EPILEPSY GENETICS

Newsletter

ISSUE NUMBER 1 NOVEMBER 2001

EPILEPSY RESEARCH INSTITUTE
Austin & Repatriation Medical Centre
(Repat Campus),
Banksia Street, West Heidelberg,
Victoria 3081
Tel: (03) 9496 2737
Fax: (03) 9496 2291

Professor Samuel Berkovic

Associate Professor Ingrid Scheffer

INTRODUCTION

Welcome to the first edition of this newsletter, which we aim to produce regularly to update participants and supporters about our research.

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, and to date approximately three thousand people have been involved.

The research team is headed by Professor Samuel Berkovic, Consultant Neurologist and Epileptologist and Professor of Medicine (Neurology) at the University of Melbourne. The team is based at the University of Melbourne Department of Medicine at the Austin and Repatriation Medical Centre, Heidelberg Victoria.

Dr. Ingrid Scheffer is a Paediatric Neurologist and Epileptologist who has worked with Professor Berkovic for many years, and gained her degree of Doctor of Philosophy (PhD) in the field of epilepsy genetic research. She has recently been appointed as an Associate Professor in the Department of Medicine at Melbourne University

Together Professor Berkovic and Dr. Scheffer coordinate a team of clinical research officers and higher degree students, and contribute extensively to the ongoing success of the research effort through liaison with a large network of collaborating doctors and scientists in Australia and around the world.

RECENT NEWS

In a recent breakthrough, the Epilepsy Genetic research team have identified a genetic mutation responsible for two of the most common types of childhood epilepsy. The involvement of Jessica (photographed) and 39 members of her family was crucial to the detection of the gene. The full details of the research are published in the May edition of the science journal Nature Genetics, and there was also television coverage of the discovery.

COLLABORATION: THE KEY TO SUCCESS

The clinical research group in Melbourne diagnoses individuals, twins and families with epilepsy. This has led to the discovery of many forms of inherited epilepsy. We work closely with a large molecular genetics group at the Women's and Children's Hospital in South Australia headed by Professor Grant Sutherland and Dr. John Mulley. This laboratory receives the blood samples collected from study participants. The staff extract the DNA (genetic material) and perform the analyses that enable us to identify genes for epilepsy.

Laboratory Staff, Dept. of Physiology, Melbourne University.

At the University of Melbourne Department of Physiology, a team headed by Dr. Steven Petrou and Associate Professor David Williamson, have been helping us understand how some of the genetic changes we have identified with our work on families may cause seizures.

A basic science laboratory at Monash University headed by Dr. John Drago is also studying the fundamental consequences of these genetic changes.

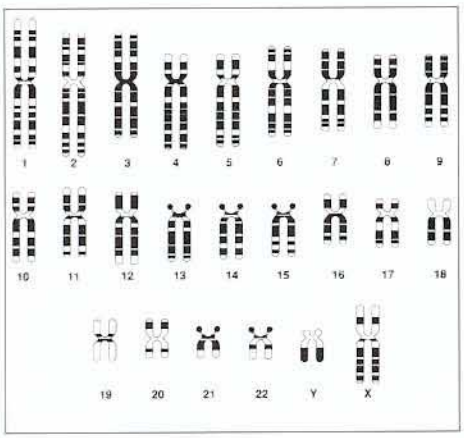
Laboratory Staff, Women's & Children's Hospital, Thebarton, S.Australia.

THE UNIVERSITY OF MELBOURNE

Austin & Repatriation Medical Centre

The discoveries of the Melbourne-Adelaide team have also been assisted by a relationship with some doctors and scientists in North America and Europe.

The success of this collaborative research was recognised at the 2001 International Epilepsy Congress by the awarding of



A set of human chromosomes.

the Novartis Epilepsy Prize, an international award given only every 4 years, to Professor Berkovic. In addition, the group has just received a prestigious Program Grant from the National Health and Medical Research Council (NHMRC), which offers funding for a period of several years to groups with a proven track record of successful inter-disciplinary collaboration.

CAUSES OF EPILEPSY:

There are many types of epilepsy, with many different causes. Some epilepsies are due to damage to the brain from a head injury or the result of other brain diseases such as stroke. However, in many cases there is no detectable change in the brain structure or underlying illness that can be associated with the onset of seizures. Many of these common forms of epilepsy that arise in an otherwise healthy person have an inherited component, and the inheritance (genetics) of epilepsy is a subject of intense world-wide interest.

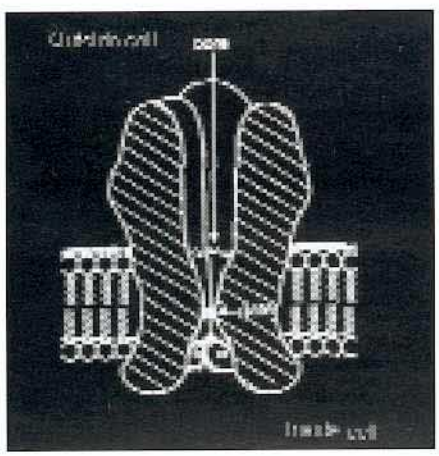
By understanding the genetic causes of epilepsy we hope that the way seizures occur can be identified, and that this knowledge will result in better treatments in the future.

Our collaborative group is the world leader in this area. We have performed clinical studies and obtained blood from a large number of twins, families and individuals with epilepsy over the last 12 years.

WHAT HAS BEEN DISCOVERED SO FAR?

To date, 8 genes that cause different types of epilepsy have been found, and our group has been involved in 5 of these discoveries. A revolutionary insight from this research has been that such epilepsies are associated with subtle changes in *ion channels*.

What are ion channels? All cells in the body, including brain cells, have an envelope or covering around them called a membrane. This membrane has gate-ways or channels within it, that allow water and natural substances to flow in and out of the cells. Electrically charged particles (ions) such as sodium and



An ion channel.

calcium also flow in and out of these cells and the regulation of this flow by ion channels is extremely important for normal brain activity. Changes in these ion channels cause epilepsy in some patients.

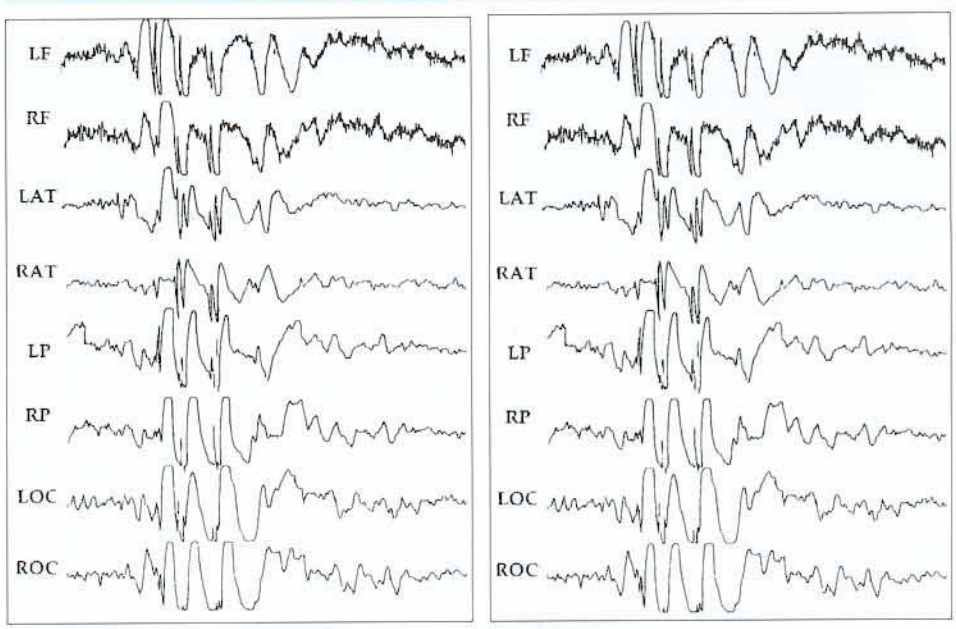
The team of scientists who work with us at Melbourne University study the ion channels in their various forms in individual animal cells. Normal and variant forms of the ion channels are inserted into the membrane, and the effect of the different channels on the cell's electrical currents is observed. This research will enable us to understand how the ion channel changes we have detected in people cause seizures.

WHAT DO TWINS TELL US?

Twins *do not* have a greater chance of having epilepsy than the general population but they can provide special insights into the causes of epilepsy. Where both individuals in a pair of identical twins have the same condition, it is very likely that it is due to an inherited factor. Together with Professor John Hopper of the Australian National Health and Medical Research Council (NHMRC) Twin Registry we have studied over 400 twins with epilepsy. We have discovered new inherited forms of epilepsy and gained a deeper understanding into which forms of epilepsy have a major inherited component.

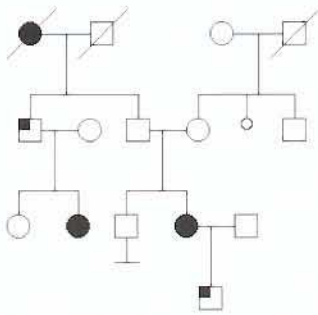
Similarly, by studying twins where only one has epilepsy we are gaining insights into the acquired causes of epilepsy. We continue to recruit volunteer twins with epilepsy and have begun to look for subtle differences in their brain magnetic resonance (MRI) scans that offer clues as to the causes of some forms of epilepsy.

ARTHUR & BILLY'S EEGS: EEGS (BRAIN WAVE RECORDINGS) OF IDENTICAL TWINS ARE IDENTICAL



FAMILIES WITH EPILEPSY:

We have been studying large families with epilepsy where many individuals have seizures. This has also led to the recognition of new types of epilepsy and to the isolation of genes causing epilepsy in some of these families.

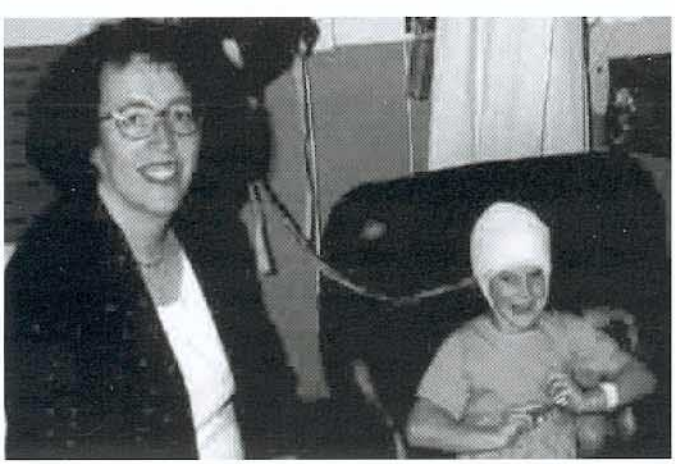


A Family Pedigree.

Large families in which many family members have seizures are uncommon, but so far they have given us valuable insights into how seizures may be inherited. We study both affected and unaffected individuals from such families. This allows us to classify the types of seizures occurring in the family and to see if the affected members all have a related seizure disorder. If a large number of members from a family do appear to share a related seizure disorder, we can then compare the DNA from affected and unaffected individuals and try to find the gene that may be causing the epilepsy in the family members. If the family is small, we cannot look for a new gene, but we can test for the relevant known genes. If no genes are currently known for the type of epilepsy, the DNA can be stored and tested as discoveries are made.

INDIVIDUALS:

It is also of great value to our research to study individuals with no family history who have well characterised epilepsy.



Video-EEG monitoring can be done to characterize seizure types.

We cannot look for new genes using DNA from a single individual. However, we can test the person for known genetic changes if genes have already been discovered that are known to cause their type of epilepsy. This helps us to understand how important each epilepsy gene is in causing particular types of epilepsy. It may also give the individual some useful information about the cause of their seizures, although only a small proportion of people have seizures caused by a known gene. In the common situation where no genes are currently known for a person's type of epilepsy, the DNA can be stored and tested later as discoveries are made.

WHERE IS THIS RESEARCH LEADING US?

So far it appears that the newly discovered single genes are not causing seizures in the majority of people with epilepsy. Whilst it is likely that more single genes will be found that can cause epilepsy in their own right, these disorders are likely to remain rare.

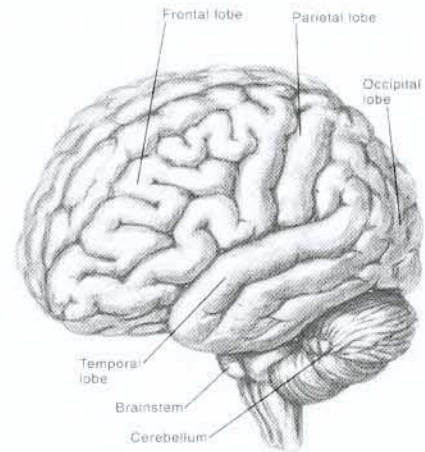
For most of the common forms of epilepsy due to a genetic cause, it is believed that a number of genes are working together to produce the seizures. This is an area of current research focus.

To study the inheritance of conditions which result from many genes working together is much more difficult than looking for disorders caused by single genes. This is because the effect of each gene may be very small and therefore difficult to detect.

Thus, whilst we will continue to study large multi-generation families where many members have seizures, a new method of research needs to be adopted to look at the more common situation where a person with epilepsy may not have (m)any affected close relatives. This will involve doing large scale population studies of affected individuals and their closest relatives, such as parents or siblings.

Eventually, we hope that by finding the genes contributing to the development of seizures that we will be able to discover

Anatomy of a Brain



their role in the brain. The next step will be to understand how the different genes alter the brain's electrical activity to produce seizures. Once this is known, development of treatments based on an understanding of how the brain function has been altered by the different genes involved may be possible. This will be a medium to long-term process, as the complexity of the brain presents a great challenge to researchers.

WHEN WILL NEW TREATMENTS BE DEVELOPED?

Understanding the causes of epilepsy is the first step and great strides have been made. Developing new treatments will take many years but this research is a major step along the way. Our group is a major contributor to the discovery of knowledge that will facilitate the development of new treatments.

HOW IS THIS WORK SUPPORTED?

The research has been heavily supported over the years by the National Health and Medical Research Council of Australia as well as by grants from other bodies, such as the Austin Hospital Medical Research Foundation, the Royal Children's Hospital Research Foundation, The Epilepsy Foundation of Victoria and private donations. Recently we have been supported by Bionomics Limited, a publicly listed biotechnology company. Bionomics will undertake further work to apply our research discoveries to the practical development of new treatments for epilepsy.

We are also indebted to all the study participants over the years who have generously given of their time and resources to support the research effort, and to those people from many walks of life who have referred twins, families and individuals to the research programme.

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 the research. Study participants enrolled from July 2000 onwards are required to state how long their DNA sample is allowed to be used for our research when they agree to participate. In addition, people who were enrolled as children are now required to give their consent when they reach 18 years of age.

If you have any concerns or queries about the research, please do not hesitate to contact us. 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.

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:

Dr. Judith Adams
(03) 9496 2990

Dr. Carla Marini
(03) 9496 2757

Mary Connellan
(03) 9496 2721

Bronwyn Grinton
(03) 9496 2761

Kathryn Crossland
(03) 9496 2737

Lisa Johnson
(03) 9496 2330

Fiona Phillips
(03) 9496 2764

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.