One of the first grants made by Epilepsy Ireland under our Research Funding Scheme back in 2009 was to Dr Cavalleri and colleagues for their work in identifying genetic predictors of epilepsy. Below Dr Cavalleri outlines his team's work over the past four years and explains some of the key findings to come from the study.

What is DNA?

Our bodies consist of billions of cells, and the building blocks of these cells are called 'proteins'. Indeed all life on earth is made up of proteins and millions of proteins exist on the planet. We read about proteins in health books and hear about them on TV but where do proteins actually come from?

Well, our bodies can make proteins on demand. Contained within cells from all living organisms including humans is a substance called DNA. This incredible molecule represent a code made up of four different letters ('A', 'T', 'C' and 'G'). The code is over 3 billion bases in length. If you joined all of the DNA in your body and stretched it out end-to-end, it would reach over 700 million miles, that's to the sun and back about 4 times! Critically, this code contains the instructions for making all the proteins our body requires. It is the book of life, and we each have our own copy.

We each have our own, unique copy of DNA because our DNA is slightly different from our parents, with each generation the code changes slightly. Any two individuals will be 99.9% identical at the level of their DNA, but the 0.1% of the code that differs is critical as that, at least in part, explain the wonderful diversity that exists in life on earth. But crucially, these differences can sometimes influence our health. If a difference occurs in the code for a protein involved in lung function, it might cause a condition such as cystic fibrosis. If it occurs in a protein involved in cell signalling in the brain, it might lead to epilepsy.

It's only in the last decade that scientists have been able to read our DNA in its entirety. Indeed, the first human genome (we refer to all of a persons DNA as their 'genome') was sequenced in 2002, as part of the Human Genome Project. This was the result of a massive global effort that cost almost 3 billion dollars and took the best part of 10 years to complete. But since 2002, technology has changed dramatically. Today, researchers can sequence all of your DNA in a day, at a cost of just $3,000. But although it's relatively easy to generate all this information, interpreting what it actually means is a massive challenge. Researchers are currently working to address this challenge.

What did we set out to do in this particular study?

Epilepsy Ireland partnered with the Health Research Board (HRB) to fund researchers at the Royal College of Surgeons in Ireland in their efforts to better understand the genetics of very difficult to treat epilepsy. Around two thirds of patients with epilepsy will respond well to medication and manage to control their seizures. However, the remaining one-third of patients continue to experience regular seizures despite trying several different drugs. Prof. Delanty, Dr. Doherty and Dr. Cavalleri (of Beaumont Hospital, St. James's Hospital and RCSI) together with collaborators, set out to identify key regions of our DNA that might be important in the development of difficult to treat epilepsy. If you can identify such regions you might be able to develop new treatments that correct or target the underlying problem.

As part of this work over 400 people with epilepsy were recruited through the clinics of Prof. Delanty at Beaumont Hospital patients and Dr. Doherty at St James's Hospital. These patients were studied very carefully by our clinical team, so as to prepare detailed, individual profiles on how each responded to their epilepsy treatment. We then generated extensive genetic profiles on all participants. When we analysed the data we observed some interesting signals but nothing that clearly predicted chronic refractory epilepsy. More powerful and focused studies are required.

The funding has contributed to important parallel discoveries

But the work has helped establish important resources that can now be integrated with collaborative efforts with scientists in other countries that are seeking to extend the research but using much larger numbers of patient participants. This should improve the power of the study to detect genetic effects considerably.

Indeed the resource established by this study has already helped contribute to parallel discoveries in epilepsy. For example, Epilepsy Ireland support has helped us identify a gene type that is a predictor of severe skin-related adverse reactions to carbamazepine (1). We hope this test might be integrated to the clinic in the future, to help avoid these severe, but extremely rare, reactions. We have also helped to show that common genetic variation in a gene called SCN1A is a risk factor for mesial temporal lobe epilepsy with hippocampal sclerosis (2) - the same gene was previously known to be important in epilepsy with a strong family history such as GEFS+ or Dravet Syndrome. Epilepsy Ireland funding has also helped us contribute to the identification of genetic variation as predictors of the volume of the hippocampus (a brain structure known to be important in epilepsy)(3). Together, these discoveries represent small but

significant steps in helping us understand the biological factors underlying epilepsy.

But perhaps the most exciting discovery to be supported by the Epilepsy Ireland funding was the recent finding that genetic changes in a gene called TDP2 can cause a very rare but difficult to treat and debilitating seizure disorder (4). Together with collaborators from the UK and Netherlands, we showed that genetic changes in this gene can lead to the development of seizures. The gene itself helps control how DNA is coiled. When a gene is producing a protein, the DNA containing that gene needs to be relaxed (or unwound) and vice-versa when it is not. If TDP2 is damaged, we lose some of that control over DNA coiling which can lead to differences in the levels of certain proteins in the brain, which can lead to epilepsy.

We need your help!

Genetics plays an important role in epilepsy and recent technological breakthroughs in research are allowing us to understand this role with more clarity. But there is still a lot of work to do and we need your help. If you are under the care of Prof Delanty or Dr. Doherty, and have any or a combination of a) a strong family history of epilepsy, b) difficult to treat epilepsy or c) experienced side effects from anti-epileptic drugs please contact our Research Nurse, Lisa Slattery, at 087-983-1043 or email lisaslattery@rcsi.ie

References:

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2. Kasperaviciute D et al,. Epilepsy, hippocampal sclerosis and febrile seizures linked by common genetic variation around SCN1A. Brain. 2013 Sep 6.

3. The ENIGMA Consortium. Identification of common variants associated with human hippocampal and intracranial volumes. Nat Genet. 2012 Apr 15;44(5):552-61.

4. Gómez-Herreros F, et al TDP2 protects transcription from abortive topoisomerase activity and is required for normal neural function. Nat Genet. 2014 Mar 23.

REPORT SHOWS IMPACT OF CUTS ON PEOPLE WITH NEUROLOGICAL CONDITIONS

Caoimhghín Ó Caoláin TD and Alexis Donnelly who has MS at the launch of the NAI report in March.

A survey conducted by the Neurological Alliance of Ireland (NAI) of 600 people living with neurological conditions and their families showed that it has become more difficult to access a range of basic services and supports over the past three years.

The findings, announced in March during Brain Awareness Week highlight again the impact of on-going cuts in health, benefits and entitlements on top of historical underdevelopment of neurological services.

Among its findings are that:

- 42% had their medical card withdrawn.
- 68% of respondents had been affected by changes to the mobility allowance
- 64% were affected by cuts to home care packages
- In addition, there were high rates of people finding it more difficult to access community services over the last three years, or getting no service at all, including 74% for personal assistance services, 70% for respite care and 55% for speech and language therapy.

The study highlights alarming changes since a similar study was conducted in 2011. For example, in 2011, 11% said they did not have access to a specialist nurse but this is now 20%. In 2011, 16% said they had difficulty accessing psychology services and this is now 24%. Figures for physiotherapy, occupational therapy and home adaption services show similar trends.

Almost half of respondents had to give up work as a result of their condition, whilst some 40% were paying privately for physiotherapy, neurology and aids and equipment.

Speaking at the launch of the report in the Mansion House, Chris Macey, chairman of the NAI, which represents 30 organisations in the neurological sector including Epilepsy Ireland said that "these are worrying findings which show that people with neurological conditions are being hit extremely hard by the cumulative impact of cuts to community services and to benefits that have a massive impact on their quality of life".

NAI is calling on the Government to show commitment to prioritising neurological services, to make no further cuts to entitlements and to invest in rather than further cut community services.

A number of prominent politicians speaking at the launch outlined their commitment to neurological issues and to highlighting the findings of the report within Leinster House, including Deputies Denis Naughten and Caoimhghín Ó Caoláin and Senators Marie Moloney and Jillian Van Turnhout.

GO http://bit.ly/1cMPsyb