Scientists identify the first genetic marker for multiple sclerosis severity

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A study of more than 22,000 people with multiple sclerosis has discovered the first genetic variant associated with faster disease progression, which can rob patients of their mobility and independence over time.

Multiple sclerosis (MS) is the result of the immune system mistakenly

attacking the brain and the spinal cord, resulting in symptom flares known as relapses as well as longer-term degeneration, known as progression. Despite the development of effective treatments for relapses, some of which were pioneered at the University of Cambridge, none can reliably prevent the accumulation of disability.

In findings published in *Nature*, an international collaboration of researchers report a genetic variant that increases disease severity, providing the first real progress in understanding and eventually fighting this aspect of MS.

The work was the result of a large international collaboration of more than 70 institutions from around the world, led by researchers from UCSF (U.S.) and the University of Cambridge (UK).

"Inheriting this genetic variant from both parents accelerates the time to needing a walking aid by almost four years," said Professor Sergio Baranzini at UCSF, co-senior author of the study.

"Understanding how the variant exerts its effects on MS severity will hopefully pave the way to a new generation of treatments that are able to prevent disease progression," said Professor Stephen Sawcer from the University of Cambridge and Cambridge University Hospitals NHS Foundation Trust, the other co-senior author of the study.

A renewed focus on the nervous system

To address the mystery of MS severity, two large MS research consortia joined forces: The International Multiple Sclerosis Genetics Consortium (IMSGC) and The MultipleMS Consortium. This enabled MS researchers from around the world to pool the resources needed to begin to identify the genetic factors influencing MS outcomes.

Previous studies have shown that MS susceptibility, or risk, stems in large part from dysfunction in the immune system, and some of this dysfunction can be treated, slowing down the disease. But, explained Baranzini, "these risk factors don't explain why, 10 years after diagnosis, some MS patients are in wheelchairs while others continue to run marathons."

The two consortia combined data from over 12,000 people with MS to complete a genome-wide association study (GWAS), which uses statistics to carefully link genetic variants to particular traits. In this case, the traits of interest were related to MS severity, including the years it took for each individual to advance from diagnosis to a certain level of disability.

After sifting through more than seven million genetic variants, the scientists found one that was associated with faster disease progression. The variant sits between two genes with no prior connection to MS, called DYSF and ZNF638. The first is involved in repairing damaged cells, and the second helps to control viral infections. The variant's proximity to these genes suggests that they may be involved in disease progression.

"These genes are normally active within the brain and spinal cord, rather than the immune system," said Dr. Adil Harroud, lead author of the study and former postdoctoral researcher in the Baranzini Lab. "Our findings suggest that resilience and repair in the nervous system determine the course of MS progression and that we should focus on these parts of human biology for better therapies."

The findings give the field its first leads to address the nervous system component of MS.

The team also used statistical methods known as "Mendelian

randomization" to explore the importance of environmental effects and found that years of education and parental age reduced the severity of MS, while smoking worsened it. Finding correlation with these indirect measures of brain health further underlines the importance of resilience in determining the outcome of MS.

"Although it seems obvious that your brain's resilience to injury would determine the severity of a disease like MS, this new study has pointed us towards the key processes that underlie this resilience," Sawcer said.

An ever-expanding coalition to address MS severity

To confirm their findings, the scientists investigated the genetics of nearly 10,000 additional MS patients. Those with two copies of the variant became disabled faster.

Further work will be necessary to determine exactly how this genetic variant affects DYSF, ZNF638, and the nervous system more generally. The researchers are also collecting an even larger set of DNA samples from people with MS, expecting to find other variants that contribute to long-term disability in MS.

"This gives us a new opportunity to develop new drugs that may help preserve the health of all who suffer from MS," said Harroud.

Studying the genetics of multiple sclerosis has been a major theme of neurological research in Cambridge since the late 1980s. With others, members of the Department of Clinical Neurosciences have been closely involved in discovery of the vast majority of gene variants that increase susceptibility.

Professor Alastair Compston from the University of Cambridge and a founding member of the IMSGC added, "Having been personally

involved with the identification of susceptibility genes for multiple sclerosis since the 1970s, it is a tribute to those within IMSGC who led this project that fully independent risk variants for progression have now been discovered.

"Once more, the work illustrates the benefits of international collaboration for advancing the understanding of disease mechanisms in multiple sclerosis and other medical conditions."

More information: Sergio Baranzini, Locus for severity implicates CNS resilience in progression of multiple sclerosis, *Nature* (2023). DOI: 10.1038/s41586-023-06250-x. www.nature.com/articles/s41586-023-06250-x

Insights into the genetic architecture of multiple sclerosis severity, *Nature* (2023). DOI: 10.1038/d41586-023-01787-3 , www.nature.com/articles/d41586-023-01787-3

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