EPILEPSY RESEARCH CENTRE NEWSLETTER 2023

>825 GENES CAUSE DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES
EARLY DIAGNOSIS OF DRAVET SYNDROME
TRACING AN EPILEPSY GENE BACK 800 YEARS

Professor Samuel Berkovic
Neurologist

Professor Ingrid Scheffer
Paediatric Neurologist

It is wonderful to reconnect after the last few years of pandemic disruption and uncertainty. We hope you have weathered this challenging time and life is returning to normal. Our team pivoted to remote working through the pandemic but are delighted to be back working together in person, where we have a critical mass to take our understanding of epilepsy and genetics forward.

We were keen to continue supporting individuals with epilepsy in novel ways through the COVID-19 pandemic. We contributed to a paper advising clinicians on how to manage their patients with epilepsy at such a distressing time (free download at: https://n.neurology.org/content/94/23/1032.long). We were also delighted to work with the US Dravet Syndrome Foundation on an analysis showing that individuals with Dravet Syndrome coped well with COVID-19 vaccination. We showed that it posed much less risk than the COVID-19 infection for patients with Dravet Syndrome (free download at: https://onlinelibrary.wiley.com/doi/10.1111/epi.17250).

Here, we capture just a small number of our research projects which we hope you will find interesting reading. Our research focuses on all forms of epilepsy from common epilepsies to rare, severe epilepsies. These studies depend on your participation, which now includes more than 25,000 people! We are also indebted to our referring doctors and our other supporters for their wonderful contributions. We can't thank you enough for working with us to understand the epilepsies as we seek to improve outcomes for people living with epilepsy.

Covid & Epilepsy

Covid & Dravet Syndrome

The Epilepsy Research Centre Team

We were delighted to have our 28th Epilepsy Research Retreat in person on the fair shores of Geelong. We had the Research Retreat online during the covid years and certainly missed the opportunity to network and be as creative together.

We have welcomed an adult neurologist to our leadership team, Associate Professor Piero Perucca, a long-time collaborator from Monash University, the Royal Melbourne Hospital and Alfred Health. Piero has joined as Director of the Comprehensive Epilepsy Program at Austin Health and Associate Professor of Adult Epilepsy at the University of Melbourne. Piero is a wonderful neurologist who has major interests in the genetics of epilepsies, trials of new epilepsy medications, epilepsy and pregnancy, and evaluating patients for epilepsy surgery.

Brialie Forster, who has been nursing on our Austin pediatric ward for 20+ years, has established a world first role of a Developmental and Epileptic Encephalopathy (DEE) nurse. The demand for this role has already been overwhelming and she brings a superb skillset to our team. We also welcomed Talia Allan, Olivia Hoeper and Shannyn Genders as new clinical research assistants. Susan Cooke has taken up the new role of Research Finance Officer for the Epilepsy Research Centre and Eliza Honybun is the Neuropsychology Co-ordinator for the newly established DEER program. We are fortunate to have the following technical assistants: Olivia Adrian, Ned Solly, Josh Stent and Chloe Tomaras, supporting our team. In our laboratory we welcomed research assistant Tom Witkowski, bioinformatician Neblina Sitka and Sian McDonald as a technical assistant.

Now that the covid pandemic is further behind us, Dr Sindhu Viswanathan is a paediatric Neurology Fellow who has joined us from Malaysia and Dr Annie Chiu is a paediatric Neurology Fellow from Hong Kong. Dr Michelle Dang, Dr Sam Gooley and Dr Shuyu Wang joined us as PhD students and adult Epilepsy Fellows.

We are delighted to have Professor Emilio Perucca join us from Italy as Honorary Clinical Professor in the Department of Medicine, (Austin Health) of the University of Melbourne. He was previously Professor at the University of Pavia and Director of the Clinical Trial Center of the 'C. Mondino' National Neurological Institute in Pavia, Italy. Professor Perucca has served as President of the International League against Epilepsy and his research activities have focused on the clinical pharmacology of antiseizure medications, the treatment of seizure disorders and outcome assessment in people with epilepsy.

28th Epilepsy Research Retreat 2022

THE UNIVERSITY OF MELBOURNE

Austin HEALTH

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EPILEPSY RESEARCH CENTRE
Melbourne, Australia

Want to know more?
Watch the talks on Epileptic Encephalopathies at www.genes4epilepsy.org

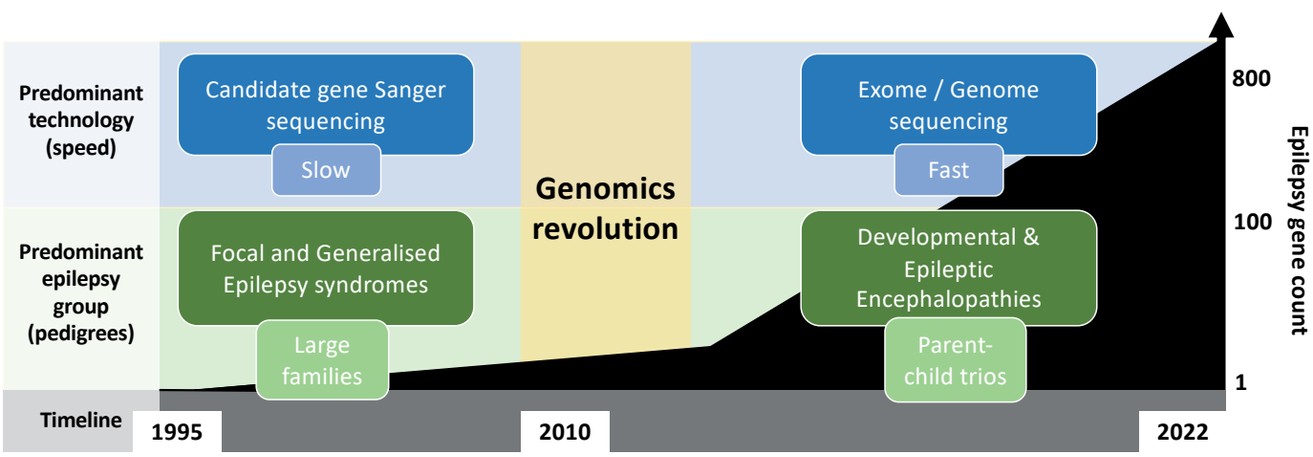
>825 genes cause DEEs

Karen Oliver

Senior bioinformatician and PhD scholar, Karen Oliver, recently analyzed the number of genes that are a monogenic cause of epilepsy, monogenic means that one gene causes the disorder.

Of the 926 genes that Karen identified, 825 cause DEEs. Interestingly, Karen found that there are more genes causing autosomal recessive DEEs, than autosomal dominant DEEs. In Australia, autosomal dominant DEEs are far more frequent, whereas, autosomal recessive DEEs are more frequent in inbred populations. The other fascinating finding was that some DEE genes are also relevant to milder, common epilepsies.

This paper is available for free download at
https://onlinelibrary.wiley.com/doi/epdf/10.1111/epi.17547



Approximate timeline and impact of monogenic epilepsy gene discoveries over the last 27 years.

Developmental and Epileptic Encephalopathy Research - (DEER) Program

Developmental and Epileptic Encephalopathy Research Program

Developmental and epileptic encephalopathies are the most severe group of epilepsies where patients typically have many seizure types that are difficult to control, together with slowing of development, and often loss of skills. The frequent epileptic activity on their EEG is associated with developmental slowing or regression. The DEEs typically begin in infancy or childhood and are usually associated with a range of other features, such as sleep, behaviour, movement, and feeding problems. These serious disorders also carry higher risk of early death.

The DEER program brings together our 30-year history of DEE research at the Epilepsy Research Centre and, while we have always been keen to include people from around Australia and beyond, we now have research funding to design a formal Australia-wide study. We are always keen to include people from around the world. We have brought together experts in all areas of DEE research and healthcare to enable to us ask critical research questions that will improve outcomes. We have hosted 2 wonderful symposia where we have heard from doctors, scientists and allied health professionals working on clinical, laboratory, genetic, bioinformatic, psychosocial, health economic and implementation science aspects of DEEs.

First inaugural DEER Symposium 2022

We have developed a DEE Natural History Study (NHS), where we will focus on epilepsy, development, other medical issues and psychosocial outcomes over the life of each DEE disease. As there are now more than 825 genes that cause DEEs, this means we are effectively studying at least 825 different diseases. To support this research, we have developed a new online database and are designing researcher, doctor and patient portals within our new website that will allow all parties to contribute and learn from this important work. With help from the doctors from around Australia who have joined our new DEER Australian Paediatric Neurology Network, the Genetic Epilepsy Team Australia (GETA) and our DEE consumer engagement committee, we hope to start enrolling families in our DEE Natural History Study in the next few months.

Defining Dravet syndrome to enable early diagnosis and be ready for precision medicine therapies

Building on our 25-year history of research in Dravet syndrome, we analysed the presentation of 205 individuals with Dravet syndrome from around the world. We found that many patients did not fit the description often used to diagnose Dravet syndrome. For some this means that that a diagnosis of Dravet syndrome may be delayed which in turn means the wrong anti-seizure medications may be prescribed, potentially impacting long term outcomes. Early diagnosis is becoming even more important as we enter the era of precision medicine with gene therapies under development.

Doctors are taught that patients with Dravet syndrome start having seizures at 6 months of age, however, we found that some patients started having seizures from as young as 6 weeks or as late as 20 months of age. Doctors are also taught that their first seizure is a long, febrile (fit with fever), hemiclonic (jerking down one side) seizure, however, the first seizure for most patients was tonic-clonic (both sides stiff and jerking) and only half had a fever. One third of patients had a short seizure at onset, lasting 5 minutes or less rather than a very long, 30+ minute seizure.

Development is often thought to be typical in the first year of life, however, we found that ¼ had developmental delay prior to age one year. In some patients, development was normal up to the age of 5 years. Tonic (stiffening) and atonic (sudden loss of tone) seizures are often not considered part of Dravet syndrome in childhood, yet we found that a fifth of patients had these seizure types.

By refining the definition of Dravet syndrome based on evidence from a large group of patients, we will help doctors to recognise and diagnose Dravet syndrome earlier, ensuring patients receive appropriate treatment.

This paper is available for free download (courtesy of a grant from The Dravet Syndrome Foundation Spain) at https://onlinelibrary.wiley.com/doi/epdf/10.1111/epi.17015

Natural History Studies and Clinical Trial Readiness

Natural History Studies (NHS) are observational studies designed to track the course of a disease and identify genetic, environmental, and other factors that occur through the patient's life. They differ from patient registries, which include basic facts about patients and their genetic variant. Natural History Studies have greater breadth and depth about each disease, and track disease progress over time. Because each genetic DEE is rare, it is important that DEE Natural History Studies are properly designed, supported and can be accessed by patients from around the world. Natural History Studies for DEEs are critical to establish whether new therapies are effective, as they allow us to evaluate whether the new therapy improves the long term outcome.

Clinical trial readiness relies on understanding the relationship between the causative genetic abnormality and the features of the disease. It also needs knowledge of how the disease progresses over time, to select appropriate patients for clinical trials.

Natural history studies are extremely important for patient care to ensure appropriate medical surveillance for medical complications as the person ages. They also inform reproductive counselling for the individual and family members. We have carefully designed a DEE Natural History Study as a critical basis for assessing the value of novel therapies to improve patient outcomes.

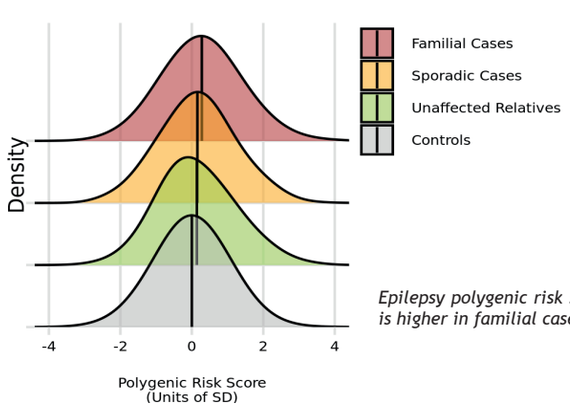
Palmer EE, Howell KB, Scheffer IE. Natural History Studies and Clinical Trial Readiness for Genetic Developmental and Epileptic Encephalopathies. Neurotherapeutics 2021; 18: 1432-44. doi: 10.1007/s13311-021-01133-3. PMID: 34708325

Finding genes for common epilepsies

There has been great success in finding single genes that cause epilepsy, especially in the severe group of Developmental and Epileptic Encephalopathies. There are many families where several people have had seizures, but no gene of major effect (monogenic) has been found. It is likely these families have polygenic (multiple genes) epilepsies where many genes of small effect contribute to their epilepsy. A relatively new method to try and identify these common gene changes of minor effect uses polygenic risk scores (PRS). Our study investigated whether common gene changes are more likely to be found in individuals with familial epilepsies compared with those with non-familial epilepsies, where no one else in the family has epilepsy.

PRS estimate the risk for an individual that combine common changes (variants) linked to epilepsy through large population studies (see ILAE study below).

Results show that patients with familial epilepsy have a higher epilepsy polygenic risk score compared to the general population, non-familial epilepsy patients and relatives without epilepsy. The results demonstrate that common epilepsy risk variants can help explain why some family members develop epilepsy while others do not, and why some families develop specific types of epilepsy.



Epilepsy polygenic risk score is higher in familial cases.

This paper is available for free download at https://www.thelancet.com/action/showPdf?pii=S2352-3964%2822%2900260-2

Tracing a mutation back to its founder 800 years ago

In 1998, we were the first to identify that sodium channel genes could cause epilepsy. We discovered *SCN1B*, the gene that encodes the β-1 subunit of the sodium channel, which led others to identify *SCN1A* which encodes the *α*-1 subunit. We found the abnormal change (pathogenic variant) in *SCN1B* in a large Australian family. Since, our research program has identified 9 families with exactly the same change.

Recently our global collaboration in Epi25 found exactly the same abnormality in 5 families. We wanted to discover if the variant had occurred newly in these families or whether they were related long ago.

If two people have a large section of DNA that is identical, it is likely this section has come from a common ancestor. We examined the DNA around the *SCN1B* variant and found that all families did in fact share a section of DNA. This suggests all families are indeed distantly related and that the variant we have seen multiple times came from a single person long ago, rather than it having occurred independently in each family.

We estimated that all families have descended from an ancestor approximately 800 years ago. It is extraordinary to see this type of genetic variant persist in the population for so many generations, particularly beginning so early in childhood, but it is likely because it is associated with a mild form of epilepsy.

We also wanted to see how often this variant is present in a large group of people from the general population. We looked for the *SCN1B* variant in individuals who participated in the large UK Biobank study of 500,000 individuals. We found another 74 people with this same variant, and all 74 also have the identical DNA segment around the variant, suggesting they are distantly related. This tells us it is very likely this *SCN1B* variant first occurred in one single individual and then has been passed down through many generations to the different families around the world today.

This paper is available for free download at
https://www.cell.com/ajhg/fulltext/S0002-9297(22)00452-9

ILAE papers x5

Following our leading role in the major revision of epilepsy classification in 2017, we were pleased to join colleagues from around the world in papers formally defining epilepsy syndromes for the first time in five papers in Epilepsia. The classification system is designed to clearly define and communicate effectively regarding the diagnosis of different seizure types and epilepsy syndromes. The classification guides diagnosis for every patient in the world with epilepsy to establish their epilepsy syndrome. This, in turn leads to optimal management and understanding long term outcomes.

Epilepsy syndromes are often age-dependent, so the ILAE classification papers have grouped syndromes as neonates and infants, childhood, and onset at variable ages, which means the epilepsy is diagnosed in both child and adult patients. The new changes are designed to improve diagnosis, inform in providing the most appropriate treatment, and provide more accurate information around other medical features and long-term outcomes.

More information on the ILAE classification of the epilepsies can be found at www.epilepsydiagnosis.org

These papers are available for free download at

https://onlinelibrary.wiley.com/doi/epdf/10.1111/epi.17236
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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.

In order to assist us with 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). 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, or email us at **epilepsy-austin@unimelb.edu.au**

We continue to be at the forefront of Epilepsy Genetics research. We have two websites that may be of interest. **www.epilepsyresearch.org.au** 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 our newsletters and links to other useful sites can also be found.

Our new website **www.genes4epilepsy.org** has information about developmental and epileptic encephalopathies. This includes the talks from our last genetic epilepsies conference where there are many practical tips for looking after children or adults with these diseases. We are always keen to recruit new patients if they are interested.

Bladin-Berkovic Comprehensive Epilepsy Program

In June 2022, the Comprehensive Epilepsy Program at Austin Health was officially named the 'Bladin-Berkovic Comprehensive Epilepsy Program', after Professor Peter Bladin AO, and Laureate Professor Sam Berkovic AC. Sadly, Professor Bladin passed away in May 2022, aged 93 years, but Professor Bladin's son, Professor Chris Bladin, joined us together with Laureate Professor Sam Berkovic at Austin Health for the special event to officially name the Program.

Associate Professor Piero Perucca, the Director of the Bladin-Berkovic Comprehensive Epilepsy Program, said the naming of the Epilepsy Program is a well-deserved acknowledgement of their outstanding, lifetime contributions to epilepsy.

> "The work they have led and been part of has influenced the way we care for patients not only at Austin Health, but across the world."

Professor Peter Bladin AO - 1928-2022

Professors Ingrid Scheffer, Sam Berkovic, Chris Bladin (son of Professor Peter Bladin), Geoff Donnan, Richard MacDonnell and Piero Perucca

Ethical Considerations

The conduct of our research is over-seen by Human Research Ethics Committees. Study participants are asked to allow the indefinite use of their DNA sample for our research. People who were enrolled as children are asked to give their own consent when they reach 18 years of age provided we are able to contact them. If you have any concerns about this, please contact us so we can discuss this with you. If you have recently turned 18 and have not heard from us, please complete the change of address form or email us at epilepsy-austin@unimelb.edu.au to check we have your current details. 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 after you contact us to discuss the result.

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.

Information will be shared with parents of children in the study if they are under 18 years of age. Some information may be shared with collaborating scientists to identify or better understand epilepsy genes.

Donations

We are always in need of support to take our research forward.

Donations can be made via credit card, direct bank transfer and cheque.

- Credit card donations can be made online at https://giving.unimelb.edu.au/epilepsy-research-1?startcustomization=1
- **Cheques** should be made payable to the ***University of Melbourne***.
- Complete your contact details below and return this slip with your cheque to:

Epilepsy Research Centre, Lvl 2 Melbourne Brain Centre

245 Burgundy St, Heidelberg VIC 3084

For details on **direct bank transfer**, please contact Natasha Crawford on **03 9035 7344** or **epilepsy-austin@unimelb.edu.au**

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

Please find enclosed a cheque for my tax-deductible donation of $ .....

Name ..... Phone ..... Email .....

Address .....

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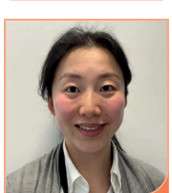

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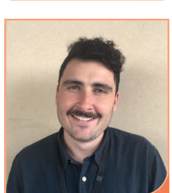

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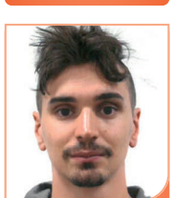

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Thank you

We would like to thank everyone who has contributed to our research 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 have sent donations. This reinforces that our families, as well as the researchers, value our work.

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