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RECENT NEWS

In September 2002 the Epilepsy genetics research team discovered the gene for a new syndrome in infancy, "Benign Familial Neonatal-Infantile Seizures". We reported the syndrome in the scientific journal "The Lancet". Seizures start anywhere from birth up to 6 months of age, and are benign as babies usually grow out of the seizures. The gene we identified was an ion channel called SCN2A, encoding the alpha 2 subunit of the sodium channel. See page 3 for more information about ion channels.

THE UNIVERSITY OF MELBOURNE

Austin & Repatriation Medical Centre

EPILEPSY GENETICS *Newsletter*

ISSUE NUMBER 2 **2003**

Welcome to the second edition of our Epilepsy Genetics Newsletter. We aim to keep you updated regularly on the progress of our research. Thank you to everyone who provided such positive feedback about our last newsletter. We welcome any suggestions you may have including any ideas of what you would like to see in future editions of the newsletter.

The Epilepsy Genetics Group at the Austin and Repatriation Medical Centre has been studying the inheritance of seizures in twins and families for over a decade. To date, approximately three and a half thousand people have participated. We are grateful forthe enthusiasm and time of our participants and supporters which are essential for the success of our studies.

The research team is headed by Professor Samuel Berkovic, Consultant Neurologist and Epileptologist, and Professor of Medicine (Neurology) at the University of Melbourne, and Associate Professor Ingrid Scheffer, a Paediatric Neurologist and Epileptologist who has worked with Professor Berkovic for many years. The team is based at The University of Melbourne Department of Medicine at the Austin and Repatriation Medical Centre, Heidelberg, Victoria.

Together Professor Berkovic and Associate Professor Scheffer coordinate an ever expanding team of clinical research officers and PhD students, and contribute extensively to the ongoing success of our research effort through liaison with a large network of collaborating doctors and scientists in Australia and around the world.

This newsletter discusses some recent discoveries in Epilepsy Genetics made by our group and others around the world and more about how different genes may be causing epilepsy.

TEAM CHANGES

PhD student Dr Carla Marini recently passed her thesis investigating the Genetics of the Idiopathic Epilepsies, including the discovery of the first gene for Childhood Absence Epilepsy. During her PhD Carla was awarded several Young Investigator Awards from the International Epilepsy Congress, the Austin Biomedical Alliance and the American Epilepsy Society. She is looking forward to returning to Italy in early 2003 where she will be working on epilepsy genetics research with a team in Pisa. Her work at the Epilepsy Research Institute will be continued by the remaining research staff.

Dr Judith Adams spent two years working at the Epilepsy Research Institute, finishing during 2002. Kathryn Crossland, our "oldest" research assistant, worked with our group for seven years on the genetics of epilepsy. More recently she has been focusing on the genetics of speech and language disorders and received an outstanding result for her thesis on this topic, which she completed as part of her Masters of Speech Pathology.

Dr Lata Vadlamudi comenced a PhD in 2002 investigating the reasons why identical twins do not always both have seizures.

Three new research assistants Jacinta McMahon (Wiegerink), Jo-Anne Dean and Samantha Turner also joined the team in 2002 and are conducting detailed family studies in order to better understand the genetic causes of epilepsy.

In 2003, we are fortunate to welcome two new members to our team: Dr Jim Pelekanos, a paediatric neurologist from Brisbane, and Dr Isabella Taylor, an adult neurologist who will be commencing a PhD.

Recent Achievements/Awards

The success of our research has been acknowledged in a number of ways in 2002. Professor Berkovic was awarded the prestigious Eccles lectureship from the Australian Neuroscience Society and the GlaxoSmithKline Australia Award for Research Excellence. These awards indicate the high esteem that our work is held in the wider scientific community.

Together with other researchers at the University of Melbourne and the Austin and Repatriation Medical Centre we have been awarded a "Clinical Research Centre of Excellence Grant" from the National Health and Medical Research Council. This prestigious grant recognizes the high quality of clinical research practised by our group and the training opportunities for young researchers.

Associate Professor Scheffer has been awarded a National Health and Medical Research Council Practitioner Fellowship for five years. This fellowship is awarded to doctors practising clinical medicine who devote part of their time to clinical research. Dr Vadlamudi has also been awarded a scholarship from the NH&MRC enabling her to conduct her PhD research with us.

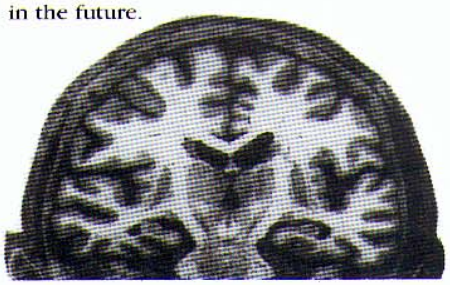
The Epilepsy Research Institute and collaborators at the annual Epilepsy Research Retreat 2002

Collaboration: The Key to Success

In our last newsletter we introduced you to some of our key collaborators: the molecular genetics group at the Women's and Children's Hospital in Adelaide, the Department of Physiology at the University of Melbourne, and Associate Professor John Drago's laboratory at Monash University.

We have continued to work closely with these groups as well as with the Brain Research Institute and the Centre for Nuclear Medicine and PET who conduct research looking at the structure and function of the brain. Due to these successful collaborations, we were awarded a very prestigious research grant for the period 2002-2006. This Program Grant from the National Health and Medical Research Council recognises groups with a proven track record of successful inter-disciplinary collaboration, and provides funding for our research for several years.

This collaboration between groups specialising in different disciplines helps us take our research beyond the identification of genes involved in causing epilepsy. The grant will enable research into how the changes we discover in genes alter the function of the proteins made from these genes. Tests done with these genes and proteins in the laboratory will allow us to understand which pathways in the brain are involved and how seizures arise. This in turn will help us to better understand the results of imaging and metabolic tests performed in patients with epilepsy, and to develop new tests and hopefully new treatments in the future.



An MRI scan of the brain

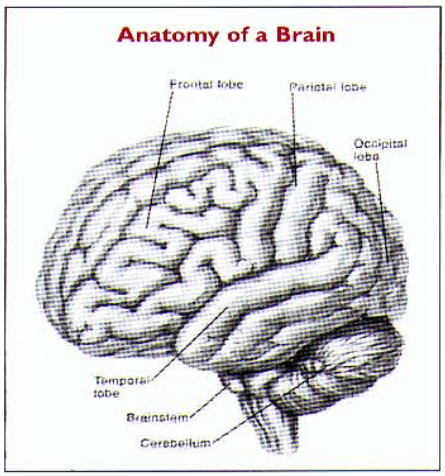
Recent Epilepsy Gene Discoveries

In addition to our discovery of the "BFNIS" gene (page 1) we have also been involved in identifying a gene for a very different type of epilepsy – one causing very severe epilepsy called infantile spasms. Changes in this gene, called *ARX*, usually also cause intellectual disability, and have so far only been seen in boys. We don't yet understand much about this gene's normal function in the brain, but we believe it probably plays an important role in brain development.

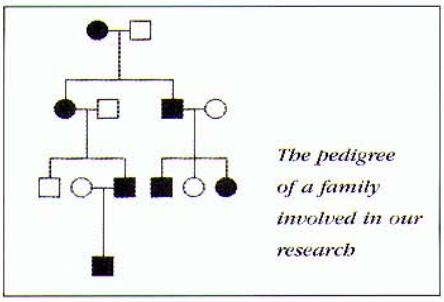
TEMPORAL LOBE EPILEPSY

In early 2002 a group of researchers in New York, discovered a gene called *LGI1* which causes a specific type of temporal lobe epilepsy where the patients experience auditory symptoms before the seizures such as hearing unusual voices, ringing in the ears, changes in volume and whistling noises. After this discovery was reported we also tested some of our families with this rare type of inherited epilepsy and found two families who have changes in the same gene.

One of these families was initially studied eight years ago but was too small for us to analyse on its own to identify the responsible gene. This finding demonstrates why it is important for us to have many families and individual patients participating in our research, even if the families are not large enough for us to actively look for a gene causing the seizures in that family on its own. This is also the reason why we ask to store your DNA samples for an extended period of time. When a gene is discovered either by us or by other researchers, we need to test many other patients with similar epilepsy syndromes for changes in the same gene. In this way we can develop an understanding of exactly what types of epilepsy that gene might cause and how important the gene is as a cause of epilepsy in the broader community.



The discovery of these genes brings the total number of known "epilepsy genes" up to 11, and our group is proud to have been involved in identifying seven of these 11 genes.



The pedigree of a family involved in our research

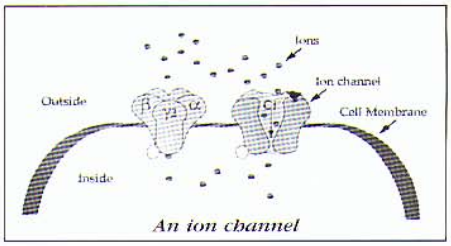
SEVERE MYOCLONIC EPILEPSY OF INFANCY

Severe Myoclonic Epilepsy of Infancy (SMEI) is a rare type of severe epilepsy in which an infant usually presents with febrile seizures and then goes on to develop several other seizure types over the next few years. These patients often have a family history of seizures but the syndrome has only recently been recognized as having a genetic cause.

In May 2001, a group of researchers in Belgium published a study in which a number of patients with SMEI were found to have mutations in the ion channel gene called *SCN1A*, a gene already known to be associated with epilepsy. Since this report, our group and others have studied a number of patients with SMEI who have *SCN1A* mutations. The most interesting observation has been that the mutations are *not* seen in the patient's parents, indicating it has arisen newly in the patient rather than being passed on from a parent. This finding is important because it tells us a patient's epilepsy may have a genetic cause, even though it has not actually been inherited. Nevertheless, we think there is still more to the story because of the frequent family histories of seizures in children with SMEI which cannot be accounted for by these newly arisen mutations.

HOW DO MUTATIONS IN ION CHANNEL GENES CAUSE EPILEPSY?

Most of the known genes causing epilepsy are ion channel genes. Ion channels are gateways or pores located in the envelope or membrane surrounding cells. The channels allow water and other substances such as electrically charged sodium and calcium particles (ions) to flow in and out of the cells. Most of the epilepsy genes identified have been ion channels. When charged particles move through an ion channel, an electrical current is produced. Our cells use these electrical currents to pass messages around our bodies and brains. Experiments show that changes identified in epilepsy genes affect how long the channels are open or closed and consequently the amount of current produced. When an excess amount of current is produced, the cells become *hyperexcitable*. A hyperexcitable group or network of cells can be more easily triggered to discharge all of their current at once, leading to a seizure.



An ion channel

TWINS AND EPILEPSY: ANALYSIS OF ACQUIRED FACTORS

In our last newsletter we explained that twins do not have a greater chance of having epilepsy than the general population but twins can provide special insights into the causes of epilepsy. It is commonly believed that events during pregnancy and birth (obstetric factors) may contribute to the development of epilepsy and that second born twins are at greater risk of developing epilepsy compared with first born twins because pregnancy and birth pose more risks for them. Using 63 twin pairs discordant for epilepsy (i.e. only one twin of the pair had seizures), we investigated the role that obstetric factors may have on the development of epilepsy. This involved studying exhaustive pregnancy, birth and posnatal histories obtained from the mothers, hospitals of birth, obstetricians and paediatricians. The data from this study suggests that the order of birth has no impact on the twins' probability of developing epilepsy and also that obstetric factors do not have a major role in causing epilepsy.

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 procedures to do with research. 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 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:

We can be reached at the above numbers and would be happy to answer any questions.

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.