EPILEPSY GENETICS

Newsletter

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RECENT NEWS

After 15 years of twin research, in 2003 we saw our 500th twin pair.

THE UNIVERSITY OF MELBOURNE

Austin Health

Welcome to the 2004 edition of the Epilepsy Genetics Newsletter. Each year we publish a brief newsletter keeping our research participants and other supporters up to date with the progress of the research being conducted by the Epilepsy Genetics group at Austin Health, the new name for the Austin and Repatriation Medical Centre.

The research team, headed by Professor Sam Berkovic and Associate Professor Ingrid Scheffer, has been studying the inheritance of seizures in twins and families for well over a decade. The success of the group and the ability to produce the work mentioned in this newsletter is due to the time and enthusiasm of the four thousand participants and supporters who have kindly assisted us in our research. We would like to extend our thanks to you all.

THE TEAM

This year has seen our group receive a number of awards. The major awards include a National Health and Medical Research Council scholarship to support Dr Isabella Taylor's PhD research and a highly prized National Association of Research Fellows of the NHMRC post-doctoral investigator award for Associate Professor Ingrid Scheffer's work in epilepsy genetics. Our work was also recognized at the Austin Health research week where we were awarded the Clinical Research Award.

Four new research assistants have joined the epilepsy genetics team in 2003. Danya Vears, Sarah McInnes, Jodie Malone and Deborah Glencross are all involved in conducting Family Studies, with Deborah and Sarah also coordinating the Twin Studies. Liliana Velick also joins us as Ingrid's new personal assistant.

Dr Jim Pelekanos, paediatric neurologist from Queensland joined us for a year in 2003 and his expertise provided valuable insights for our research. During 2003 we said farewell to Mary Connellan, the Twin Studies coordinator, and research assistant Jo-Anne Dean.

SCNIA - THE STORY CONTINUES

In our last newsletter, we discussed our first SCN1A study looking for mutations in an ion channel gene (SCN1A, the gene encoding the alpha 1 subunit of the sodium channel) in patients with a severe type of epilepsy called Severe Myoclonic Epilepsy of Infancy (SMEI). This study has now been completed and published in the scientific journal "Neurology". We found that of the 24 patients with SMEI tested, 8 (33%) had a mutation in the SCN1A gene.

This is an important finding as groups from Belgium and Japan, conducting similar research have found much higher rates, with over 75% of patients tested having a mutation in this gene.

Trying to understand how often patients with SMEI have SCN1A mutations is important for determining if testing this gene might be used to help confirm a diagnosis of SMEI. This could be very useful in terms of guiding anti-epileptic therapy and understanding a child's prognosis. In addition, as we know there are patients with SMEI who do not have mutations in the SCN1A gene, then there must be another gene, not yet identified, causing the same condition.

One explanation why different research groups are getting such variable results may relate to SMEI being a very complicated type of epilepsy that can sometimes be difficult to diagnose. There are also many patients who show some, but not all, of the characteristics of SMEI. So it is possible that different research groups are using different criteria for diagnosis of SMEI and therefore including significantly different patients in their studies.

To explore this idea further, we have embarked on our second SCN1A study. This large, collaborative study of more than 100 patients with severe epilepsies beginning in the first year of life explores the spectrum of epilepsy syndromes that may be caused by abnormalities in the SCN1A gene. We are very grateful to the many families and their clinicians involved in the study which includes children from Australia and New Zealand as well as other countries around the world including the UK, USA, Canada, Israel and Denmark.

We've Changed Our Name

As you can see from the top of this newsletter we have changed our name from the Epilepsy Research Institute to the Epilepsy Research Centre (ERC). This change was made in order to reflect the true nature of the research group.

The ERC is focused on understanding more about all aspects of epilepsy, drawing together people employed by many different institutions across Melbourne. Our cohesive team of research collaborators come from institutions including the University of Melbourne, Austin Health, Monash Medical Centre, the Royal Children's Hospital and the Brain Research Institute as well as many overseas centres.

We continue our strong collaboration with our molecular genetic laboratory at the Women's and Children's Hospital in Adelaide, headed by Associate Professor John Mulley and Professor Grant Sutherland with support from an Adelaide biotechnology company, Bionomics.

In conjunction with the change of name we have also unveiled our new website: *www.epilepsyresearch.org.au.*

This site provides information about some of the research projects being conducted by the Epilepsy Research Centre, as well as information for patients seeking treatment through Austin Health and details of how to contact the Centre. Helpful links for more information about epilepsy can also be found.

The Epilepsy Research Centre and collaborators at the annual Epilepsy Research Retreat 2003 with leading epilepsy researchers Prof Jerome Engel (Los Angeles) and Prof Alan Connelly (London).

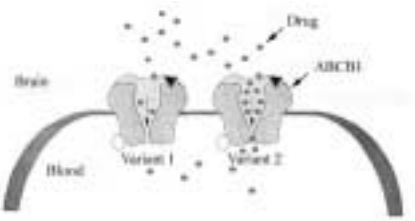
Pharmacogenetics – Can genes affect how well drugs work?

Anti-epileptic drugs remain the cornerstone of medical treatment in epilepsy. They provide good seizure control for most patients. However, some patients keep having seizures despite taking multiple anti-epileptic drugs.

What makes one person respond to a drug, and not another? The type of epilepsy, the cause and the age of onset may all play a role.

A recent study from England suggested that genetics might also be important. The study looked at a gene (called ABCB1) that "pushes" anti-epileptic drugs out of the brain and into the blood stream. Several variations of the gene exist and they found that patients with difficult to control epilepsy usually had one particular variant. It is thought that this variant may be more active than others, stopping the drug getting into or staying in the brain and preventing it from doing its job.

We are studying this gene and a number of other genes that may act in a similar way to see whether we find the same result. We will study a group of people with difficult to control epilepsy and a group with easily-controlled epilepsy, and look for genetic differences between the two groups. We hope that learning more about these genes will help us understand the exact role they play in our brains. This may explain why it is easier to control seizures in some people than in others, help us to understand how different drugs work, and possibly lead to new medications or new approaches in how we use medications in the future.

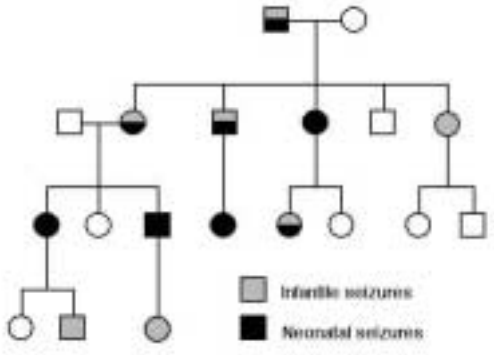


Two channels which "push" different amounts of anti-epileptic drug out of the brain and may be important in drug responsiveness.

Benign Familial Neonatal-Infantile Seizures – 6 more families

At the time of our last newsletter, we had recently published an article in the scientific journal "The Lancet" identifying the gene, SCN2A, which encodes the alpha 2 subunit of the sodium channel that causes a rare epilepsy syndrome that runs in families known as Benign Familial Neonatal-Infantile Seizures (BFNIS). BFNIS occurs at around two months of age, falling between two similar epilepsy syndromes that begin in either the newborn period or at about six months of age. Importantly the diagnosis of BFNIS can only be made when the family history is investigated in detail.

During the past year we have studied a number of families who were thought to have BFNIS. To better understand the boundaries of this condition we investigated the type of seizures each family member experienced, including the age the seizures started and finished. Six families from Italy and the USA were diagnosed with BFNIS. Our collaborating laboratory in Adelaide identified SCN2A mutations in all six families. By studying these families in detail we were able to define the characteristics of BFNIS more clearly. These results will be published soon in the scientific journal Annals of Neurology. This information will help doctors make more accurate diagnoses of patients and families with epilepsy starting in infancy and allow them to provide better information regarding treatment, progress and outcome of this condition.



BFNIS family where the shading represents the age the seizures began (females are circles, males are squares).

Genetics of epilepsy and sensitivity to light

Idiopathic Photosensitive Occipital Epilepsy (IPOE) and Juvenile Myoclonic Epilepsy (JME) are two different types of epilepsy. They are characterised by different seizure types and different patterns on the EEG recording. However the two epilepsy syndromes have one important feature in common – seizures can be induced by flashing lights (photosensitivity). Previously this similarity was considered coincidental and IPOE and JME were thought to be completely unrelated.

Through the course of our research, we have identified a few families where individuals have experienced features of both these epilepsy syndromes. This overlap in the same person or the same family was not expected. Although rare, this suggests to us that IPOE and JME may be more closely related than previously thought and may possibly have a common genetic cause in some cases.

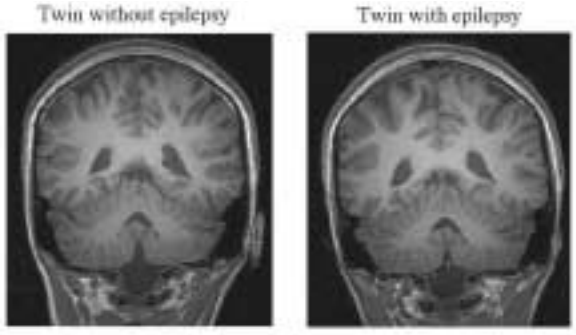
Understanding more about these families and the characteristics of the seizures they experience may provide clues that can help us identify the gene(s) involved. It is also important for doctors to recognise this overlap so that the best treatment options are considered.

Twins research – twin brains

Studying twins allows us to investigate both genetic and acquired causes of epilepsy. We have previously found that events during pregnancy and birth (obstetric factors) do not have a major role in causing epilepsy and we are continuing to investigate the relationship between genetic and environmental factors in epilepsy.

We are currently working in collaboration with the Brain Research Institute to look for subtle differences in the brain scans of twin pairs where only one twin has seizures. We know that in some people seizures can be caused by obvious structural variations in the brain, but in other individuals there is no clear cause.

As the brains of monozygous (identical) twins are more similar than the brains of unrelated individuals, it is possible to look for slight variations in brain structure. We hope to compare the brain scans of up to 20 twin pairs to look for subtle differences that may explain why one twin has seizures and the other does not and help us to recognise these changes in other patients with epilepsy.



MRI brain scan of twins

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 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.