Ethical Considerations:

The conduct of our research is over-seen by Human Research Ethics Committees. In recent times there have been some changes to the guidelines for certain research procedures. Study participants enrolled from July 2000 onwards 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 required 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.

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).

Our Team:

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Kate Lawrence
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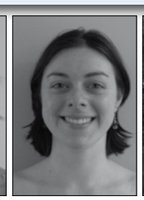

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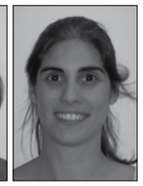

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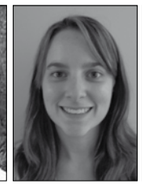

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FOR FURTHER INFORMATION:

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 and return it as requested.

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

$_____

Name:_____

Address:_____

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

Please return to: Epilepsy Research Centre, Level 1, Neurosciences Building, Repatriation Hospital, Austin Health
Banksia St, West Heidelberg VIC 3081 Tel. (03) 9496-2737 Fax (03) 9496-2291

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Professor Samuel Berkovic
Neurologist

Professor Ingrid Scheffer
Paediatric Neurologist

RECENT NEWS

We have recently identified the gene, SCARB2, as the cause of a rare form of Progressive Myoclonus Epilepsy associated with renal failure. This exciting finding has just been published (see Berkovic et al., Am J Hum Genet. 2008 Mar 3;82(3):673-684 for details).

THE UNIVERSITY OF MELBOURNE

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EPILEPSY GENETICS

Newsletter

ISSUE NUMBER 7 **2008**

Welcome to the Epilepsy Genetics Newsletter, 2008 edition. As we enter our 19th year of investigating the genetics of epilepsy and other related conditions, we would like to thank everyone who has made our research possible. From the referring clinicians to the participants and their families, our research is impossible without you and we greatly appreciate the time you take to contribute to our research. We are making progress in our quest to discover the genes that cause epilepsy and as the number of participants we have included in our research soars to 9000, we continue to learn more about how seizures occur with the aim of helping people with epilepsy now and in the future.

In 2007 we bade a fond farewell to Dr Ingo Helbig as he returned to Germany to continue his training as a Paediatric Neurologist. We also said goodbye to Katie Kron who worked as a research assistant with our team for three years and has returned home to the USA to study genetic counselling. Four new research assistants joined our team in 2007. Karen Oliver, Georgie Scales, Carla Bruce and Alex Fischer continue our ongoing study of individuals, twins and families with epilepsy.

In December, Prof Ingrid Scheffer was honoured with the American Epilepsy Society Research Recognition Award for Clinical Research for 2007. This award recognises an outstanding contribution to clinical research in epilepsy at an international level and is rarely awarded outside the US.

Prof Sam Berkovic's ongoing contribution to the field of epilepsy genetics was acknowledged when he was elected a fellow of the Royal Society (London), one of only two Australians in all fields of science to be elected in 2007. He was also appointed a Laureate Professor at the University of Melbourne and was awarded an inaugural NHMRC Australia Fellowship. This brings more funding to our group, which will allow us to expand our research over the next five years. In particular, we will establish a new molecular genetics laboratory at Austin Health, which will collaborate with our existing laboratory at the Women's and Children's Hospital in Adelaide.

Our website, ***www.epilepsyresearch.org.au,*** provides a range of information about the Epilepsy Research Centre, the research projects we are conducting and also information for epilepsy patients interested in seeking treatment through Austin Health. Past issues of the newsletter and links to other useful sites can also be found on the website. If you would like to contact us with any specific queries about any of our studies, please email us at ***epilepsy-austin@unimelb.edu.au.***

The Epilepsy Research Centre team and our collaborators at the 2007 Epilepsy Research Retreat. Our international moderator for 2007 was Professor Dan Lowenstein, (University of California, USA)

NZ & NSW Epilepsy Research Groups

New Zealand

Dr Lynette Sadleir, Paediatric Epileptologist and Senior Lecturer, University of Otago, Wellington, New Zealand, has worked with Professor Ingrid Scheffer from afar since 2000 on a number of projects including a video-EEG study examining the features of 509 absence seizures in 70 children in collaboration with paediatric neurologists at the children's hospital in Vancouver. Another study has investigated the best type of EEG recordings for children with new onset seizures. This year saw the formal expansion of our Epilepsy Genetics research group to New Zealand. Collaborative ties have been strengthened with the input of two research grants, including one from the Health Research Council of New Zealand. This has enabled the employment of two NZ research assistants, Natalie Redshaw and Rosie Harty, to work with Dr Sadleir. The New Zealand group will recruit children and families with epilepsy and thereby contribute significantly to new and exciting genetic discoveries.

Lynette Sadleir, paediatric epileptologist, leading the New Zealand team.

New South Wales

Our first interstate team has also been established and is based at the Children's Hospital at Westmead and the Westmead Hospital in Sydney.

This team comprises Dr Deepak Gill and Associate Professor Andrew Bleasel with research assistant Sarah Bowen.

Although we have been studying patients with epilepsy in NSW for years with the help of many referring clinicians, this has expanded our ability to involve participants from NSW in our research studies.

Functional Brain Imaging in Childhood Epilepsies

Benign Epilepsy with Centro-Temporal Spikes (BECTS), also known as Benign Rolandic Epilepsy (BRE) and Benign Focal Epilepsy of Childhood (BFEC), is the most common epilepsy syndrome in children. Onset is between 3 and 12 years of age. Seizures usually occur during sleep and may only occur once or a few times. Children may be aware during their seizures, which may begin with tingling in their mouth and then involve twitching of the face and arm. Sometimes only convulsive attacks occur. The electroencephalogram (EEG) shows spikes coming from a particular area, the central and temporal region, on one or both sides of the brain.

A collaborative study between the Brain Research Institute (BRI) and the ERC has been underway since 2005 to investigate the precise location of these spikes in the brain. This study has used a technique called functional magnetic resonance imaging (fMRI) to help us see which parts of the brain "light up" or are active at exactly the same time the spikes occur on the EEG.

To date, thirty children with new onset BECTS have been scanned from Austin Health, the Royal Children's Hospital and Monash Medical Centre. The study has been very successful and has shown that these spikes can be localized to a very small area of the brain. We are also investigating whether these spikes have any effect on language development.

Family trees of these children are also being obtained to determine whether family members of children with BECTS are more likely to have seizures than people in the general population. We are keen to determine the types of seizures occurring in family members if they are happy to participate. Dr Patrick Carney, Epilepsy Fellow, is also utilising the fMRI technique in the hope of unravelling the mysteries of Childhood Absence Epilepsy (CAE). In this condition absence seizures, which involve brief staring spells, appear to come from both sides of the brain at once. He hopes to study children with absence seizures in order to see which networks in the brain are most important for generating these seizures.

Participant in the Magnetic Resonance Imaging machine used to obtain functional brain images

Gene-Hunting in Fainting and Breath Holding Families

Fainting, or syncope, is a common phenomenon often with an unknown cause. A related problem, affecting younger children, is that of breath holding spells where the toddler stops breathing and will then blackout. This is very alarming for parents, although it is usually not dangerous.

Syncope and breath holding attacks can occasionally display features similar to seizures. During our large study of families with epilepsy, we have encountered many individuals with syncope or breath holding attacks who were incorrectly thought to have epilepsy.

Syncope and breath holding can also run in families but this has been poorly studied. In 2008 we are commencing a new research study that will try to identify how these conditions are inherited with the aim of discovering the genes involved. The study will involve structured interviews with individuals from large families where multiple family members have experienced fainting or breath holding attacks and tracking the condition back through the generations. Gene discovery will provide significant insights into the fundamental cause of fainting that should lead to better diagnostic methods and improve knowledge to counsel parents.

Genetic Copy Number Variations in Epilepsy

It is normal for us all to have changes in the sequence of our DNA that do not cause problems. One of the newest discoveries in the field of human genetics is that we all have whole segments of our DNA where we may have multiple copies (duplications) or are missing copies (deletions) of one or more genes.

Most of the alterations in the number of copies (or copy numbers) of these DNA sequences are not harmful and contribute to our individuality. However, if these copy number changes involve an important gene, they can alter that gene's function in a critical way.

We have recently discovered, for the first time, that copy number variation underlies some epilepsy syndromes. Dravet syndrome (or Severe Myoclonic Epilepsy of Infancy) is caused by conventional mutations (abnormal sequence changes) of the sodium channel gene SCN1A in 70-80% of patients. Similarly, Benign Familial Neonatal Seizures (BFNS) is frequently caused by mutations of the potassium channel gene KCNQ2. In both of these rare epilepsy syndromes, we have shown that some children with Dravet syndrome have deletions of SCN1A, and some babies with BFNS have copy number variation (deletions or duplications) of KCNQ2.

There are still some patients with these syndromes for which no genetic mutation has been found. Our hope is that as technology continues to advance, and our understanding of our genes expands, we will discover the genetic cause for the remaining patients.

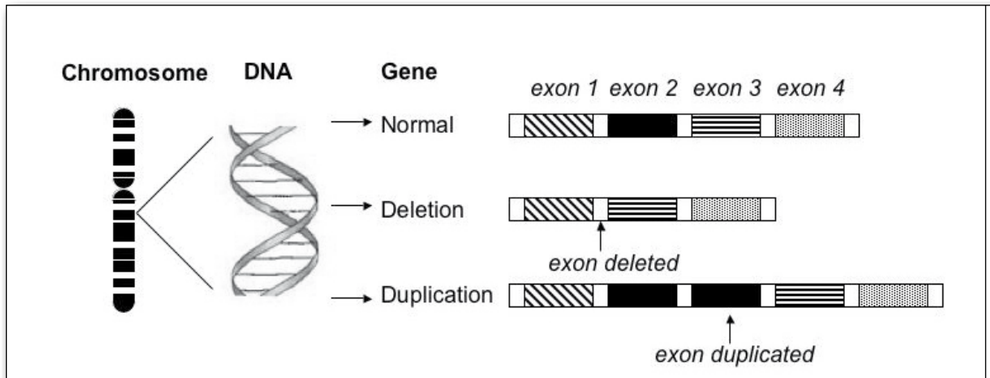

Diagram shows variations in copy number from a normal DNA structure which may involve deletion or duplication of a segment (exon) of a gene.

Febrile Seizures and Epilepsy: Spreading the Word

The International Brain Research Organization (IBRO) World Congress of Neuroscience was held in Melbourne in July 2007. As part of the conference, a Special Interest Forum entitled 'Febrile seizures and Epilepsy: What is the link?' was organised by Prof Ingrid Scheffer and Prof Tallie Z Baram (University of California, USA). The forum included talks from Prof Scheffer and Prof Baram, as well as Prof Michael Frotscher from the University of Freiburg, Germany.
Importantly, the forum provided an opportunity for individuals who had had febrile seizures and epilepsy to talk about their experiences. We were very fortunate to have research participants who spoke about how seizures had influenced their lives. From a family in whom we discovered a GABA gene receptor mutation, a mother and grandmother spoke about dealing with febrile seizures in their young children and the help they had derived from our research. The huge impact of the tale of an eloquent young woman's plight describing her temporal lobe epilepsy and the benefit that she had derived by being seizure free after epilepsy surgery left a lasting impression with the two hundred people present. The transcript of this talk can be found on our website ***www.epilepsyresearch.org.au.***

The opportunity for communication between participants and researchers was treasured by all and inspired the researchers to work even harder to understand epilepsy.

Prof Ingrid Scheffer receiving the American Epilepsy Society Research Recognition Award for Clinical Research in Philadelphia, USA

Thank-you

We would like to thank everyone who has contributed to our research in 2007, 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. This year we wish to extend our heartfelt thanks to the students of Suzuki Music who played beautiful music, gained sponsors and performed in concerts to aid us in helping children with epilepsy.

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.

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