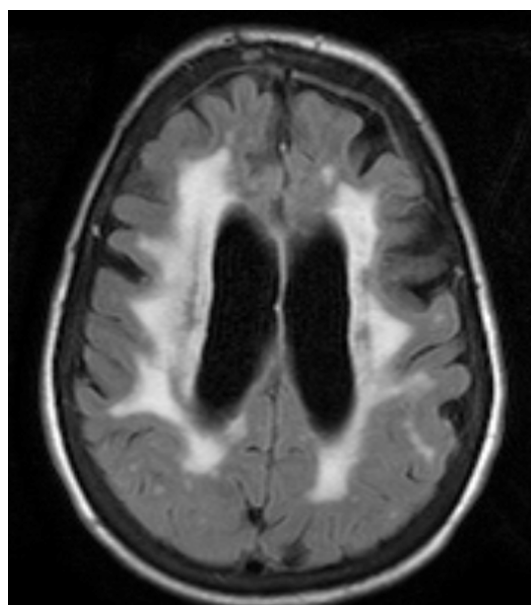
Previous research has suggested that there is a strong genetic component to a person's risk of developing SVD, and one way of finding new information about the disease is to carry out genetic studies<sup>2, 3, 4</sup>.

Genetics is the study of genes, units of biological code which are inherited from a person's parents. Genes provide instructions for how the body is made and how it functions, and are organised into thread-like structures called chromosomes.

Using a new technique called Genome-wide Association Study (GWAS), it is possible to look at genetic variations within each chromosome. This allows the detection of distinct patterns of genes that are associated with a disease which could not previously be found. By detecting patterns within genes that are associated with diseases, tests can be developed to identify them as 'biomarkers' of disease and new treatment approaches can be developed to directly target the genes involved. The GWAS approach has been successful in a number of other diseases including diabetes and heart attack.

## What did the researchers do?

This study used GWAS to investigate whether there are differences in people's genes which contribute to the development of SVD. If patterns can be found, this allows identification of genetic 'risk factors'. The amount of SVD present in the brain is represented by a marker of SVD called 'white matter hyperintensities' (WMH) or 'leukoaraiosis', which is observable on an MRI brain scan.



**Magnetic Resonance Imaging brain scan with white areas indicating 'white matter hyperintensities' (WMH), also known as leukoaraiosis.**

The researchers collected MRI brain scans of patients who had presented with a stroke caused by a blockage of blood to the brain (ischaemic stroke). A computer programme was then used to measure the amount of WMH on the scans. All of the patients had already submitted blood samples for GWAS analysis as part of previous studies. The genetic markers from the GWAS (over one million) were then compared with the WMH so that areas with high levels of WMH may be linked to specific genetic patterns, which can therefore be used as biomarker tests for high levels of WMH – an indicator of vascular dementia. This would allow a simple blood test to be used to detect this disease.

As well as using existing data from previous studies, the study recruited 1,380 further patients who had just had a stroke. With data from collaborators this meant the study involved data from about 3,600 patients.

## What did the research find?

A genetic marker on chromosome 17 was shown to be associated with a higher level of WMH, confirming previous findings and leading to a publication in the journal *Stroke* in 2013<sup>5</sup>. A number of other potentially new genetic markers were also linked to the amount of WMH found, and could represent new mechanisms by which people can develop SVD.

Genetic profiles of people who have high blood pressure, and people who do not, were also compared and showed some very different patterns. This finding suggests that the causes of SVD in those with high blood pressure may be very different to the causes of SVD in those without high blood pressure.

The Stroke Association has granted the researchers further funding to continue this genetic research into SVD in a different population of patients (Project Code: TSA 2013/02), and they will analyse new data from that project in combination with the data from this study.

## References

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## What does this mean for stroke survivors?

The development of cerebral small vessel disease (SVD) may be different in patients who have high blood pressure, and those who do not. Understanding this difference could mean more appropriate early treatment of patients, as well as better, more tailored management of blood pressure in these patients, leading to a reduced risk of stroke and vascular dementia.

There is also a growing database of genetic information that can be built upon and shared by researchers world-wide. This increases the likelihood of finding more important links between a person's genetics and risk of both stroke and vascular dementia in the future.

## We are the Stroke Association

The Stroke Association is the leading stroke charity in the UK. We believe in the power of research to save lives, prevent stroke and ensure that people make the best recovery they can after a stroke.

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