RESEARCH BLOG ROUNDUP

In this ediion...

DR KATE BAKER
SCIENTIFIC ADVISORY COMMITTEE (SAC) MEMBERT

REBECCA
SHAPE NETWORK STEERING GROUP MEMBER

DR SUKHVIR WRIGHT
EMERGING LEADER FELLOW

KIM MORLEY
EPILEPSY NURSE AND MIDWIFE

DR CAOIMHE TWOHIG-BENNET HEAD OF RESEARCH EPILEPSY RESEARCH UK

SHINING A SPOTLIGHT ON #WOMENINSCIENCE

To mark International Day of Women and Girls in Science, we're celebrating the incredible contribution of women to epilepsy research. From developing targeted treatments, to pioneering specialist epilepsy services, to safeguarding the integrity of our own grant making , these women are the backbone of research into epilepsy.

Download, share, print – ENJOY!

EPILEPSY RESEARCH UK

11th February 2022

IF GENETICS IS THE ANSWER, WHAT'S THE QUESTION?

Dr Kate Baker is a clinical geneticist at the University of Cambridge and a member of the Epilepsy Research UK Scientific Advisory Committee (SAC). She frequently works with families with genetic conditions including epilepsy and is often asked what the future holds for those affected and how can we improve it? In this blog, Kate shares the progress genetic testing has made in the last 10 years, including her own research into a specific genetic mutation, and explains why more research is still needed to provide answers for families.

It is easy to forget how far and how fast genetic testing has progressed for people with epilepsy. When I started training as a clinical geneticist 10 years ago, we could diagnose some rare epilepsy-associated syndromes, for example, Angelman syndrome or tuberous sclerosis, by spotting shared physical features.

Chromosome microarray testing, which looks for small deletions or duplications of genetic information, was just starting to become available. DNA sequence differences ("variants") in a handful of genes had been tracked down in some children with early-onset, severe epilepsies but it cost thousands of pounds to test any one gene, and we had to argue long and hard for permission from testing committees to request these tests on a case-by-case basis.

Then in the mid-2010s Next Generation Sequencing (NGS) methods were introduced, the costs fell, and large research studies (such as Deciphering Developmental Disorders, Epi4K, and the 100,000 Genomes Project) showed that NGS is efficient for diagnosing known rare disorders and discovering new diagnoses. Now, NGS is available as an NHS test for anyone whose epilepsy started before the age of two, or who has epilepsy plus intellectual disability, autism or physical features suggesting a genetic syndrome.

The chance of finding a genetic diagnosis is somewhere between 25% and 50%, depending on how much DNA sequence is analysed (a selective gene panel or the entire genome – the complete set of genes) and which research paper you read. If a diagnosis is found, we can give clear advice about risks for other family members, and we can (sometimes) provide useful pointers towards safe and effective antiepileptic medications.

So, if genetic diagnosis is now so good, why do we need more research into epilepsy and genetics? For at least 50% of individuals that are currently offered genetic testing, no diagnosis is reached. So we need more research to discover more genetic causes to add to the existing tests. Testing is not routinely on offer for people with later-onset epilepsies or milder (but still very significant) cognitive difficulties, even if these symptoms run in families, because the chance of making a diagnosis is currently low. Test results are plagued by "variants of uncertain significance" (VUS) which might indicate a cause or might be a red herring – these results generate a lot of worry for families (and doctors!).

To improve this situation, we need research into new ways to tell the difference between a harmless variant and a true diagnosis. We also need to understand why the same genetic diagnosis can cause vastly different symptoms in different people, even within the same family.

If testing continues to improve, and a genetic diagnosis can be found for an ever-increasing number of people with epilepsy, will this be the "end of the odyssey" as genetic diagnosis is sometimes termed? Well, no. When I meet patients and families in clinic to discuss a new genetic diagnosis, they are hungry for information. I am usually asked two questions: does this genetic diagnosis predict

IF GENETICS IS THE ANSWER, WHAT'S THE QUESTION?

future problems with learning, social interaction and mental health, and is there a treatment targeted at the genetic problem which will improve quality of life. It is very frustrating for families (and for me!) that we lack answers to these questions and solutions to these problems.

In very small steps, we are starting to find some answers. Here is one example. A few years ago I carried out a research project with families who had received a genetic diagnosis through the GOLD (Genetics of Learning Disability) study led by Professor Lucy Raymond. I travelled across the UK to meet people with variants in many different genes, to find out if people with similar variants shared the same sorts of problems.

In the space of a few weeks, I met 11 people from three families who all had variants in one gene, called ZDHHC9.

Unexpectedly, I found that most of these individuals had experienced a similar form of epilepsy during childhood – Rolandic seizures, which usually occur at night and start with facial twitching. Rolandic epilepsy is a common form of childhood epilepsy, usually without a known genetic cause, and is often associated with speech and language problems, which continue even if seizures stop. I found that people with ZDHHC9 variants had these speech problems too. This is important for children who are diagnosed with ZDHHC9 variants now because their epilepsy risk can be anticipated and their seizures treated effectively at an early stage. It also means their communication difficulties are recognised and not written off as part of broader learning disabilities. Finding out more about this genetic diagnosis has, in a sense, given these individuals a voice.

My colleagues and I decided to go one step further. We invited the ZDHHC9 group to visit Cambridge to take part in research brain scans, which they were all keen to do! Again, the results were surprising. We found that their deep brain "control" structures were smaller and less well connected to the rest of the brain. Using a type of functional brain scan called MEG (magnetoencephalography) we found that the normal "maps" of brain activity were present but were switched on and off less frequently.

Putting these observations together, we now think that ZDHHC9 is important for controlling the "dynamics" of brain electrical activity, which might explain why individuals with ZDHHC9 variants are at risk of seizures and have difficulties with communication and concentration. This idea could be important for other people with Rolandic epilepsy and might even lead to a targeted treatment – but a lot more research is needed to get there.

In essence, research with people who share the same genetic diagnosis is one way to move beyond understanding and treating epilepsy symptoms, to understanding and treating the brain differences influencing each individual's epilepsy risk and their long-term outcomes.

So, if genetics is the answer, what do YOU think should be the question?

Dr Kate Baker
Scientific Advisory Committee (SAC) Member
University of Cambridge

THE IMPORTANCE OF RESEARCH INVOLVEMENT

Rebecca has lived with drug-resistant focal epilepsy for the past 30 years. In April, she joined our SHAPE NETWORK Steering Group to help develop the strategy for the network. Here, Rebecca explains why she wanted to be part of this network and why it's so important for those affected by epilepsy to become involved in research.

Why did you want to be part of the SHAPE NETWORK?

I first heard about the SHAPE NETWORK on Facebook and signed up right away – it was a very straightforward process. I am excited to be involved in the network as it offers a great opportunity for people living with epilepsy to have a direct impact on the types and quality of research that is carried out. Research is central to improving the lives of people living with epilepsy now, and for those who will either develop or be born with the condition in the future. I have been involved in research in a number of ways over the past eight years. As someone living with epilepsy, I feel it's a way of turning a negative into a positive – taking my years of lived knowledge and experience into forward motion.

What have you been involved in as a SHAPE NETWORK member?

I successfully applied to be a member of the SHAPE NETWORK Steering Group, along with nine other people who are also affected by epilepsy. Being a Steering Group member has so far involved attending virtual meetings to discuss ideas on the development of the SHAPE NETWORK strategy. The process of being on the Steering Group has been a positive experience and I have felt valued in my ideas and contributions. As a group, we have appropriately 'shaped' a set of clear ideas and goals of how Epilepsy Research UK can progress with genuine involvement of people with epilepsy. I also joined discussions around the review of grant applications and as to how people affected by epilepsy can become meaningfully involved in research. I am really excited to see this work in action in the coming months.

What do you hope the SHAPE NETWORK can achieve for people with epilepsy?

I hope it can encourage and engage people to come forward to be involved in a range of research and advocacy opportunities. Patient involvement has the ability to make research relevant, focused and hopefully more successful in its aims. It also has the potential to give people with epilepsy a sense of real purpose, to raise self-esteem and perhaps even help develop additional skills.

What do you hope research can achieve for people with epilepsy?

I hope for more effective treatments, with fewer medication side effects. A third of people still live with uncontrolled epilepsy – I would hope this can be markedly reduced.

Why do you think it's important that people affected by epilepsy are actively involved in research?

Living with epilepsy gives you the insight of walking in the epilepsy shoes every day. So, you know where they are tight, where they rub and how you want to cast them off. You also have first-hand individual experience of medication side effects. Both these things give you the knowledge and coping strategies that can inform and shape research. You're an expert in your own epilepsy and your voice should be included in shaping research directions and decisions.

Rebecca
SHAPE NETWORK
Steering Group member

THE IMMUNE SYSTEM AND EPILEPSY

In this Research Blog, we hear from Dr Sukhvir Wright who is investigating autoimmune-associated epilepsy, a condition in which seizures can be caused by the body's immune system interfering with brain cells. Dr Wright explains how an Epilepsy Research UK Emerging Leader Fellowship in 2016 has helped researchers gain an understanding of how autoimmune-associated epilepsies work, as well as aiding the search for targeted treatments.

I appreciate everyone has heard A LOT about antibodies in relation to COVID-19 over the last few months. But people rarely discuss how antibodies can affect seizures...

Antibodies are the molecular soldiers in our immune system's army, fighting to protect us from, yes, you guessed it, VIRUSES, as well as other bugs and threats that may cause disease. However, sometimes these antibodies get distracted or confused (for example, by viruses or a tumour) and instead of protecting us and our vital organs, they start attacking them, and become autoantibodies. When these autoantibodies target proteins within the brain, this can result in an autoimmune neurological condition known as autoimmune encephalitis. Affected patients, adults or children, will display changes in behaviour, seizures and abnormal movements among other symptoms. The seizures mostly occur during the condition, but some patients can be left with ongoing seizures and develop an autoimmune associated epilepsy. We also know that although most patients make a good recovery, sufferers of autoimmune encephalitis and associated epilepsy can be left with longstanding cognitive problems. This has recently been identified as a particular problem in children. My research has been focused on trying to understand how these antibodies cause seizures and whether there are ways of improving treatments so that we can prevent any long-term problems.

The autoantibodies that I have focused on in my Epilepsy Research UK-funded project target a protein in the brain called the NMDA receptor (NMDAR), which is crucial to making brain cells communicate with one another – known as 'firing'. Using a wide range of laboratory methods, we have managed to make an experimental seizure model caused by the NMDAR antibodies and used this to understand why seizures occur when the NMDAR brain protein is disrupted. Turns out it's not as simple as we thought...

The good news is we managed to partially reverse the change in neuron firing pattern that happens when a seizure occurs caused by NMDAR antibodies, with a treatment targeting the NMDAR brain protein. We also showed this treatment had the same effect on human brain tissue (kindly donated by patients undergoing epilepsy surgery, as part of another project funded by Epilepsy Research UK!) which is the first step towards translating this treatment from lab bench to bedside. We hope this research will lead to additional targeted treatments for patients and allow refinement of immune-targeting drug therapy and minimizing of side effects.

It continues to be an absolute privilege to be able to conduct research which could be directly applicable to the patients I see in the clinic. I am frequently humbled by how eager patients are to participate in research, even when the findings may have no direct impact on them or their loved ones; their motivation – a selfless act of compassion to help others. Similarly, I am also amazed and excited by other researchers and clinicians, always keen to collaborate in these same research studies, even when competing pressures are high (COVID-19!). I am very thankful to Epilepsy Research UK and their incredible supporters for their continued efforts to drive research into epilepsy and keep it in the spotlight. With one new patient diagnosed with epilepsy every minute within the UK and Europe, there is an urgent clinical need to understand seizure-inducing pathways in brain networks, particularly for those patients that will not be helped with standard treatments.

Dr Sukhvir Wright
2016 Emerging Leader Fellow
Aston University and Birmingham Children's Hospital

EPILEPSY IN PREGNANCY IN THE CLINIC

For two decades, Advanced Clinical Practitioner, nurse and midwife Kim Morley has been a pioneer of specialist epilepsy maternity services, with a particular focus on anti-epileptic drug (AED) management. Through her, work Kim has established community and hospital-based services in Winchester, Southampton and across Hampshire. Kim is also involved in research and is a dedicated advocate working with MBRRACE UK (Mother and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK) and represents the Royal College of Midwives on the Medicines and Healthcare products Regulatory Agency (MHRA) Valproate Stakeholders Committee. In this Research Blog, Kim discusses her career providing specialist care to women with epilepsy, and how being a voice for patients has led to real change.

I first wanted to investigate the effects of anti-epileptic drugs (AEDs) after hearing about the sudden unexpected death of a young mother with epilepsy (SUDEP), whose bereaved child had facial irregularities and learning difficulties. I already knew that birth defects had been linked to sodium valproate in pregnancy, but after some initial research, I learnt there was also a syndromic effect. The developmental and learning difficulties were very similar to cases where babies had been exposed to alcohol.

I immediately recognised that more needed to be done to inform and educate women and healthcare professionals on foetal anticonvulsant syndrome – a group of malformations that can affect babies if exposed to certain AEDs. I joined a national foetal anticonvulsant support group and offered to help raise awareness and share the experiences of families whose children had been affected. But in order to properly inform and educate, I needed the relevant evidence. At the time Dr Pam Crawford, Professor John Dean and Professor Peter Turnpenny were conducting research into women with epilepsy and the effect of AEDs on their children. They shared their published research with me and I began presenting this information to healthcare professionals around the UK through lectures and seminars.

After realising our hospital had no services tailored for women with epilepsy, I was determined that should change. With support from our lead consultant obstetrician and Head of Midwifery, I established a unique epilepsy specialist midwifery service providing pre-conceptual and pregnancy counselling. My aim was to prevent any baby from being harmed by AEDs whilst ensuring women became experts in their own health condition. I wanted to make sure every woman I met was correctly diagnosed with epilepsy, prescribed the AED most likely to control their seizures in the lowest therapeutic dose and least likely to cause harm to a future developing baby in pregnancy. With some small voluntary donations, I was able to found a hospital registered charity, 'Women with Epilepsy', which partly funded my work. The service became entirely NHS funded in 2017, and we launched a new website to provide free information for women with epilepsy and their families.

Research has moulded my career. My journey started with reading articles about foetal valproate syndrome and SUDEP and learning how to critique

EPILEPSY IN PREGNANCY IN THE CLINIC

research. My passion for the topic was ignited and I started studying to become our first independent and supplementary non-medical prescriber. I then became our NHS Trust's co-investigator for a multi-centre study researching AED management in pregnancy. I've now completed my own dissertation research study for a master's degree in advanced clinical practice. (Morley K, 2020). The study explored experiences of using a toolkit I designed at the antenatal booking appointment and has provided valuable insights into the opinions of midwives, which are rarely sought in the epilepsy research paradigm.

Research has enabled me to support women and their prescribers with evidence-based advice during the transition from preconception years to pregnancy and beyond. To inform decision making, it is imperative women are provided with research evidence on the effects of medication exposure during pregnancy and whilst breastfeeding. This must be balanced with information about any potential risks associated with changing or withdrawing from their current medicine regime, including the risk of SUDEP and, importantly, providing a pillar of support during that process. As I specialise in AED management, it is rewarding to read research findings that have mirrored my clinical experience with these medicines.

It also highlights the imbalance in therapeutics available for women of child-bearing potential with generalised epilepsy versus the options available for men, and the dilemmas this can lead to in decision-making and research design.

It was such a privilege to share my clinical experience at the European Medicines Agency first public hearing into valproate (2017), and in the Cumberlege Review (2020) and MRHA valproate guidance (2021). Being part of the epilepsy community has enabled me to be a voice for my patient group nationally and internationally, ensuring care and future research is inclusive of all women with epilepsy irrespective of race, ethnicity, gender, socioeconomic status, and health provider. I am forever grateful for the opportunities I have had, but mostly to the women and families I have had the privilege of working with along the way.

Kim Morley
Advanced Clinical Practioner
Epilepsy nurse and midwife

WHY WE HAVE A SCIENTIFIC ADVISORY COMMITTEE. WHY THEY'RE IMPORTANT. AND WHY YOU SHOULD CARE...

Dr Caoimhe Twohig-Bennet is Head of Research at Epilepsy Research UK and works closely with the SAC – a panel of some of the country's leading neurologists, neuroscientists and epilepsy researchers – to decide which projects we fund. In her Research Blog, Caoimhe explains exactly who the SAC are and why they are vital to our grant funding process.

If you've ever read an ERUK annual report or browsed our website, you will have noticed a number of words and phrases that we repeat over and over again: 'independent', 'rigorous', 'scrutiny', 'peer review', 'multi-stage process', 'AMRC standards' and so on.

Antibodies are the molecular soldiers Of course, we know what we mean, but we thought it might be worth explaining why these over used verbs are the guiding principles of our funding programmes and why, as a supporter, they should be something you look for in research investment...

But first things first... who are the SAC?

The Epilepsy Research UK Scientific Advisory Committee (or SAC to you and me) is a panel of some the country's leading neurologists, neuroscientists and epilepsy researchers. As individuals they have decades of experience and work at the highest levels of clinical or scientific research. From a governance perspective the panel are a sub-committee of the ERUK Board. The SAC is committed to supporting ERUK's overall mission and vision while maintaining enough distance to ensure that recommendations for funding are independent of the Board Trustees and the Charity's Executive team.

And why exactly are they so important?

Well, each year ERUK invites researchers from clinical and academic institutions across the UK to submit their research ideas. The research will focus on a specific aspect of epilepsy, for example:
- developing more accurate diagnosis
- improving seizure control
- exploring new treatments

It is the responsibility of the SAC to triage these ideas and concepts, select the most promising, and invite the primary investigator to submit a second stage, more in-depth proposal. This in-depth proposal outlines exactly how the researcher intends to explore this area of epilepsy; what equipment or techniques will be used, what expertise it will involve, how their institution will support their research, and how this research will benefit people with epilepsy.

As members of the Association of Medical Research Charities (AMRC) – we are required to adhere to a set of strict guidelines, ensuring that the assessment of research applications by the SAC is independent and thoroughly examined to the required standards. When we talk about appropriate scrutiny and rigorous process, this is what we mean. If you haven't heard of the AMRC, it is worth checking their website to understand a little more about the work they do to ensure that medical research charities achieve the greatest impact for our beneficiaries. Membership of the AMRC is a hallmark of quality research.

How does the SAC reach a decision about what to fund?

The whole assessment process usually takes around 7 months and during this time all applications are reviewed not only by the SAC, but by international epilepsy experts from across the globe – a process known as 'peer review'.
The feedback is then collated from the expert analysis, and the SAC then come together to discuss each application.
This is where the SAC's decades of experience and knowledge are put to the test with each member debating the applicants expertise, the methodologies, the capability of the research group, the backing of the host institution... and challenging every data source. After a full day of exhaustive discussion, the final scoring for each application is agreed.
The SAC's highest scored applications are then recommended to the ERUK Board of Trustees for funding.

Together, these steps form an independent multi-stage process that ensures only the highest quality research, showing potential to impact the lives of people with epilepsy, is awarded funding.

But why should you care?!

As a supporter investing in research, it is essential to know that every penny of your gift is going to research that has been assessed for funding by a world class, uniquely qualified panel of scientific and clinical experts. The only way to achieve this is through a transparent and entirely independent Scientific Advisory Committee.

Dr Caoimhe Twohig-Bennett
Head of Research
Epilepsy Research UK

RESEARCH BLOG ROUNDUP

You can find more of our Research Blog posts on our website here.

We want to know which topics you'd be interested to know more about on the #ERUKResearchBlog. Have you ever wondered what 'drug repurposing' is? Maybe you want to find out about the latest epilepsy surgery techniques? Whatever the project, topic, or theme you'd like to see discussed by the experts, please get in touch here!

@EpilepsyRUK @epilepsyresearchuk @epilepsyresearchuk

EPILEPSY RESEARCH UK