# EPILEPSY GENETICS Newsletter

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**Professor Samuel Berkovic**

**Associate Professor Ingrid Scheffer**

## RECENT NEWS

Our research investigating changes in the SCN1A gene in people with Severe Myoclonic Epilepsy of Infancy (see page 2) has been a major contributor to the development of a diagnostic test for this gene becoming commercially available. Many patients who have been involved in our research have already been tested for changes in this gene.

Welcome to the 2005 edition of the Epilepsy Genetics Newsletter. We like to keep you informed of all our exciting developments from our last year of hard work here at the Epilepsy Research Centre at Austin Health, Melbourne and the University of Melbourne. We also take this opportunity to thank all of our five and a half thousand research participants and supporters for their time and energy in helping our research to continue. Without their kind assistance and enthusiastic attitude to the research, our continuing success and progress in the field would not be possible.

The research team, headed by Professor Sam Berkovic and Associate Professor Ingrid Scheffer, is now in its 16th year and we continue striving to unravel the inheritance of seizures in both families and twin studies. The last couple of years have also seen our interest expand to interrelated areas of research including cerebral malformations and pharmacogenetics (how genes influence the way the body handles drugs).

### THE TEAM

We have had a number of additions to the genetics team in 2004. Kate Lawrence and Katie Kron are our new research assistants, both involved in conducting Family Studies, with Kate also coordinating Twin Studies. We also have the pleasure of hosting three international fellows; paediatric neurologists, Dr Floor Jansen (Utrecht, The Netherlands), Dr Yue Hua (Helen) Zhang (Beijing, China) and adult neurologist, Dr Gunay Gul (Turkey), who are each spending six months with our group learning more about epilepsy and research into epilepsy genetics. Dr Zhang, Dr Jansen and Dr Gul bring valuable experience from their countries, and we all benefit enormously from the opportunity to exchange ideas.

Sadly, during 2004 we said farewell to several members of our team. Dr Lata Vadlamudi moved to become an academic neurologist in Canberra where she will complete her PhD thesis, and Dr Nigel Tan returned to Singapore after spending 18 months with us. We hope to keep working closely with both Dr Vadlamudi and Dr Tan in the coming years. Two research assistants, Sarah McInnes and Deborah Keay (Glencross), also left the team during 2004.

Our work in the area of the genetics of epilepsy continues to progress well with a number of important scientific publications throughout the year. This ongoing success is made possible by our strong collaborative links with researchers from hospitals across Melbourne, Australia and around the world. In particular our collaboration with the molecular genetic laboratory headed by A/Prof John Mulley at the Women's and Children's Hospital in Adelaide is integral to our success.

More information about the Epilepsy Research Centre, the range of research studies performed here and also 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 for us we can be contacted by email at ***epilepsy-austin@unimelb.edu.au***.

*The Epilepsy Research Centre genetics team 2004*

THE UNIVERSITY OF MELBOURNE

Austin Health

## SCN1A Progress Report

Our last two newsletters highlighted our recent work studying the gene that encodes the alpha-one subunit of the neuronal sodium channel, SCN1A, in patients with a severe type of epilepsy called Severe Myoclonic Epilepsy of Infancy (SMEI).

We have extended this study further and have been looking for changes in this gene in patients not only with SMEI, but also with other severe epilepsies beginning in the first year of life. We thought changes in this gene might be the cause of other forms of severe epilepsy. We originally aimed to study approximately 100 patients, but due to demand from all around the world, we now have close to 250 patients enrolled. This has meant a delay in finalizing this complex set of results and we thank the study participants for their patience.

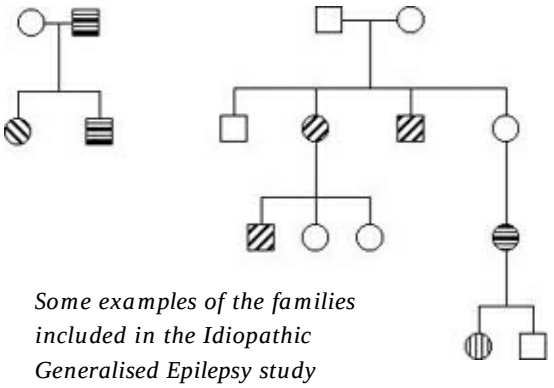
In order to thank the local families who kindly participated in this major study Associate Professor Ingrid Scheffer recently gave two information sessions on Severe Myoclonic Epilepsy in Infancy. A small group was organised by the Epilepsy Association of South Australia in Adelaide, whilst we organised a gathering at Austin Health for about 20 parents and grandparents of children involved in our SCN1A research including one Tasmanian family. The gatherings were an opportunity for family members to be able to share their experiences with others, whilst learning more about SMEI.

## Idiopathic Generalised Epilepsy Study

This year we began collaborating with the Gene Mapping Centre in Berlin, Germany, headed by Dr. Thomas Sander. The aim of this collaboration is to identify new genes that are involved in causing several of the common Idiopathic Generalised Epilepsies (IGEs) such as Childhood Absence Epilepsy (CAE), Juvenile Absence Epilepsy (JAE), and Juvenile Myoclonic Epilepsy (JME). DNA from 35 of our Australian and Israeli families was sent to the Gene Mapping Centre to undergo a genome wide scan to identify chromosome regions likely to contain epilepsy genes. Because of the statistical methods used to analyse the data, we only included families where two or more siblings have IGE.

Idiopathic Generalised Epilepsies are thought to be genetic, even though most cases do not have a family history of epilepsy. IGEs are relatively common, accounting for about 20-30% of people with epilepsy. Seizures generally begin during childhood or adolescence, although some people first experience seizures in adulthood. People with IGE are of normal intelligence, do not have structural brain abnormalities, and often outgrow their seizures, such as in CAE.

Because of the variety of IGE syndromes within families, there are likely to be a number of genes that contribute together to produce a specific epilepsy syndrome. We hope the genome scan will identify gene combinations that may cause susceptibility to these epilepsy syndromes.



*Some examples of the families included in the Idiopathic Generalised Epilepsy study*

## Benign Rolandic Epilepsy – Is it Genetic?

Benign Rolandic Epilepsy (BRE) is the most common childhood epilepsy syndrome thought to have a genetic basis. In the past, researchers have published articles about twin pairs who are concordant (both have) for BRE, suggesting that this particular epilepsy syndrome is highly genetic.

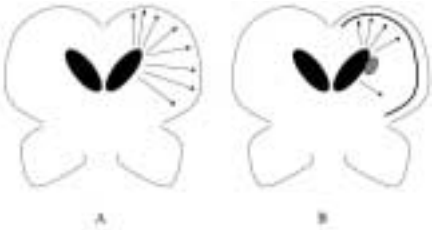
During 2004 Dr. Lata Vadlamudi travelled to a number of countries to identify cases of BRE in databases of both identical and non-identical twins. She reviewed data on 1761 twin pairs from Australia, Denmark, Norway and the United States and found no cases of twins who were concordant for BRE. This indicates that although patients with BRE may still have an underlying genetic predisposition to seizures, other, so far unidentified factors, must be contributing to their epilepsy. Indeed, we believe it may be the characteristic EEG feature of centro-temporal spikes seen in BRE that has a genetic basis rather than the seizures themselves.

Together with our colleagues at the Brain Research Institute at Austin Health we are studying MRI brain images of children with Benign Rolandic Epilepsy, as well as collecting clinical information and blood samples for future genetic studies to help us better understand this condition and the impact it has on children's lives.

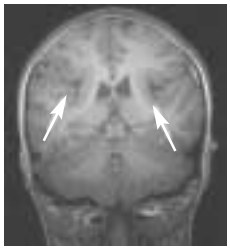
# Epilepsy and Brain Malformations

Certain genes, which are switched on in the early stages of embryonic development, regulate how neuronal cells migrate and form the human brain. It is likely that mutations in these genes affect cell migration and give rise to structural abnormalities in the brain, or malformations. Seizures may occur secondary to these malformations.

We have a long-standing collaboration with the Walsh Laboratory at the Harvard Institutes of Medicine (USA), who lead the field in malformations genetics research. In the past we have studied some families with certain malformations and have successfully collaborated with the Walsh lab, and with other groups overseas, to identify genes causing brain malformations and seizures. Earlier this year, a collection of DNA samples and MRI's (pictures of the brain) of patients with different types of structural abnormalities, where the causative genes have not yet been found, were sent to the Walsh Laboratory. This information will help the laboratory better define the conditions caused by these malformations, and hopefully lead to identification of the causative genes. We hope that by identifying genes linked to these disorders we can learn more about how the brain develops and better counsel patients and their families regarding these disorders.



*In normal brain development cells migrate from the middle of the brain to the outside edge (Figure A). In brain malformations cells may never migrate (grey circle, eg periventricular heterotopia), or may not reach the edge (black line, eg double cortex) (figure B).*



*MRI of a brain showing a malformation called polymicrogyria (arrows) where normal folding of the brain surface is replaced by lots of small, abnormal folds.*

# ABCB1 in Temporal Lobe Epilepsy

The ABCB1 gene is important for transporting drugs in and out of the brain. In last year's newsletter we mentioned a study conducted in the UK that had suggested a common change in this gene may increase the chance of antiepileptic drug resistance, by pumping the drug out of the brain more quickly. These types of studies, called genetic association studies, often produce inconsistent results when repeated in different populations. It was thus important for us to validate these results to see if this gene has an effect in Australians as well.

This study was completed in early 2004 and the results published in the scientific journal Neurology. We did not confirm the findings of the UK group, despite recruiting a group of patients that was twice the size of the original UK study. An Editorial by a geneticist in the same issue of the journal suggested that the varying results may be due to differences in statistical interpretation of the results of these studies.

In a separate genetic association study a link between a gene called GABBR1 and Temporal Lobe Epilepsy (TLE) was found. A rare variant of this gene appeared to increase the risk of developing TLE by over 30 times in a population studied in Italy.

Such rare changes may be present in some populations but not others. In other words, although Italians may be at risk if they had this GABBR1 variant, other caucasian populations from other European countries may not have the same risk. We looked at a large group of over 230 caucasian Australian TLE patients from diverse backgrounds, and found the GABBR1 variant did not appear to increase the risk of developing temporal lobe epilepsy. It may be that this particular rare variant only increases the risk of developing TLE in Italian populations. These results will be published in the scientific literature this year.

# Thank-yous

We would like to thank everyone who has contributed to our research in 2004, by participating in the research studies, referring patients and families, or making financial contributions. In particular we would like to thank the Lions Club of Mooroolbark for their generous support and contribution to our research program.

We have also been especially delighted when the families who have participated in our studies have sent donations to our research. This reinforces that our families as well as the researchers value the significance of our research.

If you would like to assist our important research into better understanding epilepsy by making a donation to the Epilepsy Research Centre please contact us by phone on (03) 9496 2330, email epilepsy-austin@unimelb.edu.au, or complete the section on the bottom of the attached form. Cheques should be made payable to the Epilepsy Research Centre. Donations over $2 are tax deductible.

## ETHICAL CONSIDERATIONS:

The conduct of our research is overseen by Ethics Committees at the various 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.**