

HRB/MRCG 2011/7

Genome-wide DNA methylation analysis of hippocampus from patients with intractable temporal lobe epilepsy

Lay summary:

This project investigated the role of epigenetics – non-heritable changes to DNA - in human temporal lobe epilepsy (TLE). The background to this was the knowledge that TLE is associated large-scale, wide-ranging changes in gene expression. Identifying mechanisms controlling those gene changes could lead to deeper understanding of causes of the disease and also new approaches to treatment.

We obtained surgically-resected brain tissue from epilepsy patients and analyzed chemical modifications to DNA called methylation. These are known to act as “switches” which enable genes to be turned on or off. We analyzed the methylation state of the entire human genome. A total of 146 protein-coding genes exhibited altered DNA methylation in human TLE, with 81.5% of the promoters of these genes undergoing hypermethylation (suggesting “turn-off”). Unique methylation changes were found in the brain of patients with TLE as well as according to pathology. An analysis of what the genes do found many to be involved in brain development and structure, neurotransmission, cell death and DNA transcription.

We also identified methylation changes to what are known as “non-coding RNA” in TLE. These are DNA-like sequences within the human genome that are transcribed but not “read” to form proteins, remaining instead as RNA. Our genome comprises about 80% of this form of non-coding RNA but we still know very little about what it does. We identified methylation-sensitive short and long non-coding RNAs, including microRNA (miRNA), which were recently implicated in seizure control and epilepsy development.

Our studies represent the first analysis of genome-wide DNA methylation changes in TLE. The findings contribute to our understanding of how gene expression is controlled in epilepsy and identify epigenetic control of non-coding RNA in epilepsy.

Outputs from HRB DNA methylation grants

Original research publications:

1. Miller-Delaney S.F.C., Das S., Stallings R.L., **Henshall D.C.** Investigating gene promoter methylation in a mouse model of *status epilepticus*. in "Tiling Arrays: Methods and Protocols". Methods Mol Biol. 2013;1067:87-101
2. **Henshall D.C.** and Jimenez-Mateos E.M. Epilepsy, in Innate neuroprotection for stroke. Ch 24. Springer
3. Miller-Delaney S. F. C., Das, S., Sano, T., Jimenez-Mateos, E. M., Bryan, K., Buckley, P. G., Stallings, R. L. and **Henshall, D. C.** (2012) Differential DNA methylation patterns define *status epilepticus* and epileptic tolerance. *Journal of Neuroscience*, 32(5): 1577-1588.
4. Miller-Delaney, S.F.C., Bryan' K., McKiernan, R., Das, S., Bray, I., Gwinn, R., Stallings, R., and **Henshall, D. C.** (2013) Differential DNA methylation profiles of coding and non-coding genes define hippocampal sclerosis in Temporal Lobe Epilepsy . *In preparation*

Presentations:

1. Invited speaker "Molecular mechanisms of seizure-induced neuronal death", University College Cork, Cork, Ireland, Apr 2012
2. Invited speaker "Status epilepticus: new targets for neuroprotection and anti-epileptogenesis" at the Second National Epilepsy Research Conference, Dublin, May 28 2012 (conference organizer with G. Cavalleri).
3. Invited speaker ""Getting the brain to put up a fight: Tolerance and the molecular basis for endogenous programmes of neuroprotection in epilepsy" at the Epilepsy Society, Chalfont, U.K., June 14th 2013
4. Invited speaker, "Differential methylation patterns define status epilepticus & epileptic tolerance", 10th European Congress on Epileptology, London, U.K. Sep 2012.
5. Invited speaker "DNA methylation in endogenous neuroprotection mechanisms", Neuroscience Ireland meeting, Dublin, Ireland, Sep 2012
6. "Differential DNA methylation patterns define *status epilepticus* and epileptic tolerance", RCSI research day talk, Dublin, Ireland March 2012

Other outputs/disseminations

- 2013 Organizer: Neuroscience workshop as part of “European Month of the Brain” RCSI (with 3U partners), Dublin, May 21 2013
- 2012 Conference Organizer, “7th Annual Neuroscience Ireland conference (Sep 5th & 6th 2012), RCSI, Dublin
- 2012 Conference Organizer, “Second National Epilepsy Research Conference” RCSI, Dublin, May 2012