

Kelly Cervantes: 00:00 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 My daughter Adelaide has been through more tests than I care to remember, from MRIs, biopsies, and countless blood draws. Some of the most informative tests, though, can be related to genetics. That is why I'm excited to have Dr. John Millichap on the show today talking about the connection between epilepsy and genetics. This evolving field of study is a key element in identifying many forms of epilepsy and finding their cures in the future.

Kelly Cervantes: 00:43 Dr. Millichap is an attending physician for neurology and epilepsy at Ann and Robert H. Lurie Children's Hospital here in Chicago. He is also an associate professor of pediatrics and neurology at Northwestern University's Feinberg School of Medicine. Thank you so much for being with us today, Dr. Millichap.

John Millichap: 01:00 I'm glad to be here.

Kelly Cervantes: 01:01 We know that our DNA determines our eye color, hair color, and body type, but what is the connection between our DNA and epilepsy?

John Millichap: 01:09 Sure. So, we know a lot about the causes of epilepsy. But, in the same breath, I'll say we also know very little. What we do know is there are hundreds of genes that are related to epilepsy. We also know that variations in genes alter the functioning of those genes within the body's machinery. For example, a very common cause of epilepsy is related to what we call "ion channels." A channel is like a hole.

John Millichap: 01:45 Imagine a brain cell with a protective wall around it. Then imagine a small hole, an ion channel, in that wall, where salts like sodium and potassium can enter and exit. When these salts remain in balance, the electrical activity of the brain cells remains stable. Any variation in the gene that controls that cell's ion channel could cause a salt imbalance. When you have more electricity in that brain cell and more electricity leads to more seizures.

John Millichap: 02:22 That's just one example. There are also genes that are related to the actual structure of the brain can lead to actual brain malformations, which could be detected in an MRI.

- Kelly Cervantes: 02:35 Talking about variants in the genetic code, not all forms of epilepsy are necessarily hereditary. But when you get your test results back, they're talking about this variant and that variant. What causes those variants if it's not hereditary?
- John Millichap: 02:50 Sure. This is one of the first things I talk to parents about when bringing up the option of genetic testing. I explain that most early-onset childhood epilepsies are actually new variations within the child's genetic code, rather than being inherited from the parents. Consider basic biology: once the egg and the sperm come together, the child is formed. Every time cells split in the developing child, DNA is copied. Every time DNA is copied, there are little mistakes, little changes to the DNA.
- John Millichap: 03:32 Sometimes those changes, or variations, don't make any difference whatsoever and we just go on being ourselves. But sometimes, early in development, one little variation will alter the function of one gene, thus altering the body's machinery and cause epilepsy.
- Kelly Cervantes: 03:53 For my family, we saw a developmental delay in our daughter. That was when our neurologist started to order the genetic testing. But for a lot of people, the testing may come *after* that initial epilepsy diagnosis. Are there other tests available that can be administered earlier? As a clinician, what tests do you find most beneficial and why?
- John Millichap: 04:23 Sure. When I got into neurology about 11 years ago, genetic testing was not used as a first-line test. Things have changed to the point where almost every patient that I see today, once I've established the diagnosis of epilepsy, taking a history, and looked at the EEG, the MRI, my examination, and I haven't determined a cause of the epilepsy, I'll then talk to parents about the availability of genetic tests. In many cases, the first test would focus on isolating the genes we know to be associated with epilepsy. This test is called the "epilepsy gene panel," and it has a high sensitivity for detecting those specific epilepsy-related genes.
- John Millichap: 05:15 Maybe 100- 200 genes with a strong association to epilepsy are included on the panel. Once we've ruled out that there's been no change in those genes because it looks at it with such depth and accuracy. And if that's unrevealing, we can go to the next step, which involves the parents even more. We compare blood samples from both the child and the parents, focusing on the relevant DNA sections. This is called "whole exome sequencing."

John Millichap: 05:56 The reason we take the parents' blood is because, as I said, we all have little variations that don't affect anything in our bodies, so we subtract those inherited variations from the child's sequencing.

Kelly Cervantes: 06:15 Right. So, if you see the variant in the parent and also in the child, but the parent is symptom- free, then that's probably not your culprit.

John Millichap: 06:23 Exactly. The GI testing company has a huge computer that does a lot of this initial sifting. Another thing that I'll constantly be reminding other doctors, trainees, and parents is that the genetic testing is not a static test. For example, if you had an MRI last week, the results would be fixed. Meaning, they would be the same results a year from now, or five years from now. But if you had a genetic test last month, or six months ago, or a year ago, the results are not fixed. They are constantly re-evaluated and re-analyzed, since we're always learning new things. The variations that seemed meaningless, or the genes that appeared unrelated to epilepsy, a year ago may today be the cause for your child's epilepsy.

Kelly Cervantes: 07:14 Let's say you get through "whole exome sequencing," as this was the case with our daughter. There were some variants of unknown significance, but there was no smoking gun, if you will. What does "variants of unknown significance" mean? And what do you do next when you still don't have an answer after completing the "whole exome sequencing"?

John Millichap: 07:42 The terms that we use today have changed over the last five years or so. Instead of using the word "mutation" to describe a variation in DNA that leads to disease, the genetics professional association convened and established clear criteria for how doctors should discuss these findings with families and individuals. Now we have this vague and confusing designation, "variant of unknown significance" (VUS), which falls right in the middle of the new terminology spectrum. Above this, we have "likely pathogenic," or likely causing the disease, and "straight pathogenic," or clearly causing the disease.

John Millichap: 08:29 On the lower end, we have "likely benign," or likely not significant, and just "plain benign," or not the cause of the disease. As you can imagine, VUS means we're not sure. It has neither the criteria to make it definitely the cause or definitely not the cause. I'll always caution parents when I send them for genetic testing that it may lead to uncertainty and more tests.

Kelly Cervantes: 09:00 Sure. So, now then, very recently, within the last year or so, “whole *genome* sequencing” has become available. It seems to me, and correct me if I'm wrong, that, on a research level, it's not available commercially. What is the difference between “whole exome” and “whole genome” sequencing? How can someone get submitted for testing for “whole genome sequencing” and when should they?

John Millichap: 09:35 “Whole genome sequencing” has some differences from the panel that I referred to previously, having 200 genes that are analyzed deeply to be sure there were no variations in those genes. The “whole exome” is still very good, but it doesn't have as many, we call them, “reads.” Let's say you have a gene like KCNQ2, one cause of epilepsy that I'm very familiar with. With “whole genome,” KCNQ2 would be “read” over 200 times. It's like reading a book 200 times; you really know that book, right?

John Millichap: 10:15 On the other hand, “whole exome sequencing” may only “read” it 30 times or less. It covers it, but not quite as deeply.

Kelly Cervantes: 10:24 Okay.

John Millichap: 10:25 This is also the problem with “whole genome sequencing.” There's an enormous amount of data. We imagine “whole exome” as the parts of the book we can read, what makes the story. “Whole genome,” then, is everything, including the binding, the cover, the white spaces, the margins, everything. The entire book. There are parts of DNA that we don't know how they relate to bodily functions or mechanisms. And that's an enormous amount of data.

John Millichap: 11:07 We're still learning more and more about how a variance *outside* of the traditional readable portions of DNA can lead to disease. So, “whole genome sequencing” is now available clinically, and there are different companies making it available. The cost is still at a higher level, but that will surely come down.

John Millichap: 11:42 I would say that, in the next few years, technology will probably take over the technologies we currently have. At that point, if somebody had testing several years ago, it would probably be a good time to get retested, if no cause had been found. Again, the number of “reads” will continue to increase as the technology improves and the cost drops.

Kelly Cervantes: 12:17 So we've got the tests, we know what we're looking for, the variance, the number of different tests progressively going up. On an individual, fundamental level, why should someone get

tested? What is the benefit of knowing what's causing the epilepsy, aside from peace of mind, or having somewhere to direct her/his frustrations?

John Millichap: 12:42 I think this is a really an important point. I was trained in neurology, and we knew a little something about genetics back in 2007-2008. We kept looking for various genetic causes of epilepsy, but it wasn't until 2012 when I really saw the power of genetic testing. A patient of mine was having gene test after gene test. They had been going on almost two years at that point. Then we tested for KCNQ2. The patient had had seizures since they were born, and the test came back showing a variation. This was how we found out the cause of the epilepsy.

John Millichap: 13:28 The way it affected the family really struck me more than anything else I could see as to the value of genetic testing. It just changed the way they looked at their child, and the way they approached me and the rest of the community. It allowed them to reach out and meet other families of children with the same genetic cause. It gave them a lot of support which otherwise they wouldn't have. They would say, "We don't know why our child can't talk and-"

Kelly Cervantes: 14:11 Under prognosis.

John Millichap: 14:13 Now it gives us a better idea.

Kelly Cervantes: 14:14 Or at least a better idea of what the future looks like. If you can connect with other similar children and families, you can be like, "okay, this is what we can look out for. This is what we can expect." There's so much peace of mind in that.

John Millichap: 14:28 There are one of about 20 genes where it may change our approach. We may prescribe different available seizure medications based on the genetic-testing result. For example, tuberous sclerosis is a common cause of infantile spasms and other types of seizures. In the case of infantile spasms, we may prefer to recommend one treatment over another if we know that's their cause. A genetic diagnosis there can really help us.

John Millichap: 15:01 And in the cases of KCNQ2, SCN2a, SCN8a, these are all names of ion channels, or the holes in the wall of the cell. We may now prescribe specific types of medicine, very common ones that we currently use to treat adults, that we may not have thought to use in babies, because we now have this specific genetic diagnosis. It's changed my practice. I look for the clinical signs of

these genetic causes of epilepsy, confirm them, and then prescribe specific medicines for that specific cause of epilepsy.

- Kelly Cervantes: 15:42 Genetic testing can clearly be very helpful in terms of treatment. I also imagine that it can be incredibly useful on the research side of things. If you start to understand the cause behind some of these epilepsies, then research can focus our research and get closer to find a cure for some types of epilepsy. Do you have a sense of how genetics is changing epilepsy research?
- Speaker 3: 16:13 Absolutely. This goes along with some of my research interests as well. Let's go back to that KCNQ2; it's actually one of the precision-medicine genes, so to speak. Even before we knew that KCNQ2 was a cause of serious epilepsy, a seizure medication that was approved and released only for use in adults and was going to be approved for children, but it was only released for adults, focused on that gene, or the channel, that gene makes.
- Speaker 3: 16:49 Just by increasing the amount of this potassium salt that goes out of the cell stabilizes things for everybody. For example, a veteran who has a concussion, or a person who has had a stroke, or an adult who had a stroke and has epilepsy, all these people benefit from this medicine that targets that specific gene. Once we learned it also causes newborn-onset epilepsy, it really opened our eyes to how important this system is for epilepsy and as a potential target for treatment.
- Speaker 3: 17:29 The work we've been doing for the last five years has been to try and see how we can use that drug, or ones that are similar to it, to hopefully reverse not only the seizures, but also all the developmental consequences as well.
- Kelly Cervantes: 17:46 These genetic tests can be so beneficial for prognosis and treatment, but it can sometimes be difficult to get insurance companies to cover them because they are very expensive. What advice can you give to parents who are trying to fight the insurance companies to approve this genetic testing, which can be so beneficial? What conversations should they have with their doctors to increase their chances of getting this testing for themselves or their child?
- John Millichap: 18:17 I think when things are new, the insurance companies and the hospital systems have to take some time to catch up. I'm sure in the 1980s, when the MRI procedure was new, there were doctors who said, "well, we've been doing just fine with our CT scans, why do I need this newfangled test?" But we've seen how

helpful the MRI has been in diagnosing epilepsy in both children and adults more accurately, as well as leading to improved results and lower costs overall.

- John Millichap: 18:50 I think genetic testing is there now too. If I have a positive genetic testing result, I may do a fewer EEGs, MRIs, or other invasive tests like lumbar punctures and muscle biopsies. Lumbar punctures put a small needle in the back to get the fluid from around the brain. Muscle biopsies is where you take a portion of the muscle to look at under the microscope.
- John Millichap: 19:14 Those tests were much more common just 10 years ago, but they are less frequently done now because of genetic testing. Once we have testing as a viably consistent option, there should be enormous cost savings. The insurance companies should realize that early and accurate diagnoses will lead to more efficient use of our resources in the long-term. The cost has already dropped so much. Compared to an EEG, especially one that's done overnight, the EEG is much more expensive.
- Kelly Cervantes: 19:57 Really?
- John Millichap: 19:57 Yes. Also, an MRI that requires sedation with anesthesia makes that test much more expensive. But I think these tests have really come down as far as costs are concerned. It's more now a matter of being covered or not covered, and we have to change the understanding.
- Kelly Cervantes: 20:20 I have to constantly remind myself how new all this testing is, that insurance companies and doctors are really just learning how useful it can be, and how it can reduce costs. I know I have found, in speaking with parents who have children who are 10 years old, they've never had the genetic testing done because it wasn't available to them when their child was first diagnosed. As opposed to my daughter Adelaide, one of her first tests was a genetics test. It's just so shocking to me how quickly genetic testing has taken off. Where do you see it going? What new studies are being done? What's on the horizon for genetics and epilepsy research?
- John Millichap: 21:13 I think the testing will become a part of our common practice. Once we've determined that the patient has had a seizure or epilepsy, we'll then do our usual history, including taking an exam, a picture of the brain, an MRI likely, and then an EEG. In most cases, we'll get a good idea of what the cause is from those tests. But beyond that, I think we will want to know what the underlying genetic cause is, and how that affects the patient going forward.

John Millichap: 21:54 I'm going to go out and say now that I think we'll be doing genetic testing on almost everybody very shortly because, even if we have a malformation of the brain, that malformation must've come from somewhere. There must be some genetic variation. Even if your child had a stroke, an infection, or had a particularly bad response to the brain infection. In some cases, it might not be an epilepsy gene, there's going to be some genetic predisposition to that child's over-exaggerated immune response to the bacteria. This may result in treatments that infectious disease specialists are currently investigating.

John Millichap: 22:41 "Everything is genetic," I think, will be the mantra going forward.

Kelly Cervantes: 22:46 Tell your kids to go into genetics.

John Millichap: 22:49 Well, I do a lot of this myself, obviously. I'm able to talk to you about it, but genetic counselors are really helping us specialists with this explosion in genetic testing. They're very important for talking about cultural inheritance and other genetic questions that are beyond my epilepsy wheelhouse, so to speak.

Kelly Cervantes: 23:15 I think one of the things that's so concerning to me is that we have these staggering statistics where over half of those who are diagnosed with epilepsy still don't know what is causing their seizures, which simply adds to their feelings of helplessness. How do you treat something if you don't know the cause? But I have to imagine that, with the availability of genetic testing, we'll start to see those numbers come down, that we'll start to see more and more people with better information, and less people being undiagnosed.

John Millichap: 23:49 Absolutely. As we talked about in the beginning of our conversation, just knowing a cause is so much more reassuring for families. Even if it's not a cure or we don't have an answer today, just meeting other families who are going through a similar experience; it can also avoid unnecessary further testing that can be invasive and expensive. And our goal of precision medicine is still there. It's very complicated, but we're continually inching towards it in different ways.

Kelly Cervantes: 24:30 Wow. Crossing fingers that we get there sooner rather than later. Thank you so much for joining us today and for helping keep this very "sciencey" conversation accessible to a lay person like myself. I really do appreciate your time and letting me pick your brain.



John Millichap:	24:49	It was great talking with you. Thank you.
Kelly Cervantes:	24:54	I'd like to thank Dr Millichap for his insights and experience on the genetics of epilepsy. While we have made steps towards understanding how genetics causes epilepsy, we have so much more to do. More than 50% of people with epilepsy still do not know the cause. Without this information, it can be extremely challenging to find the best treatment. But further funding of genetic epilepsy research could close this gap. Cure has been instrumental in leading us towards personalized medicine based on epilepsy and genetics. Help us do more by donating to citizens United for Research in Epilepsy at <a href="http://www.cureepilepsy.org/seizing-life">www.cureepilepsy.org/seizing-life</a>
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