Key Findings from the Largest Genetic Study Ever Performed
A CURE Epilepsy Webinar
(Transcript)

Dr. Laura Lubbers: Welcome everyone to today's webinar. I'm Laura Lubbers and I'm the Chief Scientific Officer for CURE Epilepsy. November is National Epilepsy Awareness Month and I want to thank you for taking the time to come and educate yourself this month and for many of you, who I'm sure are on the call, throughout the year to learn about research on epilepsy.

Since our founding in 1998, CURE Epilepsy has raised millions of dollars to fund epilepsy research. CURE Epilepsy provides grants that support novel research projects to advance the search for cures and more effective treatments. Today we are excited to bring you the final installment of our 2024 CURE Epilepsy webinar series with a webinar entitled Key Findings from the Largest Genetic Study Ever Performed. This genetic analysis of people with epilepsy, which was coordinated by the International League Against Epilepsy and published in the Journal Nature Genetics sought to advance our knowledge of why epilepsy develops and potentially inform the development of new treatments.

Working together, researchers from around the globe identified 26 distinct areas of our DNA that appear to be involved in epilepsy. This includes 19 regions which are specific to a particular form of epilepsy called genetic generalized epilepsy. They were also able to point to 29 genes within these DNA regions that are probably contributing to epilepsy. The scientists found that the genetic picture was quite different when comparing distinct types of epilepsy, especially focal and generalized epilepsies were compared. The results also suggest that proteins that carry electrical impulses across the gaps between neurons, which are called synapses, contribute to some of the risk of epilepsy, of generalized forms of epilepsy.

Attendees of today's webinar will learn about the epilepsy genes that have been identified, the different mechanisms by which genetic changes increase the risk of epilepsy and how polygenic risk scores might be integrated into clinical practice. Today's webinar, like all of our webinars, is being recorded for later viewing on the CURE Epilepsy website. You can also download transcripts of all of our webinars for reading.

This webinar is presented by Dr. Sam Berkovic, who is the Laureate professor in the Department of Medicine at the University of Melbourne in Australia, and he's also the director of the Epilepsy Research Center at Austin Health. His work in collaboration with Laureate professor Ingrid Scheffer and International Collaborators in Adelaide, Australia and Germany, aided the discovery of the first gene related to epilepsy in 1995. Subsequently, he's been central to the discovery of many epilepsy genes. Dr. Berkovic was a member of the steering committee for CURE Epilepsy's Epilepsy Genetics Initiative or also known as EGI, and he's currently leading a global initiative called Epi25K with the Broad Institute to genetically sequence over 25,000 individuals with epilepsy.

Before I turn it over to Dr. Berkovic, I'd like to encourage everyone to ask questions. We'll address the questions during the Q and A portion of the webinar. And keep in mind you can submit your questions anytime during the presentation by typing them into the Q and A tab located on your WebEx panel, and then click send. We'll do our best to get through as many of the questions as possible. We do want this webinar to be as interactive and informative as possible. However, to respect everyone's privacy, we ask that you make your questions general and not specific to a loved one's epilepsy. Now I'll turn it over to Dr. Berkovic. Welcome, Sam.

Dr. Samuel Berkovic: Thank you very much Laura and thank you and CURE for inviting me to give this presentation. I've taken the liberty of slightly changing the title and I'll certainly be addressing the large study that we had published last year, but I thought particularly as the audience is general, I thought I'll first give you sort of a helicopter view about the genetics of epilepsy so you can understand how this particular study fits in.

Now, the overall motivation for this is that when patients and families come to their neurologist, they want to know whether the problem can be fixed, which is something that we attempt to do, but importantly they want to know what caused it. And that's a really fundamental issue that people have, as well as the cause being a route for development of further therapies. And what's become clear is that genetics is relevant to most and certainly many patients with epilepsy, and that's why the subtitle is unpacking a very complex condition because the genetics of epilepsy is complex, it can be simplified and I hope I'll present to you an understandable version that you can take away with you, but that's sort of the background to the thinking.

Okay, so the idea that genetics might be important to epilepsy is not new. And here's a quote from a very prominent 19th century British neurologist and you can read it there, that his view was that it was pre-eminently an hereditary affection. In the United States, the famous neurologist William Lennox said that a genetic factor in epilepsy is no longer in question, but only its nature and extent. Lennox had a complex view about genetics, and I'll explain why in a moment. He stressed that genetic factors had been underestimated, and I'll show you some of the evidence why he sort of realized that. But he also said it's not as heritable as other diseases. Now, that's actually not true. Epilepsy is one of the most heritable diseases as we know now. The answer to why there was this paradox is unfortunately not very nice as I'll get onto in a moment. Some of the best evidence that Lennox generated to suggest that epilepsy did have a heritable component was a very large study of twins that he did around the 1940s.

And here's an example of his sort of pin up twin girls, Catherine Constance, who had childhood absence epilepsy, absence is switching on at the age of six. In both of them, they switched off at the age of about 16, and they grew up to be very healthy women. In fact, I was able to track them down a number of years ago, still living in Boston. You can see they still like being twins with their

matching shirts. They'd been seizure free since teenage, they'd had a number of children and a number of grandchildren and none of them had epilepsy. And one of the sort of paradoxes, if you will, is that where one twin has epilepsy, the second twin very often does, but then again, it's not strongly familial. In other words, it doesn't affect a large proportion of other relatives. And I'll explain that paradox as we get through the talk.

Now, a great shadow came over the world and in particular in genetics with the field of eugenics, which was a terrible movement initially started with apparently good intentions and highlighting the alleged detrimental effect on society that people with disabilities have. And epilepsy was unfortunately wrapped up in this and it reached its awful conclusion with the Nazis in the middle of the last century. And why is this important? Well, this shadow hung over the field for many, many years and to some extent still hangs over the field in terms of stigma. Certainly when I started working on the genetics of epilepsy around 1980, it was still something that was awkward to do to talk to families about family history because of this stigma. And this is all trace backable to the awful legacy of this.Now, I think we've largely shaken off that epilepsy in the western world. It's still present in other countries, but I always like to acknowledge that this is a very unfortunate issue in the history of epilepsy genetics.

Now, I said briefly that essentially many, if not most epilepsies have a genetic component. And let me explain that with a bit of history. Here's a traditional view, again, going back nearly 50 years now, of the causes of epilepsy. And what you can see is that there's about a quarter of the cases that are due to obvious acquired lesions like head trauma, like stroke, like knee plasms, et cetera. But about three quarters of the cases were so-called idiopathic. In other words, the cause wasn't known. And this was very solid epidemiological work done centered in the Mayo Clinic, and it's sort of generally accepted and replicated. At that time, genetics was acknowledged, but it was minimized for the reasons I've just explained.

And in the 1980s, the first attempts at molecular genetic characterization of the epilepsies began, and we had a fairly simplistic view at that time, myself included. As you know, there are evolving classifications of epilepsy and we had the view from sort of classical genetics that a particular syndrome, epilepsy syndrome for example, absence epilepsy, that I just showed you the twins of, there'd be one syndrome and one gene, and it's turned out to be a lot more complicated than that. So let's go back to basic genetics 101 or high school genetics. How do we know that a disorder is genetic? Now, that's not hard and it's sort of common in just everyday conversation to talk about diseases running in families. Well, Joe got this particular disease or that's not surprising because his dad had it or his granddad had it. And it's generally known that many diseases do have an aggregation in families.

So we've learned that from family studies where we formally study the occurrence of disorders in families from twins, as I've just shown you, and more

recently using gene discovery, which we'll get to. So does epilepsy run in families? The answer is yes, it may. Having said that, do most people with epilepsy have a family history? The answer to that is no. And in fact, do most known genes, and I'll tell you how many genes we know about already in a moment, do most known genes for epilepsy run in families? So the answer to that is paradoxically no. And again, I'll explain why that paradox occurs in a moment. So just to talk a bit more about basic genetics, many of you will have done some high school genetics. There may be some people on the webinar with much more sophisticated information.

So we can divide genetic disorders basically into two very broad groups. The first are so-called single gene or monogenic one gene, also known as Mendelian, named after the famous Austrian monk who worked out the basics of genetics working on peas. So amongst these monogenic or single gene disorders, there are so-called dominant disorders where one abnormal copy of a gene, and we have two copies of all the genes in our DNA in the famous double helix, one copy causes the condition or increases the risk of the condition. And well-known examples of that include the breast cancer genes, BRCA1 and 2, and also famously the disorder Huntington's disease. And there are also a number of epilepsies which are caused by dominant disorders that run in families and they're usually mild, and part of the reason they're usually mild is if they're severe, those people often don't have offspring and we don't see the family trees that we are used to in classical dominant disorders.

The other common type of single gene inheritance is called recessive inheritance where two abnormal copies are required. The commonest example of that that everyone has heard of is cystic fibrosis, which is of course not an epilepsy, but there are numerous rare and typically severe epilepsies that are caused by recessive inheritance. These are seen with increased risk in countries where consanguineous marriage, that is where people are allowed or encouraged to marry cousins. And these disorders are the reason that cousin marriages are often discouraged. But recessive inheritance is also important, and we'll get to in a moment, there are many rare epilepsies that are due to recessive inheritance. But most of the epilepsies, particularly things like genetic generalized or idiopathic generalized epilepsy, and certainly some forms of focal epilepsy are not due to single gene disorders, but they're polygenic multiple genes, sometimes called non-Mendelian, and the best sort of term for them is that their inheritance is complex. By which we mean the interaction of a number of genes and sometimes additional environmental factors.

So as has been already mentioned, the first gene for epilepsy was discovered by our group collaborating with others, and this was a part of Ingrid Scheffer's PhD that she did with me many, many years ago. And it all went back to this very large family that Ingrid traced. And in this pedigree, men are represented with squares, women with circles, and where the figure is black, they have the condition. And this is a rare condition called autosomal dominant nocturnal frontal lobe epilepsy or now called sleep-related hypermotor epilepsy. And by working with this very large family, we with our collaborators, were able to

narrow down the gene for this disorder and it turned out to be a gene for an iron channel receptor. And the story about iron channels in epilepsy subsequently grew from there, although this particular one has turned out to be reasonably rare. But that's sort of the principle of how we got started in molecular discovery in epilepsy.

Now, one's often asked how many epilepsy genes are there? And 20 years ago I would've said, oh, maybe there'll be a few dozen or 100. It turns out now that we've got nearly 1000 and it's growing, and we publish this and keep it updated on our website called Genes for Epilepsy, where this shows the number of genes with particular disorders. Now there are a few interesting facts here. On the top is genetic generalized epilepsy, a condition that accounts for about 40% of all people with epilepsy. I'm sorry, 20% of people with all epilepsy. And there are a relatively small number of known genes for that. Similarly, in focal epilepsy, which is responsible for about 60% of people with epilepsy, there are a relatively small number known, and the colors show the mode of inheritance. Ad is autosomal dominant, AR autosomal recessive, et cetera, and the others are more rare.

A particular form of epilepsy, which I've been interested in but is quite rare, is called progressive myoclonus epilepsy, which as you can see is often recessive in blue and often occurs in inbred communities, and we've solved most of the progressive myoclonus epilepsies, but again, it's a small fraction of all people with epilepsy. Here are patients with malformations of cortical development, MCDs, and they have a large number of genes. But by far the largest number is in what I call the DEs, or the developmental and epileptic encephalopathies, whereas you can see, there are well over 800 genes, some of them recessive as I've mentioned before, but some of them dominant. And yet these people don't have a family history.

Now why is that? Because these dominant mutations occur de novo, in other words, they're new and they occur spontaneously in the sperm or the egg. So a healthy couple who have no family history of epilepsy unfortunately have a child with one of these devastating diseases, and the cause historically was just not known. We didn't know. But now it's clear that many of them are genetic due to novel mutations, novel de novo mutations, and discovering that can be really important for counseling the family, for getting them in touch with other similarly afflicted families and for developing new therapies which are very much on the way. So that's the big picture of the epilepsy gene number now, and the number continues to grow literally weekly.

Now, let's go back to a helicopter view of epilepsy and to explain how genes fit in. Now, it's long been stated and really known that in people with epilepsy there are often genetic factors and there are also acquired factors. Brandon, something has gone wrong with this slide with the transfer, there is a figure picture in here, which if you can't unblock, then I'll do without, and I'll move on. Maybe too fiddly to do that, but there should be a red and blue figure in here, and it hasn't transferred

Brandon: Unfortunately. I'm unable to at this point.

Dr. Samuel Berkovic: Okay. Okay, we'll do without it. So what this figure shows is that there is about a quarter of cases over here where there are known acquired factors for epilepsy such as trauma, stroke, et cetera, as we've mentioned before, and way over here, there were so-called single gene epilepsies, which we thought were rare, but we now know as shown by the picture I've just shown, that this new mechanism of de novo mutations, new mutations, accounts for a lot of it. And in fact, most of the known genes now are over here. And in the middle we've got epilepsies with polygenic inheritance, which are, as I've already mentioned, the commoner types of epilepsy, and they are due to multiple genes, which the study that I'm going to tell you about is starting to unpack. And this is sometimes referred to as a so-called genetic background. That is you see epilepsy running through the family with increased frequency, not affecting everybody and not even affecting people from one generation to the next, but just an increased propensity to epilepsy.

Okay, so to go on, when we go to the lab, there are three particular forms of changes in the DNA that we can look at. The first is called rare variation, and these are sort of classical mutations where a change occurs in the DNA, it typically occurs in a protein coding region, and you get a change in the protein that affects its function or in fact may stop it being translated at all. So this is a big change, a dramatic change. This is what we typically get in those de novo mutations, and we detect that now by so-called whole exome sequencing, which is now commonly done and done by many labs and many gene sequencing companies.

The second form is what we call common variation, also known as SNPs or single nucleotide polymorphisms, and we all carry these. There are tens of thousands of these in every one of us where just simple changes to base pairing are results in a variation from the so-called consensus sequence. Now, most of these changes are in non-coding parts of the DNA. Parts of the DNA that don't result in proteins, and we think that or we sort of know that they're likely to be regulatory changes. And these are tested by so-called genome wide association studies, which is what this major study that I'm going to tell you about in a moment has revealed.

And finally, and I won't be talking about this today, there are larger changes in the genome that can occur, so-called copy number variation where large bits of the chromosome can be cut out or duplicated, and these also can raise risk for epilepsy and other neurodevelopmental disorders. So what I'll be focusing on are the common variation changes. So this is the study that came out last year and it was done through the International League Against Epilepsy Consortium on Complex Epilepsies. There were over 300 contributors to this from many countries, and as Laura said, we identified 26 risk loci for epilepsy. The sort of senior people in the consortium, in addition to myself, were Gianpiero Cavallari from Dublin and Bobby Koeleman from Utrecht. And we had a wonderful group

of younger analysts from all around the world who contributed to this, and it was a sort of delight to work with this consortium.

So this is the key result, and let me spend a bit of time explaining this. This is called a Manhattan plot because it looks like the Manhattan skyline with skyscrapers. What it shows is the set of human chromosomes from number one to number 23, and we've got 23 pairs of chromosomes. And each little dot on the graph represents a particular gene, and the dots indicate whether the gene is enriched in people who have epilepsy compared to controls. And the higher the peak, the more significant the effect is. And the red line shows the level above which we start to believe the peak and know that it is... Sorry. And know that it is significant. So there are about 26 peaks getting above the red line here, and these represent SNPs or groups of SNPs where it is significant and they can be attributed to particular genes which are shown on the labels.

Now, I won't go through all the names of the genes, but suffice to say that some of them are ion channels like the original gene discovered in 1995, but many or most of them are involved with synaptic processing. That is the synapses of the gaps between brain cells that allow them to talk to one another, and that's not surprising given that epilepsy is a disease of the brain where cell communication is so important. So the key findings were that with this large sample size of nearly 30,000 patients, we got many more hits and we're in fact now attempting to double this again. And in the fourth iteration of this consortium, we hope we'll get even more information, but that will be a couple of years in the making.

Secondly, as Laura has already indicated, the genetic architecture of focal and generalized epilepsy differ. Most of the hits occurred in generalized epilepsy, where previously we've had very little understanding of the actual genetic underpinnings of this. So common variants are more important in generalized epilepsy than in focal epilepsy. As I've already said, the genes implicated affect synaptic processes. And interestingly, some of the genes that we found with these relatively small effects overlap with genes that are found in the monogenic epilepsies like the ones with that family tree that I showed you initially.

Now, there are now clever ways to use these findings to point the way to potential alternate drugs for epilepsy or new drugs for epilepsy, and that's being done. But perhaps the most practical thing now is what we call the application of polygenic risk scores. Now, the trouble with these hits are that they only change your risk for epilepsy by a very small amount, individually far less than 1%. But what one can do is sum up all these hits on the genome wide association study and generate what's called a polygenic risk score. And this has been shown to be really quite valuable, and I want to spend a couple of minutes explaining polygenic risk scores and how it is and will be applied to epilepsy.

So a way I like to explain this is by looking at height. Now, we all know that height runs in families. If you've got small parents, you are likely to be small.

And if you've got tall parents, you are likely to be tall. And if you've got one tall and one small parent, you're likely to be in the middle. Now, here's a very tall man, Shawn Bradley, an ex-NBA basketball at nearly 2.3 meters tall, and he doesn't have a medical condition. He's very fit, very healthy, he's just incredibly tall. And what this graph shows is the polygenic risk score for height. That there've been very large studies looking at the SNPs in people against their height, and the risk score follows what we call a normal distribution, a bell-shaped curve like most physiological variables. And where does Shawn fit on this bell-shaped curve? Sorry, my mouse is slipping. He fits way over here. So he's got sort of an, if you like, an out-of-court polygenic risk score for height, and that's part of the reason that he's so tall and indeed otherwise healthy.

So I hope that sort of simple explanation gets this concept in your head. This is the aggregation of many genes or if you like, the genetic background that explains this. Now, this has been cleverly applied to a number of common conditions where genetic information has been much more available than it has been so far in epilepsy. Now, you all know that high cholesterol increases your risk of heart disease, but there are some people with very high cholesterols who live happily ever after and don't have any trouble. And there are others that sort of die young often with a very high cholesterol. Now, there are a small group of people, about one in 500, who have rare variants, in other words, mutations in genes for cholesterol. And they are known to be at particularly high risk, and the risk of them is shown in the blue line compared to the risk in people without these mutations in the black line. But that risk is motivated by their polygenic risk score.

In other words, those people with this rare variant in the cholesterol gene, their risk of a heart attack is determined or is influenced by their polygenic risk score. If their polygenic risk score is low, then their risk of a heart attack is relatively low, down at 20% way here, whereas it goes up to nearly 100% if they have a high polygenic risk score. So that's how these common variants interact with rare variants and go on to explain the sort of complex interaction that determines our risk for disease.

Now, does this apply to epilepsy? Well, it does. So here's another one of these unusual pedigrees. This is another family that Ingrid and I worked up with a condition called genetic epilepsy with febrile seizures plus or GEFs plus. And this family was subsequently shown to have a major mutation in the gene SCN1A. And the question is that the colors here represent the severity of the epilepsy. There are some patients here just with febrile seizures, which technically isn't an epilepsy, and others with more severe epilepsy shown in yellow and in other colors. And how do we explain this in a family with a single gene mutation that's been discovered? So this is again another way of showing the spectrum of disorders in this family.

And what we did was we took not just that family, but 58 GEFS plus families, and many of these were taken from the Epi25 consortium that's been looked at, and we looked at their polygenic risk score versus their particular syndrome.

And this was work done by Melanie Barlow and Karen Oliver, one of our really great post-docs now. And we graded the severity of the epilepsy from one to five amongst the carriers. Not everybody with this variant in their gene has seizures. There are ones going right to the other end of some patients with developmental and epileptic encephalopathy, really severe epilepsies like Dravet syndrome, and we graded them like that. And the hypothesis was that with an increased polygenic risk score burden, they'd have a more severe phenotype. Is this true? Well, broadly, yes. Here's a graph showing the polygenic risk score in controls. And you can see it doesn't differ from those with very mild epilepsy. And in those with more severe epilepsy, it's significantly higher. So this is telling us the same story as I showed you from that familial cholesterol graph.

Now, we can look deeper into this, and here's another large family that where we describe the first GABA receptor mutation and inhibitory receptor mutation many years ago. And it's quite, if you like, refreshing and exciting as a researcher to go back to stuff you did 20 years ago and still find you can get new information from it. So here's a very large GEFS plus family with a big variation in severity. And what we did here is we matched each patient in the family to everyone else in the family and asked is the more severely affected person, do they have a higher PRS score? And the answer is, yes, they do. It's only relatively mild, but it's there. So here it's telling the same story within a family that the PRS determines or influences the severity of the family. And here it's shown in more detail with the severity of the epilepsy, grade one to five shown in the colors. The redder color being the more severe, and the PRS score shown on this sliding scale, which is under each individual person.

So to break this down, here are patients with relatively low PRS. They're green as you can see, and they by and large have very mild epilepsies, whereas those that are red have deeper colors and have more severe epilepsies. So this is telling us again, in a different way, that the PRS is influenced, these SNPs are influencing the expression of the epilepsy, and this goes a long way to explaining the mystery of so-called phenotypic variation in patients.

So to come back to this first picture that I showed you, how have things changed? Well, the idiopathic group has sort of more or less changed into genetics. And in this three quarters of the pie, we've got some single gene epilepsies, we've got some epilepsies with complex inheritance, and we're now really getting into this area of modifiers or things that influence the major genes. And much of this is explained by the SNPs. So this is the reason that we believe that really most people with epilepsy have at least some genetic component to their epilepsy.

So again, to take a helicopter view about what's happened in the field broadly, there've been enormous advances in monogenic gene discoveries. That histogram I showed you with 900 going on a 1000 genes. It's part of clinical practice now, particularly in child neurology, but increasing now in adult neurology, and it certainly should be. This has been made possible by enormous

leaps in genomics technology, and there are some major research challenges in the next five years, and that's particularly developing therapies based on the monogenic discoveries and that's already happening. There are trials going on now in this. Solving the remaining monogenic epilepsies. We still don't solve all the children with we believe de novo mutations and a deeper understanding of the complex epilepsies, which I've shown you the sort of first opening in that with this landmark study that I discussed today.

Turning to the common variants themselves to summarize, there are critical cause of certain epilepsies, particularly generalized epilepsies, although they contribute to all, they modify the phenotype in disorders with major genes as I've shown you, and they're an important component of phenotypic variability. We hope this is then going to have applications in clinical practice. These are unproven and perhaps it will predict whether you're going to develop recurrent seizures or epilepsy after a first seizure, and that's something that can be tested. Perhaps it can help predict phenotypic severity in families of a newly affected child, and I think that's very likely. And there are also hopes that the polygenic risk scores may be modifiable, that we'll be able to develop therapies that look at the end product of what they do and help it.

So as I've emphasized, this work was due to a very large number of people, the ILE Consortium I've already mentioned, but also Epi25. Many people in my group in Melbourne, particularly Karen Oliver and Melanie Barlow for the bioinformatics work, and clinically my long-standing colleague, Ingrid Scheffer, who was responsible for the first pedigree and is now very much a leader in pediatric epilepsy genetics. Thank you for listening to me.

Dr. Laura Lubbers: Thank you so much, Sam, for a terrific presentation. So rich in teaching us about the genetics of epilepsy. So we'll now start the Q&A portion of the webinar. I know that there's already a question in place. If you want to submit a question, please go to the Q&A, which might be down at the bottom of your WebEx panel. Put your question into the Q&A area and click send and then we'll address them.

So the first question we have is when carrying out a clinical assessment, do you suggest whole genome or whole exome sequencing as a first pass versus doing an epilepsy panel?

Dr. Samuel Berkovic: Yeah, so it depends when you ask me. If you would've asked me five years ago, we weren't even dreaming of doing regular whole genome sequencing because it was so expensive and now it's sort of tractable. One of the problems is that you've got to do it, but then you've got to analyze it. So in a lab, in a center where one has a research lab and one has Bioinformaticians, we now go for a whole genome sequencing. You get all the information, you can look at it quickly, but then you can look at it again and again as the years go by. Panels are limited because you only find what you look for, but they're also relatively efficient. So it's not a one-size-fits-all answer. It really depends on your patient, the circumstances you're in and the sort of question you're asking. I'm sorry, I

can't be more definitive about that, but that's the pragmatics about how it works.

Dr. Laura Lubbers: Thank you, Sam. As a part of that, can you describe, because I think people hear this acronym or this terminology and don't know what to make of it. So a VUS is a variant of unknown significance. Can you talk about what that means and then address it in your paper? Did you find VUS's, did you report these and how do they correlate with clinical symptoms?

Dr. Samuel Berkovic: Okay, so as you've defined it, VUS's are variants of unknown significance. It does not apply to the common variants. As I said, each of us have got 10,000 or so of these. So they're not things that are reported in genetic testing. They are reported where people have done whole exome sequencing or whole genome sequencing and looked at the particular genes. And there are some changes or variants that occur in those studies that are instantly recognizable as important. Why would they be instantly recognizable as important or first that they've been seen in other patients with a similar disorder? That's probably the strongest evidence. So there are now excellent databases that the genomics people look up and you get, for example, a change in SCN1A, perhaps a child who you think has Dravet syndrome and you go to the databases and there it is. There are multiple reports of this. So bingo, that's the answer. And this is a variant that is significant.

However, you may find, and we'll just stick with SCN1A to keep it simple, you may find a variant that has never been reported before. And here you've got to be careful because just because it's a variant doesn't mean it is significant and may be of unknown significance. So you have to be very careful there not to say, well, look, this patient's got to change in this gene and therefore it must be significant. Big mistakes can happen with that. You've got to really validate that there's a case for saying it's significant. So the evidence for that is, I've already mentioned, if it's been seen before. Secondly, if it occurs in a part of the gene or part of the protein that's known to be really important for function, then you've got a sort of stronger case for it.

And sometimes, but this is sort of research testing and not available usually clinically, is that you can do so-called functional testing and actually measure the effect of the change in the lab. Now, this is the only way we used to have to do it. There are now incredibly powerful programs that can predict what might happen to a gene. And many of the people on the webinar might be aware that the Nobel Prize for chemistry... For medicine, sorry, was given to a group of scientists that developed what we called AlphaFold or what they called AlphaFold, which predicts the structure of all our proteins. So programs such as this can sort of tell us what the effect of a variant may be on the protein. Now we're not at the stage yet where you go Dr. AlphaFold, tell you if it's likely be important, but these are the tools now that labs have to build a case that it's important.

But I appreciate that it's hard for patients and families to integrate or comprehend what VUS means because it's written there on the piece of paper, it's written there on the genetic report, it's there. But just like MRIs, there are MRI changes that are absolutely definitive. You see a focal cortical dysplasia, you see hippocampal sclerosis. There are also changes on MRI in people with epilepsy that are of dubious or uncertain significance. So it's true in genetics as well. So I hope that helps. It's a bit of a roundabout explanation, but that's sort of how the situation sits. And I think the good news is the proportion of VUSs that we report or see is going down simply because of the fact that these databases are growing and the genetics community sort of worldwide I think is good at reporting information where they found something that they believe is important, and if the same variant in your patient, one has got a match.

Dr. Laura Lubbers: That's the power of research. We've come a long way. We still have a long way to go, but the power of research.

Dr. Samuel Berkovic: Exactly.

Dr. Laura Lubbers: Other questions have come up. So this one relates to two children in a family, one with Doose syndrome diagnosed at the age of three and another that had JME at 18. Looking through family history, no evidence of a genetic mutation. Is it uncommon to find families with two different kinds of epilepsy or diagnoses in generation?

Dr. Samuel Berkovic: Yes and no. So the association of JME with Doose syndrome is unlikely but not heard of, but it is unlikely. And unfortunately you can have well, both Doose syndrome and JME. Doose syndrome has some single gene variants, but may well be a polygenic disorder also, and JME certainly is. So unfortunately the genetic lightning might've struck twice in this family, unfortunately in different ways, or there may be some other modifying factors. I discussed the polygenic risk score as one way of looking at that, but both answers are possible that they are genetic related or unrelated. But because that's an unusual combination, I would've thought more likely unrelated, but one can't say for sure.

Dr. Laura Lubbers: Okay, thank you. More research is needed for sure. Speaking of polygenic risk scores, is there a simple way to describe how that's calculated?

Dr. Samuel Berkovic: Yeah. So the heights of the peak on that Manhattan plot, those individual scenes that sort of describe the effect size, how big an effect that particular variant has. So these are computed relatively simply. I mean, you need a Bioinformatician to do it, but you take each gene that is significant or above a certain threshold and multiply it by its so-called effect size, which in simple terms is the height of those peaks and sum them all together.

Dr. Laura Lubbers: Okay. Very straightforward with a Bioinformatician.

Dr. Samuel Berkovic: Yeah, it's not a hard concept. Maybe it's a little more difficult in the application, but that's the basis of it.

Dr. Laura Lubbers: Okay, great. Thank you. Yeah, more questions have rolled in. Could you speak briefly to the POLG gene? Is it a big player in genetic epilepsies?

Dr. Samuel Berkovic: Okay, so POLG is a polymerase gamma, which is a gene related to the mitochondrial system, which are the powerhouses of cells where we break down glucose and other nutrients for them to do their job. It is a rare cause of epilepsy, a quite rare cause of epilepsy, but it's a very important one because it has important treatment applications. So in people with POLG mutations, the drug sodium valproate or valproic acid as it's known in the US, can have nasty adverse effects. And that drug needs to be avoided in people with POLG mutations. But it is rare. But on the other hand, it's also important for the neurologist to recognize.

Dr. Laura Lubbers: Great, thank you. This is a question. You touched on this a little bit, and I have this question for myself and then somebody has asked it. Is it possible for adults to ask for genetic testing? Can you speak to the value? And perhaps if there is resistance from a provider to get genetic testing, is there a way to provide a convincing argument about it, about its value?

Dr. Samuel Berkovic: Yeah. Look, it depends on the disorder.

Dr. Laura Lubbers: Okay.

Dr. Samuel Berkovic: So for example, in 2024, the role of doing genetic testing through a gene testing company for something like Juvenile Myoclonic Epilepsy or Regular Temporal Lobe Epilepsy is pretty low. And I think it'd be hard to mount an argument. However, children with developmental and epileptic encephalopathies grow up and many of them are seen by adult neurologists, if they survive, and they live often somewhat limited lives. And again, finding out the cause in them can sometimes make a difference.

For example, the best recognized one of this is unrecognized Dravet syndrome, which is a condition that adult neurologists are not necessarily that familiar with, and the child is just sort of regarded as somebody with epilepsy and intellectual disability. But in fact, if you pick through it, they've got the characteristic evolution of Dravet syndrome and what do you know, they're on carbamazepine or oxcarbazepine, drugs which make them worse, or phenytoin. So recognizing the right diagnosis can get them put on drugs that are known to be better for that. And as we know, there are now some much more specific treatments for Dravet syndrome, so it can make a difference. So look, I think it needs to be tailored to the case. I don't think we're at the stage where we want to do it willy-nilly on people with epilepsy, but there are specific situations where it can be very valuable.

Dr. Laura Lubbers: Thank you. And you've just, I think, addressed one of the questions that's come in, but you could speak to it again and just clarify. It is about using genetics to tailor treatment, and it sounds like we're doing this using genetics to decide what medications may work best rather than using just a general approach to using anti-seizure medications. That's correct, right?

Dr. Samuel Berkovic: Yeah, yeah, that's a summary of it. So I've already given the example of Dravet syndrome and there are other genetic disorders where it's known that some drugs work well and some don't work so well or indeed may make the patient worse. There's also a field of pharmacogenomics, which is a field where genetic changes alter the way our bodies handle the drugs, and that can be used to help tailor a medication. One would have to say that the impact of that, and we've been talking about pharmacogenomics for 20 years, has been less than expected. The one major exception to that has been prediction of side effects, and in particular Stevens-Johnson syndrome.

So for example, it's known that a particular genetic change, which is of higher prevalence in people of East Asian origin, predisposes you to Stevens-Johnson syndrome with those drugs with carbamazepine and to a lesser extent, oxcarbazepine and phenytoin. So here, if one has a patient of East Asian extraction and there's black box warnings for this, that you ought to test for the particular genetic variants that predispose to this sometimes fatal side effect. So that is another sort of important use, but it's not something that one thinks about with every patient.

Dr. Laura Lubbers: Thank you. And one last question and then we'll wrap up. Are there specific SNPs associated with epilepsy with eyelid myoclonia?

Dr. Samuel Berkovic: So, no, not to my knowledge. And again, the story with SNPs is that we're largely not at the stage where we can narrow it down to a particular SNP. It's sort of a large group of SNPs that are put together, and these are aggregated in the polygenic risk scores. I'm not aware of anything that's been shown to be specific to epilepsy with eyelid myoclonia, and I doubt that we'll find it, but it may change.

Dr. Laura Lubbers: Thank you so much for this presentation and educating us about genetics and what we're finding and how rapidly things are changing in this field. And of course, thanks to our audience for always the great questions and getting us to think about different topics beyond those presented in the presentation. If you have additional questions about this topic or wish to learn more about CURE Epilepsy's research programs, please visit our website or email us at research@CUREepilepsy.org. We'd also appreciate if you would complete a brief survey that we're going to be emailing out to all of our webinar attendees in the next 24 hours. The survey will help us improve our webinars and also provide you an opportunity to suggest topics you'd like to learn more about in 2025. In addition, I want to encourage everyone who'd like to learn even more during Epilepsy Awareness Month to participate in another webinar plan for next Monday, November 18th.

That webinar will be conducted in partnership with our friends at Partners Against Mortality and Epilepsy and will be entitled State Interventions to Prevent SUDEP and other Epilepsy-Related Deaths. It will feature a panel discussion on what actions you can take within the United States to advocate for greater awareness and resources for people with epilepsy. Please visit our website in the webinars section for more information on how to register for that webinar and for information on our previous webinars. Finally, stay tuned for the announcement of our 2025 CURE Epilepsy Webinar series that will come out in January. And with that, I wish you all a happy and safe year-end. Thank you for all of your support throughout this year, and thank you, Sam.