EPILEPSY RESEARCH CENTRE NEWSLETTER 2011

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- Glucose Transporter 1 Deficiency
- Special Insights from Twins
- Temporal Lobe Epilepsy

Professor Samuel Berkovic
Neurologist

Professor Ingrid Scheffer
Paediatric Neurologist

We are excited to be writing to you from our new purpose-built research facility, the Melbourne Brain Centre, a collaboration between the University of Melbourne, the Florey Neuroscience Institutes, and Austin Health. This is the first stage of a twin facility being built for researchers, with the second campus located at Parkville. The new Melbourne Brain Centre is the largest brain research centre in the Southern Hemisphere and will help treat and prevent brain disorders that affect millions of people suffering from conditions such as epilepsy, stroke, and other neurological and psychiatric disorders. It encompasses the Epilepsy Research Centre, the Brain Research Institute and the National Stroke Research Institute. The Melbourne Brain Centre at the Austin Hospital includes laboratories, two MRI machines, research clinic rooms and offices. Please note our change of address and contact details below.

The Epilepsy Research Centre, together with our collaborators in Adelaide and at the Florey Neuroscience Institutes, has again been recognised as a world leader in the field of epilepsy genetics research, being awarded our third consecutive Program Grant from the National Health and Medical Research Council (NHMRC). This grant will aid us as we search for genes associated with epilepsy, how they are inherited and how genetic variations actually cause seizures. However, our research would not be possible without the involvement of our 14,500 research participants and family members as well as their referring doctors. We would like to take this opportunity to thank you all for the time and effort you contribute to our research. Without your assistance, we would not be able to keep striving towards our goal of understanding the mechanisms that cause epilepsy, which will hopefully lead to improvements in the treatment and the lives of people with seizures.

Our team has grown with Dr Henrik Dahl, molecular geneticist, bringing 30 years experience to lead our molecular laboratory on the Austin Campus. We have been fortunate to have talented young neurologists from other countries join our team. They include paediatric neurologists Dr Young-Ok Kim from Korea for 18 months, Dr Mel Villaluz from the Phillipines for 12 months and Dr Utcharee Intusoma from Thailand for 10 months. Adult neurologist Dr Lysa Boissé from Canada has joined us for two years. We have welcomed two new research assistants: Sinéad Heavin and Rosie Burgess, and bid farewell to Tarishi Desai and Lexie Slingerland. Alexandra Sandow, who joined us as a research assistant in 2007 moved to Texas, but fortunately continues to work with us remotely.

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Austin Health

THE UNIVERSITY OF MELBOURNE

Florey Neuroscience Institutes

The 2nd Australian and New Zealand Dravet Family Conference, March 2011.

On 19 March 2011 the second Australian and New Zealand Dravet Family Conference was held at the Royal Children's Hospital. Professor Ingrid Scheffer organized the program together with Jean Ewing, Epilepsy Foundation of Victoria, and an incredible group of Dravet family parents led by Tom Philbin and Sam Jackson. A number of parents shared their stories, and other speakers included Judy Nation, Ketogenic dietician; Dr Sian Hughes, Developmental Paediatrician; Helen McCoy, Principal of Monash SDS; Helen Hatherly, Principal of Ashwood SDS and President of the Specialist Schools Principals Association; Kathryn McEvoy and Jean Ewing. We were also joined by Dr Angela Black, Co-Chair of the International Medical Advisory Board of Dravet.org (formerly IDEA-League).

When identical twins are not quite identical

Each of us contains new genetic changes not found in our parents. These contribute to making each of us unique. In some cases, the genes that change may create a significant abnormality that causes a disease. Identical twins are usually genetically identical so that if one has a genetic disorder, the other twin will also have it.

We have spent the last twelve years studying Dravet syndrome, a severe infantile-onset epilepsy syndrome caused by abnormalities (mutations) of a sodium channel subunit gene *SCN1A*. 90% of these mutations are not inherited from either parent but are new, or *de novo*, in the affected person. We have studied three sets of identical twins with Dravet syndrome. In two pairs, both twins had the disorder as would be expected. However, the third pair was quite remarkable as only one twin had Dravet syndrome. We tested both twins for an *SCN1A* mutation and found that the affected twin had a severe *SCN1A* mutation while her unaffected co-twin did not.

We then looked at different cell lines such as blood, hair, skin and nerve cells (taken by a biopsy from the nose) from both twins to see if we could determine when the mutation occurred in terms of embryonic development. We showed that the *SCN1A* mutation was present in all cell lines of the twin with Dravet syndrome and not present in any of the cell lines in the unaffected co-twin even at minute levels.

For this to be the case, the *SCN1A* mutation must have occurred at the time of twinning when the embryo split into two embryos. This is the first time that a disease-causing genetic change has been proven to occur after twinning creating "not quite identical identical-twins". This novel biological insight was recently published in the *New England Journal of Medicine*, the highest impact medical journal.

We were delighted that our twin with Dravet syndrome was able to speak at the Second Australian and New Zealand Dravet Family Conference. She spoke to more than 120 people about her life experience and she was clearly the highlight of the meeting. This was a great opportunity for families to meet and support each other whilst learning more about their child's condition and the many new developments in the field.

Professor Scheffer and twins

Continuing success in solving the Progressive Myoclonus Epilepsies

The Progressive Myoclonus Epilepsies (PMEs) are a group of rare epilepsy syndromes where patients develop myoclonus (jerks) that progressively worsens over time. Patients also have convulsive seizures and, depending on the type of PME, can experience unsteadiness (ataxia) and sometimes dementia. Although the genes causing many PMEs are known, there still remains a group of patients for whom no cause has been found. We have been involved in a large-scale international collaboration with researchers from Finland, Italy and Canada, to try and discover the remaining genes causing PME.

As we have previously reported, we identified a gene called *SCARB2* as the gene for a rare type of PME called Action Myoclonus-Renal Failure syndrome (AMRF), a condition which involves both epilepsy and kidney failure. This international collaboration allowed us to identify that *SCARB2* is also responsible for some cases of Progressive Myoclonus Epilepsy without kidney failure, expanding our knowledge about this gene.

Since then, we have also found a new gene that causes early onset ataxia, myoclonus and tonic-clonic seizures. This gene is called *GOSR2* and it is involved in the processing of proteins inside brain cells. This finding was recently published in the *American Journal of Human Genetics*. Another recent finding has been in a rare condition called Kufs disease where patients can initially have Progressive Myoclonus Epilepsy, often with deterioration in their memory and thinking abilities. We identified a gene called *CLN6* as a cause of Kufs disease. This is an important finding because this type of PME is very difficult to diagnose and this information will be helpful for genetic counselling purposes in these families.

This series of discoveries was made possible thanks to clever statistical strategies performed by Dr Melanie Bahlo and her team at the Walter and Eliza Hall Institute working together with our teams at the ERC and in Adelaide. These discoveries were enabled by the power of the Human Genome Project and novel gene technologies that we are now applying to commoner forms of epilepsy.

A distinctive seizure type in *CDKL5* encephalopathy

Abnormalities in the gene *CDKL5* affect girls who have a severe epilepsy (*CDKL5* encephalopathy) characterised by seizure onset before 3 months of age and significant developmental delay. Early recognition of this disorder is important as it determines the cause of the epilepsy, guides genetic counselling and may also avoid further investigations.

We recently identified a distinctive seizure sequence that was present in 4 out of 5 girls with *CDKL5* encephalopathy. The sequence begins with a hypermotor phase with rocking of the body and kicking of the legs. This is followed by a tonic phase when the body stiffens and then culminates in a prolonged series of spasms consisting of brief extension of the arms and/or legs that often continues for more than 15 minutes.

Our findings were published in the journal *Neurology*. We hope that the recognition of the hypermotor-tonic-spasms sequence will facilitate earlier diagnosis of *CDKL5* encephalopathy. Interestingly, we have already received feedback that many parents have recognised this seizure type in their children with *CDKL5* encephalopathy which confirms our observations.

Donations

To **make a donation** to support our research please complete your contact details and return with your cheque to us at the address below. Cheques should be made payable to the **Brain Research Institute**.

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 to: EPILEPSY RESEARCH CENTRE
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The Epilepsy Research Centre and our collaborators at the 2010 Epilepsy Research Retreat. Our moderator was Professor Anne Berg, Children's Memorial Hospital, Chicago, USA.

GLUT1-deficiency causes a wide range of epilepsies

GLUT1 deficiency, caused by mutations of the gene *SLC2A1*, has been increasingly recognised as an important cause of epilepsy. Glucose is the main source of energy for the brain. The protein GLUT1 is the glucose transporter that moves glucose from the blood to the brain. As the brain cannot use glucose if GLUT1 is not functioning, the brain is starved of energy. GLUT1 deficiency was initially described as a very severe disorder where lack of glucose caused failure of development, seizures and movement disorders. However, it is now clear that GLUT1 deficiency causes a broader range of epilepsies than previously thought.

Diagnosing GLUT1 deficiency is particularly important. Not only does it provide a clear cause for the epilepsy but also may significantly influence treatment choices. In particular, the ketogenic diet is effective in GLUT1 deficiency. The ketogenic diet is a treatment that has been used for severe childhood epilepsy in which almost all glucose or carbohydrates are removed from the diet. This causes a radical change in metabolism such that fats are broken down to produce ketone bodies as a source of energy for the brain, bypassing the need for glucose. How the ketogenic diet works for other epilepsies is debated.

GLUT1 deficiency appears particularly important as a cause of absence epilepsy. Together with collaborators in Belgium, we found that over 10% of children with early-onset absence epilepsy, where absence seizures start under 4 years of age, have GLUT1 deficiency. We have now studied the relatives of these children, who also carry the *SLC2A1* mutation causing GLUT1 deficiency, and we found that they have mainly absence epilepsy syndromes. Affected family members have onset of seizures from childhood to adult life. This means that GLUT1 deficiency is not only a common cause of early-onset absence epilepsy but also a cause of the common, classical idiopathic generalised epilepsies such as childhood absence epilepsy and juvenile absence epilepsy.

In addition to such relatively mild epilepsies, GLUT1 deficiency is also important in severe childhood epilepsies. In our study with Italian collaborators, we have recently shown that 5% of children with myoclonic-astatic epilepsy, a rare childhood epileptic encephalopathy, have *SLC2A1* mutations and thus GLUT1 deficiency. This is particularly important as early diagnosis and commencement of the ketogenic diet has the potential to both control seizures and possibly improve learning, thereby preventing intellectual difficulties.

Familial mesial temporal lobe epilepsy (FTLE): What do family studies tell us?

Temporal lobe epilepsy (TLE) is the most common focal epilepsy. TLE is often thought to be due to injury or other acquired causes such as scarring of the middle (mesial) part of the temporal lobe, known as hippocampal sclerosis. However, twin studies provide compelling evidence of a genetic basis for some forms of temporal lobe epilepsy. Several forms of familial temporal lobe epilepsy (FTLE) have been described including one form from the lateral part of the temporal lobe and a second form from the mesial part.

Lateral temporal lobe epilepsy, also known as Autosomal Dominant Epilepsy with Auditory Features, is a rare single gene disorder due to mutations in the gene *LGI1*. Despite mutations of *LGI1* accounting for 50% of families with lateral TLE, the genetic causes of the more common familial mesial temporal lobe epilepsy are not known.

Recently Dr Douglas Crompton studied 20 families in which two or more first degree relatives had FTLE. 51 individuals in 20 families had TLE which was usually mild and responsive to medication. Familial mesial temporal lobe epilepsy is a relatively benign epilepsy syndrome with adolescent or adult onset of temporal lobe seizures. These seizures are characterised by déjà vu, a dreamlike state, fear and nausea, seizures with or without altered awareness, and infrequent convulsions. No factors predisposing to brain injury, such as birth trauma or CNS infections, were present. Brain MRIs were usually normal and did not show hippocampal sclerosis.

Inheritance patterns of these 20 families, together with 19 other families we reported previously, including 100 individuals with TLE were analyzed. We found that FTLE is likely to be due to complex inheritance, where multiple genes are involved, possibly with an environmental contribution.

Ever wanted to visit the United States of America? A part of you just might be able to….

2010 was the first year of an exciting new international collaboration at the Epilepsy Research Centre. The Epilepsy Phenome/Genome Project (EPGP) is an United States National Institutes of Health funded project. The aim is to identify genes that may be causing epilepsy by studying patients where a genetic cause for their epilepsy is more likely.

The study is divided into two groups. The Trios group focuses on people with rare types of epilepsy such as Lennox-Gastaut syndrome, Infantile Spasms and brain malformations. To be eligible, the participant's parents must also be willing to be involved. The Sibling Pairs and Parent-Child Pairs group studies families with more common epilepsies. Two first-degree relatives (the patient and a sibling or parent) with epilepsy are required. There are various other eligibility criteria that each participant must meet before they can participate in the study.

Once we have determined their eligibility, participants are asked to provide a blood sample, which will be flown across the Pacific to the USA. So far 110 people have kindly participated. We are still very interested in including more people in this study so if you or someone you know may be interested in being involved please contact us. We look forward to hearing from you!

Trios Patient + Mum + Dad		
Lennox - Gastaut Syndrome	Infantile Spasms	Brain Malformations

Sibling Pairs & Parent-Child Pairs	
Idiopathic generalized epilepsy	Focal epilepsy
Childhood Absence Epilepsy Juvenile Absence Epilepsy Juvenile Myoclonic Epilepsy	Frontal Lobe Epilepsy Temporal Lobe Epilepsy Occipital Lobe Epilepsy

Ethical Considerations

The conduct of our research is over-seen by Human Research Ethics Committees. Study participants are asked to state how long they permit their DNA sample to be used for our research. In addition, people who were enrolled as children are asked to give their own consent when they reach 18 years of age. 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. Some information may be shared with collaborating scientists to identify or better understand epilepsy genes.

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 the process of 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 the field 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 the newsletter 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***

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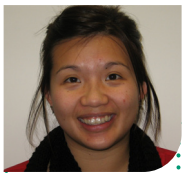

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Thank you

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 the fact that our families as well as the researchers value the significance of 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 us on 03 9035 7344 or 03 9035 7330, by email epilepsy-austin@unimelb.edu.au, or complete the section on the back of this page. Cheques should be made payable to the Brain Research Institute. Donations over $2 are tax deductible.