EPILEPSY RESEARCH CENTRE NEWSLETTER 2010

HIGHLIGHTS

- Epileptic Encephalopathies
- Absence Epilepsies
- Idiopathic Generalised Epilepsies
- Syncope
- Receiving Genetic Results

Professor Samuel Berkovic
Neurologist

Professor Ingrid Scheffer
Paediatric Neurologist

Welcome to the 2010 edition of the Epilepsy Genetics Newsletter. This year, the Epilepsy Research Centre celebrates its 21st birthday! Therefore, we would like to take this opportunity to express our gratitude to all of the 12,300 participants, referring clinicians and collaborators without whom our ongoing success would not be possible. The field of epilepsy genetic research is progressing rapidly and, as always, we are excited to share our latest discoveries with you.

The international professional body for epilepsy is called the International League Against Epilepsy. It has a range of commissions that cover important areas related to clinical and research practice in epilepsy at a global level. Prof Ingrid Scheffer has been appointed Chair of the Commission for Classification and Terminology for 2009-2013 and Prof Sam Berkovic is Chair of the Genetics Commission over the same period. It is most unusual for two chairs to be appointed from one centre so we are very excited by the opportunities this provides at an international level to help people with epilepsy.

The ERC has had a very successful year in terms of both achievements and new discoveries. Prof Ingrid Scheffer received the RACP Eric Susman prize, which is awarded to a Fellow of the Royal Australasian College of Physicians for the most outstanding contribution to the knowledge of any branch of internal medicine. We congratulate Prof Sam Berkovic on receiving the Bethlehem Griffiths Research Foundation medal in July last year for his ongoing commitment and leadership in epilepsy research. PhD student and epileptologist, Dr Saul Mullen won the American Epilepsy Society Young Investigator Award for his presentation about GLUT-1 deficiency in absence epilepsy. Research assistant, Danya Vears was awarded the Austin Health Medical Research Foundation Young Investigator award during Austin Health Research Week for her oral presentation on *SCARB2* mutations in Progressive Myoclonus Epilepsy without Renal Failure.

We have recently been joined by two research fellows, Dr Kheng Seang Lim from Malaysia and Dr Meng-Han Tsai from Taiwan. We also welcome a new research assistant, Lyndal Douglas, who started working at our New South Wales site and Brigid Regan and Lexie Slingerland have joined our Melbourne team. As always, researchers move on to the next phase of their careers. We were sad to farewell Dr Doug Crompton who investigated the genetics of familial epilepsy with our group for almost three years. He has returned to his homeland of Newcastle, England as an academic neurologist, but we look forward to our ongoing collaboration with him. Paediatric neurologist, Dr Daniel Carranza Rojo also returned to Barcelona, Spain, after spending almost 2 years with our team. One of our Wellington research assistants, Rosie Harty has recently moved to Melbourne to take up a PhD scholarship in the laboratory of Dr Steven Petrou, our physiology collaborator at the Florey Neurosciences Institute. Steven's laboratory investigates the functional aspects of genetic mutations in cells and delves into how these mutations lead to seizures so Rosie will be continuing in the field of epilepsy genetics.

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The Epilepsy Research Centre and our collaborators at the 2009 Epilepsy Research Retreat. Our moderator this year was Gary Mathern, University of California, Los Angeles, USA. We also welcomed guest scientists Helen Cross, Great Ormond Street Hospital for Children, London, UK and Stephen Robertson, University of Otago, Dunedin, New Zealand.

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 involve severe seizures in infants and children accompanied by developmental slowing and intellectual problems. There are many different epileptic encephalopathies including Dravet syndrome and West syndrome. A few years ago, thanks to the participation of many families and the assistance of national and international collaborators, we tested 300 patients with epileptic encephalopathies for changes in the sodium channel gene *SCN1A*. This work, together with other groups, has now established that *SCN1A* causes Dravet syndrome in about 80% of patients. We also found a small proportion of patients with other epileptic encephalopathies that were caused by *SCN1A* mutations.

In 2009, we extended our research into looking for genetic causes of epileptic encephalopathies with the help of international collaborators. Working with a French group, we were able to identify five girls whose epileptic encephalopathy was due to mutations in a gene called *CDKL5*. Mutations in this gene have previously been associated with atypical Rett syndrome. Another child was found to have a mutation in a gene called *STXBP1* through a Belgian collaboration. Although the majority of cases remain unsolved, we know that it may help each patient and their family when we do find the answer in a myriad of ways. Having a definite cause is important in its own right, it may guide which antiepileptic therapies are likely to work, and it may have implications for prognosis and genetic counselling for the patient, their parents and their siblings. We are sure that more answers for the epileptic encephalopathies will emerge with our ongoing studies and the wonderful help of our patients and their families.

Broadening our understanding of absence Seizures

Absence seizures are brief staring spells that are characterised by loss of awareness and are a result of generalized epileptic activity in the brain. These seizures often begin in childhood but they can also start in adolescence and continue into adulthood. We have been studying these seizures for many years and have found several genes that are associated with absence seizures (see GLUT-1 article). Our team has also been using a range of methods to better understand absence seizures, including different approaches to classification and brain imaging.

Dr Sadleir leads our research team in New Zealand, and is a member of the International League Against Epilepsy (ILAE) classification taskforce. Her research has shown that past ideas about how we might classify patients with absence seizures into different groups are too simplistic and do not consider the complex interaction of both genetic and environmental factors which influence absence seizures (Sadleir et al. Epilepsia. 2009 Dec; 49(12):2100-7).

PhD student and epileptologist, Dr Patrick Carney, in conjunction with the Brain Research Institute (BRI), has been using functional magnetic resonance imaging (fMRI) to understand the parts of the brain that are involved in absence seizures. This is a technique which detects changes in blood flow in the brain during absence seizures and can therefore tell us which parts of the brain become active or inactive. A large number of children and teenagers with absence seizures have had EEG studies performed while they are in the MRI scanner. The most important finding has been that a specific network of structures in the brain is involved in the generation of absence seizures. Dr Carney now hopes to see whether particular parts of the brain, particularly the frontal lobes, may be important in initiating these seizures. We hope this research will enhance our understanding of where in the brain absence seizures originate and which may, one day, lead to more targeted treatments. This study will be published in Neurology (in press, 2010).

A genetic risk factor for Idiopathic Generalised Epilepsy

Idiopathic Generalised Epilepsy (IGE) accounts for 30% of the epilepsies in the general population, and affects 1 in 200 people. IGE usually begins in childhood and adolescence and includes the syndromes of Childhood Absence Epilepsy (CAE), Juvenile Myoclonic Epilepsy (JME), Juvenile Absence Epilepsy (JAE) and Generalised Tonic Clonic Seizures Alone (GTCSA). IGE typically follows a complex pattern of inheritance, meaning that it is due to multiple genes which interact with each other. This means that, in most patients, there is no family history of epilepsy. Although major insights into the genetics of epilepsy have been achieved, little is known about the genes involved in the common IGE syndromes.

In recent years, we have learned that, somewhat surprisingly, everyone has variation in the number of copies of their genes. We all carry small deletions and duplications within our DNA called copy number variants (CNVs). Most CNVs are normal and harmless however, in some cases, larger duplications and deletions cause disease. Recently, a small deletion (microdeletion) on chromosome 15 at location 15q13.3 has been found to occur more frequently in the genes of people with autism (0.4%), intellectual disability (0.3%) and schizophrenia (0.2%) compared to the general population (0.02%). Recently, this microdeletion was shown to have an even stronger association with IGE, occurring in 1% of patients with IGE. To better understand the significance of this finding, with the help of our collaborators in Adelaide, we looked for the microdeletion in our IGE participants and then examined how the CNV was inherited in families.

The 15q13.3 microdeletion was found in 1.3% (7 of 539) of our IGE patients, and was found within different IGE syndromes. The relatively high frequency of this microdeletion in IGE patients means that an individual who has the 15q13.3 microdeletion has an increased risk of having IGE (a 1 in 3 chance) compared to the general population (a 1 in 200 chance). Family studies revealed that the 15q13.3 microdeletion could be inherited but this was not always the case. In 3 participants, the microdeletion was a new change in that individual rather than being inherited.

We also found that not everyone with the microdeletion had epilepsy, and that not all individuals with IGE in the families had the microdeletion. As such, the microdeletion could be inherited from an unaffected parent or passed on to unaffected offspring. Therefore, rather than being a gene causing epilepsy, the 15q13.3 microdeletion acts as a risk factor (or gene increasing susceptibility) for IGE. The 15q13.3 microdeletion is likely to be one of many rare susceptibility gene variants that collectively contribute to the complex inheritance of IGE. This research was published in the scientific journal "Human Molecular Genetics" (Dibbens et al., HMG 2009 Vol. 18, No. 19:3626-3631).

How do people feel many years after an epilepsy gene is discovered in their family?

Danya Vears recently completed a thesis as part of her Masters degree in Genetic Counselling through the University of Melbourne. With the help of Prof Ingrid Scheffer, Dr Samantha Wake from the Murdoch Childrens Research Institute and Dr Karen Dunn from the Royal Children's Hospital, she interviewed people in whom we had previously identified a gene as a cause for the epilepsy in their family. This study looked at how people felt about receiving a positive genetic result indicating the cause of the family's epilepsy and the impact on that individual and their family.

The findings showed that research participants hope for benefits from the research for themselves, their families and for others with epilepsy. As well as wanting to receive more information about the gene identified, participants explained their need to understand what having the gene meant for them and how this information could be used to help them and their families, both now and in the future. Participants also wish for the research findings to be made available to their doctors to assist with their clinical care which, with their permission, is our usual practice.

Communication about genetic results within families was sometimes problematic. Stigma associated with epilepsy was identified as a possible barrier to communication and family members may need additional support in the communication process, especially when communicating genetic information to future generations. The results of this study will help to develop guidelines for how both research participants and patients in the clinical setting are told their genetic results and the follow up they receive.

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 now 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.

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.

If you would like further information regarding any of these issues please do not hesitate to contact us. 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).

GLUT1-deficiency causes early onset absence epilepsy

GLUT1-deficiency syndrome is a genetic condition where glucose, the sugar used by the body as fuel, fails to cross from the blood to the brain. Under normal circumstances, the brain cannot use fat as an energy source so this lack of glucose leaves the brain starved for energy. GLUT1-deficiency is caused by mutations in the gene, *SLC2A1*. GLUT1-deficiency has long been known to cause a very severe disease of early childhood where the child has difficult to treat epilepsy, intellectual disability and failure of the brain to grow properly due to inadequate glucose. Over the last few years the Epilepsy Research Centre, in collaboration with Belgian collaborators, has been involved in the discovery that GLUT1-deficiency is responsible for a much broader range of conditions.

The first condition is paroxysmal exercise-induced dyskinesia (PED). In PED, exercise for 20 or more minutes, causes unusual muscle cramps where the legs take up an uncomfortable and fixed posture, often causing the person to fall. Similar cramping symptoms can occur in the arms with arm exercises. When PED runs in families, we have discovered that it may be due to GLUT1-deficiency. Some members of these families also have epilepsy or learning difficulties.

Our second discovery relates to absence epilepsy. Absence epilepsy in childhood typically starts between 4 and 10 years. We recently tested a group of patients with early-onset absence epilepsy beginning under the age of 4 years. This epilepsy may be more difficult to control than typical childhood absence epilepsy or may be associated with learning problems. Mutations were identified in 4 of 32 patients (over 10%) tested. Genetic testing for *SLC2A1* mutations causing GLUT1-defiency will now become a diagnostic test for early-onset absence epilepsy. This study was published in Annals of Neurology (Suls et al. Ann Neurol. 2009 Sept; 66(3):415-9).

In addition to better understanding the cause of a person's epilepsy, a diagnosis of GLUT1-deficiency can significantly change treatment. As mentioned above, under most circumstances the brain cannot use fat for energy. If, however, most sugar and starch is removed from the diet then metabolism of fat is radically altered so that the brain can use it. This occurs when people are placed on the ketogenic diet, which is a strict high fat, low carbohydrate diet that bypasses the sugar transport problem underlying GLUT1-deficiency and controls seizures. This means that the genetic test can guide treatment choices.

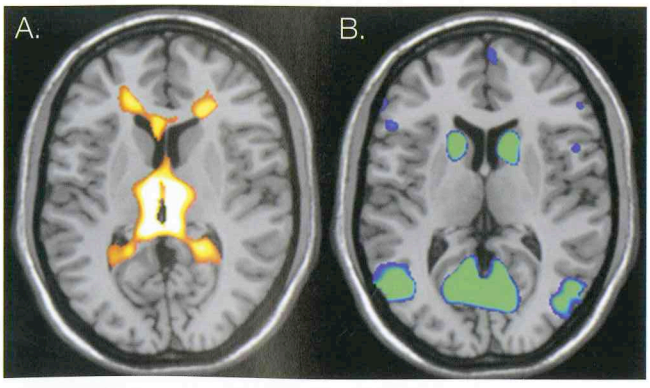


Figure A shows the areas of the brain which are activated during absence seizures where as figure B shows areas which are switched off during absence seizures using FMRI.

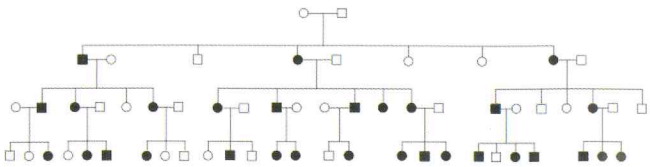
Syncope – a common condition in a large family

Syncope, also known as fainting, is a common condition that occurs in approximately 30% of people. It can mimic epilepsy as during syncope, patients lose consciousness and may have jerking or stiffening and look like they are having an epileptic seizure. However, syncope is caused by insufficient blood flow to the brain and not by epileptic activity in the brain.

The most frequently experienced type of syncope is called neurocardiogenic or vasovagal syncope, which is usually a benign, mild condition. Patients with neurocardiogenic syncope typically faint due to triggers such as prolonged standing, medical procedures, pain or emotional situations. Neurocardiogenic syncope often runs in families but no genes have been identified so far. To investigate the genetics of this form of syncope we are looking at families with this condition, using a similar research strategy to that which has proven so successful for our discovery of epilepsy genes.

We have studied a very large family with neurocardiogenic syncope with 30 affected family members in Australia, New Zealand, England and Ireland (see below). Syncope in this family seems to follow an autosomal dominant pattern of inheritance where each child has a 50% chance of inheriting the condition from an affected parent. Family members experienced the typical triggers and warning symptoms for fainting yet interestingly, the relevant triggers were quite variable between different family members. For example, some family members fainted after standing for a long time, whereas others fainted during blood taking, or when they experienced pain or frightening thoughts. About 40% developed jerking or stiffening during their fainting spells.

Through our ongoing collaboration with Dr Melanie Bahlo from the Walter and Eliza Hall Institute, and Dr Leanne Dibbens at the Women's and Children's Hospital Adelaide, work is underway to identify the underlying syncope gene within this family.



Family with an autosomal dominant form of neurocardiogenic syncope. The family tree has been modified to maintain confidentiality.

Please have a look at our website, **www.epilepsyresearch.org.au**, which 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 questions about our research, please feel free to email us at **epilepsy-austin@unimelb.edu.au.**

Musical Spectacular

We were thrilled to see the resourcefulness, enthusiasm and incredible talent of secondary students at four Melbourne schools, Scotch College, St Catherine's School, St Kevin's College and Loreto Mandeville Hall, who created a musical spectacular and raised funds to support our research. Their hard work will contribute to exciting discoveries that we hope will help adolescents with epilepsy.

Gonzo Golf Day

The annual Gonzo Golf Day was held in February this year in Sydney with the inspiration and hard work of Wayne Rowley and team. Golfers and celebrities helped raise funds to support our ongoing research into the genetics of photosensitive epilepsies. Sam Berkovic flew up to speak about our work and to accept the generous donation from organiser Wayne Rowley and patron Wally Lewis.

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.

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.

Donations

To **make a donation** 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 $ .....

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

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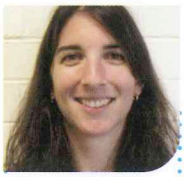

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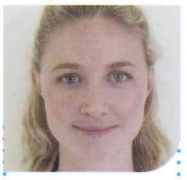

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Thank you

We would like to thank everyone who has contributed to our research in 2009 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) 9496 2330, 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.