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Gene mutation discovery could explain brain disorders in children

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Researchers have discovered that mutations in one of the brain's key genes could be responsible for impaired mental function in children born with an intellectual disability.

The research, published today in the journal, *Human Molecular Genetics*, proves that the gene, TUBB5, is essential for a healthy functioning brain.

It's estimated that intellectual disability affects up to four per cent of people worldwide, and two per cent of all Australians. One of the ways in which intellectual disability occurs is through genetic mutations, which cause problems with normal fetal brain development.

During fetal brain development, TUBB5 is essential for the proper placement and wiring of new neurons. When the gene is mutated, the brain, which sends and receives messages to the rest of the body, is impaired.

Lead researcher, Dr Julian Heng, from the Australian Regenerative Medicine Institute (ARMI) at Monash University, said genetic mutations to TUBB5 could be responsible for a range of intellectual disabilities. It could also affect the development of basic motor skills such as walking.

"TUBB5 works like a type of scaffolding inside neurons, enabling them to shape their connections to other neurons, so it's essential for healthy brain development. If the scaffolding is faulty, in this case of TUBB5 mutates, it can have serious consequences," Dr Heng said.

These new findings build on the team's collaborative work with researchers in Austria, which led to the discovery of TUBB5 mutations in human brain disorders in 2012. By looking at just three unrelated patients with microcephaly, a rare brain disease in children, the team found striking similarities – each had a mutation to TUBB5. The team also provided the first evidence that the TUBB5 mutations were responsible for each patient's disorder.

Dr Heng said the research could have important implications, not only for intellectual disabilities but also for a wide range of developmental disorders.

"Learning more about the TUBB5 gene and its mutations could reveal how it shapes the connections of neurons in normal and diseased brain states.

"We're just at the beginning of this work but if we can understand why and how mutations occur to TUBB5, we may even be able to repair these mutations. In the future, we believe this work will enable us to develop new therapies to transform people's lives," Dr Heng said.

The work may potentially lead to new information about the causes and possible treatments for other brain developmental syndromes, including autism, a condition that affects as many as 1 in 160 children.

Dr Heng said that because TUBB5 belongs to a family of genes which produce the scaffolding in neurons, it means that there is scope for further study into its impact.

"By learning what these scaffolding proteins do to help neurons make brain circuits, we might be able to pinpoint the underlying causes of a wide range of brain disorders in children, and develop more targeted treatments," Dr Heng said.

Scientists believe that in the future this knowledge, combined with regenerative medicine techniques, could also aid the replacement of neurons in times of brain injury or disease.

The next phase of the research will be to develop a working model to better understand how TUBB5 can be targeted for gene therapy.

Provided by Monash University