EPILEPSY RESEARCH CENTRE NEWSLETTER 2015-2016

Medicinal cannabis for epilepsy
Understanding the genetic basis of common epilepsies
A new genetic cause for a progressive form of myoclonic epilepsy

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We are delighted to bring you an update on our research program investigating the genetic basis of the epilepsies at the Epilepsy Research Centre, University of Melbourne, Austin Health. Once again it has been a busy and exciting year.

Professor Sam Berkovic and Professor Ingrid Scheffer were recognised for their contribution to the study of epilepsy, its diagnosis, management and treatment by being awarded the 2014 Prime Minister's Prize for Science – Australia's most prestigious and highly regarded award for excellence in science.

In addition to gene discovery, our research focus will shift a little in the next five years to translation of our research to improving treatments and outcomes for people with epilepsy. Together with our collaborators at the Florey Institute for Neuroscience and Mental Health, the University of Adelaide and the Royal Melbourne Hospital, we have been awarded our fourth consecutive Program Grant from the National Health and Medical Research Council for five years beginning in 2016. This grant will aid us as we continue to search for genes that cause epilepsy and work out how genetic mutations cause seizures. We will also determine the different types of epilepsy associated with a specific gene and associated medical disorders such as autism spectrum disorder and intellectual disability. Our genetic discoveries will help provide answers for people with epilepsy and enable genetic counselling for patients and their families. This grant will also help us to continue our work with our physiology collaborators to develop new epilepsy treatments that target the specific problem produced by the genetic mutation.

During the past year we have welcomed some new members to our team. Dr Yu-Chi Liu, a bioinformatician who analyses the complex DNA sequencing data that we receive on individuals with epilepsy, will be working in close collaboration with our colleague Associate Professor Melanie Bahlo at the Walter and Eliza Hall Institute. Six new research assistants have also joined the team – Georgie Hollingsworth, Caitlin Bennett, Esther Johns and Hannah Shilling in the clinical genetics team, Jordan Wilcox in the molecular genetics laboratory and Shannon Huskins in Hobart working on our study investigating the Infantile Epileptic Encephalopathies in Tasmania. Dr Ken Myers, a paediatric neurologist from Calgary in Canada, and Dr Dorien Weckhuysen, a neurologist from Belgium, have also joined us to work on our clinical research program.

The Epilepsy Research Centre and colleagues at the 2015 annual Epilepsy Research Retreat. Our moderator was Prof Emilio Perucca, President of the International League Against Epilepsy.

Prof Ingrid Scheffer and Prof Sam Berkovic receive the 2014 Prime Minister's Prize for Science from The Hon Ian Macfarlane MP and The Hon Tony Abbott MP

We are excited to bring you updates on our projects such as understanding how the gene *DEPDC5* causes epilepsy and investigating genes that may be associated with the tragic event known as Sudden Unexpected Death in Epilepsy. We are also working closely with large international collaborations to answer research questions in epilepsy genetics that cannot be tackled by individual research groups as large numbers of patients are needed to produce meaningful results.

The main focus of our research is the study of patients and their families with many different forms of epilepsy. We carefully compile detailed information about seizures and related conditions and obtain DNA for genetic analysis. This important collection of research information and DNA samples, provided by our generous research participants, is critical to improving our understanding of the genetic causes of epilepsy, how these genetic changes cause seizures, and ultimately to generate knowledge that will enable the development of targeted treatments that will improve outcomes for patients. We would like to thank all our research participants (now more than 16,000 people!), referring doctors and other supporters for your fantastic contributions in helping us understand this complex and fascinating field.

New insights into how the *DEPDC5* gene causes focal epilepsy

Focal seizures begin in one part of the brain, and in the past were considered to be caused by a brain injury or tumour. Our research over many years has pioneered understanding that rare forms of focal epilepsy can be inherited, leading to the discovery of several genes for focal epilepsy. These genes have only accounted for a very small proportion of the patients with focal epilepsy in the community.

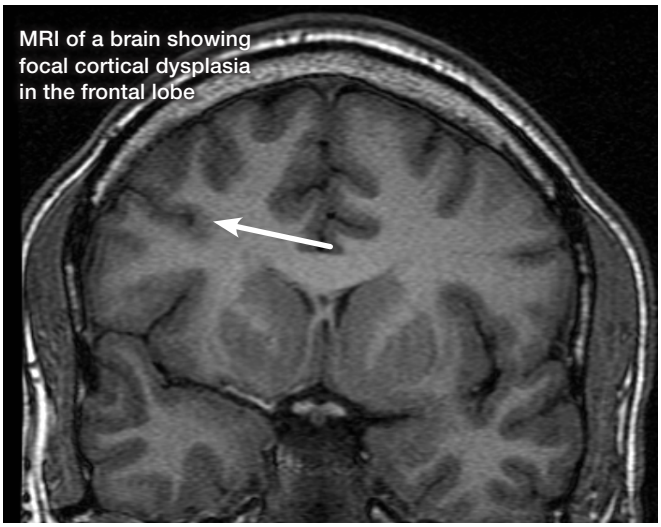
Last year we shared our discovery of the most common gene known to date for focal epilepsy with *normal* brain imaging – *DEPDC5*. We showed that *DEPDC5* mutations were found in more than 10% of small families with two or more individuals with focal epilepsy with normal brain imaging. At that time, little was known about how *DEPDC5* caused focal epilepsy.

More recently, we discovered a *DEPDC5* mutation in a family with focal epilepsy in which some family members had normal brain MR imaging and some had *abnormal* imaging. Two individuals in this family had a subtle type of malformation of the brain called 'focal cortical dysplasia'. This refers to an area of the brain where the brain has not formed properly as the nerve cells have not migrated to the right region of the brain during brain development, when the baby was in the mother's womb. This abnormal area results in abnormal brain networks, which lead to seizures.

By carefully reviewing the MRI brain scans of our participants with *DEPDC5* mutations to look more closely for focal cortical dysplasia, we identified more individuals with subtle malformations. This shows that *DEPDC5* mutations can be associated with both normal brain imaging and also brain imaging with malformations.

DEPDC5 is normally involved in stopping uncontrolled growth of brain cells through an important pathway called the 'mTOR pathway'. Other genes in the same pathway cause another condition, tuberous sclerosis which is an inherited disorder causing seizures, intellectual disability and autism spectrum disorder. Mutations in *DEPDC5* prevent the gene from functioning as the "stop light", therefore leading to too much cell growth in areas of the brain during development.

This research shows that focal epilepsy caused by *DEPDC5* is biologically similar to tuberous sclerosis and that understanding the mTOR pathway may help us to discover other genes causing common focal epilepsy and malformations. It also opens the door to new therapeutic approaches.



MRI of a brain showing focal cortical dysplasia in the frontal lobe

Medicinal cannabis for epilepsy

You cannot have missed the media attention devoted to medicinal cannabis as a treatment for epilepsy, particularly for children with severe childhood epilepsies such as Dravet syndrome. Newspapers declare that medicinal cannabis may be the panacea for many ills from nausea associated with chemotherapy to pain control to uncontrolled epilepsy. Families in the media have accessed a range of cannabis-related products from growers within Australia and companies further afield. These products vary greatly in the nature and purity of the compounds as there are many components within a cannabis plant ranging from many different cannabidiols to the THC (tetrahydrocannabinol) component which is the psychoactive constituent associated with the feeling of 'being high'. In Australia at present there is no access to pure cannabidiol made at pharmaceutical grade level where one is assured that each dose is accurate and the compound comprises exactly what it states on the label. While some families report promising benefits in their children with epilepsy, the media reports are biased to those in whom the cannabis has had a positive effect as the many families who have tried cannabis without success do not usually seek media attention. This is partly because cannabis has been an illegal substance in Australia but the laws are being changed to allow access to the group of cannabidiol drugs.

What is desperately needed for people with epilepsy is definite evidence that medicinal cannabis can improve seizure control. The good news is that large scale studies are underway in different regions of the world. One large European-US study is focused on Dravet syndrome while others are for severe childhood epilepsies. These include well designed randomized double-blind placebo-controlled trials in which patients receive cannabidiol or placebo medication in which there is no active ingredient. Neither the doctor, the patient nor their family know who is receiving the drug or the non-active placebo. The seizures and side effects are then carefully monitored. Once recruitment is completed, the "blind" is broken and the data are analysed to see if there is objective evidence that medicinal cannabis has improved seizure control. Once these results are to hand, we will know how effective cannabis is and which patients are most likely to benefit from it. Cannabidiol trials are likely to start in Victoria in the very near future.

New gene for epilepsy with myoclonic-atonic seizures

Together with Dr Heather Mefford's research group at the University of Washington in Seattle, we have discovered a new gene for the syndrome of epilepsy with myoclonic-atonic seizures, described by Doose in 1970. This gene is called *SLC6A1* and it encodes a protein that prevents the brain from having too many electrical discharges by helping an important chemical called GABA to be taken up into the nerve cells of the brain. Children with *SLC6A1* abnormalities have many types of seizures and intellectual disability, with some having autistic features. This work was published in the *American Journal of Human Genetics* recently.

Epi4K: gene discovery in 4000 genomes

Epi4K is a large, international collaboration investigating the genetic basis of epilepsy. In this project 4000 people with epilepsy are having their DNA studied using the most modern genetic technologies to identify genes that cause epilepsy. We will also look for genetic factors that influence how different people respond to different treatments. The Epi4K project includes participants from a study called the Epilepsy Phenome Genome Project (EPGP), on which we previously collaborated. Over 2000 genomes have been analysed to date, and we are in the final stages of recruitment for the last phase of the study.

The Epi4K study of epileptic encephalopathies continues to be highly successful, with seven new genes causing this severe group of epilepsies identified. The second major focus of Epi4K is to study families in which three or more members have focal or generalized epilepsies. Over 300 families have been studied and their DNA collected for analysis. The majority of these families are Australian, with others from Israel, New Zealand, Canada, USA, Ireland and Wales. As well as studying these families to identify new genes that increase the risk of epilepsy, the clinical data will be carefully analyzed to improve our understanding of familial epilepsy syndromes.

Sudden Unexpected Death in Epilepsy

Rarely and tragically, some people with epilepsy die unexpectedly. This is known as Sudden Unexpected Death in Epilepsy (SUDEP). The causes of SUDEP are not yet understood. Recently a study showed that some people who die of SUDEP may have a problem with the control of their breathing at the end of a seizure, which leads to their death.

Congenital central hypoventilation syndrome is a rare genetic disorder in which brain cells that activate breathing muscles fail to develop normally. People with this condition breathe too little, particularly during sleep. Congenital central hypoventilation syndrome is caused by mutations in the gene *PHOX2B*. We explored whether mild mutations (or variants) in *PHOX2B* affect breathing after seizures and so contribute to an increased risk of SUDEP. Together with cardiologist, Professor Chris Semsarian, and geneticist, Dr Richard Bagnall, from the Centenary Institute in Sydney, we sequenced the *PHOX2B* gene in 68 people who have died from SUDEP but did not find any significant changes. This suggests that *PHOX2B* mutations are not a common risk factor for SUDEP.

This project forms part of our continuing studies investigating the causes of SUDEP. We are investigating clinical features that put people at risk of SUDEP and working closely with our collaborators at the Centenary Institute to search for genes that might be involved in SUDEP. We hope to gain a better understanding of the causes of SUDEP, so that we can work towards prevention. If you are interested in learning more about this study, please contact our team on 9035 7075 or at epilepsy-austin@unimelb.edu.au

> ***"We hope to gain a better understanding of the causes of SUDEP, so that we can work towards prevention."***

Donations

We are always in need of support to take our research forward. Donations can be made via direct bank transfer and cheque.

- **Cheques** made payable to the ***Florey Institute of Neuroscience and Mental Health***.
- Complete your contact details below and return this slip with your cheque to:
  Epilepsy Research Centre, Lvl 2 Melbourne Brain Centre
  245 Burgundy St, Heidelberg VIC 3084
- For details on **direct bank transfer**, please contact Lorraine Green on (03) 9035 7096 or grel@unimelb.edu.au.

We greatly appreciate all the assistance we receive from our supporters.

Please find enclosed a cheque for my tax-deductible donation of $ .....

Name ..... Phone .....

Address .....

Understanding the genetic basis of common epilepsies

Identifying the variants within genes that increase an individual's risk of having the common generalized and focal epilepsies has been challenging and not very successful, despite many research groups around the world trying to discover genes that put us at higher risk. The main reason for this is that these studies need many thousands of participants to be able to understand what is normal genetic variation and what variation might make it more likely that a person will have epilepsy. It is virtually impossible for any single research group to have enough people enrolled in their research to be able to answer these questions on their own.

In a large, international collaborative research study, we have started to solve this problem by combining data from many groups. Data was combined from researchers in the United Kingdom, Europe, North America, Hong Kong and Australia to perform what is known as a meta-genome-wide association study. Samples from over 34,000 people, of whom more than 8,000 had epilepsy, contributed to this research.

The study was successful in identifying two genes that are strongly associated with epilepsy. One, the gene encoding the sodium channel alpha 1 subunit (*SCN1A*), is known for familial epilepsies and severe childhood epilepsies including Dravet syndrome; this finding suggests that *SCN1A* plays an even broader role in epilepsy. Another gene that was also strongly associated with epilepsy is a member of the protocadherin family of proteins (*PCDH7*), which help cells bind together. When the data was subdivided into specific types of epilepsy, we found that other genetic risk factors may be associated with specific types of epilepsy, such as variants in the genes *VRK2* or *FANCL* in the generalized epilepsies.

Overall this study has emphasized the complexity of the genetics of epilepsy and the importance of international collaboration to understand the many genes that contribute to epilepsy. Prof Sam Berkovic led this major effort as Chair of the International League Against Epilepsy (ILAE) Consortium on Complex Epilepsies.

> ***"Overall this study has emphasized the complexity of the genetics of epilepsy and the importance of international collaboration to understand the many genes that contribute to epilepsy."***

CHD2 encephalopathy

Last year we discovered that the gene *CHD2* was a cause of the epileptic encephalopathies. Epileptic encephalopathies are severe epilepsies in which infants or children have multiple different types of seizures that are difficult to control along with slowing in development or loss of skills and very frequent epileptic activity on their EEG (brainwave tracing).

More recently, we have studied in depth the clinical features of children with *CHD2* encephalopathy. Our aim was to identify features that might help doctors to make a diagnosis in similar patients. We studied 10 patients and all had myoclonic seizures as part of their disorder. Seizures began between 1 year and 3½ years of age, often with an explosive onset of multiple types of seizures. Our patients had many other seizure types, including one we described as a complex atonic-myoclonic-absence seizure. In these seizures, patients would suddenly crumple to the ground or drop their head and their arms would then jerk away from their body a few times. Patients were not aware during these seizures which lasted for only 2 to 8 seconds.

All individuals had intellectual disability, which varied in severity, and was more severe with earlier onset of seizures. Most of the patients were also photosensitive and some liked to put their face in front of the television screen to induce a seizure.

We hope that describing the clinical features of this disease will mean that children with a similar clinical picture will receive a diagnosis earlier and that it will help doctors and families understand more about their child's condition and which treatments help. Further research is needed to assist in the development of therapies specifically for *CHD2* encephalopathy.

For further information

Please do not hesitate to contact us at any time if you have questions about our research. Thank you again for your participation and support.

In order to assist us with keeping in touch with you, if you change your address we would be very grateful if you could advise us of your new contact details (see attached sheet). If you do not wish to receive future editions of this newsletter, please fill in the check box on the attached contact sheet along with your name and address and return it to us, or email us at *epilepsy-austin@unimelb.edu.au*

We continue to be at the forefront of Epilepsy Genetics Research. Our website, ***www.epilepsyresearch.org.au***, provides a range of information about the Epilepsy Research Centre, our research projects and also information for epilepsy patients interested in seeking treatment through the Comprehensive Epilepsy Program at Austin Health. Past issues of our newsletters and links to other useful sites can also be found. If you would like to contact us with any specific queries about our research, please do so via email at ***epilepsy-austin@unimelb.edu.au***

Participants at the Fourth Australian and New Zealand Dravet Family Conference

Dravet syndrome: new discoveries and 4th Family Conference

Our research program in Dravet syndrome continues apace. Dravet syndrome is due to a new abnormality in *SCN1A* in 80% of patients. Together with Dr Mefford's research group in the US, we recently published in *Neurology* that Dravet syndrome can be caused by mutations in genes other than *SCN1A* in rare patients. These genes include *GABRA1* which encodes a GABA receptor subunit and *STXBP1* which is also associated with a more severe epileptic encephalopathy. These mutations were new in the child and not present in either parent.

Together with our physiology collaborators, Associate Professor Chris Reid and Professor Steve Petrou, we published a genetic mouse with a presentation resembling Dravet syndrome in the journal *Brain*. This mouse will serve as a model to understand what is going wrong in patients with Dravet syndrome.

In August 2014, the Epilepsy Research Centre together with the Epilepsy Foundation of Victoria hosted the fourth Australian and New Zealand Dravet Family Conference at the Melbourne Brain Centre in Parkville. Over 150 parents, relatives and carers of children and adults with Dravet syndrome attended from around Australia and were treated to presentations by specialists in the care and management of this devastating condition. Speakers from the fields of neurology, paediatrics, physiotherapy, gynaecology, psychology, neuropsychology, education, research and peer support presented inspiring and informative talks. Many topics were covered, from "What is Dravet syndrome?" to medication choices, gait and mobility issues, challenging behaviours, educational avenues, the National Disability Insurance Scheme and the experiences of parents and support groups. A family dinner and zoo visit the next day also provided a great opportunity to catch up with friends and share experiences.


Sarah Beck, a participant in our Dravet syndrome research studies, competes in an equestrian event

A new genetic cause for a progressive form of myoclonic epilepsy

The Progressive Myoclonus Epilepsies (PME) are a rare group of epilepsies. The core symptoms include myoclonic seizures (sudden jerks), tonic-clonic seizures and ataxia (unsteadiness), which gradually worsen over time. There are many different types of PME that vary in age of onset and severity, and they are largely regarded as genetic disorders. The PME typically begin in late childhood or early adolescence. Many genes have been identified for different PME, but a significant proportion of cases remains unsolved.

In collaboration with researchers at the University of Helsinki and the University of South Australia, we aimed to identify the genetic cause in 84 people with unsolved PME using modern DNA sequencing technology called Whole Exome Sequencing (WES).

The most important finding of our study was that the same mutation in a gene encoding a potassium channel called *KCNC1* was found in 13 patients. We determined that the mutation was a new (*de novo*) mutation in each patient, as it was not inherited from either parent. This mutation disrupts the function of a potassium channel, Kv3.1, which plays a central role in electrical transmission in the brain.

Other patients had abnormalities in genes known to cause PME or other neurological conditions. Overall, we found the genetic cause in almost one third of patients. These findings shed important light on the genetic basis of PME and will improve diagnosis and open up avenues for new targeted treatments for these severe disorders.

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Thank you

We would like to thank everyone who has contributed to our research by participating in the research studies, referring patients and families, or making donations to support our research. We have been especially delighted when the families who have participated in our studies have sent donations. This reinforces that our families, as well as the researchers, value our work.