Research Project
By Dr Fiona Bright

Dementia Australia™ Research Foundation

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> **Studying genetically modified human "mini brains" will move us closer to developing treatments for tau-related dementias.**
>
> — Dr Fiona Bright

Investigating unknown causes of tau-related dementias using 3D human "mini brains"

What is the focus of the research?

Scientists will grow human "mini brains" in a petri dish to investigate rare genetic mutations that cause dementia-like symptoms in children and adolescents.

Why is it important?

Our genes influence everything from our eye colour and temperament to the likelihood of developing disease. We have approximately 25,000 genes, which are made from our DNA. They instruct our billions of cells to create proteins that form the basis of all life and bodily functions.

One specific gene, called microtubule-associated protein tau (MAPT), has been linked to several types of dementia. MAPT encodes a protein called tau, which is important for healthy brain function. Unfortunately, in dementia, tau malfunctions. When this happens, it forms abnormal clumps that kill neurons and shrink the brain. This is what causes the fatal cognitive decline that cuts lives short and devastates families.

MAPT lives at the "genetic postcode" 17q21.31, which is known in the scientific community as a hotspot for DNA mutations. Newly discovered rare genetic mutations at 17q21.31 were identified in patients with unexplained dementia-like symptoms, who also had malfunctioning tau in their brains. Sadly, most of these patients were children and adolescents, so it is possible they could be classified as having childhood dementia. These mutations are large and act differently to those found in the brains of adults with tau-related dementias. Unfortunately, scientists understand very little about MAPT and tau in the developing brain.

Dr Bright and her team will study brain organoids, aka "mini brains", that are genetically modified to have mutations in 17q21.31. Mini brains are 3D models of human brain tissue which are grown from stem cells in a petri dish. By using human brain organoids, Dr Bright can more accurately and reliably explore how tau damages childhood and adolescent brains in disease. This will allow her to model the brain changes that occur because of these genetic mutations and move researchers closer to developing treatments for tau-related dementias in brains of all ages.

How will this happen?

Stage 1: genetically modify human stem cells to express the 17q21.31 mutation. Source stem cells from human patients who carry the mutation, to establish a 2D modelling platform.

Stage 2: cultivate these stem cells to grow into 3D brain organoids that mimic the tau changes that occur in human brains with 17q21.31 mutations.

Stage 3: use specialised technology to look for specific cells or molecular pathways that cause tau to become pathological during neurodevelopment. This will allow Dr Bright to identify targets for screening of potential drug treatments.

What will it mean for dementia research?

- More accurate modelling of how abnormal tau impacts the human brain.
- A greater understanding of the cause of dementias that exhibit abnormal tau.
- A step closer to understanding the mutations in dementia-related genes.
- New avenues to explore to identify targets for tau-related dementia treatments.
- More knowledge of the links between 17q21.31 mutations and childhood dementias.

17q21.31, explained

Human chromosomes are the building blocks of life. These thread-like structures live in the nucleus of our cells. They're made from protein and DNA and contain our unique genetic information. We typically have 23 pairs of chromosomes and the "genetic postcode" 17q21.31 is located on number 17.

The recently discovered rare genetic mutations that occur in 17q21.31 cause either a deletion or a duplication of a segment of chromosome number 17. It is important for researchers to investigate more about these rare mutations that involve the MAPT gene in the developing brain (children and adolescents).

By uncovering the cause/s of these changes, and comparing the production of malfunctioning tau in young versus older patients with dementia, they will progress the scientific field further towards the development of targeted dementia treatments.

Who's undertaking the research?

Dr Fiona Bright, Macquarie University

Dr Bright is a postdoctoral research fellow at the Dementia Research Centre within Macquarie University Medical School. She has a background in paediatric neuropathology and expertise in early-onset neurodegenerative diseases, including frontotemporal dementia. Prior to commencing at the Dementia Research Centre in 2020, Dr Bright conducted research at the University of Adelaide, Harvard University Medical School and The University of Sydney.

This project will be overseen by Dementia Research Centre director Professor Lars Ittner. Dr Ann-Na Cho and PhD Candidate Nicolle Morey will work alongside Dr Bright to achieve the research aims. Outside of her research, Dr Bright participates in running festivals and charity events throughout the year to raise funds for dementia research.

The title of her project is *Completing the tauopathy puzzle - modelling novel mutations to uncover unknown roles for tau in neurodevelopment and neurodegeneration.*

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