Seizing Life, episode 132
Rare Epilepsy Organizations: Fostering Community and Advancing Research
Guests: Dr. Justin West and Liz Ramirez
(Transcript)

Kelly Cervantes: Hi, I'm Kelly Cervantes, and this is Seizing Life, a biweekly podcast produced by Cure Epilepsy.

This week we bring you another episode recorded at Epilepsy Awareness Day at Disneyland. This annual event gathers epilepsy groups, advocates, clinicians, researchers, patients, and families for three days of awareness, education, and information, featuring seminars and presentations on the newest advances in epilepsy therapies and technology. Today we speak with two organizations that focus on a rare epilepsy syndrome. These small grassroots organizations offer community support and hope to families living with a rare epilepsy diagnosis. Groups like these are essential in raising awareness and funding research for rare epilepsy syndromes. So talking with Dr. Justin West, with the KCNT1 Foundation, and I want to start by learning how the foundation was formed.

Dr. Justin West: Several years ago, there was a father who started the initial version of our foundation. He had a daughter who had been diagnosed. He was an attorney, and he was given some advice that if you wanted to be able to interact with pharma teams, that he should have a foundation, if he wanted to be able to bring a potential trial to an academic center that he needed a foundation. So he did that. We ended up meeting, because everybody in our community is small and you get to know each other. My wife and I had been talking about starting a foundation, and we thought, "Well, if there's already a foundation, maybe rather than have multiple competitive foundations, we should start a way to work together."

So I approached Seth and it seemed that we were clearly on the same page. That advocacy for our children was paramount. It was the single most important thing that we were doing in our lives. So we started working together and we took what was a small foundation, brought in some very important people, like our executive director who's somewhere behind me, and we turned it into a 501(c)(3), and we brought in all the core elements that gives a foundation some power.

Kelly Cervantes: That's amazing. And now tell us about your connection to the foundation and why you are so passionate about this.

Dr. Justin West: So my 6-year-old son, Andrew, he's our third. He was born right around the corner at Hoag Hospital in Newport Beach. When he was born, he had a very normal pregnancy, normal delivery. He had been meeting all his milestones. We had what we thought was a very normal healthy child. And then when he was about four months old, my wife called and said, he's doing something I don't understand. He had had this subtle movement of his foot. We're both physicians, but neither of us had ever seen a seizure in our lives other than what you see on TV, which is overdramatized, and it's not what typically we see here probably. So that brought us to an ER visit, and we found this diagnosis. It took

about three months to get the genetic diagnosis, but we essentially had an epilepsy diagnosis By the time he was, let's say, four months old, cause unknown at the time. Fast-forward to seven months, now we know we have a KCNT1 child.

Kelly Cervantes: Okay. And what are the goals of the foundation?

Dr. Justin West: So we put a lot of thought into that, whether we wanted to be a parent support organization or if we wanted to focus on research and drug discovery. As a surgeon, in a space where there was essentially no dedicated therapeutics for KCNT1, I decided early on that my philosophy was we should be all about driving therapeutics. We do some nice things to support our community on the side, but really the focus is drug discovery, doing everything we can to de-risk and to create programs and initiatives that support IND enabling studies.

Kelly Cervantes: Yeah. Well, research is at my heart as well, so I completely understand that. Can you explain to us how the KCNT1 mutation affects children?

Dr. Justin West: Sure. Yeah. So KCNT1 codes for something called the Slack channel, which is a sodium gated potassium channel in the brain. You can find it throughout the body, but the biggest concentration is in the brain. So what happens when you have that mutation is that you get an imbalance, like a lot of our epilepsies, between inhibition and neck citation. So Andrew has to gain-of-function mutation. His channel is just firing way too actively. And so the strategy is to not either block those channels or to knock down the production of those aberrant channels.

Kelly Cervantes: So what epilepsy syndromes does that cause? What kind of seizures do KCNT1 patients experience?

Dr. Justin West: There's a couple of different phenotypes, three. But in general, we have groups of children who start having seizures in the first few days, weeks, or months of life. They can have anywhere from 10 to 150 seizures a day, very heavy seizure burden. Essentially, once those children start having seizures, they end up in the hospital, multiple medications. They essentially arrest in development at that point, whether it's the seizure burden or the heavily sedating medications. And there's two phenotypes that sort of overlap in that category. Then we have kids who are affected a little bit later. Developmentally, they're actually pretty normal. They have nocturnal seizures predominantly, and they can sometimes have some psychiatric issues, but they can be really high function. So we have these extremely sick children and then some children who can kind of go out and have a relatively normal life. Our focus tends to be because they're so sick and we have this high mortality in these younger groups to help those families. So those are the people that we end up interacting with the most.

Kelly Cervantes: And what is when you're talking about the wide spectrum that KCNT1 patients experience, and it sounds a lot like your regular epilepsy where you have the

severely impacted, and then those that can ideally lead more typical lives. I wonder what is the prognosis difference there?

Dr. Justin West: So of the three phenotypes, if you're in that first two categories of these very early onset seizures where it's happening 24/7, the life expectancy is kind of scary. Up to 25% of our children die within the first five years, whether it's respiratory complications, sudep, any of their number of complications. So those are the ones that we would call medically fragile. They're the ones that we worry about on a daily basis. In our community, those are the parents posting their children in the ICU, in and out, over and over, multiple times per year.

So our goal, I think, in the short term is how do we support these families with the drugs that exist and optimize their care for now with what we have to keep them as strong and healthy so that when targeted therapies come along in a year or three or five, they're ready and they meet the criteria to enter those trials and they're not too sick and therefore excluded. So in the short term, we're really focusing on managing to the best that our doctors can, managing the care of these very sick children in preparation for trials, and they're coming, which is exciting.

Kelly Cervantes: That is incredible. And you're sort of leading me into my next piece, which is I know that KCNT1 and Cure Epilepsy were able to partner on a grant to help push that science forward. Can you tell us about that grant that we were able to partner on?

Dr. Justin West: Yeah, so we're fortunate KCNT1 it happens to be on the mind of a lot of really smart researchers and drug developers. And so we had a team that had a proposal to try to get a better understanding of the distribution of channels with the brain. And the thought was, if we can potentially super selectively target not just the whole brain, but specific areas of the brain that we might be able to save children from the impact of the side effects of the drug targeting the whole brain. So it's a really interesting idea. I've not encountered anybody else working on it. So we were excited by the proposal and excited that somebody cared enough about KCNT1 to submit that, and we were really excited that Cure Epilepsy was really excited about. So it was one of those kind of magical moments where we thought, "Wow, we're all really excited about the same thing. Let's do something with this."

Kelly Cervantes: It's incredible.

Dr. Justin West: Yeah, excited to see what happens. It'll probably take time for that to translate into something actionable, but I think it addresses some of these really core questions about what part, is it the whole brain or is it parts of the brain? And I think you have to understand these core biological questions so that you can create therapeutics that are most meaningful.

Kelly Cervantes: Absolutely. I feel like that is so much at the core of why so little of epilepsy and seizures are understood because there are these core mechanisms that we just don't understand in the brain that we understand in spades, say, in the heart. And so I appreciate you bringing that up. Where do you see KCNT1 research going in the next five years?

Dr. Justin West: It's an interesting question. So that's the kind of question that we ask our science advisory board is to say, "What are the knowledge gaps? What are the areas that we know well enough and which should we ignore because we have enough information, but what are the areas that we still need to... And do we even know what those areas are?" So some of them I think are fairly obvious to our scientific team, and that means getting somebody to pick up a project and then fund that project and then sit and let it cook and hopefully put something out that's actionable. So I think that the question being answered specifically by this proposal was one of those key questions. Is it the whole brain or part of the brain? In terms of other areas, this came up just the other day actually finding opportunities to cluster different types of epilepsies together.

So for example, we're a potassium channel and there's lots of channelopathies, and we have some evidence out there sometimes that for a specific, we have an ASO that was created for KCNT1 and there's data out there that ASO that was super selectively targeted to our mutations.

Kelly Cervantes: What's an ASO?

Dr. Justin West: An antisense oligonucleotide.

Kelly Cervantes: Oh my word.

Dr. Justin West: Okay. So here's the quick and easy dirty version, and please don't show this in your scientists, but DNA is a double-stranded molecule, and all of our bodies essentially function on proteins. The way you get a protein is the DNA separates. You create what's called messenger RNA, which is a single strand, and that messenger RNA gets translated, translates into proteins. In our case, it's a protein that goes into the cells of the cell membrane, and that controls ion channel flow. If you have a bad protein being made, a strategy can be to make essentially a piece of Velcro that is complimentary to a part of that mRNA. Once it binds, you can essentially tell this thing to degrade itself so that you don't make the bad copy.

Kelly Cervantes: Amazing.

Dr. Justin West: Yeah, it's really cool science, and there's lots of people working on this. I think it's one of the most exciting things going on in medicine in general and specifically for epilepsy.

Kelly Cervantes: That's incredible. Justin, thank you so much for sharing all of this with us and wishing you and your family the best.

Dr. Justin West: Thank you so much. I really appreciate it.

Kelly Cervantes: So nice to meet you.

Brandon: Hi, this is Brandon from Cure Epilepsy. Since 1998, cure epilepsy has raised over $90 million to fund more than 280 epilepsy research grants in 17 countries. Learn what you can do to support epilepsy research by going to cureepilepsy.org. Now back to Seizing Life.

Kelly Cervantes: So we're here with Liz Ramirez who's going to talk to us about the Acute Syndrome Foundation. Share with us how the organization began and what the mission is.

Elizabeth Ramirez: Sure. Our founding director was Hillary Savoie, and her daughter had a suite of symptoms that was at that time undiagnosed. And so when people would ask her, we get the questions sometimes, "What's wrong with her?" She said, "Oh, it's the acute syndrome that she has." And turns out that her daughter, Esme, had a couple of genetic differences, and one of those was actually a genetic mutation to the SCN8 gene, which is a gene that encodes sodium channels, which are prevalent in our brain, and which when they aren't working the right way, cause epilepsy for most of our patients. So the foundation was created to increase awareness and to support clinicians and researchers so we can find out more about it and support families and individuals living with an SCN8 genetic disorder.

Kelly Cervantes: Well, we certainly love research in Cure Epilepsy. And so can you explain to us what some of the symptoms are that experience with this particular diagnosis?

Elizabeth Ramirez: Well, we see with our kids, they kind of run a wide variety kind of a spectrum depending on where on the SSN8 gene, the genetic kind change happens. So some of our kids will be much more severely impacted. The vast majority of our families do have, or patients have, some kind of epilepsy, but not all of them. Some of them have more autistic like features, or some of those kids used to have seizures and then they outgrew them or they stopped having the seizures. Some of them have cortical visual impairment. Some of them have digestive challenges like gastrointestinal. A lot of them have developmental delays or disabilities, learning disabilities, learning challenges.

Kelly Cervantes: Can you tell us, you mentioned, I think it's interesting, the spectrum and not all SCN8A patients experience seizures, but the ones that do, what kind of seizures do they typically experience?

Elizabeth Ramirez: Every kind, we are finding, some of them have infantile spasms from very young, absence, generalized tonic-clonic.

Kelly Cervantes: And do they appear over the course of their life or do they typically appear when they're younger?

Elizabeth Ramirez: For a lot of them it's younger, like as infants. My son started having them at 10 months old. Some moms actually have reported that they're pretty sure their kids had started having seizures in utero.

Kelly Cervantes: Oh, wow.

Elizabeth Ramirez: But generally, it happens fairly early on for our patients.

Kelly Cervantes: And then, I imagine that because the way that it affects patients is so varied, the prognosis is probably also varied, but can you speak to that a little bit and what the prognosis does look like?

Elizabeth Ramirez: Well, I think probably the number one thing is keeping the seizures under control, which can be a challenge. A lot of our families have tried every different medication out there, BNS, all sorts of things. And sometimes the efficacy of those medications kind of wears off, and so you end up trying different things. So really I think that's a huge determinant in quality of life. But we have some families in our support group, we have a Facebook online support group, and we have adults who are living happy, healthy lives, which is awesome.

Kelly Cervantes: That's amazing.

Elizabeth Ramirez: Yeah, one of my co-volunteers here has a daughter, an adult daughter, who she struggles with seizures and things like that, but I think she knows she's well-loved and she has happy days and she has rough days too. So I think a lot of our wellbeing of our patients and our kids really does depend on the quality of seizure control that they have. And that was true for us too when we had decent seizure control, which for us was maybe a few a month, we had decent quality of life.

But for a lot of us, we will kind of go through ups and downs where we'll have semi-decent seizure control, but sometimes the medication will wear stop working as well. And we'll have so many seizures and we'll have clustering of seizures, status epilepticus, and then our kids will land it in the hospital. So we see a lot of different varied outcomes in our kids.

Kelly Cervantes: And I know very exciting that Cure Epilepsy and Acute Syndrome were able to partner on a research grant. Tell us what the aims of that grant are.

Elizabeth Ramirez: Sure. We're partnering with Cure Epilepsy to fund some research done out of Children's Hospital of Philadelphia. Dr. McKee is looking at the longitudinal data of SSN8 patients that has been collected by and compiled by Citizen. And what we're doing is we're analyzing or they're analyzing that data just to see if we can

better understand, like I said, the longitudinal progression of our kids who are impacted by SCN8 related disorders.

Kelly Cervantes: I think it's so interesting and important for people to understand that these medical records are out there, and a lot of times it's fairly easy to make them anonymous so that we're not crossing HIPAA lines, but that this data is out there and it just needs to be mined for information. But all of that takes money and it takes someone to sit down and actually look through it. Who has that information, who has that knowledge and that experience that knows what to look for? But it does, it takes effort. It takes these grants, it takes money and organizations like ours that will go through and mine it and try and pull this information out.

Elizabeth Ramirez: Yes, and I think there's especially some particular challenges with our kids because a lot of us... I had taken my son to all sorts of specialty hospitals, so his medical records were at Children's Hospital, Orange County and Kaiser and Cedars-Sinai.

And on top of being a parent of a medically involved child, then you're having to track medical records. And so it's really nice to have them all in one place with Citizen. They've done that for us, compiled them, they collect them, we can even update them. And so it's all there. And then like you said, that data can be mined for important information in treating our patients. Yeah.

Kelly Cervantes: Yeah. That's amazing. Where do you see research for SCN8A going in the future?

Elizabeth Ramirez: Well, we would love to see, and we are actually already seeing some clinical trials for precision medicine.

Kelly Cervantes: Amazing.

Elizabeth Ramirez: Yeah, it is really incredible the amount of work that has been done over the past few years. Because a lot of the anti-epileptic medications, they may help with the seizures, but then there's a lot of other impacts on their organs or on their functioning.

And so with precision medicine, there's an opportunity to just focus on the part that is dysfunctional and not impact as much the other areas so that we can control the seizures and whatever else, what other dysfunction-

Kelly Cervantes: Make the patient more alert.

Elizabeth Ramirez: Yes. And that's a huge challenge. Sometimes there's alertness issues, but also sometimes insomnia, which is terrible because the more tired you are, then the more-

Kelly Cervantes: Seizures you're going to have.

Elizabeth Ramirez: So it's a really tough decision where you have to control the seizures, but it comes at a really high cost to our community. So I think precision medicine is really, really exciting for us, and I feel like it's around the corner.

Kelly Cervantes: That's incredible. Liz, thank you so much for sharing your journey and this whole experience with us, Acute Syndrome, and Cure Epilepsy is just so thrilled that we can partner with your organization on this research.

Elizabeth Ramirez: Thank you so much. It was really nice meeting you.

Kelly Cervantes: Nice to meet you too.

Thank you to Dr. Justin West of the KCNT1 Foundation and Liz Ramirez of the Acute Syndrome Foundation for taking time to speak with us at Epilepsy Awareness Day. And thank you to both organizations for their work. On behalf of families living with a rare form of epilepsy. Cure Epilepsy understands the importance of grassroots organizations. That's why we have collaborated with these organizations on the Rare Epilepsy Partnership Award. Like the organizations we profiled today, Cure Epilepsy began with a handful of mothers gathered around a kitchen table, desperate to find answers and improve epilepsy care for their children. 25 years later, Cure Epilepsy has raised more than $90 million to fund epilepsy research and other initiatives that will lead us to a cure. If you would like to help us achieve our goal of a world without epilepsy, please visit cureepilepsy.org/donate. Cure Epilepsy, inspiring hope, and delivering impact. Thank you.