EPILEPSY GENETICS Newsletter

ISSUE NUMBER 5 2006

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Melbourne, Australia

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Professor Samuel Berkovic
Neurologist

Professor Ingrid Scheffer
Paediatric Neurologist

RECENT NEWS

On 4th April the State Government announced a plan to build a new Australian Centre for Neuroscience and Mental Health Research at two nodes – Austin Health and Parkville. At Austin Health this will bring together researchers from a number of Institutes and University departments, including the Epilepsy Research Centre.

THE UNIVERSITY OF MELBOURNE

Austin Health

2005 was a very busy and fulfilling year at the Epilepsy Research Centre with a number of important scientific publications, many projects underway, and the ongoing recruitment of families, twins and individuals into our studies. Around 500 people have participated in our studies in the past 12 months, bringing our total number of participants to nearly 6000. We wish to thank all our participants and all the doctors who refer individuals and families to our study for their time and effort. Without your assistance, we would not be able to keep striving towards our goal of understanding the genetic patterns and causes of epilepsy that, in turn, will hopefully help people with epilepsy in the future.

Our team continues to grow and we have recently welcomed Dr Ingo Helbig from Germany who will be spending two years working on our twin studies. Ingo is training to be a paediatric neurologist when he returns to Germany. Dr Saul Mullen, who worked at the Austin as a neurology registrar in 2004, has recently commenced his PhD with us. Dr Isabella Taylor has just submitted her PhD after three years studying the genetics of the Idiopathic Generalised Epilepsies, the occipital epilepsies and photosensitivity. Isabella has now returned to her hometown of Perth where she will take up an appointment as a consultant neurologist with an interest in epilepsy. Alison Noa worked with us as a research assistant through 2005 on the ever-growing family studies.

It is an exciting time for studies of the genetic causes of disease with the emergence of new techniques, which allow us to tackle problems that were previously very difficult, time consuming and expensive. We hope these techniques will be very powerful in helping to understand the genetic causes of the common epilepsies. These techniques require very large numbers of participants and this is one reason why we are always keen to hear about new individuals and families with seizures and specific forms of epilepsy. In addition, there are many different types of epilepsy, so it is not until we have a large group of people with each form of epilepsy (say 1000 individuals with a specific epilepsy syndrome) that we can start recognising patterns within each particular type. This has been one of the many positive outcomes from the SCN1A study that we have been working on over the last 3 years (see page 3 for the latest update).

More information about the Epilepsy Research Centre, the range of research studies performed here as well as information for patients seeking treatment for their epilepsy through Austin Health can be found on our website: ***www.epilepsyresearch.org.au***. The website contains previous editions of this newsletter and helpful links for more information about epilepsy. If you have any specific queries we can be contacted by email at ***epilepsy-austin@unimelb.edu.au***.

The Epilepsy Research Centre and our collaborators at our annual Epilepsy Research Retreat

Achievements in 2005

Ingrid Scheffer's hard work and significant contributions to research over the years were recognised and rewarded last year when she was promoted to Professor as the Chair of Paediatric Neurology Research through the Departments of Medicine and Paediatrics at The University of Melbourne. This position is based across the Austin and Royal Children's Hospitals. This new role will help foster stronger links between the research in neurology and paediatrics at the University and at Austin Health and RCH. Everyone at ERC is very proud of Professor Scheffer's achievements and congratulates her on her promotion.

This year we have been successful in our application for a prestigious new Program Grant from the National Health and Medical Research Council to support our research, ensuring we have the resources to continue our work over the next five years. This grant builds on the strong collaborations we have developed with the Women's and Children's Hospital in Adelaide, the Brain Research Institute, the Howard Florey Institute, Austin Health and many other research groups around Australia and the world. This grant allows us to continue investigating many aspects of the causes, diagnosis and management of epilepsy.

Professor Sam Berkovic has received four prestigious national and international awards in the last twelve months largely for work in genetics of epilepsy. Internationally, he was made an "Ambassador for Epilepsy" by the Joint Executive of the International League Against Epilepsy and the International Bureau for Epilepsy and he was awarded the Zülch Prize for Basic Neurological Research from the Max Planck Society, Germany, for outstanding achievements in the field of basic neurological research. Nationally he was made a Member of the Order of Australia and a Fellow of the Australian Academy of Science, an honour rarely given to clinical researchers.

INGRID'S CELEBRATION
Professors Glenn Bowes, Jeffery Zajac, Sam Berkovic and James Angus congratulate Professor Scheffer (centre) on her promotion.

Photosensitivity in Epilepsy

Many people know that photosensitivity can be associated with epilepsy. Photosensitivity is a sensitivity to flashing or flickering lights that shows a specific response on the electroencephalogram or EEG. However there is a general misconception that all people with epilepsy need to avoid flashing lights or risk having a seizure. Photosensitivity in epilepsy is actually quite uncommon, playing a role in only a small number of people who have seizures. Indeed, most people who find the flashing lights uncomfortable do not have photosensitivity. Photosensitivity is most commonly associated with a particular type of epilepsy known as Juvenile Myoclonic Epilepsy (JME) although not all patients with JME are photosensitive. People with JME typically start having seizures during their teenage years and usually are quite easily controlled with a combination of medication and a sensible lifestyle.

We have been conducting a study looking at a small group of families where several people in each family have JME or a related type of epilepsy, and some of the family members are photosensitive. We have identified changes in a gene that are only present in the family members with photosensitivity. The changes are not seen in the other family members who have seizures without photosensitivity. This indicates that this gene does not cause the seizures to occur in the first place, but may play a role in determining the type of seizures a person experiences. In these families, this gene is likely to be one of several genes contributing to their seizure disorder. These findings may help us to understand the biological mechanisms of photosensitivity and why people within a family may experience different types of seizures triggered by different stimuli.

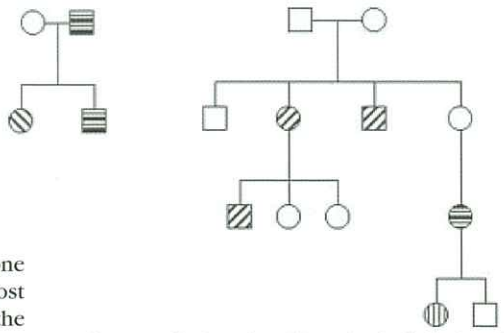
Clustering of Generalised Epilepsy Types in Families

Although there are many families where multiple people in the family have had seizures, it is quite common for each person to have a different type of epilepsy. This is particularly true in a group of common epilepsies called the Idiopathic Generalised Epilepsies (IGE). This group includes the specific syndromes of Childhood Absence Epilepsy (CAE), Juvenile Myoclonic Epilepsy (JME) and Juvenile Absence Epilepsy (JAE). These syndromes are characterised by the seizure types seen (myoclonic jerks, absences and generalized tonic-clonic seizures) and by the age at which the seizures start. We believe that the variability seen in families is due to a number of genes coming together to cause the seizures in each person. Some of these genes will be shared by all the people in the family, and some will be different – leading to the different seizure types and age of onset. So far these genes have been very difficult to identify.

In order to develop a better understanding of the relationship between each of these epilepsy syndromes, we conducted a study of 55 families where a number of family members have IGE and examined the pattern of syndromes within families. This initial study was published in the scientific journal "Epilepsia" in 2004.

We then embarked on a second study in conjunction with Dr Melodie Winawer and Professor Ruth Ottman at Columbia University, New York. In this study, the data from our families was combined with the data from a group of families studied at Columbia University. We analysed the pattern of seizure types, as opposed to the syndrome types, within families. This study was recently published in "Neurology".

The families fell into two subgroups. In one subgroup, affected family members most commonly had myoclonic seizures, or the syndrome JME. In the other subgroup, absence seizures tended to cluster, typically as part of the syndromes CAE and JAE. Only occasional mixing of myoclonic seizures and absence seizures was seen within families. This indicates that while there may still be an underlying gene in these families that makes people more susceptible to developing seizures, the genes causing JME are likely to be separate from the genes causing CAE and JAE. This information will help us design studies to identify these genes.



Some of the families included in the Idiopathic Generalised Epilepsy study, showing different family members with different types of seizures.

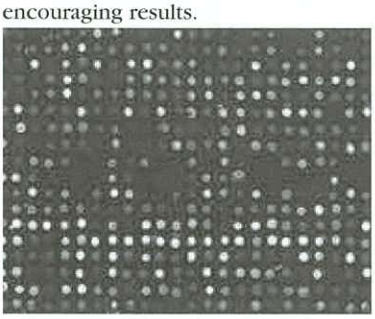
Twins Research Studies

Twins do not have a greater chance of having epilepsy than the general population, however they can provide us with important insights into the causes of epilepsy. For many years, we have been studying twin pairs where one or both have had seizures and we now have more than 500 pairs enrolled in the study. We are currently conducting a number of special projects with these twins.

We thank all the twins who have participated in our research study

Microarray studies

The use of "microarrays" is an emerging technique being used in genetics research. We have been conducting a small study with twins to try to identify genetic causes of epilepsy. We all have a complete set of our genes in every cell of our body, however only certain genes are turned on, or expressed, in each cell. This is why our muscle cells are different to our skin cells and why our organs differ in their function. Genes are also expressed differently in each person due to age, ethnicity, medications, diseases and environmental effects. Identical twins have an almost identical pattern of expression of genes compared with other relatives or unrelated people because their genes are virtually identical and they usually grow up in a similar environment. By looking at which genes are expressed differently between twins where one has epilepsy and one does not, we hope to identify candidate genes for epilepsy. This study is in its early stages with encouraging results.



A section of a microarray chip. Each spot represents part of a gene. The spots appear different colours depending on how much the gene is expressed in each person.

Brain imaging

Working in collaboration with the Brain Research Institute, we have been looking at MRI brain scans of identical twins where only one twin has had seizures. By comparing the brain images of twins with seizures with the images of their twin, we are investigating whether subtle differences in brain structure explain why only one twin has had seizures. We are still interested in recruiting twins for this study.

Effect of complications at birth

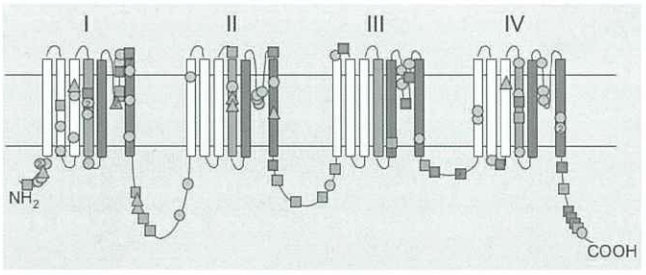
Seizures are often blamed on events or problems that occur during pregnancy or birth. While in rare cases these events can be quite severe and may contribute to seizures, in many cases the events are relatively minor and their role in causing seizures has been unclear. We have conducted a study analysing the birth records and histories of twins in detail. The results of our study indicate that "minor" events during pregnancy and birth do not play a significant role in causing seizures.

SCN1A

Over the last three years we have been working on a large study looking for changes in the alpha-one subunit of the neuronal sodium channel gene, SCN1A. We included over 250 patients from around the world in this study who had Severe Myoclonic Epilepsy of Infancy (SMEI) and other severe epilepsies beginning in the first year of life. The results of this study show that changes are found in SCN1A in over 70% of people with SMEI. These results are similar to those published by other research groups around the world. We are currently finalising the analysis of our data and hope to publish the results of this study in the scientific literature this year.

Through this study, we have been able to evaluate the clinical details of some of these severe and complicated types of epilepsy. As these conditions are rare, it is often difficult to detect patterns and similarities between groups of patients. However, as we have had many patients referred to us from around Australia and the world, we have been able to detect patterns not previously recognised and find the cause in some of these severe conditions. Recognition of these patterns will allow earlier diagnosis of similarly affected infants and children in the future; leading to earlier use of optimal treatment which hopefully will improve the outcome of these severe epilepsy syndromes.

The interest generated by this study, and the resulting evidence that changes in SCN1A account for so many cases of SMEI, has led to the development of a commercially available test to detect changes in the SCN1A gene. Several companies now offer this test: Genetic Technologies Ltd in Australia and Athena Diagnostics in the US, as well as several laboratories in Europe. This has made the test more widely and quickly available than would be possible by testing through research laboratories.



A cartoon of the SCN1A gene showing the changes identified in our study. The different shapes represent different types of changes.

Thank-you

We would like to thank everyone who has contributed to our research in 2005, by participating in the research studies, referring patients and families, or making financial contributions. We have been especially delighted when the families who have participated in our studies have sent donations to our research. This reinforces the fact that our families as well as the researchers value the significance of our research.

If you would like to assist our important research into developing a better understanding of epilepsy by making a donation to the Epilepsy Research Centre, please contact us on (03) 9496 2330, 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.

Ethical Considerations

The conduct of our research is over-seen by Human Research Ethics Committees at the hospitals where we recruit people for our studies. 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.

The recent introduction of the *Health Records Act 2001 (Vic)* may affect the way we store your personal information. 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).**

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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:_____

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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
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