RCSI MAKE BREAKTHROUGH IN UNDERSTANDING GENE ACTIVITY

Prof David Henshall and lead author Dr Suzanne Miller-Delaney from the Royal College of Surgeons.

Epilepsy is one of the most common neurological diseases, affecting about 40,000 people in Ireland. Patients with epilepsy have an enduring predisposition to seizures – brief electrical storms that result from abnormal and excessive firing of brain cells. But what maintains the hyper-excitable state in epilepsy? This is a question that many researchers working in the field are trying to answer since it may lead to new ways to treat or prevent seizures. Although we have a solid understanding of what is different about the brain of a patient with epilepsy – changes to the structure and function of neurones and their support cells, as well as inflammation and re-wiring of brain networks - what has been unclear until now is why they are so persistent and why is it so difficult for the brain to reverse epilepsy after it is established?

To answer this, researchers at the Royal College of Surgeons in Ireland led by Dr Suzanne Miller-Delaney from Prof David Henshall's group, explored mechanisms by which cells "store" biochemical memories over long periods of time. They looked for chemical changes to DNA - the addition of a methyl molecule - which act as "on/off" switches for gene activity. Studies show that increased amounts of methylated DNA tends to shut off genes whereas reduced DNA methylation makes genes particularly accessible and more likely to be turned on.

The RCSI team studied DNA methylation in over 30,000 sites of the human genome in brain tissue. Samples came from patients with temporal lobe epilepsy who had undergone surgery to remove part of their brain as treatment for drug-resistant epilepsy at the Swedish Neuroscience Institute in Seattle, USA. The team analysed the overall methylation state and looked for differences from normal brains. They found that each sample showed significant variation in the DNA methylation landscape, indicating individual experiences are probably influencing the function of genes in brain cells. While unique methylation differences were only found for 146 genes in epilepsy, many of these changes were found to be specifically aligned with the tissue deterioration in the brain associated with repeated seizures. Furthermore, increased methylation was found to be most common, consistent with gene turn-off. Among the affected genes were several coding for ion channels as well as a number involved in early development and remodelling, suggesting adaptive changes that may affect network organisation and excitability.

The team also looked at whether methylation affected DNA sequences that code for molecules called microRNAs – these originate from non-coding regions of the genome and are sometimes referred to as our genome's "dark matter". The tiny microRNA sequences act as regulators of gene expression and the team actually found stronger effects of DNA methylation on their expression than traditional genes, suggesting DNA methylation may have unequal effects according to gene type.

Dr. Suzanne Miller-Delaney, lead author of the study, commented that "this study is the first of its kind in human temporal lobe epilepsy. It specifically aligns structural changes in patient DNA with anatomical deterioration and gene activity." Professor Henshall adds "our findings help us to understand at a molecular level what is controlling gene activity in epilepsy and why the epileptic state can be so persistent. It may also offer new targets for reversing epilepsy once established."

The research, which included members of professor Ray Stallings group, also at RCSI, was funded in part by Epilepsy Ireland and Science Foundation Ireland. It was published online in Decemeber in the journal *Brain*, the second highest ranked neurology journal, and will appear in the March issue this year.

Epilepsy Research Explained

Epilepsy Ireland and the RCSI will hold an information evening on April 23rd in Dublin where people with epilepsy and all with an interest in the condition can find out more about the latest discoveries in epilepsy. You can hear experts like Prof Henshall explain – in plain English – what these discoveries mean for people with epilepsy. See back cover for full details.

Thank You

So many people volunteer their time and money to support Epilepsy Ireland every month. Without everyone's support we simply couldn't provide our services, work to raise awareness and support epilepsy research. Just some of our recent supporters we want to thank are: Abbey School, Tipperary; Trim Vintage & Veteran Car Rally; Paul Ryan & Bakers Pub; Newtown NS, Crettyard; the Sweetman Family; Ladbrokes, Ballyhaunis; 6th Class Pupils in Ballyagran National School; Barbara Golec Regiec; Sarah Mechan; DCC Management Services; Mount Anville School Transition Year.