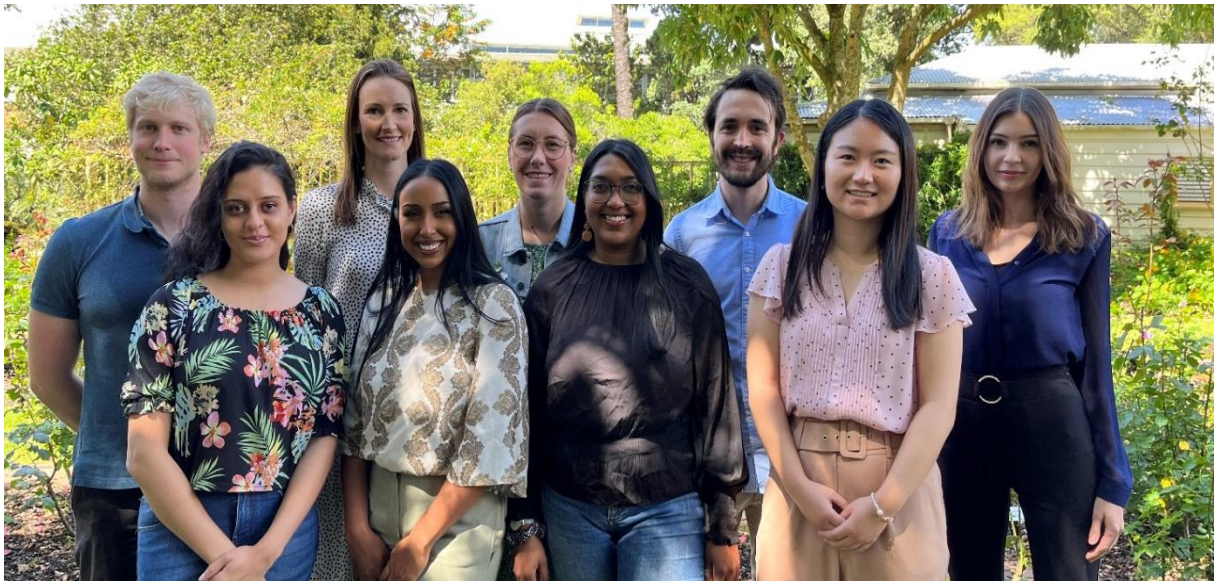
UNIVERSITY OF AUCKLAND
Waipapa Taumata Rau
NEW ZEALAND

MEDICAL AND HEALTH SCIENCES

2023 UPDATE TO DONORS: Motor Neuron Disease Research



THANK YOU

Thank you for your generous support of Motor Neuron Disease (MND) research at Waipapa Taumata Rau, University of Auckland. Your generosity continues to drive our progress, and we're excited to share our latest updates with you.

With your support, the Motor Neuron Disease Research Hub coordinates current MND research conducted at the University, including a national genetics study to get New Zealanders with MND 'clinical trial ready'. The Hub benefits from close collaboration between the University of Auckland (MND Research Lab, and Neurological Foundation Human Brain Bank), Auckland City Hospital (Neurogenetics Clinic run by Dr Richard Roxburgh), and national and internal MND research consortia.

Our most important and vital collaborations are with the individuals and families living with MND who participate in our research, and with the donors who provide philanthropic support for our work. Your philanthropic donations have hugely improved our capacity to test people genetically for MND-causing genes, and to recruit and retain New Zealand's most talented biomedical scientists.

We thank you for your extraordinary support, your interest in our work, and your faith in our desire to create real change for people in New Zealand with MND through research.

With kindest regards,

Dr Emma Scotter
Head, Motor Neuron Disease Lab

BACKGROUND

New Zealand has one of the highest rates of Motor Neuron Disease (MND) worldwide, but it is unknown whether our high rate relates to environmental or genetic risk factors. A number of therapies for MND which are being trialled or developed will target genetic risk factors. Genetic risk factors are most common in people with a family history of MND, but around 12% of people with sporadic MND have genetic mutations we can identify right now.

To better understand MND risk in NZ and to connect people with MND to genetic therapies on the horizon, we must have a means of screening all New Zealanders with MND for MND-causing genes.

Dr Scotter heads the Motor Neuron Disease Lab at the Centre for Brain Research. Her team is focused on understanding the relationship between genetic errors, the deposition of protein aggregates, and the death and dysfunction of various brain cells.

OUTCOMES AND IMPACT

With the partnership of our donors, the following has been achieved:

The NZ Motor Neuron Disease Genetics Study has provided nationwide access to genetic testing that is fully supported by genetic counsellors. The study has genetically tested 183 people with MND, or at risk of MND, and 14 controls.

We identified 46 families with clear familial MND, found an MND-causing genetic error in 32 people, and found that MND in New Zealanders may be due to relatedness to globally distributed MND 'mega-families'.

Providing certainty over whether or not their MND was caused by a genetic error has given New Zealand families greater agency over the disease; including knowing whether children are at genetic risk of MND, access to clinical trial entry for gene-targeting drugs, and clinical testing to select embryos free of MND-causing genes to implant back into mum.

Increasingly, we are investigating rare genetic causes of MND, testing whether certain genetic errors we find in MND families increase the risk of developing MND or if they are simply normal variation between individuals. This will aid clinical decision making for people with those rare genetic errors.

By using patient skin cells and brain tissues we are accelerating understanding of how those rare genetic errors affect the biology of cells, and designing interventions.

RESEARCH ACTIVITY

With your support, we are soon to submit manuscripts on; i) our findings for the first 120 participants in the NZ Motor Neuron Disease Genetics Study, and ii) using distant relationships between people with MND to find genetic causes.

In addition to presenting at various conferences around the world, we have also had multiple manuscripts published this year, contributing to the global knowledge and resources on MND.

You may also be interested in these public engagement and press coverage pieces:

- Neurological Foundation of New Zealand public webinar: https://youtu.be/Ul9bDYw8PZw
- Profiled in University of Auckland News and Opinion: https://www.auckland.ac.nz/en/news/2022/04/11/the-heart-and-soul-of-brain-research.html

NZ MND GENETICS STUDY

In our ongoing research, we've conducted genetic screening for 197 participants and

analysed 42 skin biopsies to bank cells. Notably, 32 individuals (16%) showed MND-causing mutations, including 23 with *C9orf72* repeat expansions and nine with *SOD1* mutations. Six of these cases, initially thought to be without a family history of MND, were revealed to have connections through collaborative genetic reconstruction at Macquarie University. This challenges the perception of sporadic MND cases.

Our NZ MND Family Study, supported by the Neurological Foundation of NZ, continues, with 46 families providing valuable insights. Among them, 6.5% identify as NZ Māori, 48% have a *C9orf72* mutation, 13% have an *SOD1* mutation, and 17% have an unidentified gene mutation.

We're now closely engaged with a sizable *SOD1* gene-related MND family and two families (one NZ European/Māori) with a potential newly identified gene.

RARE GENETIC CAUSES OF MND

With your support we are exploring genetic errors unique to family members with MND, aiming to distinguish between potential causes of MND and harmless variations. Investigating rare and previously unreported genetic errors in the *UBQLN2* gene, we collaborated internationally, studying brain tissue from individuals who had both MND and *UBQLN2* gene errors.

Our findings unveiled a distinctive protein clumping 'signature' that distinguishes between benign and MND-causing errors in the *UBQLN2* gene. Additionally, we've identified a rare genetic error impacting the editing process of RNA for a specific gene, potentially influencing protein function and contributing to motor neuron degeneration—a critical aspect we're actively testing.

CURRENT & FUTURE IMPACT

NZ MND GENETICS STUDY

This study has enabled us to reassure over 100 people with sporadic MND that their children are unlikely to be at greater risk of developing MND, and to identify genetic errors in people with sporadic MND that are actionable (gene therapy, family planning decisions). We will continue to advocate for access to genetic testing for everyone with MND.

We have also referred 11 people with MND caused by a genetic error in *C9orf72* to a clinical trial for a gene-specific therapy. Although the trial was unsuccessful and was terminated, NZ are well positioned to act as a site for future gene therapy trials.

Finally, one of our proudest achievements is that our study enabled genetic testing for embryo selection so that a child could be born without the MND-causing genetic error.

RARE GENETIC CAUSES OF MND

Our work testing the biological effects of genetic errors will inform clinical decision making. If we find that a genetic error is the cause of MND in a family, other family members can be tested, and family planning decisions can be made (including pre-implantation testing).

It is an absolute privilege and an honour to conduct this work with, and for, people with MND. Thank you.

If you would like to know more about supporting MND research, contact:

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