Genetic test unlocks cause of Brisbane boy's rare disease

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Steve, Seth and Chris de Rooy with Dr Cas Simons from UQ's IMB

Queensland researchers have led an international effort to uncover the gene behind a young Brisbane boy's rare developmental condition, in a discovery his family hopes will pave the way for future treatments.

Eleven-year-old Seth De Rooy is one of only seven people in the world diagnosed with Temple-Baraitser syndrome (TBS), which causes severe epilepsy, intellectual disability, low muscle tone and missing nails on the thumbs and big toes.

In their search for answers for Seth, Dr Cas Simons from The University of Queensland's Institute for Molecular Bioscience and Dr Michael Gabbett and Dr Julie McGaughran from Genetic Health Queensland teamed up with colleagues around the world to create a genetic profile for six of the patients and their parents.

"From a small blood sample from each individual we were able to sequence and analyse their exomes, which are the protein-coding sections of our genes that are home to many of the disease-causing mutations in our DNA," Dr Simons said.

"We then compared the genetic differences between patients and their parents and found a number of damaging mutations in each patient's KCNH1 gene," he said.

"KCNH1 is known to be important for the function of the central nervous system, but hasn't been associated with human disease before."

Dr Simons said the critical part of the discovery was confirming their findings in the lab.

"Once we knew what these mutations were, we recreated versions of the human KCNH1 protein with and without the mutations, and designed a series of experiments to understand how the function of the protein was changed by the mutations," he said.

"From these tests, we found that all of the mutated versions of KCNH1 were hyperactive, which is consistent with our understanding of how defects in potassium channels can result in epilepsy."

Dr Michael Gabbett said he hoped the team's work would be used as a model for diagnosing and treating rare diseases.

"Rare diseases affect more than 1.2 million Australians, and around 80 per cent of rare diseases are caused by mutations in our genes," he said.

"The rare nature of TBS has made it challenging to identify the genetic basis of the disease, and because its symptoms are quite common, we also expect there is a high degree of underreporting by the global medical community.

"Through this study we found that some of the parents of TBS patients have a very small amount of these mutations in their own cells – nowhere near as many as their children, but still enough that could be immediately useful in prenatal genetic screening to help future parents make informed choices.

"These findings could also help us identify existing drugs that could be effective on this gene and help minimise some of the symptoms of TBS."

Ms Chris de Rooy, Seth's mother, said the findings brought hope to her family and helped remove some of the mystery around Seth's condition.

"Seth was only the second person in the world to be diagnosed with TBS and is now the eldest known patient, so we have no idea about what the future holds for him, which can be scary at times," she said.

"It's hard to think about it now, but for many years I blamed myself for Seth's condition – 'what did I do wrong?' I'd ask myself; 'why is he developing differently to his brother and sister?' and 'when will he learn to walk and talk?'

"Now we know the genetic cause of this disease, and we've seen Seth lead the way for others with his treatment and progress, it's easier for us to take each day as it comes.

"We hope this discovery can inspire more awareness and research into treatments to improve quality of life for Seth and other families like ours living with rare genetic conditions."

The discovery is the first from an innovative partnership between scientists at IMB's Centre for Rare Diseases Research and clinicians at Genetic Health Queensland, who have teamed up to help find answers to some of Queensland's most challenging genetic health conditions.

The study was published in *Nature Genetics*.

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