A rare genetic brain condition

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The Murdoch Children's Research Institute (MCRI) is launching an Australian-first research project into a genetic brain disorder that causes intellectual disability, seizures and degeneration. Affected children appear to have a static disorder but then lose developmental skills and have a reduced lifespan.

The cutting-edge project, made possible by generous philanthropic support, aims to discover how the genetic cause results in the condition and begin large scale drug screening of potential therapies.

MCRI researchers have a long history of investigating and finding disease genes and developing therapies for childhood disorders. They are hoping for a breakthrough into this condition—beta-propeller protein-associated neurodegeneration (BPAN).

This is the first BPAN project in Australia and one of only a few globally. It was only made possible by the dedication and tenacity of David and Edwina Hunter, who have garnered significant philanthropic funding. Their son, Angus, was diagnosed with BPAN in 2016 when he was two years of age.

Mr Hunter said, "The clock is ticking; a cure or treatment must be found for Angus and other children diagnosed with BPAN before they reach their late teens or early twenties, which is when the deterioration starts. We have so far raised about half the funds needed to begin scientific research into BPAN, and I'm calling on everyday Australians to help us help these brilliant scientists."

MCRI Professor Martin Delatycki said BPAN was not an inherited condition, but caused by a random genetic mutation in a gene called WDR45.

"The disorder interferes with normal childhood progress, so children with BPAN are slow to develop some skills and never develop others. Many children never learn to walk or talk. Tragically they lose skills and have reduced life expectancy."

Professor Delatycki said the impact of BPAN accelerates when a child reaches their teens, at which point they decline, losing skills from sitting

up, to eating and swallowing. Premature death is the result.

"BPAN was considered extremely rare, and most of those affected were female. However, boys with the condition are now being identified, and with the advances in genetic testing, children who in the past were diagnosed with an unknown developmental disorder can now be given a definitive BPAN diagnosis," he said.

Professor Delatycki and his colleagues have identified five children with BPAN in the past two years.

"More children are being diagnosed as genetic testing becomes more widely available, and more doctors are ordering genetic tests," he said.

Worldwide, about 125 children have been diagnosed, including 11 people in Australia—ranging from toddlers to a 36-year-old woman. Only two boys worldwide have been diagnosed, including Angus.

Co-Director of the Bruce Lefroy Centre at MCRI, Associate Professor Paul Lockhart, said the new research program would use laboratory-grown human nerve cells to try to understand how faults in the WDR45 gene cause BPAN, and to test new treatments.

Skin or blood cells from children with BPAN will be reprogrammed using cutting-edge stem cell technologies to become nerve cell types affected by the condition.

"This 'brain in a dish' model lets us directly test how BPAN affects brain cells function, and offers a way to rapidly screen large numbers of drugs for potential treatment options," Lockhart said.

Dr. Jay Shukla has been appointed as the project's inaugural research officer. Dr. Shukla has extensive experience investigating iron-mediated

brain degeneration.

Associate Professor Lockhart said the research may offer unprecedented and life changing opportunities for individuals and families affected by BPAN.

"Little is known about the biology of BPAN, and there are no drugs that can cure or even slow the progression of this devastating disorder," he said.

"Current treatments only aim to alleviate symptoms. There is a critical need for this research to understand the disease and begin to look for treatments. These advances will improve long-term health outcomes for this vulnerable group of children, and deepen our knowledge about a range of different but related rare genetic diseases."

Patient story

Four-year-old Angus Hunter is one of only two boys worldwide known to have BPAN.

His father David Hunter had mixed feelings when his son was finally diagnosed.

"I guess I wanted to hear that there was some magic panacea that would make everything better, but there is not," he said. "I was shocked, and I think I will always be in shock."

Mr Hunter admits to "why me, why us" moments, which he tries to resist.

"He is a beautiful, happy, happy boy," he said of Angus. "No matter what the circumstances, he always manages to look on the bright side.

No matter how many visits there are to the Children's Hospital, he is always happy to a fault, and in some respects, it makes the burden on us easier, but also harder because we love him so much."

Provided by Murdoch Children's Research Institute (MCRI)