EPILEPSY RESEARCH CENTRE NEWSLETTER 2013-2014

HIGHLIGHTS

Genes found for focal epilepsy

Epileptic Encephalopathies

Epi4K: gene discovery in 4000 genomes

Professor Samuel Berkovic
Neurologist

Professor Ingrid Scheffer
Paediatric Neurologist

Research recognized with top honors

The high quality of the research conducted by the Epilepsy Research Centre continues to receive recognition from the scientific community, as well as local and international organizations. This is reflected by several high impact publications in the most prestigious scientific journals including *Nature* and *Nature Genetics* during 2013.

Prof Sam Berkovic has recently been awarded the highest possible honour in the Australian honour system, receiving the Companion of the Order of Australia (AC), on Australia Day 2014. This is a rare and singular award in recognition of his exceptional contribution to the field of epilepsy.

Prof Ingrid Scheffer has been honoured with the GlaxoSmithKline Award for Research Excellence, the Ambassador for Epilepsy Award from the International League Against Epilepsy for outstanding international contribution to epilepsy, and the Emil Becker Prize for outstanding contribution to paediatric neurology from Gesellschaft Neuropädiatrie, the German speaking society for neuropaediatrics.

During the past year we welcomed international researchers visiting our group including Dr Linmei Zhang, a paediatric neurologist from Shanghai, China, Dr Rhys Thomas, a lecturer in adult neurology from Wales, UK, and Prof Eliane Roulet Perez, Director of Paediatric Neurology from Lausanne, Switzerland. Four new research assistants have joined us - Elisa Cops, Amy Schneider and Sarah Garry in Melbourne and Emily Mountier in Wellington, New Zealand. We were sad to see Sinéad Heavin return to Ireland and Viger Yang (New Zealand) moved on to other roles. Dr Hans Henrik Dahl, who played a key role in establishing our molecular genetics laboratory at Austin Health, is now enjoying his well-earned retirement. We thank him for this hard work and significant contribution.

The landscape of genetic research has changed rapidly as advances in technology open up areas of investigation that we could only dream about a few years ago. While we must constantly adapt to these changes, we are very fortunate to work with many talented researchers both within Australia and around the world who help us to expand our understanding of the genetic basis of epilepsy. A major recent highlight has been our discovery, together with colleagues at the University of South Australia, that a new gene, *DEPDC5*, causes focal epilepsy. It is the first gene for the more common group of focal epilepsies. Together with Heather Mefford's group in Seattle, US, we are finding new genes for the severe epilepsies of childhood. Meanwhile, we are working with a large international epilepsy research collaboration called Epi4K funded by the National Institutes of Health in the US. Epi4K aims to use the latest genetic sequencing technology to look for mutations causing epilepsy in 4000 individuals.

Our main focus is the study of patients and their families with many different forms of epilepsy. We carefully compile detailed information about seizures (including EEG and MRI) 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 better targeted treatments.

EPILEPSY RESEARCH CENTRE
Melbourne, Australia

EPILEPSY RESEARCH CENTRE
Austin Health
Melbourne Brain Centre
245 Burgundy Street
Heidelberg, Victoria, 3084
P: +61 3 9035 7344/7330
F: +61 3 9035 7307
E: epilepsy-austin@unimelb.edu.au
W: www.epilepsyresearch.org.au

Austin Health

THE UNIVERSITY OF MELBOURNE

THE FLOREY

The Epilepsy Research Centre and our collaborators at the 2013 Epilepsy Research Retreat. Our moderator was Professor Peter Crino, Temple University, Philadelphia, USA and special guest Professor David Goldstein from the Duke Center for Human Genome Variation.

Finding the genetic cause of focal epilepsy

Familial focal epilepsy with variable foci (FFEVF) is a rare autosomal dominant epilepsy syndrome first described by our group in 1998 in a large Australian family. FFEVF describes a monogenic form of epilepsy in which individuals in the same family have focal epilepsy arising from different regions of the brain. Seven additional large families have been subsequently described around the world including our work with a second large Australian family.

Using a technique called Whole Exome Sequencing (WES) with our collaborators, we showed that FFEVF is caused by mutations in a gene called *DEPDC5*. Of the eight families with FFEVF, seven have mutations in *DEPDC5*, essentially solving the quest for the genetic cause of FFEVF. Even more excitingly, we went on to study small families in which 2 or more individuals had focal epilepsy and found mutations in 10 of 84 families (12%). This means that *DEPDC5* is the first gene for the large group of patients without a strong family history of epilepsy.

DEPDC5 is currently the most common known genetic cause of focal epilepsy which accounts for 60% of all epilepsies. Focal seizures come from one part of the brain. In some people they can be the result of a structural abnormality such as a brain injury or tumour. In the families with *DEPDC5* mutation, individuals with epilepsy had normal brain imaging. We are now extending our studies to see whether mutations in *DEPDC5* are associated with structural malformations of the brain.

When we discovered *DEPDC5*, its function was unknown, but science can work in remarkable ways. Contemporaneously, a basic science group in Boston found that *DEPDC5* regulates a pathway essential for cell growth (the 'mTOR pathway'). This pathway is also regulated by genes that cause tuberous sclerosis, a well known inherited disorder causing seizures. The link between focal epilepsy and *DEPDC5* was a surprise; it provides a major advance in understanding focal epilepsy.

This discovery promises to change clinical practice as a genetic cause can now be tested for in patients with focal epilepsy. In cases where a mutation is found, other investigations may be avoided, accurate genetic counselling can be offered and, in the future, specific treatments will hopefully be developed. Moreover, drugs that influence the mTOR pathway are already known, providing potential new avenues for treatment.

A new gene for Autosomal Dominant Nocturnal Frontal Lobe Epilepsy

In 1995 our group identified the first epilepsy gene. This discovery was made in a large Australian family with a rare epilepsy syndrome which we described called Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE). We found a mutation in the *CHRNA4* gene which encodes an acetylcholine receptor subunit, part of a gateway through which ions (charged particles) pass into the cell. Nocturnal frontal lobe seizures are very striking seizures that occur abruptly from sleep with screaming, violent thrashing movements of the arms and legs, sometimes accompanied by a feeling of choking.

Since 1995 we, and other research groups, have continued to look for genes that cause ADNFLE. There are now three known genes for ADNFLE which all encode different subunits that make up the acetylcholine receptor.

Together with our gene finding scientists, we recently discovered a new ADNFLE gene called *KCNT1* in an Australian family. *KCNT1* encodes a different type of ion channel gateway called a potassium channel. We went on to identify *KCNT1* mutations in three additional ADNFLE families from Australia, Israel and Italy. We found that the people with *KCNT1* mutations had more severe epilepsy than in other families with ADNFLE and some also had intellectual and psychiatric problems. Our collaborating physiology scientists at the Florey Institute of Neuroscience and Mental Health are conducting experiments to determine how and why *KCNT1* mutations cause ADNFLE.

Epileptic Encephalopathies: Finding the cause

One of our major areas of interest over recent years has been identifying the genes involved in causing epileptic encephalopathies. Epileptic encephalopathies are rare severe disorders in which infants or children have multiple different types of seizures that are extremely difficult to control. They are usually accompanied by slowing in development, sometimes with loss of skills. Often there is no family history of epilepsy and no cause has been found.

We have been working with research collaborators in America who have developed a rapid and inexpensive method to look for changes in many genes at once. In 2013, we published a large study in *Nature Genetics* looking for the cause in 500 children with epileptic encephalopathies. We studied each child's DNA looking for changes in 19 known epilepsy genes and 46 genes that we considered potential epilepsy genes. We found the genetic cause in 52 patients. While some changes were found in known epilepsy genes, 15 patients had mutations in new genes including *CHD2* and *SYNGAP1*, each accounting for 1% of patients. These genes will be important new causes of epileptic encephalopathies.

Knowing the genetic cause of epileptic encephalopathies is of critical importance for patients and their families. It often guides which antiepileptic therapies are likely to work and which may make seizures worse, thereby influencing long term outcome. It may provide information about prognosis and enables genetic counseling for future pregnancies. More answers regarding the causes and therapies for epileptic encephalopathies will emerge with our ongoing work and the wonderful and committed help we receive from our patients and their families.

Abbi and her family very kindly starred in an episode of ABC's 7:30 report by Lisa Whitehead, highlighting the positive impact this research has had on epilepsy diagnosis and genetic counseling.

How many patients have epileptic encephalopathies in Tasmania and Victoria?

Together with neurologists and paediatricians in Hobart, and paediatric neurologists at the Royal Children's Hospital in Melbourne, we would like to identify all children in Victoria and Tasmania who develop an epileptic encephalopathy between 2011 and 2015. By collecting information about all children with these conditions in a specific population, we hope to develop a better understanding of how many children are affected, exactly what type of epileptic encephalopathy they have and how often a specific gene is causative.

We believe that this research will lead to faster testing and diagnosis for children with epileptic encephalopathies and will also provide information that will help organizations in Victoria, Tasmania and more globally provide appropriate health care and other support for these children and their families.

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.

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**.

Sudden Unexpected Death in Epilepsy (SUDEP) study

People with epilepsy almost always make a full recovery within minutes or hours of their seizures. Sometimes injuries can happen, or urgent medical treatment may be needed because seizures or seizure clusters are prolonged (status epilepticus). Very rarely, people with epilepsy can have a seizure (usually a convulsion) and die soon after. This tragic event is known as Sudden Unexpected Death in Epilepsy (SUDEP). Optimal treatment of epilepsy (so that seizures are prevented, or seizure frequency is minimised) is vital to minimize the risk of SUDEP.

In order to work towards preventing SUDEP, we need better understanding of how and why it happens. Together with Prof Chris Semsarian, cardiologist, and Dr Richard Bagnall, genetic scientist, from the Centenary Institute in Sydney, we are searching for genes that cause SUDEP by looking for gene changes in people who have died of SUDEP. We are also meeting the close relatives of people who have died of SUDEP, as studying the wider family may give additional useful information about the causes of SUDEP. With the wonderful support of caring families, we hope to make vital discoveries about the causes of SUDEP. If you are interested in learning more about this study, please contact our team on (03) 9035 7012 or epilepsy-austin@unimelb.edu.au

> ***"In order to work towards preventing SUDEP, we need better understanding of how and why it happens"***

Epi4K: gene discovery in 4000 genomes

Epi4K is a large, international collaboration aiming to identify genes causing epilepsy. In this project 4000 people with epilepsy will have their DNA studied using the most modern genetic technologies to look for mutations that increase the risk of developing epilepsy. Epi4K follows on from a project we have written about previously called the Epilepsy Phenome Genome Project (EPGP).

Over the last year the recruitment of participants for EPGP ended and the next phase of the collaboration began. The Epi4K project includes EPGP participants, as well as many families we have studied over the years in which at least three people have generalised or focal epilepsy.

The first stage of Epi4K has been a great success with our exciting results recently published in Nature, the top-ranking scientific journal. The first group of patients to be studied were those with the epileptic encephalopathies of Lennox-Gastaut syndrome and Infantile Spasms. We discovered two new epilepsy genes and identified the genetic cause in about 10% of those patients. As we expected, the genetic changes found were new in the patient and were not inherited from their mother or father.

The analysis of the second major Epi4K project, consisting of the genetic testing of brother-sister pairs, parent-child pairs and families is well underway. We have had a major role in the US based study and look forward to sharing the results with you in our next newsletter.

Donations

We are always in need of support to take our research forward. Donations can be made via direct bank transfer and cheque. To **make a donation via cheque** please complete your contact details and return with your cheque to us at the address below. Cheques should be made payable to **The Florey Institute of Neuroscience and Mental Health**.

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

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

Address .....

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

Please return cheque to:

EPILEPSY RESEARCH CENTRE
Epilepsy Research Centre, Level 2 Melbourne Brain Centre,
245 Burgundy Street, Heidelberg Vic 3084
P: (03) 9035 7344 or (03) 9035 7330 F: (03) 9035 7307

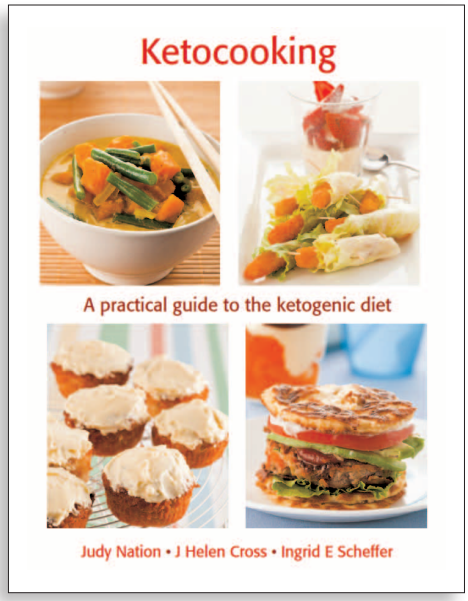
For further details on **direct bank transfer**, please contact:

Lorraine Green
P: (03) 9035 7096
F: (03) 9496 4183
E: grel@unimelb.edu.au

GLUT1 Translational Service

Several years ago we recognised that mutations in the GLUT1 gene that makes the glucose transporter 1 protein cause various forms of genetic generalised epilepsy. GLUT1 is responsible for getting glucose, the major form of energy, into cells in the brain. GLUT1 mutations have been seen in 5% of patients with early-onset absence epilepsy (beginning under 4 years) and 10% of patients with the syndrome of epilepsy with myoclonic atonic seizures described by Doose. Based on these findings our Translational Neurogenetics Laboratory at the Epilepsy Research Centre has established a commercial service to screen the GLUT1 gene in appropriate patients. Importantly, the ketogenic diet is the first choice of treatment for patients with GLUT1 mutations.

"the ketogenic diet is the first choice of treatment for patients with GLUT1 mutations"



Ketocooking is a beautiful and practical guide for those who want inspiration and guidance when providing a ketogenic diet in combination with support from the medical team.

Fainting in twins

Twins play an important role in understanding genetic and environmental factors involved in the development of different conditions

Approximately 25% of the population faint at some time in their life, but the causes of fainting, or syncope, are not well understood. More information about the genetic and environmental causes is needed to improve diagnosis and treatment options for people who have frequent fainting attacks. We conducted a study of twins where at least one twin had a history of fainting. Twins were questioned about their fainting spells, including what triggers these events and whether there is any family history of note.

Our study found that both twins in identical twin pairs fainted more often than both twins in non-identical twin pairs. The frequency of fainting in other family members was low, indicating that while fainting does appear to have a strong genetic component there may be multiple genes, and potentially environmental factors, that influence the condition.

Ethical Considerations

The conduct of our research is over-seen by Human Research Ethics Committees. Study participants are asked to allow the indefinite use of their DNA sample for our research. People who were enrolled as children may be asked to give their own consent when they reach 18 years of age provided we are able to contact them. If you have any concerns about us contacting your child when they turn 18, please contact us so we can discuss this with you. If you have recently turned 18 and have not heard from us, please complete the change of address form or email us at epilepsy-austin@unimelb.edu.au to check we have your current details. Participants are free to withdraw from the study at any time.

If we obtain a positive result on your sample or in your family, we will send you a letter stating that we have obtained a result. If you would like further information about this, we will be happy to provide it after you contact us to discuss the result.

All information collected for our research is strictly confidential and is not used for any purpose other than for research to understand epilepsy and related conditions. In particular we do not share any of your information with other members of your family, including any results. Information will be shared with parents of children in the study if they are under 18 years of age. Some information may be shared with collaborating scientists to identify or better understand epilepsy genes.

Our team

Prof Sam Berkovic
03 9035 7093

Prof Ingrid Scheffer
03 9035 7112

Dr Saul Mullen
03 9035 7137

A/Prof Doug Crompton
03 9035 7090

Prof Eliane Roulet Perez
Visiting Fellow

Dr Patrick Carney
03 9035 7115

Karen Oliver
03 9035 7075

Brigid Regan
03 9035 7012

Bronwyn Grinton
03 9035 7013

Jacinta McMahon
03 9035 7062

Susannah Bellows
03 9035 7145

Kate Lawrence
03 9035 7078

Rosie Burgess
03 9035 4199

Elisa Cops
03 9035 7328

Amy Schneider
03 9035 7349

Sarah Garry
03 9035 7293

Lisa Johnson
03 9035 7093/7330
PA: Sam Berkovic

Natalie Bryant
03 9035 7112/7344
PA: Ingrid Scheffer

Jana Vukcevic
03 9035 7112/7344
PA: Ingrid Scheffer

Dr Michael Hildebrand
03 9035 7143

John Damiano
03 9035 7070

Elena Aleksoska
03 9035 7034

Dr Lynette Sadleir
+64 4 918 6138

Emily Mountier
+64 4 918 6292

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 the fact that our families, as well as the researchers, value our work.

If you would like to assist our important research to help us understand epilepsy, you can make a donation to the Epilepsy Research Centre. Please contact Lorraine Green on 9035 7096, by email grel@unimelb.edu.au or epilepsy-austin@unimelb.edu.au, or complete the section on the back of this page.