MS RESEARCH ADVOCACY CURE AUSTRALIA

MEDIA RELEASE

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New clues in the hunt for a cure for multiple sclerosis

Scientists identify the first genetic marker for MS severity, opening the door to treatments for long-term disability

29 June 2023: 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 people 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, none can reliably prevent the accumulation of disability.

The findings, published in *Nature* on June 28, point to a genetic variant that increases disease severity, providing the first real progress in understanding and eventually fighting this aspect of MS.

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

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

“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 Stephen Sawcer, a professor at the University of Cambridge and the other co-senior author of the study.

There was strong Australian and New Zealand involvement as part of MS Australia’s national collaborative platform, the Australian and New Zealand MS Genetics Consortium (ANZgene). This study represents the most recent of this platform’s considerable contribution to the genetics of MS. ANZgene is funded and coordinated by MS Australia and consists of clinicians and scientists from Australia and New Zealand with an interest in the genetics of MS.

“A study of this magnitude requires samples and clinical information from thousands of people with MS and is therefore only possible by combining forces with many groups internationally. This current study has been coordinated through the International Multiple Sclerosis Genetics Consortium, of which multiple Australian MS research groups have been important contributors to over many years,” said Dr Grant Parnell, research fellow at The Westmead Institute for Medical Research and The University of Sydney, and co-author of the study.

A renewed focus on the brain and spinal cord

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 "these risk factors don't explain why, ten years after diagnosis, some people with MS are in wheelchairs while others continue to run marathons," explained Baranzini.

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 Adil Harroud, MD, lead author of the study and former postdoctoral researcher in the Baranzini Lab. "Our findings suggest that resilience and repair in the brain and spinal cord 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 brain and spinal cord components 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 people with MS. Those with two copies of the variant experienced faster disease progression.

Further work will be necessary to determine exactly how this genetic variant affects DYSF, ZNF638, and the brain and spinal cord 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 live with MS,” said Harroud.

MS Australia would like to thank the ANZgene researchers involved in this study, including:

- Professor Bruce Taylor, IMSGC representative, Menzies Institute for Medical Research, University of Tasmania
- Dr Grant Parnell, IMSGC representative, Westmead Institute for Medical Research, University of Sydney
- Associate Professor Justin Rubio, Chair of ANZgene, The Florey Institute of Neuroscience and Mental Health, University of Melbourne
- Professor Trevor Kilpatrick, The Florey Institute of Neuroscience and Mental Health, University of Melbourne
- Professor Jeannette Lechner-Scott, Hunter Medical Research Institute, University of Newcastle
- Professor Allan Kermode, Perron Institute for Neurological and Translational Science, University of Western Australia
- Dr Marzena Pedrini, Perron Institute for Neurological and Translational Science, University of Western Australia

MS Australia would also like to thank the people living with MS who contributed to this study.

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MEDIA CONTACTS:
media@msaustralia.org.au
Sarah Morrison – 0400 477 527
Jayme Markus – 0401 944 905
www.msaustralia.org.au

About MS

MS is the most common acquired chronic neurological disease affecting young adults, often diagnosed between the ages of 20 to 40 and, in Australia, affects three times more women than men. As yet, there is no cure. There is no known single cause of MS, but many genetic and environmental factors have been shown to contribute to its development.

In MS, the body's own immune system mistakenly attacks and damages the fatty material – called myelin – around the nerves. Myelin is important for protecting and insulating nerves so that the electrical messages that the brain sends to the rest of the body, travel quickly and efficiently.

As the myelin breaks down during an MS attack – a process called demyelination – patches of nerves become exposed and then scarred, which renders the nerves unable to communicate messages properly and at risk of subsequent degeneration. This means that the brain cannot talk to other parts of the body, resulting in a range of symptoms that can include a loss of motor function (e.g., walking and hand and arm function, loss of sensation, pain, vision changes and changes to thinking and memory).

About MS Australia

MS Australia is Australia's national multiple sclerosis (MS) not-for-profit organisation that empowers researchers to identify ways to treat, prevent and cure MS, seeks sustained and systemic policy change via advocacy, and acts as the national champion for Australia's community of people affected by MS.

MS Australia represents and collaborates with its state and territory MS Member Organisations, people with MS, their carers, families and friends and various national and international bodies to:

- Fund, coordinate, educate and advocate for MS research as part of the worldwide effort to solve MS
- Provide the latest evidence-based information and resources
- Help meet the needs of people affected by MS.