Medical Xpress

New gene for intellectual disability discovered

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A gene linked to intellectual disability was found in a study involving the Centre for Addiction and Mental Health (CAMH) – a discovery that was greatly accelerated by international collaboration and new genetic sequencing technology, which is now being used at CAMH.

CAMH Senior Scientist Dr. John Vincent and colleagues identified defects on the gene, MAN1B1, among five families in which 12 children had intellectual disability. The results will be published in the July issue of the *American Journal of Human Genetics*.

Intellectual disability is a broad term describing individuals with limitations in mental abilities and in functioning in daily life. It affects one to three per cent of the population, and is often caused by genetic defects.

The individuals affected had similar physical features, and all had delays in walking and speaking. Some learned to care for themselves, while others needed help bathing and dressing. In addition, some had epilepsy or problems with overeating.

All were found to have two copies of a defective MAN1B1 gene, one inherited from each parent. These were different types of mutations on the same gene – yet the outcome, intellectual disability, was the same in different families – confirming that this gene was the cause of the disorder.

"This mutation was seen in five families, which is one of the most seen so far for genes causing this form of recessive intellectual disability," said Dr. Vincent, who last year made a breakthrough by identifying the PTCHD1 gene responsible for autism.

MAN1B1 codes an enzyme that has a quality control function in cells. This enzyme is believed to have a role in "proofreading" specific proteins after they are created in cells, and then recycling faulty ones, rather than allowing them to be released from the cell into the body. With the defective gene, this does not occur.

"This is a process that occurs throughout a person's lifetime, and is probably involved in most tissues in the body, so it is surprising that the children affected didn't have more symptoms," said Dr. Vincent, who is also head of the Molecular Neuropsychiatry and Development Laboratory at CAMH.

The discovery benefited from collaboration and the availability of new technology. Initially, the CAMH-Pakistani research team identified four families in Pakistan with multiple affected family members. As there had been intermarriage among cousins in these families, it enabled the researchers to begin mapping genes in particular regions of risk.

By teaming up with researchers from the Max Planck Institute in Berlin, Germany, conducting similar work on a family in Iran, they were able to focus on three genes of interest. These three genes were identified using next-generation sequencing, which sped the process in identifying the MAN1B1 gene. In addition, a University of Georgia scientist, Dr. Kelley Moremen, recreated one of the mutations in MAN1B1 in cells, which resulted in 1300-fold decrease in enzyme activity.

To date, MAN1B1 is the eighth known gene connected with recessive intellectual disability, but there are likely many more involved. "We

would like to screen children with intellectual disability in a western population," said Dr. Vincent.

Provided by Centre for Addiction and Mental Health