

Final report summary:

**Can genetics explain
why disease of the
small blood vessels in
the brain happens?**

Understanding disease mechanisms in cerebral small vessel disease;
a genetic study

PROJECT CODE: TSA 2013-01

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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. It is also a major cause of vascular cognitive impairment and vascular dementia, the second most common form of dementia in the UK¹.

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

Some research has suggested that there may actually be two very different types of SVD. The first type producing larger, isolated lacunar (meaning 'hole') type strokes in the brain, and the second producing smaller, diffuse lacunar strokes^{2,3,4}. This means that different types of treatment may be required for different types of SVD.

Previous research has also suggested that there is a strong genetic component to a person's risk of developing SVD, and one way of finding new information about this disease is to carry out genetic studies^{5,6,7}.

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

Using a technique called Genome-Wide Association Study (GWAS), it is possible to look at genetic variations within each chromosome. This allows the detection of genes that are associated with a disease which could not previously be found⁸. By detecting genes associated SVD we can discover entirely new information about what causes the disease and this may help us develop new treatment approaches. It may also help us develop "genetic biomarkers" to help us predict who is at risk from the disease.

This study builds on previous research funded by the Stroke Association; a GWAS study (TSA 2010-08) and The Young Lacunar Stroke study co-funded by the Medical Research Council (MRC) and the Stroke Association.



What did the researchers do?

There were three stages to the study. For the first stage, GWAS were performed on the DNA of 1,000 people with lacunar stroke, and who were below 70 years of age. The DNA and brain scans of these stroke survivors had already been collected as part of the Young Lacunar Stroke Study.

The second stage involved analysis of this information on its own, and together with what was aimed to be information of up to 1,000 further stroke survivors, collected through the International Stroke Genetic Consortium (ISGC). To date, the information from 400 people from the ISGC has been analysed in this way. For comparison against the information from stroke survivors, information from 1,000 people without stroke was also analysed, the 'control' group.

Analyses included those to identify new genetic variants associated with SVD as a whole, and a type of analysis called Genome Complex Trait Analysis (GCTA), which would be able to show whether there were any genetic patterns associated with either of the two proposed types of SVD.

A third analysis was performed to try and repeat the findings of a smaller, previous study which suggested that the development of SVD was associated with 'OXPHOS' genes, which are involved in the release of chemical energy inside the cells of the body. We wanted to know whether defective OXPHOS genes were associated with either of the two proposed types of SVD.

What did the research find?

Using the GCTA analysis, the study showed that genetic influences are important in SVD, accounting for about 20-25% of the risk of developing the disease. MRI brain scans used to diagnose SVD were found to be crucial to identifying the genes involved. When MRI is not used the inaccuracy of the diagnosis makes it much harder to identify such genes. This finding was published in the journal *Stroke* in 2015¹.

In collaboration with a group in the USA, abnormalities in OXPHOS genes were found to contribute to SVD, with a particularly strong contribution to the type of SVD that results in smaller, diffuse, lacunar strokes.

In addition to the main work from this grant, further work was conducted on the NOTCH3 gene. Variations within this gene are known to cause CADASIL, a form of SVD with a high risk of inheritance in families. The work investigated whether other variations in the NOTCH3 gene, which are more common than those which cause CADASIL, could also predisposes people to SVD and increased risk of stroke. This was not found to be the case, and the result was published in the journal *Stroke* in 2015⁹.

The collective findings from this study will help inform further collaborative work within the ISGC and beyond, and bring us closer to being able to identify who may be at most risk of developing SVD, and could help us find ways to prevent and also treat the disease.

What does this mean for people with SVD?

This study suggests that up to 25% of the risk of developing SVD is down to a person's genetics. It provides early evidence to suggest that there are two distinct types of SVD with different genetic risk factors and which may need to be treated in different ways.

References

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