Gene-editing to Reveal Regulators of Protein Aggregation and Toxicity in Motor Neuron Disease and Frontotemporal Dementia

Research

Motor neuron disease (MND) is characterised by the degeneration of motor neurons in the brain and spinal cord that leads to muscle weakness, wasting, and paralysis. It is an inevitably lethal disease with a lifetime risk of ~ 1 in 400 Australians. Interestingly, some people with MND also develop frontotemporal dementia (FTD), suggesting that the two diseases are related. Frontotemporal dementia (FTD) is characterised by the loss of neurons in the brain, which causes changes in personality, emotional state, and language difficulties, accounting for 1 in 20 cases of dementia. The incidence of both of these diseases is increasing and there are no effective treatments that slow or stop the progression of either of these diseases.

One of the first events, at the molecular level, involved in 97% of MND and 50% of FTD cases is the abnormal build-up of a protein called TDP-43 in motor neurons. TDP-43 proteins stick together to form toxic clumps and over time the accumulation of these TDP-43 clumps leads to the death of neurons in MND/FTD. Therefore, one potential therapeutic strategy is to prevent this toxic process of TDP-43 clumping. Unfortunately, there is currently a limited understanding of how TDP-43 clumps in neurons and why it is toxic. The primary aim of this project is to identify the cellular pathways that increase or decrease TDP-43 clumping and its associated toxicity to neurons. This project will use revolutionary gene editing technology to scan every gene in the human genome to identify the genes involved in triggering TDP-43 clumping. This is extremely important because it will broaden the scope of new therapeutic targets to treat people living with MND and FTD. This approach has great potential to put us on the path towards more effective treatments for people living with MND and FTD.

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Outcome

The Brain Foundation Research Gift has enabled our lab to screen the function of ~20,000 genes in cells. The samples from these screens have been sequenced and analysed to generate "top hit" lists. This dataset has revealed that there are hundreds of genes that may play a role in protecting cells from TDP-43 toxicity. In addition, there are other genes that demonstrated involvement in inhibiting and enhancing the formation of TDP-43 clumps. The next step is to test each gene individually to determine which is the most effective at enhancing survival of cells. The best genes will become lead candidates for future therapeutic targeting studies for treatment of motor neuron disease and frontotemporal dementia.

Thank you very much to the Brain foundation and its supporters for the generous award of this research gift.