Mutant gene causes epilepsy, intellectual disability in women

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A mutated gene has been discovered as the key behind epilepsy and mental retardation specific to women, thanks to new research at Adelaide's Women's & Children's Hospital and the University of Adelaide, Australia.

The world-first discovery, published today in *Nature Genetics*, shows that although men carry the 'bad' gene, only women are affected.

The research has been led by Dr Leanne Dibbens and Associate Professor Jozef Gecz from the Department of Genetic Medicine, Women's & Children's Hospital, and the Discipline of Paediatrics at the University of Adelaide. The discovery is a result of a major international collaboration involving the Sanger Institute in Cambridge (UK), Wellcome Trust (UK) and many other collaborators in Australia, the United States, Ireland and Israel.

Their work has linked, for the first time, a large family of genes known as protocadherins with a condition known as "epilepsy and mental retardation limited to females" (EFMR).

Although a relatively uncommon disorder, the condition is hereditary, with successive generations of women affected. In just one of seven families studied across the world, 23 women were affected by the disorder across five generations. This discovery will now enable such families to benefit from genetic counselling, including screening for the genetic mutation at pregnancy.

"This is the first time this type of gene has been found to be involved in epilepsy," Dr Dibbens says.

"One of the most important discoveries we've made is that women in families affected by EFMR carry both a 'good' gene and a 'bad' (mutated) gene, while the men carry only the bad gene. For some reason, the men remain unaffected by the condition," Dr Dibbens says.

"We suspect this may have something to do with the male Y chromosome, but more research will be needed to find out exactly how or why."

Dr Dibbens says the gene involved in this discovery is important for cell-to-cell communication in the brain, and could also hold the key to better understanding related issues, such as autism and obsessive disorders.

"With 100 related proteins involved in this gene family, this study could lead to many new areas of research, with the need to understand the role and function of each protein," she says.

Clinically, the disorder EFMR was first described more than 10 years ago, but the cause of EFMR has been unknown until now. Why females rather males are affected – as is usual for X chromosome associated disorders – makes this a unique disorder among the epilepsies and mental retardations.

For this study, seven families were studied in Australia, the United States, Israel and Ireland. The genetic mutation was discovered in each family.

Crucial to this research was access to state-of-the-art technological support including the sequencing of 737 genes on the X chromosome, which was conducted by collaborators at the Wellcome Trust Sanger Institute in the UK.

Source: University of Adelaide