Protein regulation linked to intellectual disability

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Genetics researchers at the University of Adelaide have solved a 40-year mystery for a family beset by a rare intellectual disability – and they've discovered something new about the causes of intellectual disability in the process.

While many intellectual disabilities are caused directly by a genetic mutation in the so-called "protein coding" part of our genes, the researchers found that in their case the answer laid outside the gene and in the regulation of proteins.

Protein regulation involves the switching on or off of a protein by specific genes. As a consequence in this case, either too much or too little of this protein can trigger the disability.

The team has studied a large (anonymous) Australian family of 100 people, who for generations have not known the source of their genetically inherited condition.

The disability – which results in a lower IQ, behavioral problems such as aggression, and memory loss, and is linked with developmental delays, epilepsy, schizophrenia and other problems – affects only the male family members and can be passed on by the female family members to their children.

Genetic samples taken from the family and laboratory testing involving mice have confirmed that the protein produced by the HCFC1 (host cell factor C1) gene is the cause of this disability.

"The causes of intellectual disability generally are highly variable and the genetic causes in particular are numerous. The vast majority of intellectual disabilities are due to genetic mutations in proteins, so it was rather unexpected that we found this particular disability to be due to a regulatory mutation," says the leader of the study, Professor Jozef Gecz from the University of Adelaide's School of Pediatrics and Reproductive Health.

"We've been researching this specific disability for 10 years and it's taken us the last three years to convince ourselves that the protein regulation is the key," he says.

"For the family, this means we now have a genetic test that will determine whether or not a female member of the family is a carrier, which brings various benefits for the family.

"From a scientific point of view, this widens our viewpoint on the causes of these disabilities and tells us where we should also look for answers for those families and individuals without answers.

"This is just the tip of the iceberg in understanding the impact of altered gene regulation on intellectual disability – the gene regulatory landscape is much bigger than the protein coding landscape. We have already found, and I would expect to continue finding, a number of other intellectual disabilities linked with protein regulation over the next 20 years or so."

Professor Gecz and his team have published their findings in this month's issue of the *American Journal of Human Genetics.*

Provided by University of Adelaide