Finding Answers for Savannah

Until recently, the first thing Tracy Dixon-Salazar did every morning was check her daughter Savannah to see if she was still breathing.

When she was a toddler, Savannah started having seizures. The first time it happened, Tracy and her husband thought she might be choking, but it turned out to be much worse. Savannah has a severe form of epilepsy called Lennox-Gastaut Syndrome (LGS).

The seizures come fast and furious. Now a teenager, Savannah has experienced more than 27,000, and they have taken a huge toll. She is a happy, social girl, but her condition has put her way behind developmentally.

There is no single cause for LGS and no specific treatment. Savannah has been on every anti-seizure medicine that made sense—and a few that didn't. Her parents tried changing her diet and changing it again. They scoured epilepsy message boards for anecdotal successes, but nothing controlled her condition.

Mother and Researcher

With no family history, or any other explanation, physicians were mystified. “I couldn’t get over the fact that no one could tell me why this was happening,” says Tracy.

She started taking biology classes to better understand her daughter’s condition, found she loved the science and decided to get her degree. She also met Dr. Joseph Gleeson.

A practicing neurologist and dedicated researcher, Dr. Gleeson investigates the genetic causes of neurological diseases, including epilepsy. As an undergraduate, Tracy volunteered in his lab and quickly demonstrated her organizational skills and attention to detail. She helped author important papers, orchestrated research and contributed to our understanding of epilepsy. Then she went to work on her PhD.

“I never thought for a minute I would be able to help Savannah,” says Tracy. “But I enjoyed the opportunity to help other kids.”

New Technology

Tracy left the Gleeson lab for graduate school, but recently returned as a newly minted Ph.D. Much has changed. Advances in genomic sequencing have given scientists greater insights into the molecular causes of disease. Now a doctor herself, Tracy encouraged Dr. Gleeson to embrace exome sequencing, which captures information on the small portion of our genome that codes for proteins.

Savannah’s condition was not improving. She had non-stop seizures two or three times a week, events that could last for hours or even days. But Dr. Gleeson had an idea. “I said to Tracy, let’s sequence her. Maybe we can find something treatable.”

Savannah’s exome sequencing showed 25,000 genetic variations, which had to be painstakingly analyzed to understand which ones might be causing her condition. Dr. Dixon-Salazar pored over the data for months to find the disease-causing mutations in Savannah’s DNA. In late 2011, she succeeded.

Savannah has mutations in several calcium channel genes, which can affect muscle contractions. Her family already knew that calcium supplements increased her seizures. Perhaps calcium channel blockers could control them.

Treatment began in December and the results are amazing. Savannah’s seizures have been reduced by 80 percent. “She goes entire days seizure-free,” says Tracy. “That’s unheard of.”

Though Savannah will never regain function, without constant seizures she can have a more normal life. In the big picture, sequencing may help identify the underlying causes of other conditions.

“There is no disease described that has ten different calcium channel mutations,” says Dr. Gleeson. “We would never have looked for that cause. Sequencing gave us the answers we needed.”

The Promise of Genomics

The ability to sequence genes and determine how different mutations affect our health will have a profound impact on medicine. In cancer, it will allow physicians to understand each tumor’s genetic “flavor” and custom-prescribe treatments. In heart disease, genomic data will help identify how each patient responds to specific medications. But perhaps the greatest payoff will be understanding genetic diseases.

Dr. Joseph Gleeson, a senior neurologist at Rady Children’s Hospital and professor of neurosciences at UC San Diego, is already harnessing this technology to decipher neurodevelopmental diseases.

“We want to understand the parts lists,” says Dr. Gleeson. “The list of genes that is important in putting the human brain together and the diseases that result when one or more of those genes is missing.”

Dr. Gleeson’s lab is making progress. Recently, the team analyzed the exomes (genes that code for proteins) for a small group of children suffering from both autism and epilepsy. They found a mutation in a gene not previously linked to human disease. Even better, they found the condition could be treated with a simple change in diet.

“This was a previously unknown metabolic cause for autism and epilepsy,” says Dr. Gleeson. “We have similar cases. By finding the gene, we can determine a treatment.”