EPILEPSY GENETICS

Newsletter

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Epilepsy Research Centre

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RECENT NEWS

A new pattern of inheritance has been identified with a form of epilepsy only found in girls. We recently identified the gene responsible and this exciting finding has been published (more on page 2).

Welcome to the 2009 edition of the Epilepsy Genetics Newsletter. This year marks our 20th anniversary of research into the genetics of epilepsy and what better time to acknowledge all the people that make our research possible. We would like to take a moment to thank the 11,000 participants and families for the time and effort they contribute to our studies as well as all the clinicians for referring patients. Each year brings steady progress in the field of epilepsy genetics with identification of genes that cause seizures and related conditions. Our big picture aim is to develop new therapies, help understand prognosis and inform genetic counselling.

We are fortunate that two outstanding international research fellows have recently joined our team. Dr Daniel Carranza Rojo from Barcelona, Spain, is a Paediatric Neurologist who is working on epilepsies beginning in childhood. Dr Karl Martin Klein from Marburg, Germany, is an adult neurologist who is working on our syncope (fainting) project as well as epilepsy genetics. Two new research assistants, Susannah Bellows and Simone Yendle, are enthusiastic new members of our group. We said goodbye to research assistants Carla Bruce and Alicia Calderone, and in February 2009, Sarah Bowen, our Sydney based research assistant, will leave us to pursue a career in pharmacy. We wish them well. We are excited that our group in Melbourne has grown to include a new molecular genetics laboratory at Austin Heath which will enable even more projects to be undertaken (see page 2 for more details).

We remain keen to study large families in which a number of people have seizures as this is a proven way to find epilepsy genes. We have had further success this year in the disorder described below called Epilepsy in Females with Mental Retardation (see page 2). However, it is clear that the way to find genes relevant to epilepsy in most people is through large-scale studies in collaboration with international groups. This is because most people with genetic forms of epilepsy do not have a family history of seizures at all. The reason is that their epilepsy follows "complex inheritance" which means it is due to the interaction of a number of genes, possibly with an environmental contribution. The way to find genes involved in complex inheritance is to study 1000s of individuals with the same type of epilepsy. Such a study is beyond the reach of independent research groups making it necessary to collaborate in large-scale international research studies. We will also involve individuals with a family history in these studies. So we are now keen to recruit anybody with epilepsy where genes are likely to play a role, not just those with a family history.

Please have a look at our website, ***www.epilepsyresearch.org.au***, which provides a range of information about the Epilepsy Research Centre, our research projects and also information for epilepsy patients interested in seeking treatment through the Comprehensive Epilepsy Program at Austin Health. Past issues of the newsletter and links to other useful sites can also be found. If you would like to contact us with any specific queries about our research, please do so via email at ***epilepsy-austin@unimelb.edu.au***.

The Epilepsy Research Centre team and our collaborators at the 2008 Epilepsy Research Retreat. Our international moderator was Professor David Chadwick, University of Liverpool, UK.

THE UNIVERSITY OF MELBOURNE

Austin Health

New Molecular Genetics Laboratory at the University of Melbourne, Austin Health

Over the last 14 years, we have had a highly successful collaboration with the molecular genetics laboratory of Associate Professor John Mulley at the Women's and Children's Hospital in Adelaide. As you may know, blood samples collected for our genetic research studies are sent to Adelaide. This fruitful collaboration has led to many important discoveries, including the identification of the first epilepsy gene in 1995, and subsequently ten of the sixteen epilepsy genes currently known.

This year, we have established a second epilepsy genetics laboratory at Austin Health in Melbourne to work in collaboration with the Adelaide group and the clinical genetics team. As our knowledge of epilepsy genetics increases, there are more and more questions being asked that we are keen to investigate. This new laboratory will greatly increase our capacity to investigate the role of genes in causing epilepsy and related conditions.

The new laboratory is under the leadership of Prof Sam Berkovic. Dr Todor Arsov has joined the lab as a postdoctoral scientist in molecular genetics. He did his PhD at the Australian National University and recently completed his postdoctoral research at Stanford University, California. Research assistant John Damiano is working with Todor. The team will grow with the addition of PhD scholar Felicity Jackling in 2009.

Todor Arsov and John Damiano working hard in the new laboratory.

Epilepsy and Mental Retardation Limited to Females

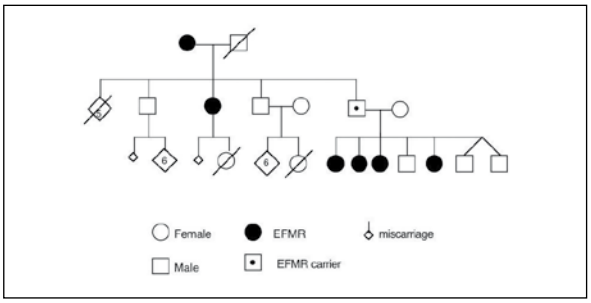
Epilepsy and Mental Retardation limited to females (EFMR) is a rare epilepsy syndrome that only affects females. EFMR follows an extraordinary form of inheritance where females have the condition and males transmit it but are not affected. This form of inheritance is novel and is almost the reverse of X-linked recessive disorders, such as Duchenne muscular dystrophy, where boys are affected and their mothers transmit the disorder. EFMR is distinctive as only girls are affected in the family tree.

Seizures begin in infancy or early childhood between 6 and 36 months of age. Affected girls may show normal development initially, but then their development may slow and they have mild to severe intellectual disability. Some affected girls have normal intellect. EFMR was previously reported in only one large family from the USA, however, over the past few years we have identified five new families. By carefully studying these families, we were able to further describe the characteristics of EFMR. We found that psychiatric features were also an important part of EFMR with autistic features, obsessive features, depression, panic attacks, aggressive behaviour and self injury in some affected women. This research was published in the scientific journal "Brain" in 2008 (Scheffer et al., Brain. 2008 Apr;131(Pt 4):918-27).

Subsequently, based on these clinical studies, our molecular genetic collaborators in Adelaide, Leanne Dibbens, Jozef Gecz and John Mulley identified protocadherin 19 (PCDH19) as the gene that causes EFMR. Mutations in PCDH19 have been found in seven unrelated families with EFMR, which we published in "Nature Genetics" earlier this year (Dibbens et al. Nat Genet. 2008 Jun;40(6):776-81). PCDH19 is located on the X chromosome. Women have two copies of this chromosome, while men have one X and one Y chromosome.

Although the biological role of the PCDH19 protein is not known, protocadherins are found in the nervous system and are involved in establishing connections between neurons (nerve cells). We do not yet fully understand how abnormal changes in this gene cause seizures, or why only females are affected, but we are continuing to conduct research to answer these questions.

Our work on EFMR will enable doctors to diagnose this rare disorder and to identify the underlying genetic mutations. This in turn will enable better treatment and very importantly, genetic counselling for family members.



A family with Epilepsy and Mental Retardation limited to Females showing the unique inheritance pattern where only females have the disorder and unaffected males transmit it.

Associated Studies

As the years progress, our team continually expands both in size and areas of research interest. Therefore, we take this opportunity to update you of some of our other related research.

Autism

Prof Ingrid Scheffer has received an NHMRC grant for three years to investigate the genetic basis of autism spectrum disorders (ASD). In collaboration with A/Prof Martin Delatycki at the Murdoch Childrens Research Institute, and Dr Sarah Wilson, from the University of Melbourne, they are studying families with ASD to help identify genes associated with autism spectrum disorders.

Syncope & Breath-holding attacks

Dr Karl Martin Klein is working on the study of families with fainting (syncope) and breath-holding attacks. In collaboration with Dr Melanie Bahlo from the Bioinformatics Division at the Walter and Eliza Hall Institute, we wish to identify genes causing syncope. We have successfully collaborated with Dr Bahlo in the past to identify an epilepsy gene (see opposite page) and hope we will achieve similar success in this exciting new field.

Twins

In 2008, medical student, Jazmin Eckhaus, studied twins who had febrile seizures as young children. This follow-up of twins studied over the last 20 years, was performed to find out how many children have seizures later in life. We continue our ongoing investigation of twins where one or both have had seizures as well as utilising twins who have had syncope for our new fainting study.

Gene-Hunting in a Rare Progressive Myoclonus Epilepsy

Action Myoclonus-Renal Failure Syndrome (AMRF) is a progressive myoclonus epilepsy characterised by jerks (myoclonic seizures) and kidney failure. The rare syndrome was initially described in the French Canadian population but has since been seen around the world. This epilepsy syndrome shows an autosomal recessive inheritance pattern which means an individual must inherit two copies of an abnormal gene, one from their mother and one from their father, in order to develop the condition.

In 2004, we identified AMRF in a patient whose parents were related. Although there was no family history of AMRF, the family structure allowed Dr Melanie Bahlo to use a new technique to find segments of the genome (DNA) where the patient had two identical copies of segments of DNA. Dr Bahlo compared this with the DNA of the patient's unaffected sibling and showed that the sibling did not have identical copies in the same region. The DNA of another patient with AMRF from Australia showed a similar pattern and helped hone down the region of DNA that we predicted would contain the gene causing AMRF. Microarray experiments comparing the proteins produced by the patients and their unaffected siblings identified SCARB2 as the gene likely to be causing AMRF. Sequencing of SCARB2 and cellular studies confirmed it as the causative gene.

Identifying genes in families where only one person has epilepsy is usually not possible. The novel way that these techniques were combined to identify SCARB2 as the gene responsible for AMRF is an exciting advance in gene-hunting methods. We hope that this will help find more genes in the future in epilepsy syndromes that follow this type of inheritance.

Investigating The Ketogenic Diet for Treating Epilepsy

The Ketogenic Diet (KD) is a high fat, low carbohydrate diet that was proposed as an epilepsy treatment in the 1920s. The KD controls seizures by inducing a state of ketosis, where the body uses fat instead of carbohydrate (sugar) as the major source of energy. In 2005, the Ketogenic Diet Program was launched at Austin Health in collaboration with the Dr Mark Mackay and the Ketogenic Diet team at the Royal Children's Hospital. Our collaborative aims were to investigate the side effects of the KD and for which epilepsy syndromes the KD is most effective.

Twelve patients with epilepsy participated in the KD program between 2005 and 2008 at Austin Health. This group included patients with Symptomatic Generalised Epilepsy (7 patients), Symptomatic Focal Epilepsy (2 patients), Childhood Absence Epilepsy (1 patient), Progressive Myoclonus Epilepsy (1 patient), and Epileptic Spasms (1 patient). Seizure frequency was measured by parents for four weeks before the diet was started and then compared to the number of seizures the children were having after the KD commenced.

Patients were deemed responsive to the diet if they experienced more than a 50% reduction in the number of seizures when they were on the KD. We are happy to be contacted about participation in our KD program.

Due to the small numbers of patients enrolled in the study so far, no specific conclusions can be drawn. However, a broad range of generalised epilepsy syndromes responded to the ketogenic diet.

Inaugural Australian and New Zealand Dravet Families Conference

In August 2008, we organised the first conference for families who have a child with Dravet syndrome together with Jean Ewing at the Epilepsy Foundation of Victoria and Very Special Kids. The conference was held in the beautiful grounds of Very Special Kids in Melbourne and 45 families from all over Australia and New Zealand attended with more than 100 participants.

Presentations from neurological, medical, allied health and community service specialists aimed to enhance parents' knowledge and coping strategies. Speakers included Prof Ingrid Scheffer, Dr Jill Rodda and Dr Sian Hughes, as well as parents of children with Dravet syndrome. Michelle Welborn, incoming President of the International Dravet syndrome Epilepsy Action (IDEA) league, also made a special visit to talk to parents about the recent advances made by the IDEA league. The event provided parents and siblings with the opportunity to meet other families and discuss shared experiences and concerns.

Overall, the day was a huge success for both parents and guests and highlighted the need for information sharing at meetings based on specific epilepsy syndromes. Plans are afoot to organise a weekend for children with Myoclonic-Astatic Epilepsy (Doose syndrome) in 2009.

Dravet Syndrome Symposium attendees at Very Special Kids House in Melbourne.

Thank-you

We would like to thank everyone who has contributed to our research in 2008 by participating in the research studies, referring patients and families, or making donations to support our research. We have been especially delighted when the families who have participated in our studies send donations. This reinforces the fact that our families as well as the researchers value the significance of our work.

If you would like to assist our important research to help us understand epilepsy, you can make a donation to the Epilepsy Research Centre. Please contact us on (03) 9496 2330, by 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. Study participants are asked to state how long they permit their DNA sample to be used for our research. When children or adolescent participants reach 18 years of age, they are now asked to give their own consent. Participants are free to withdraw from the study at any time.

Our usual practice is to write to you if we find a meaningful genetic result that is relevant to you. If you would like further information about this, we invite you to make contact with us so that we can discuss this further.

All information collected for our research is strictly confidential and is not used for any purpose other than for research to understand epilepsy and related conditions. In particular we do not share any of your information with other members of your family, including any results. Some information may be shared with collaborating scientists to identify or better understand epilepsy genes.

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 along with your name and address and return it to us.

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

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We greatly appreciate all the assistance we receive from our supporters.

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