

Gene link to multiple sclerosis

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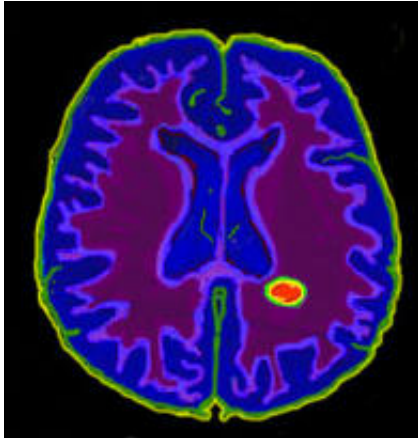


Image of cross-section of a multiple sclerosis patient brain; a lesion is shown in red. Credit: Aiden Haghikia, Calliope A Dendrou, Lars Fugger

(Medical Xpress) -- The biological role of a gene variant implicated in multiple sclerosis (MS) has been determined by researchers at Oxford University.

The finding explains why [MS patients](#) do badly on a set of drugs used successfully in other [autoimmune diseases](#), such as [rheumatoid arthritis](#) and [inflammatory bowel disease](#) - something that has been a puzzle for over 10 years.

The study illustrates that understanding the details of how some changes in the [DNA code](#) are linked to [common diseases](#) can inform clinical practice and guide the treatments that people receive so as to prevent adverse side effects.

The Oxford University team, along with German, Danish and US colleagues, has published the findings in the journal *Nature*. They were funded through the MRC Human Immunology Unit, part of the MRC Weatherall Institute of [Molecular Medicine](#), and the Wellcome Trust.

'The hope has been that analyses of the whole [human genome](#) would lead to findings that are

clinically relevant,' says Professor Lars Fugger of the Nuffield Department of Clinical Neurosciences at Oxford University, who led the work. 'We show that this is possible. It's one of the first such examples, certainly in autoimmune disease.'

'Gene scientists in recent years have been successful at identifying hundreds of individual changes, slips and alterations in our DNA that can be reliably linked to the risk of many common diseases such as MS, diabetes and heart disease. But it has been difficult to determine which of these [DNA changes](#) are causal and what biological role they play in disease. In addition, most of the gene variants only have small effects, each on their own accounting for little of the [genetic contribution](#) to disease. This has led some to question the worth of these very large genetic studies, or to suggest that the assumption that decoding the human genome would change medicine has been oversold.'

'Some people say that genomic association studies haven't delivered on the promise of decoding the human genome,' says Professor Fugger. 'But the postgenomic era has only just started.'

The researchers investigated one particular genetic variant - found in a gene called TNFRSF1A - which has previously been associated with the risk of developing MS. The Oxford-led research team used a battery of genetic, molecular, cell biology and biophysical techniques to show that the TNFRSF1A [gene variant](#) results in the production of an altered, shortened version of the TNFR1 protein encoded by the gene.

The long version of the TNFR1 protein normally sits at the surface of cells and binds TNF, an important signalling molecule involved in a number of biological pathways in the body. In contrast, the shortened form lacks an anchor to keep it at the cell surface and is instead released outside of the cell.

The researchers showed that the free, shortened protein can mop up TNF, preventing it from triggering signalling. This is essentially the same

thing TNF blocking drugs do. Drugs that block TNF are effective treatments in rheumatoid arthritis, inflammatory bowel disease and other autoimmune disorders. Yet a clinical trial over 10 years ago found the drugs make MS patients significantly worse and exacerbate the disease.

'Now we know that the functional effect of the TNFRSF1A gene variant mirrors that of TNF blocking drugs, and this promotes MS risk,' says Mr Adam Gregory, one of the joint first authors of the paper from the Nuffield Department of Clinical Neurosciences at Oxford University. 'Had we known this prior to the clinical trial of TNF blockers in MS patients, this could have helped to predict the poor outcome,' notes Dr Calliope Dendrou, the other joint first author from the same department.

Professor Fugger says the results are a 'proof of concept' that understanding the biological details of how gene variants are associated with a disease can direct which patients should or should not receive specific drugs.

'Whilst the TNFRSF1A gene variant is linked to a modest risk of developing MS, the drug that mimics the effect of the variant has a considerably greater impact. The effects of genetic variants influencing disease risk or resistance can be amplified by drugs. This has often been completely overlooked but will be critical for using genetic findings in a medical context.'

Provided by Oxford University

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