

Unravelling the causes of MS

In MS, the brain and spinal cord are mistakenly attacked by our own immune system. This involves autoimmune processes that specifically damage the myelin which forms an insulating layer around nerve fibres. Myelin allows the electrical signals to travel rapidly along the nerves, damage to this myelin leads to a delay or block in the flow of electrical signals. This leads to the symptoms of MS that can include numbness, weakness, visual loss and mobility problems.

Exactly what triggers this autoimmune process in each individual is unclear. However, we do have very good evidence on some of the factors that can contribute to the development of MS across the population as a whole.

These are a combination of genetic and environmental risk factors. Risk factors are features about a person's biology and life that can contribute to the chances of developing a disease. Each of these factors alone does not mean a person will definitely get MS, but collectively they can increase the likelihood that someone will get MS – and the exact combination of risk factors is likely to be different in each individual.

Understanding the risk factors for MS also helps us to understand the biology of the disease and how we might better treat it, as well as prevent it.

WHAT IS A RISK FACTOR?

Risk factors are anything or any exposure that increases the likelihood of developing MS, but they are not the direct or only cause of MS.

Genetics and ethnicity

MS is not considered a classical genetic disease in that there is not one single gene that causes MS. Rather, there are over 110 different known genetic factors which contribute to MS. It has been estimated that genetics may account for around half of the risk of MS, and those with a family history of MS are at greater risk than the general population. Even so, the majority of people with a family member with MS will not develop the disease – so genes on their own are not enough.

Most of these 110+ genetic factors, each only contribute a very small part of the risk of MS, although one immune system gene, known as HLA-DRB15*01 is known to contribute a much larger part of the genetic risk. This gene is also more commonly found in people of northern European ancestry, which also partially explains why these populations are more likely to develop MS than people with other ethnic backgrounds. Many of the other more minor risk genes may also play a role in regulating the immune system, but more research is needed to fully understand their role. These genes may also influence the way we respond to the other environmental, or lifestyle, risk factors.



Gender

There are clear gender differences when it comes to immune disorders. Estimates suggest about 8% of the population are affected by autoimmune diseases and of those approximately 78% are female. In Australia, three times more women than men develop MS.

Scientists have shown that this gender difference is not apparent in cases of MS that occur before puberty and after menopause, showing that it is likely to be the sex hormones that influence the immune system in a way that contributes to the development of MS – research is underway to understand this more fully.



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The vast majority of experts believe MS to be an autoimmune disease, in which the body's immune system attacks the central nervous system (CNS). There is good evidence which backs this up.

MS is complex, and what starts off as immune system-directed inflammation, does often, over time, become predominantly *degenerative* in nature.

What is also categorically true, is that most of the breakthroughs and developments in MS over the last decade have come at the earlier, immunological end of the spectrum and that many of the treatments we currently use for relapsing MS are also successfully used in other immunological diseases such as Rheumatoid Arthritis.

MS Research Australia, on the strength of our highly successful research partnership with another immunological disease charity – JDRF Australia, has convened and is leading an Alliance of over 14 different charities in the immunological field. This includes groups involved in diseases such as asthma, lung disease, type 1 diabetes, rheumatoid arthritis, Lupus and others. This Alliance recently held its second meeting. We are grateful to the Macquarie Group Foundation for hosting.

This Alliance is very important for three main reasons. One – that when we understand the basic immunological pathways that causes the body to attack one part of the body, such as it does in MS, we will be well-placed to understand how and why it attacks another. The scientific rationale for joining forces in this way is crystal clear. Secondly, we don't really understand even quite basic information around the size and scope of the immunological disease burden in Australia. This group will be the go-to body to fill in those necessary gaps which will help achieve the third aim of more powerful shared advocacy.

Dr Matthew Miles, CEO

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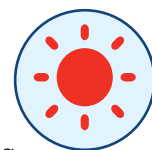
Viral infections



One virus shown to have the strongest connection to MS is the Epstein Barr virus (EBV). This virus is commonly associated with glandular fever, however the majority of the population are infected with EBV in childhood with only mild, non-specific viral symptoms. While approximately 90% of the general population has been infected with EBV, it is believed that almost 100% of people with MS have been infected (often unawares).

Although nearly everyone will be infected with EBV in their life, not everyone will develop MS – again showing that EBV is not sufficient in itself to trigger MS.

Climate and sun exposure



Where you live can also influence your risk of developing MS. The further you live away from the Equator, the greater your risk of developing MS – this is called the 'latitude effect'. In Australia, those living in northern Queensland are 7 times less likely to develop MS than those in Tasmania. One explanation of this is that sunlight, or more specifically exposure to ultraviolet (UV) radiation, decreases with increasing distance from the Equator.

Ultraviolet light is known to have a myriad of effects on the human body, including direct effects on the immune system and also playing a key role in the synthesis of vitamin D.

Vitamin D



Most of the vitamin D we need is made in our body in response to sunlight. Lack of sunlight, or low UV exposure, leads to vitamin D deficiency, and many studies around the world have strongly linked low vitamin D levels in the blood with the development of MS.

As a result, MS Research Australia is carrying out a large clinical trial testing whether vitamin D supplements could prevent MS in people at high risk, and if so, what dose is best. Results from this trial, expected in 2019, should give us key insights into the role of vitamin D in the development of MS.

Smoking



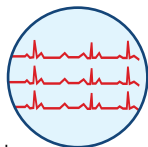
Numerous studies have shown that smoking significantly increases your chances of developing MS. Smokers, and people exposed to second hand smoke, are almost two times more likely to develop MS and more likely to develop progressive forms of MS. For people who already have MS, there is good evidence that stopping smoking reduces the risk of disability progression.

Smoking is known to cause an increase in inflammation and chemicals in smoke can also directly alter the function of some immune cells, potentially contributing to the development of MS.

Stress

Some studies have linked stress with the risk of developing MS, however, people's different coping mechanisms and response to stressful events make this connection difficult to confirm. Studies that have looked at the loss of a child or other major life events which are universally stressful for everyone, have found a only a weak connection to the development of MS.

Australian researchers have also shown that serious illness or personal injury either to yourself or a close family member can lead to an increased risk of developing MS. Other studies have linked the severe stress associated with war for example, with an increase in MS relapses.



“Understanding the risk factors for MS also helps us to understand the biology of the disease and how we might better treat it, as well as prevent it altogether.”

SUMMING IT ALL UP

So, in conclusion, how does MS develop? Well it is a complex interaction between genetics and the environment. Of course how you respond to your environment depends on your genetics. Your genetics determine how your immune system responds to an EBV infection, how you process vitamin D and which sex hormones you have also influence your immune system. Your sun exposure determines how much vitamin D your body makes and smoking adds additional inflammation into an already volatile mix. Diet, physical activity and stress may also contribute to this mix. Potentially, there are other, as yet unknown, factors which may also lead to an increase in inflammation or be able to mimic or add to the role of some of the factors listed here.

Only a few of these factors may come together in some individuals to trigger MS. In others it may be an accumulation of many of these risk factors together – the combination will be different in different people.

There is no doubt that MS is a complex and varied disease. Through research we have come a long way to understanding these complexities. In 2016, there was an international workshop assessing and summarising the extensive knowledge of the factors that contribute to MS and their report was published in the *Multiple Sclerosis Journal*. This consensus will now help us to start taking action with further targeted research and, importantly, advice and guidance to the community on how we can go about reducing the risk of developing MS.

@DrHCampbell, @lisameltonMSRA

We would like to thank Professor Robyn Lucas of the Australian National University for her feedback on this article.

Diet and physical activity

There is a great deal of interest in the role that nutrition and diet may play in the development and also the management of MS. Dietary studies are complex due to the many potential nutritional components found in our diets. This makes it difficult to isolate the influence of a particular diet or any single dietary factor. There is evidence that keeping cholesterol and fats in the blood within a healthy range may lead to better disability outcomes for those with MS, however this is an area of research which is ongoing.

There is stronger evidence when it comes to body weight and obesity and the risk of MS. Numerous studies have shown that being overweight/obese, particularly during adolescence, is associated with a 2-3 fold increase in the risk of developing MS. It is also associated with worse outcomes in people who have MS.

Lack of physical activity may also be a risk factor in developing MS but the results are very varied, possibly due to the difficulties in accurately getting people to recall their physical activity across earlier years. But we do know exercise can have a positive effect on body weight, overall health and wellbeing, as well as having direct benefits for brain health.



Risk Factors can have different effects on MS, they can enhance the risk of developing MS and/or increases the risk of disease progression once MS has developed. The evidence supports the risk of developing MS, but research is ongoing in both areas.

The table below is adapted from work by Professor Robyn Lucas of the Australian National University, an expert in epidemiology and public health.

	Risk of MS	Risk of disease progression
Genetics	●●●	●
Gender	●●●	*
EBV infection	●●●	X
Low sun Exposure	●●●	●
Low vitamin D levels	●●●	●●
Smoking	●●●	●●●
High animal fat Diet/ low Exercise	●	●
High Body Mass Index	●●	●
Stressful events	●	●
●●● Strong Evidence ●● Medium Evidence ● Low Evidence X No link found * Males are more likely to be diagnosed with progressive MS.		



Katherine Sanders, Bond University

PhD student makes a promising start to research career

Ms Katherine Sanders from Bond University QLD has recently completed her MS Research Australia PhD scholarship investigating the role of gene regulation in MS.

Katherine Sanders has made some important discoveries during her PhD studies, contributing to our understanding of immune cell function and nerve degeneration in MS. In particular, she has provided key evidence for the diminished inflammatory activity suspected to occur in secondary progressive MS and began revealing some of the mechanisms that may contribute to ongoing neurodegeneration and disability. Her work also paves the way for microRNAs (miRNAs) to be used as biomarkers to diagnose and predict disease outcomes in MS.

Katherine investigated small molecules called miRNAs in people with MS. miRNAs are part of the cell's machinery used to help switch on, or change the level of activity in different genes. This is one mechanism by which a particular gene, even though it is found in all of the cells in our bodies, can for example, be active in the brain, but dormant in the blood of the same person. They have been implicated in all sorts of normal body functions and in diseases. Since the types of miRNAs

and their functions differ between cell types, Katherine set out to look directly at the miRNAs profile in both the immune system and the brains of people with MS.

“Katherine discovered evidence that neuro-degenerative processes are occurring in the normal areas of the MS brain in SPMS, preventing other cells in the brain from making myelin.”

She found that miRNAs were generally expressed at lower levels in secondary progressive MS (SPMS) and within a specific type of immune cell, leading to a reduced activity of those cells. This may help explain why immunosuppressive therapies are generally ineffective in SPMS.

Katherine also looked at MS brain lesions and the neighbouring brain

tissues that appeared normal, or unaffected by MS, using brain tissue from the MS Research Australia Brain Bank. She discovered evidence that degeneration is occurring in areas of the MS brain thought to be healthy. This indicates that SPMS may be beginning before symptoms are clinically apparent or physical evidence can be detected by an MRI. This has important ramifications for the timing of future therapies into SPMS, indicating that they might need to be started before symptoms appear.

Dr Lisa Melton, Head of Research at MS Research Australia said ‘We are incredibly grateful to the Trish MS Research Foundation who generously supported this highly competitive postgraduate scholarship. Katherine has now completed her PhD making a significant contribution to the world of MS research and we look forward to seeing the full publication of her results. We will watch with interest as her work moves forward, hopefully leading to new approaches to treat, diagnose and predict disease outcome in MS’.

Reports show significant gaps in MS research funding

By a conservative analysis, the gap in funding for quality MS research is predicted to rise to a significant shortfall of A\$10.3 million per annum over the next couple of years. This is the gap in funding needed to fund all the quality MS research in Australia against what is available.

Over the last 14 years MS Research Australia has become the largest national for purpose funder and facilitator of MS research in Australia, and a growing contributor to MS research internationally. Since inception we have increased funding available for Australian MS research from under half a million dollars to now more than A\$4.5 million per annum - a total to date of A\$31.5 million.

Whilst MS Research Australia is the largest funder, unfortunately we are seeing an increase of MS research applications that are deemed worthy of funding by our expert panel but missed out due to lack of available funds. In 2016 alone, over A\$4.1 million worth of 'fundable' MS research applications remained unfunded.

In 2015, with support from the Macquarie Group Foundation, MS Research Australia was able to critically evaluate the size and nature of "the gap". This was then published in two large reports (*The Resource Landscape Report* and the *Research Audit 2004 - 2014*) that helped us to evaluate the impact of our funded research and identify the gaps and opportunities to prioritise our funding.

MS Research Australia currently receives less than 5% of its total annual revenue from government sources. Our own fundraising, via philanthropy and community support is the major stream of funding accounting for around 73% of our total revenue. Around 27% comes from state-based MS societies.

Australia is falling behind the rest of the world with only 7% of funds raised overall for MS (collectively by Australian MS organisations) coming to research, in comparison to between 15 – 20% in other major countries. Large MS societies such as the US, UK and Canada, have initiated successful annual funding campaigns purely for MS research.

MS UK's Director of Philanthropy and Partnerships, Emma Whitcombe, whom has begun an ambitious and exciting A\$175 million MS research-only campaign, Stop MS, said 'The UK MS Society and the global scientific community believe that we are now at a critical juncture in MS research and that a major strategic investment could unlock breakthroughs that are on the horizon.'

MS Canada recently completed a very successful 5 year A\$74 million MS research campaign called end MS and are already embarking on another campaign – this time for A\$250 million. The National MS Society (NMSS) in the US consistently fund the most MS research per annum, providing over A\$80 million to MS research funding in the 2015 financial year. They also fund MS research outside the US (including projects in Australia).

In 2015, the US completed their successful 5 year A\$336 million MS research campaign and are now embarking on a substantively larger

pioneering campaign.

The US also generously contributed over 50% of the A\$32 million funding to the first phase of the International Progressive MS Alliance, on top of their annual MS research commitment and provide significant people power to this global initiative.

Australian MS researchers have enormous potential to contribute to this global push for breakthroughs and insights about MS. But without our support their ideas and expertise will otherwise be simply left on the shelf.

Research is the only hope for a cure. More has to be done to support our Australian MS researchers who, are amongst the very best in the world. We also have many clear and unique strengths in MS research when compared to our global research counterparts. Unfortunately more and more, these researchers are getting "squeezed out" with an increasingly challenging medical research funding environment, leaving them with few options but to move overseas, transition to another area of medical research or out of science altogether.

This is really a call to action for all Australians. MS Research Australia urgently needs your support to ensure that all of the high quality Australian research can be funded to secure a better future for people affected by MS.

Summary of MS research contributions by large MS societies

	MS UK	MS Canada	NMSS (U.S)	Australia (including MS state societies and MS Research Australia)
MS research contribution (per annum)	A\$10.5 million	A\$10 million	A\$80 million	A\$4.5 million
Dedicated MS research campaign	A\$175 million existing campaign	A\$74 million completed campaign A\$250 million new campaign	A\$336 million completed campaign A\$1 billion new campaign- research and support	N/A
%allocated to MS research from annual fundraising revenue	16%	21%	26%	7%

The importance of transparency when giving

Philanthropic giving is the process where an individual or organisation gives large donations to a charity. Here at MS Research Australia a significant amount of our funds come from philanthropic donations making it a major part of our organisational strength.

One of our key philanthropic donors is former Deutsche Bank Australia CEO, Chum Darvall AM. Chum holds Board memberships for a diverse range of organisations and is one of our key supporters. Last month, we interviewed Chum learning what he and other donors look for in a charity when becoming a supporter and why he chose MS Research Australia.

He explains 'that when looking to become involved, donors should ideally be prepared to give consistently. This means before committing to a charitable organisation they should ask themselves, is this something I am prepared to make a contribution to over time?' Chum says from his observations he is 'too often seeing organisations or individuals making the mistake of becoming excited about a charity for a year or two and then losing interest'.

Citing his close relationship with a long-time friend Mike Hemingway who is living with MS (and is a Board member of MS Research Australia) as a major impetus for his giving. He highly recommends organisations to commission a simple third party report on any charity they are thinking of supporting. In our case, the report Chum commissioned looked at:

- How integrated and non-duplicative we are in terms of researching potential causes, treatments and prevention of MS.
- How our research strategy looked at research areas that are not only in the researcher's interests, but primarily addressing the priorities identified by people affected by MS.
- Our strong, international research connections, alliances and involvement, showing a collaborative and global focus. Something he feels that we are actually the "gold standard" when compared to other organisations.

It was also really important that MS Research Australia had done its own large-scale MS research audit, as it showed that our organisation is completely transparent on where we need to improve and that we are fully open to critical analysis. It also clearly shows where all the funds go. Additionally, Chum appreciated and was given comfort by our excellent Board and research governance. He explained, 'the problem with many organisations is that they are not completely focused on their stated mission, and therefore they don't get close to the outcomes they expect'. The fact that MS Research Australia showed him (and all donors) the processes we have in place to achieve our mission gave him confidence in our work and spurred him to put money aside to support us over a long duration of time.

In terms of charities wanting to attract and maintain philanthropic donors, Chum reiterates the importance of



Chum Darvall AM, former Deutsche Bank Australia CEO

reporting back to donors with detailed and clear analysis. This gives donors an informed view of what the charity is achieving and the impact it is making with the funds provided. It also keeps the donors engaged in the charity's activities. He suggests three effective ways of doing this, including: One-on-one interaction, creating a regular report and having an online information portal.

One-on-one interaction between major donors and the charity they are supporting can be achieved in many different ways which are incredibly effective, creating a positive and personal relationship. This may include having staff at your charity available to answer donor's specific questions, holding events where donors can meet key members of the charity's team, or stakeholders such as key researchers in the field.

Another way to strengthen the relationship between charities and their philanthropic donors is through the creation of an annual impact report, transparently outlining the organisations key impacts and achievements. This shows that your charity is disciplined and gives the donors confidence their funds are being effectively utilised.

Chum explains that without reporting back to philanthropic donors 'you will be in danger of donors disconnecting with the process of giving over multiple years. Meaning, that your charity will fall lower and lower on their priority list and they will either forget to donate or find a more engaging charity to donate to'. He believes 'that the size of the donation shouldn't dictate the level of reporting. It is important for people who may only be able to donate smaller amounts to still have a very good idea of what they are giving to. This is because, every donation counts. Charities need to recognise that all donors are vital enablers, advocates and accelerators who may have wider connections that may also be willing to give, given the right circumstances'.

If you are interested in making a philanthropic donation to MS Research Australia or opening up a discussion please contact us on 1300 356 467



MS researchers at Monash University

MS researchers go red for Kiss Goodbye to MS

Australia has some of the best MS researchers in the world. There are more than 900 researchers and clinicians working around Australia to help us better understand MS, dedicating their careers to solving this disease.

In the past decade the number of treatments available for MS have increased significantly, and while there is still a lot of work to do, we certainly have a better understanding of MS than we ever had before. This is simply because of the research that is being undertaken in Australia and around the world.

Each year Kiss Goodbye to MS raises in excess of \$1 million to accelerate Australian research into MS, and each year the campaign is launched with Red Lab Coat Day. Red Lab Coat Day is a chance for the MS community to say thanks to the unsung heroes of the sector. To thank the incredible minds that work day in and day out to bring us closer to the cures for MS.

Red Lab Coat Day asks our researchers to switch their traditional white lab coats for our bright red Kiss Goodbye to MS coats and upload a picture with the hashtag #RedLabCoatDay to social media. Universities and institutions around Australia got on board with more than 200

researchers proudly donning a red coat on May 1. This is a fun way for researchers to be involved with Kiss Goodbye to MS and raise awareness for the importance of the work they are doing.

As Kiss Goodbye to MS has become a global campaign, interest has grown in Red Lab Coat Day. We are excited that this year our friends in New Zealand and Ireland joined us for the first ever Global Red Lab Coat Day. More than 300 researchers from New Zealand and Ireland participated, above and beyond the originally anticipated 60 participants!

Red Lab Coat Day is a chance for our often serious researchers to shine, showing us a glimpse of their true personalities. This year the pictures were better than ever! Two very brave male Monash University researchers even puckered up for the occasion, putting on red lipstick as well as their coats! We received great team photos, pictures of 'superhero' researchers and even photos reinventing the famous Beatles Abbey Road album cover.

Red Lab Coat Day isn't just an opportunity for our researchers to connect with the Kiss Goodbye to MS campaign. It is a chance for the MS community to say thanks. Each year on Red Lab Coat Day Kiss Goodbye to MS fundraisers and supporters send messages of support and thanks to the researchers who are working hard to find a cure. While Red Lab Coat Day is a fun way to launch the Kiss Goodbye to MS campaign, it is also a reminder of the incredible brain power that goes into the work every day, with the sole intention of making the lives of people with MS better.

If you ever have the opportunity to visit an MS research institution or meet one of our brilliant Aussie researchers, be sure to say thanks. It is these people who are changing the future of what a diagnosis with MS means.

And don't be surprised if they are still wearing their Kiss Goodbye to MS red lab coat – they have become a permanent fixture in many of the labs!



MS researchers at Monash University



MS researchers at the University of Sydney's Children's Hospital at Westmead

Working to understand Progressive MS

Why do some people with relapsing remitting MS eventually transition to the secondary progressive phase but others do not?

This answer remains unclear, but researchers globally are trying to get a better understanding of this and also work out who is likely to develop progressive MS and why. This understanding will help with managing MS and help in the development of better treatments that can prevent progressive disease from developing.

Associate Professor Justin Rubio from the Florey Institute of Neuroscience and Mental Health in Melbourne has been awarded an MS Research Australia incubator grant to investigate whether any genes can be identified that may predict the development of progressive MS.

To date a number of genetic studies have revealed that there are over 110 genes involved in the risk of developing relapsing remitting MS, whereas there have been no genes identified conferring an increased risk of developing progressive MS. Associate Professor Rubio believes this is because the genetic changes associated with secondary progressive MS may specifically occur in the brain and spinal

cord tissues, and not in the rest of the body. These types of genetic changes are known as somatic mutations and can be missed in research that searches for genetic changes in people's blood samples.

To do this Associate Professor Rubio turned to the MS Research Australia Brain Bank. This is incredibly important for our Australian researchers as it collects, stores and classifies post-mortem brain and spinal cord tissues donated by people with MS. This valuable tissue is preserved for researchers to use in studies such as this one.

Using a technique called whole genome sequencing, Associate Professor Rubio and his team will look for somatic genetic changes that might be associated with progressive MS in individual cells in the brain and spinal cord. They will compare the genetic information between different cells from the same donor, and between people with and without MS.

This incubator grant will enable Associate Professor Rubio and his team to validate their methods and generate preliminary data



Associate Professor Justin Rubio from the Florey Institute of Neuroscience and Mental Health

that can be used for further investigation and will assist to leverage additional funds from other highly prestigious sources to complete the research.

Knowing what genes might be altered in the brain and spinal cords of people with progressive MS, and understanding the functions of those genes, may allow researchers to identify new ways to prevent and protect nerve cells from the damage caused by MS.

This research would not be possible without the vital tissue supplied by the MS Research Australia Brain Bank. We would like to thank all the people that have, or are considering, donating tissue. With your help we can work together to reduce and prevent the impact of MS on the lives of many people in the future.

To register visit www.msbrainbank.org.au



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