Seizing Life, episode 36

From Lab to Clinic: Genetic Research Is Changing Epilepsy Treatment (Transcript)

Dr. Gemma Carvill

Kelly Cervantes:	00:00	Hi, I'm Kelly Cervantes and this is Seizing Life, a weekly podcast produced by Citizens United for Research and Epilepsy, CURE.
Kelly Cervantes:	00:18	Today, I'm thrilled to welcome Dr. Gemma Carvill to Seizing Life. Dr Carvill is an assistant professor of neurology and pharmacology at Northwestern University Feinberg School of Medicine. She was the recipient of a CURE Taking Flight Grant in 2015, studying how genetic mutations can lead to epilepsy. Dr. Carvill is now the principal investigator in her own lab at Northwestern University, where her team focuses on underlying genetic and epigenetic mechanisms. Dr. Carvill is also a recent recipient of an NIH New Innovator Award.
Kelly Cervantes:	00:53	She is here today to discuss epilepsy genetics and help us understand how genetic discoveries in the lab can lead to better therapies and cures for epilepsy patients. Dr. Carvill, thank you so much for joining us today. I am just always so appreciative and admire our epilepsy researchers and scientists. There are not enough of you, and so thank you so much for going into this field. To that point, what drew you to epilepsy research, specifically?
Dr. Gemma Carvill:	01:26	Yeah, I guess I really, I can't say that I was particularly drawn to epilepsy research. I more fortunately fell into it, and then because I worked really closely with a lot of family foundations and a lot of folks who are affected by this disorder, I really became quite passionate about doing research here.
Dr. Gemma Carvill:	01:48	So from a background perspective, I've always loved genetics and I've always been fascinated by how the brain works. And so, I did my graduate studies in South Africa and then moved to the U.S. with the idea of I'll stay here for a year or two, I'll learn all the fancy new sequencing technologies that are coming out, and then I'll go back to South Africa and I'll set it up there. And I was here about six months and I was like, and I'm not going back.
Kelly Cervantes:	02:21	We are thrilled that you made that decision.
Dr. Gemma Carvill:	02:23	My parents weren't. I can only [inaudible 00:02:26] so much. But, yeah. And I think a lot of it was, at the time, next generation sequencing, which is really the technology that we've used to identify all these genes, was really taking off. And it was through all of this gene hunting and working with fantastic clinicians who recruit a lot of patients, and working

closely with the families, that we started to identify all of these genes that we know cause these very early onset epilepsies.

Dr. Gemma Carvill: 02:55 And through working in that community, I've formed great friendships. I'm good friends with many people who have children who are affected by these disorders. And that, for me, was incredibly attractive. I liked the idea of using science to help these kids who really need answers for what is causing their disease.

Kelly Cervantes: 03:14 I'm a little biased, but it is a pretty incredible community.

Dr. Gemma Carvill: 03:19 It honestly is.

Kelly Cervantes: 03:23 So, you became part of the CURE research family in 2015 when you were awarded our Taking Flight award. Talk to us about what that award meant to you and the research that you were able to conduct because of it.

Dr. Gemma Carvill: 03:39 Yeah. So the way it works in academics, if you're at a research center and you want to progress further with your career, is you go to grad school for five to more years. And then after grad school, you do what's called a postdoc. So a postdoc is training after graduate school. And people can stay in a postdoc anywhere from two to seven years.

Dr. Gemma Carvill: 04:02 And then the next big jump is, if you want to stay in research and specifically academic research in a university, in a medical setting, is you need to figure out what is your own independent lab going to be doing? So what is the research that you really want to focus on for the rest of your career?

Dr. Gemma Carvill: 04:19 And so, I was really at that tipping point where I was spending a lot of time towards the end of my postdoc thinking about what is my lab going to look like? What do we want to research? And I knew I wanted to stay in genetics and I wanted to keep trying to find the genes that cause these types of epilepsies. But I also knew that I wanted to take the next step, because we'd done really well in terms of finding these genetic causes. And now that we know the genes, we need to figure out what do they do in the brain. And what happens when you have a mutation in them in terms of the function in the brain, and can we use that as a tool to eventually figure out novel therapies?

Dr. Gemma Carvill: 04:55 And so, I decided to focus on a gene family of chromatin remodelers and transcription factors. And these are basically fancy names for proteins that control gene expression in the

brain. And it's really a neglected, or at the time, a pretty neglected area of research.

Dr. Gemma Carvill: 05:13 And so, what I did was I applied for the CURE Taking Flight Award, which is meant for this exact person. It's for somebody who wants to stay in epilepsy research, but needs that help in terms of securing enough funds to be able to do their own research, but also the time to be able to explore those new and novel ideas. And so, that's really what the CURE Taking Flight Award allowed me to do. It gave me the financial support to do that research. And then, from there, the early research that we did and the findings that we made, I then used to launch when I started my new lab at Northwestern. So it's really that stepping stone.

Kelly Cervantes: 05:53 So we hooked you in to the field, got you to stick around-

Dr. Gemma Carvill: 05:57 Exactly.

Kelly Cervantes: 05:58 Which I love. And now you have this incredible grant from the NIH. Tell us about the research that you're doing now that that grant has allowed you to do.

Dr. Gemma Carvill: 06:09 So it's the NIH New Innovator Award. And the idea behind this award is that it's for a completely crazy idea. But it's a completely crazy idea that if it pans out, could really transform clinical care for patients. Well, in our case, clinical care for patients.

Dr. Gemma Carvill: 06:27 And so, the idea that we had was that we may be able to use cell-free DNA as a biomarker. So what cell-free DNA is ... So most places where people have come across cell-free DNA is with non-invasive prenatal testing. So previously, particularly with advanced maternal age, you would have an amniocentesis, right? And that's a particularly invasive procedure. And the idea there is to look for any sort of chromosomal abnormalities, but there are lots of risks associated with amniocentesis.

Dr. Gemma Carvill: 07:00 And so, what a colleague of mine had this great idea that he could look in the plasma. So if you separate our blood, you get this top layer that's called plasma. And in there is what's called cell-free DNA. And cell-free DNA comes from a cell that has died and burst open. And when that cell bursts open, the DNA is released eventually into the plasma. And it exists as really short little fragments of DNA. So roughly around 150 nucleotides. They're really, really small. But what you can do is then study that DNA. So in the case of non-invasive prenatal testing, you

can actually find fetal DNA in the plasma of mom and then you can use that to determine whether the fetus has a potential chromosomal abnormality.

Dr. Gemma Carvill: 07:46 So cell-free DNA has completely transformed NIPT and now it's the first line test. Amniocentesis is not done anymore. So following on from that, we had the idea that perhaps we could use cell-free DNA from patients in epilepsy. So again, here the idea is, at least in a subset of individuals who are having seizures, those seizures can lead to cell death. And then when cell death occurs, those short little fragments of DNA may exist in the cerebral spinal fluid, as well as in the plasma of that individual.

Dr. Gemma Carvill: 08:21 So what we're trying to do is ask the question, can we find cell-free DNA that originated from the brain in the plasma of individuals with epilepsy? And the idea there is we could potentially develop it as a biomarker. One of the big challenges in epilepsy is that one of the only real biomarkers, if you will, is having an EEG or having an MRI, in the case of looking for structural abnormalities. And those are pretty tricky techniques, right, because you need, or approaches rather, because you need go into the hospital. You need to be monitored.

Kelly Cervantes: 08:56 They're very time consuming.

Dr. Gemma Carvill: 09:00 Exactly, exactly. And there is no peripheral biomarker. There's no way we can look in the blood and see if an individual has had a seizure or not. So it's a completely crazy idea, but everybody thought that looking for cell-free DNA or fetal cell- free DNA in the blood of moms was crazy. And now it's mainline. So we're hoping to try and apply some of these ideas to see if we can use cell-free DNA as a biomarker in epilepsy.

Kelly Cervantes: 09:25 So it is diagnosing epilepsy using these, using the blood, which is different than say doing whole exome sequencing or whole genome sequencing, where you're looking more for the diagnostic cause. So this way, you don't have to spend three to four days in the hospital or longer waiting for that seizure to happen. You can just test the blood and diagnose the epilepsy from that.

Dr. Gemma Carvill: 09:54 And you can potentially tell if an individual is having seizures. Yep. So it's a long, long way from being in the clinic. But that's kind of the end goal of, if this were to work and we could find that cell-free DNA, this is one potential application.

Brandon:	10:07	Hi, this is Brandon from Citizens United for Research in Epilepsy, or CURE. Since 1998, CURE has raised more than $70 million to help fund more than 235 research grants in 15 countries around the world. Learn more at cureepilepsy.org. Now back to this episode of Seizing Life.
Dr. Gemma Carvill:	10:25	You also mentioned exome and genome sequencing. So potentially we could actually do genome sequencing on the cell-free DNA as well. So there with the idea that at least a subset of patients who have epilepsy may have a genetic mutation only in a part of their brain. So we call this somatic mosaicism. So rather than every single cell in the body carrying a DNA mutation, only a very small subset of cells within the brain may carry that mutation.
Kelly Cervantes:	10:57	But those genes that carry that mutation would be the ones that would have broken down due to seizure and be the ones that you could find.
Dr. Gemma Carvill:	11:07	Exactly.
Kelly Cervantes:	11:07	That is absolutely fascinating. We're throwing around these words, whole exome sequencing, whole genome sequencing. I don't want to take the time to really dive into that, because we have done previous episodes. If anyone is interested, we did an episode with Dr. Millichap and you can go back and listen to that one.
Kelly Cervantes:	11:25	But I think that it's so interesting, because there's only so far that the commercially available genetic testing can go and there's still so many people who are left undiagnosed.
Dr. Gemma Carvill:	11:40	Yep.
Kelly Cervantes:	11:40	I've only been a part of this community for the last four years. And even the testing and the knowledge that has become available in genetics is, in those four years, is outstanding. From being deep inside the genetic research piece of it, what are the changes that you have seen in the last 10, 15 years?
Dr. Gemma Carvill:	12:03	So I started this in this field about probably 10 years ago now. And back then, there were a handful of genes that we knew caused epilepsy, maybe 10, 15, not very many at all. And some folks within the community even doubted whether genetics was going to play a big role in epilepsy. And now, 10 years later, we can do exome sequencing, we can do genome sequencing.

Dr. Gemma Carvill: 12:28 I think what's been really exciting to watch is one, for a lot of families, we can find an answer. And that's, at least in the early onset OF pediatric epilepsies, that's anywhere between 30 and 50% of cases. And I think there are a couple of fantastic things that have come out of that gene discovery piece.

Dr. Gemma Carvill: 12:50 One of them is this emergence of all these family foundations. So there is the Dravet Syndrome Foundation for individuals with SCN1A mutations, and SCN2A. Just about every gene that causes epilepsy, we now have these family foundations. And I think that's been really rewarding to watch. And I think the fantastic thing about these foundations is one, it almost gives everybody a home. It gives people a gene to coalesce around. Folks are starting to do natural history studies now, because one of the big questions that families always have is, I have this gene mutation, what does this mean? What does this mean for my child? What is he or she going to look like in terms of their progression in the next five to 10 years?

Dr. Gemma Carvill: 13:36 And I think the family foundations, while it doesn't give you all the answers and I think that's one of the frustrating things, at least you can gather with people who are in the very same situation as you, same gene. So I think that's been fantastic. The other part has been that we're really going to, in the next five to 10 years, start seeing where once you can identify a genetic mutation that there are going to be precision therapy choices.

Dr. Gemma Carvill: 14:01 So we know another good example is perhaps SCN1A. So here if you have a mutation in this gene, there are certain medications that should be avoided. So I think more and more as we identify more individuals with mutations in these genes, we can start to get a better sense of which medications work, which ones don't, but then also moving forward thinking about novel therapies. There's exciting work in antisense oligos, where they are trying to target specific genes to prevent seizures. And there'll be a lot more tailored therapies based around those genes.

Dr. Gemma Carvill: 14:39 And then lastly, it also enables us to study epilepsy in the lab. So if we know which gene can cause epilepsy, we can knock it out in fish and in mice models, and we can study what happens when you have a mutation in that gene in terms of the function of the brain.

Kelly Cervantes: 14:58 Where do you see your research going 10 years from now?

Dr. Gemma Carvill: 15:03 So I think in the next five, 10 years, like I said, I think that there are going to be precision therapies with some of these epilepsies. I think that is going to be one exciting area of

research. I think that there's still a lot of gaps. So I think we touched on biomarkers earlier. That's one of the really big challenges, right? So beyond does the therapeutic stop the seizures, we're really poor at monitoring other outcome measures. So I think there natural history studies will help a little bit.

Kelly Cervantes: 15:35 And explain, you used the term before, what is a natural history study?

Dr. Gemma Carvill: 15:39 So a natural history study is essentially trying to get an idea of what is the trajectory of a disorder. So in other words, Alzheimer's is a great example, right? So you have an individual develop certain features early on and then you know the natural progression of that disorder.

Dr. Gemma Carvill: 16:00 Whereas, in a lot of epilepsies, we don't know. So we know an individual can have seizures early on, but then we don't know how they cluster. We don't know about development. So we don't really know what the natural course of the disease is in a very robust scientific way.

Kelly Cervantes: 16:17 I think when it comes to research, a lot of families feel very powerless. How can they help? In what ways can they get out there and push science forward to help their family members or to help themselves?

Dr. Gemma Carvill: 16:35 So I think the only way we're going to solve epilepsy is obviously through research. So I think any research opportunities that arise, I would highly encourage families to participate in. So again, my bias comes from the genetics, which is what I know most about for obvious reasons. And I think that there are studies like Epi25, which is a big consortia that are enrolling individuals with epilepsy and doing genetic studies to try and again tease up what are those genetic factors.

Dr. Gemma Carvill: 17:10 There are other studies like All of Us, which is a more nationwide study. And in All of Us, it's not specifically epilepsy focus, but the idea is to enroll a million people in the U.S. and to look at both their genome or their exome, as well as capture a lot of health information. So filling in surveys, those sorts of things. And again, there the idea is it's the goal towards precision medicine. It's the goal towards, can we look at your genome and can we look at your health record and can we make choices, or smart choices rather, about which therapies are going to be the best fit for your genome?

Dr. Gemma Carvill: 17:56 So I think broadly getting involved in any research. I think academic centers are probably the best place to be involved in research, but if you go to sites like Epi25, there's long lists of clinicians who are enrolling patients. So I think any opportunity to participate in research is really what's going to help us. It's what drives my research. It's one of the reasons that I'm at an academic center like Northwestern where there is a lot of collaboration between clinicians and researchers. So I really think that's the way to drive things forward.

Kelly Cervantes: 18:30 How do organizations like CURE fit into that role or the family organizations? What place do they have in this community?

Dr. Gemma Carvill: 18:44 You heard from my own story, it was from working with family organizations that really inspired me to want to stay in this field. So I think the role of CURE and family foundations is already what these foundations are already doing, trying to capture young individuals. Because there are a lot of fantastic scientists out there who are very interested in this type of research, but it's very challenging to be able to take that next step to launch your own lab in epilepsy research when it's incredibly underfunded.

Dr. Gemma Carvill: 19:15 So there again, CURE gave me the Taking Flight Award that allowed me to launch my own career. I think that's a fantastic niche to help in smart young individuals to take the next step and explore their own ideas that also might be a little bit more crazy, if you will. We sometimes need a little bit of crazy to make advances. So I think that's where CURE and others have done a fantastic job and I would love to see that being maintained.

Kelly Cervantes: 19:41 I guess to that end, where would you like to see organizations like CURE focusing in the years to come? Where would you love to see science and research, that energy go?

Dr. Gemma Carvill: 19:53 Addressing the big gaps, so funding studies that are a little bit crazy. So biomarkers is what I've mentioned, is one of the really big things that we don't have a good gauge on whether an individual is having a seizure or not. So any sort of development of biomarkers I think it's going to be really important. And of course we're focusing on cell-free DNA, but there's a lot of other types of biological material that you can study there. So you can look at protein levels, you can look at, some folks are looking at crazy little things called exosomes.

Dr. Gemma Carvill: 20:27 There's a whole range of different approaches that we could be taking that are doing relatively well in other fields. Where I feel

like in epilepsy, it's a little bit neglected right now. And it is so important from a subclinical seizure point of view, particularly during the night in nocturnal seizures, with risk of SUDEP. All those sorts of things I think are, I think there's a great opportunity there with the technologies that we have now that really can detect very, very low levels of protein, RNA, DNA. So I think that's particularly exciting area of research that needs to be pushed forward.

Dr. Gemma Carvill: 21:03 And then, I think biomarkers aside, I think another area where we need to focus is really on disease models. So we've done a lot of work in mice over the last 10, 20 years, but I think that we need to challenge ourselves thinking about new models. Some mouse models specifically don't always recapitulate the phenotype that occurs in humans. So I think thinking about zebra fish, thinking about STEM cells, organoids, those types of things, as well, I think are already important moving forward.

Kelly Cervantes: 21:39 Absolutely. Gemma, thank you so much for joining us today and for sharing your many years of expertise in this field. And I hope that you get all of the grant money that you need in the years to come so you can keep pushing science forward for all of those who are still out there fighting and searching for their answers.

Dr. Gemma Carvill: 22:00 Yep, and it's been fantastic. Thank you for having me. And hopefully we'll find many more answers. We'll find biomarkers, we'll solve all the unsolved epilepsy and retire to the beach in 10 years.

Kelly Cervantes: 22:12 Done. Got it. There with you.

Kelly Cervantes: 22:16 Thank you, Dr. Carvill, for sharing your knowledge of genetics and your insights about how genetic discoveries can impact those living with epilepsy. As Dr. Carvill explained, there has been great progress in the area of epilepsy research during the past decade, and CURE has been at the forefront. But epilepsy research is still woefully underfunded.

Kelly Cervantes: 22:36 Epilepsy affects more people in the U.S. than multiple sclerosis, cerebral palsy, muscular dystrophy and Parkinson's combined, yet receives fewer federal dollars per patient than each of these. CURE knows that research is the only way we will develop new therapies to improve the lives of epilepsy patients and their families. To find out how you can support CURE's patient-focused research, please visit cureepilepsy.org/get involved. Thank you.

Brandon:	23:10	The opinions expressed in this podcast do not necessarily reflect the views of CURE. The information contained herein is provided for general information only and does not offer medical advice or recommendations. Individuals should not rely on this information as a substitute for consultations with qualified healthcare professionals who are familiar with individual medical conditions and needs. CURE strongly recommends that care and treatment decisions related to epilepsy and any other medical condition be made in consultation with a patient's physician or other qualified healthcare professionals who are familiar with the individual's specific health situation.