EPILEPSY RESEARCH CENTRE NEWSLETTER 2012

- Dravet syndrome
- KCNQ2 Encephalopathy
- Epileptic Encephalopathies
- GLUT1-deficiency
- Benign Familial Infantile Epilepsy
- Benign Childhood Epilepsy with Centrotemporal Spikes

Professor Samuel Berkovic
Neurologist

Professor Ingrid Scheffer
Paediatric Neurologist

Professor Ingrid Scheffer given a top international award for women in science

Recognized for her groundbreaking work in epilepsy genetics, Professor Ingrid Scheffer was awarded the Asia-Pacific L'Oréal-UNESCO *For Women in Science* Laureate for 2012. Since 1998, UNESCO has partnered with the L'Oréal Foundation to recognize women researchers who move science forward. Each year, five outstanding women scientists globally are honoured by this international prize and Professor Scheffer becomes only the third Australian laureate. She was presented with the award at a ceremony at UNESCO in Paris on 29th March 2012. Ingrid shared her experience "It has been an extraordinary accolade, not just for me but for our entire group and wider collaborating team – as well as for the wonderful individuals and families with epilepsy who work with us – and it will encourage us to take our understanding of epilepsy forward to assist in diagnosis, therapies and ultimately, cure."

The Epilepsy Research Centre has welcomed new staff, with Dr Michael Hildebrand joining our molecular genetics laboratory, and Rachel Hughan joining our team of research assistants. Dr Laura Licchetta, a neurologist from Bologna, Italy has joined us for a year and Dr Shanika Samarasekera, a neurologist from Coventry, UK is visiting us for six months. Sadly we have bid farewell to several international fellows: Dr Karl Martin Klein who returned to Germany, Dr Utcharee Intusoma to Thailand, Dr Mel Michel Villaluz to the Philippines, Dr Young Ok Kim to Korea, Dr Meng-Han Tsai to Taiwan and Dr Lysa Boissé Lomax to Canada. We wish them all the best and hope they have learned and gained much during their time with us; we have very much enjoyed having them join our team. Four of our research assistants have also moved on to new career paths, Simone Yendle from Melbourne, Viger Yang and Natalie Redshaw from New Zealand and Lyndal Douglas from Sydney. We thank them for their hard work and enthusiasm.

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The Epilepsy Research Centre and our collaborators at the 2011 Epilepsy Research Retreat. Our moderator was Professor Hal Blumenfeld, Yale School of Medicine, Connecticut, USA.

Benign Childhood Epilepsy with Centrotemporal Spikes – Is it genetic?

Benign Childhood Epilepsy with Centrotemporal Spikes (BECTS) is the most common focal epilepsy syndrome in children under the age of 16 years. Most seizures occur from sleep between the ages of three and 13 years. Seizures typically start with an aura of numbness in one side of the tongue or face, followed by twitching of the face, which may spread to include the arm. This may progress to a convulsion. BECTS is associated with a characteristic EEG pattern of centrotemporal spikes, brought out by sleep. Some children have rare seizures and do not require treatment but if seizures are more frequent, they are easily controlled with anti-epileptic medication. The cause of BECTS is not known. Genetic factors have been suggested as a cause but little scientific evidence is available.

In order to understand whether BECTS has a genetic basis, we recently studied 53 children with BECTS and their families. The inheritance pattern of BECTS appears to be complex, which means that it is likely to be determined by multiple genes in conjunction with environmental factors. We found that if other family members had seizures in the families of BECTS patients, they most frequently had febrile seizures (also known as febrile convulsions). When epilepsy was present in relatives, they generally had focal epilepsies. This suggests that there are shared genetic factors between BECTS and other focal epilepsies. This study gave us an understanding of the underlying genetic architecture of BECTS, which will pave the way for future molecular genetic studies.

Copy Number Variations in Epileptic Encephalopathies

One of the areas of greatest impact in epilepsy genetics has been in the severe epilepsies of infancy and childhood, in a group of disorders known as the epileptic encephalopathies. Epileptic encephalopathies are a rare but devastating group of disorders in which infants or children present with difficult to control seizures, beginning from as early as the first week of life to mid-childhood, and often they experience multiple seizure types. Epileptic encephalopathies are typically associated with frequent, or even continuous, epileptic activity on EEG, developmental slowing and regression. The child usually has no family history of epilepsy and for most, no cause can be identified. Recently, several genes have emerged that cause a small proportion of epileptic encephalopathies, but most cases remain unsolved.

Copy number variants (CNVs) are regions of our genetic material that have been duplicated (present in extra copies) or deleted (one copy is missing). We all have CNVs yet whether they are harmful depends on the size and location of the CNV. CNVs have been established as an important genetic cause of many disorders including intellectual disability, where CNVs are causative in more than 10% of people with severe intellectual disability. We were interested in whether CNVs cause a significant proportion of epileptic encephalopathies in which intellectual problems may be progressive.

In collaboration with a molecular genetics group in Seattle, in the US, we discovered that rare CNVs are found in almost 8% of patients with epileptic encephalopathies. Our research highlighted the significance of rare CNVs, and provided novel insights into the causes of this severe group of disorders. This study promises to change clinical practice as CNV analysis should now form a part of routine diagnostic testing for children with epileptic encephalopathies.

GLUT1-deficiency is an important cause of the most common group of genetic epilepsies

The glucose transporter 1 protein, known as GLUT1, transports sugar, in the form of glucose, to the brain from the blood stream. As glucose is the main source of energy for the brain, if GLUT1 fails to function, the brain is starved of energy. In the genetic condition called GLUT1-deficiency, a genetic abnormality causes this protein to malfunction, starving the brain of energy. This was first described over 20 years ago in children with very severe epilepsy and intellectual problems that began in the first year of life. In these cases, the energy starvation was so severe that the brain did not grow properly, leading to a small head.

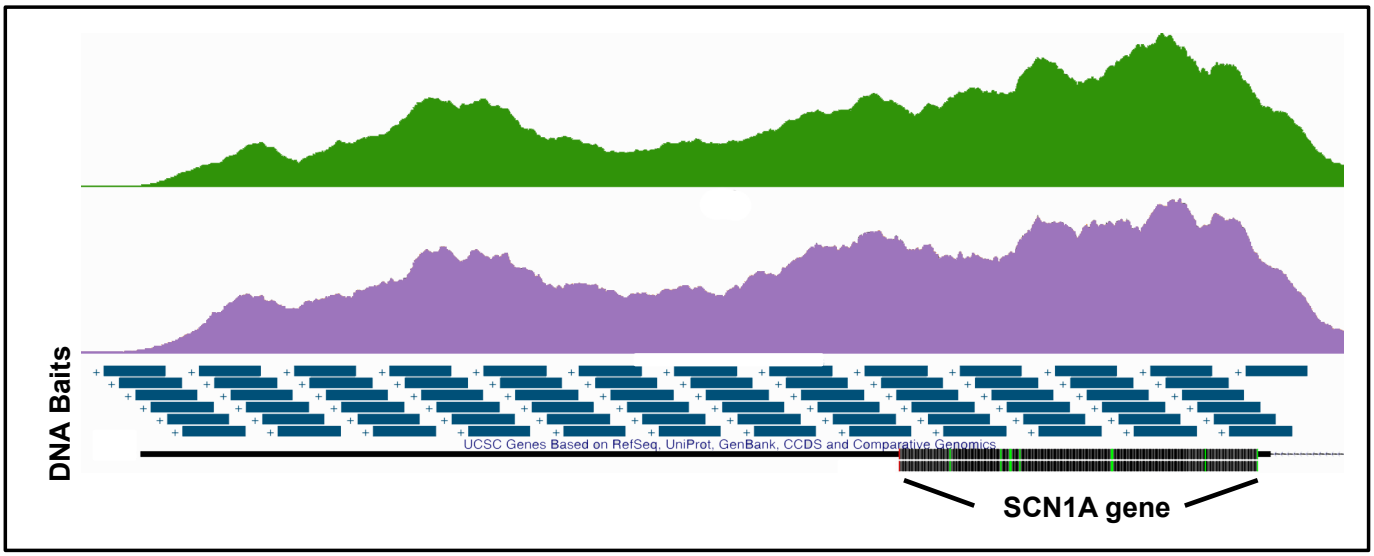
Over the last few years, it has become clear that GLUT1-deficiency is much more common than previously thought. Our work shows that GLUT1-deficiency can produce a wide range of epilepsies including much milder disorders. Together with Belgian and Italian collaborators, we found that 5% of people with the rare but severe syndrome of Myoclonic-Astatic Epilepsy, described by Dr Doose, have GLUT1-deficiency. Over 10% of patients with Early-Onset Absence Epilepsy, where absence seizures start under four years of age, also have GLUT1-deficiency.

GLUT1-deficiency is also a genetic condition that can be inherited in families. In the family members who carry a mutation causing GLUT1-deficiency, epilepsy with absence seizures is usually seen. Onset of absence epilepsy often begins in childhood or teenage life. This means GLUT1-deficiency is not only a common cause of Early-Onset Absence Epilepsy but also a potential cause of the common, classical generalised epilepsies such as Childhood Absence Epilepsy and Juvenile Absence Epilepsy.

We have recently investigated whether GLUT1-deficiency causes the common genetic (previously known as idiopathic) generalised epilepsies that make up a third of all epilepsies. A genetic mutation that causes GLUT1-deficiency was looked for in over 500 people with common generalised epilepsies. Mutations leading to GLUT1-deficiency were found in 7/500; over 1%. This ranks GLUT1-deficiency among the most common known genetic cause of epilepsy. This finding is exciting for two reasons. Firstly, GLUT1-deficiency has a specific treatment; the ketogenic diet, used in epilepsy here at the Austin Hospital and around the world. It works extremely well for GLUT1-deficiency. The ketogenic diet removes nearly all sugars from the diet so that the body starts to make ketone bodies as a source of energy from fat instead. These ketone bodies do not need GLUT1 to reach the brain. This bypasses the defective GLUT1 protein and provides energy for the brain to function and grow. What role the ketogenic diet, and milder diets such as the Modified Atkins diet, will have in common epilepsies due to GLUT1-deficiency is being studied. Secondly, GLUT1-deficiency is now a relatively common cause of epilepsy suggesting that glucose reaching and being used by the brain may be an important mechanism causing seizures. This is an ongoing area of intensive research at the Epilepsy Research Centre.

Massively Parallel Sequencing

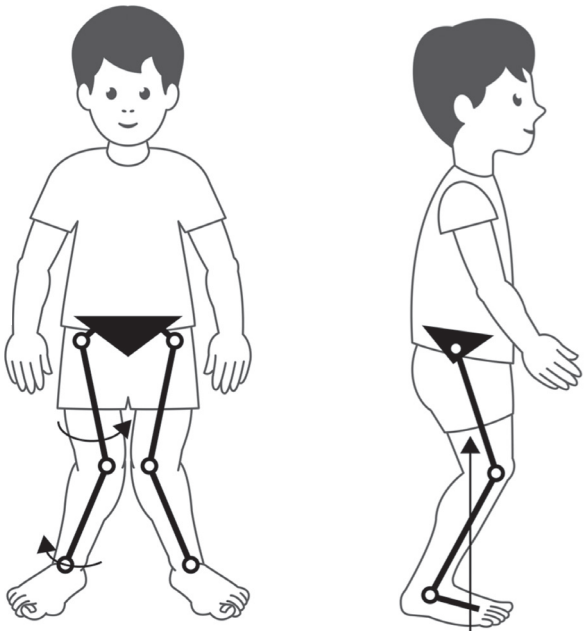
The discovery of epilepsy genes has been revolutionized over the last few years by the introduction of a new technology known as massively parallel sequencing. We are using this technology to analyse large numbers of genes that include all genes in the human genome. In these approaches short sequences (baits) are designed to capture the DNA of targeted genes, as shown for the epilepsy gene called *SCN1A* in the figure below. These DNAs are then rapidly analysed at the same time and errors in genes that cause epilepsy can be identified. In this way we can rapidly identify epilepsy genes which assists in making an epilepsy syndrome diagnosis and informing treatment options for patients. This exciting new technology has already led to the discovery of at least five epilepsy genes in the last couple of years, including three genes discovered by our group at the Epilepsy Research Centre. We anticipate identifying many new epilepsy genes in the coming years using this technology and look forward to using this knowledge to develop novel therapies for epilepsy patients.



Dravet syndrome – Does walking deteriorate in adolescence?

Over the last 15 years we have had a major research interest in Dravet syndrome, a severe infantile-onset epilepsy syndrome. While caring for patients with Dravet syndrome, we noticed that our older patients developed an unusual walking style or gait. To investigate this further we teamed up with post-doctoral physiotherapist, Dr Jill Rodda, and orthopaedic surgeon, Professor Kerr Graham, at the Royal Children's Hospital in Melbourne, to analyze the gait of individuals with Dravet syndrome.

We examined 26 patients with Dravet syndrome, ranging in age from two to 34 years. Twenty-three had abnormalities (mutations) of the sodium channel gene *SCN1A*. We found that older patients, over the age of 13 years, had significant changes in their posture and gait. They walked with a "crouch gait", meaning that their knees and hips tended to be held in a bent posture, they had flat feet which pointed outwards, and their bones in the upper (femur) and lower (tibia) legs did not show the normal developmental changes that accompany growth into adult life. These changes had a significant impact on the patients' ability to walk, especially over longer distances, so that many required assistance such as the use of a wheelchair.



Whilst these findings were quite obvious in the teenagers and young adults, signs of this gait were detectable in many of the younger participants, from about five years of age. Early identification of this deterioration in gait is the first step; now we need to devise strategies to prevent the decline in gait.

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 are asked to give their own consent when they reach 18 years of age provided we are able to contact them. 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.

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**.

Finding the genetic cause of Benign Familial Infantile Epilepsy

Benign Familial Infantile Epilepsy (BFIE) is an autosomal dominant epilepsy syndrome we have been studying for 20 years since it was first described. In BFIE, family members have seizures beginning at around six months of age which stop by two years. A related syndrome, called Infantile Convulsions and Choreoathetosis (ICCA) refers to families with BFIE in which some individuals develop a movement disorder that begins anywhere from childhood to adult life. This movement disorder, which is not a form of epilepsy, is called Paroxysmal Kinesigenic Dyskinesia (PKD). It is triggered by starting to move so that the person experiences brief muscle twisting or cramping when they initiate movement.

We found that mutations in a gene called *PRRT2* were the main cause of BFIE and ICCA. 80% of the families we had studied with BFIE had *PRRT2* mutations as did 90% of the families with ICCA. Very little is known about this gene, and we do not yet understand how the changes in the gene cause seizures. However it is interesting that a change in a single gene can cause two different conditions (seizures and a movement disorder), which arise from different parts of the brain and occur at different ages.

Recognizing the correct diagnosis in families with BFIE and ICCA is useful as it informs people that their children may be at risk of developing a movement disorder later in life. If this happens it can be quickly recognized and treated to minimize the disruption in their life. Knowing the genetic cause of the condition in a family provides more information about the chances of babies born in the future developing seizures, and can help reassure parents that their baby is likely to grow out of the seizures.

KCNQ2 Encephalopathy – a new newborn disorder

KCNQ2 is a gene that encodes a potassium channel subunit which forms a gateway allowing potassium ions (particles) into the cell. *KCNQ2* has been studied by our group for many years as it is the main cause of Benign Familial Neonatal Epilepsy (BFNE), an autosomal dominant disorder with seizures beginning in the newborn period, typically in the first week of life. Individuals with BFNE do well with normal intellect and seizures that stop usually after a few months.

As part of our ongoing search to find the cause of epileptic encephalopathies, we collaborated with a Belgian group to identify a group of children with newborn-onset epilepsy and severe developmental delay with cerebral palsy, who also had abnormalities (mutations) in *KCNQ2*. Although the seizure onset and seizure type were similar to BFNE, seizures were extremely hard to control. These children usually do not have a family history of neonatal seizures suggestive of BFNE because the mutation is new in the child.

By carefully studying this group of children, we were able to identify key features on their EEGs and brain images. Together with the seizure pattern, we have been able to describe the disorder of *KCNQ2* Encephalopathy. In future, we hope that early recognition of this disorder will lead to a more rapid diagnosis and appropriate treatments. Further work to understand why mutations in this gene can result in such different clinical disorders will also be very important.

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 **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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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 7127, by email grel@unimelb.edu.au or 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.