FIGHT MND.

Project

Disease heterogeneity

Identifying novel structural variations in MND

MND affects people differently. The age of onset, rate of progression and location in the body where MND begins can vary, making the disease difficult to diagnose and treat. In this project, investigators will study the genetics unique to people affected by MND, which is likely to be responsible for the variability that occurs. They will assess genetic markers that are linked with MND to identify groups of patients that have similar genetics and determine if patients within each group respond to specific treatments in a similar way.

Project Lead

Prof P. Anthony Akkari

Perron Institute for Neurological and Translational Science, WA

Prof Akkari started his research career in the Neurogenetics Laboratory of Professor Nigel Laing at the Australian Neuromuscular Research Institute (now the Perron Institute). Professor Laing was collaborating with Professor Teepu Siddique and contributed to the discovery of the first gene for MND, the SOD1 gene.

This sparked an interest for Prof Akkari in MND and he was determined to further study this complex disease.

Prof Akkari, Dr Flynn and Frances Theunissen conducting genotyping experiments in the lab.

Inspiring research

Prof Akkari says there are many areas of his research that he finds inspiring.

"Right up there is the thrill of examining uncharacterised regions of MND genes to see what else might reside there in terms of gene function and control," he says.

A highlight is also working with students who are coming into the MND space for the first time. *"Seeing their excitement about new discoveries they make and what light that sheds on MND genetics is very rewarding,"* he says.

The opportunity to collaborate with MND researchers around Australia and around the world, in a common commitment, is something that *"just keeps me going,"* he adds.

Variation in MND

When asked about the variation in MND and its complications, Prof Akkari explains that *"structural variations are regions of DNA that vary naturally"* and that *"there are many different kinds of gene variations within DNA"*.

Prof Akkari's group is particularly interested in Short Structural Variations (SSV). These are less than *"50 base pairs of DNA, that reside within genes but can also sit between genes. Structural variations can influence neighbouring genes but also genes far away. Many are repetitive regions of DNA."*

What this means for MND

Prof Akkari explains that *"since SSV regions of DNA vary so much between people they can be highly informative for disease risk and disease mechanisms"* and that they can be useful in clinical trials where patient responses to different therapies are measured.

"As we learn more about the SSVs in MND genes they may also identify groups of patients with similar sporadic MND disease mechanisms," he says.

This would allow these patients to be selected for clinical trials where their specific form of MND can be targeted to provide a higher chance of success for the trial.

Principle investigator Prof Akkari and Co-investigator Frances Theunissen at the Perron Institute.

How FightMND is helping

Prof Akkari says that *"funding from FightMND will allow us to fund the discovery and investigations of these difficult to examine SSV regions in novel and candidate MND genes."*

He is working with PhD student and co-investigator Frances Theunissen who has been instrumental in developing this SSV project, writing the grant application and setting up the collaboration with Prof Amar Al Chalabi's group at Kings College London, which provides access to a large patient cohort. Data sourced from this cohort will inform which SSV regions Prof Akkari and his team will follow up in the lab.

"The overall benefit of this is that it's going to significantly improve our ability to examine these SSV regions within known and novel MND genes," says Prof Akkari.

"As we examine these novel SSV gene markers in MND patient samples, we will then take this a step further and test them in MND patient DNA samples from previously conducted clinical trials," he adds.

The goal is to classify MND patients into *"sub populations"*, and if the genetic markers show promise, they would then be incorporated into futur clinical trials.

FightMND has invested $249,880 into this research.

About Prof P. Anthony Akkari

Prof P. Anthony Akkari is the Head of the Motor Neuron Disease Genetics and Therapeutics group at the Perron Institute for Neurological and Translational Science, WA.

After completing his PhD in neuromuscular disease genetics, he undertook his postdoctoral research at Duke University's Division of Neurology, where he has ongoing collaborations and an adjunct professorship. From Duke he was recruited into the USA Pharmaceutical industry at GSK, and later Eli Lilly and Cabernet Pharmaceuticals. There he focused on integrating genetic data into the drug development process to drive stratified medicines for patients. He maintains an ongoing role and interest in the pharmaceutical industry and is the Chief Scientific Officer of Black Swan Pharmaceuticals, an ALS/MND drug development company.

Prof Akkari's MND research group is focused on discovering how short structural variations within the human genome contribute to the missing heritability of MND and how these can be co-developed with therapies for improving the success of MND clinical trials. In parallel, his team works to develop antisense oligonucleotide (AO) therapeutics for MND and at present have seven AOs in development, targeted toward sporadic MND.

Prof Akkari and Frances Theunissen discussing their latest results on genetic structural variants in MND at Perron Institute.