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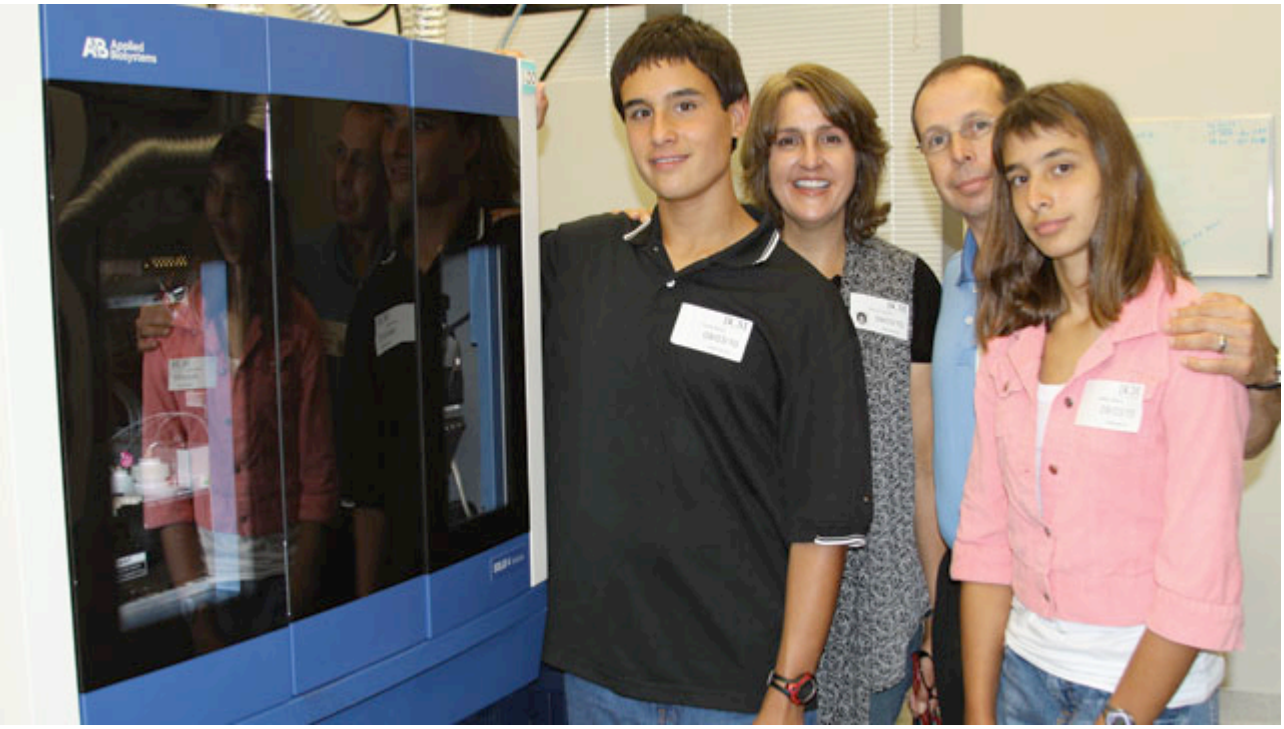
Double Blind

The mother of disabled twins doggedly pursued the root of her children's illness and found it in their genome profiles.

By Cristina Luiggi | October 1, 2011



The Beery family, standing before the sequencer that decoded the genomes of twins Noah and Alexis. Retta Beery

At two years of age, fraternal twins Alexis and Noah Beery had not met most of their developmental milestones and had such poor muscle tone they could barely walk or sit on their own. Noah drooled and vomited continually, and Alexis suffered from body tremors during which her eyes would roll back in her head for hours at a time.

An MRI scan had revealed damage in the periventricular area of Noah's brain, which led to a diagnosis of cerebral palsy. But children with cerebral palsy tend to improve with treatment; in contrast, the twins' conditions, particularly Alexis's, worsened over time. When she was 5 years old, Alexis developed respiratory problems and continued to have protracted seizures. She also had extreme difficulty walking and was always off balance.

The twins' mother, Retta Beery, was most puzzled by the fact that Alexis's symptoms seemed to fluctuate during the day—they were mild in the morning and became more severe as the day

progressed. “By 11 o’clock in the morning she was unable to sit up and unable to swallow,” Retta says. “But if I put her down for a nap, when she would wake up she could function again.”

Tired of bouncing around from specialist to specialist, Retta embarked on an exhaustive review of the medical literature. Then, one spring night in 2002, she stumbled upon an old photocopy of a 1991 *Los Angeles Times* article that described a young girl whose condition had uncanny parallels with Alexis’s. The girl, Kimberly Nelson, had been diagnosed with cerebral palsy, and the severity of her symptoms ebbed and flowed throughout the day.

John Fink, a neurologist at the University of Michigan, had determined that Nelson had been wrongly diagnosed with cerebral palsy. The fluctuations in her symptoms instead were due to a rare and poorly understood genetic disorder called dopa-responsive dystonia (DRD)—a movement disorder caused by a deficiency in the neurotransmitter dopamine.

Five weeks later, Alexis and Noah were in Fink’s office, and the doctor prescribed Alexis a daily dose of levodopa (a synthetic dopamine).

“That was the first night in Alexis’s life that she slept through the night,” a tearful Retta says. In fact, the following days were filled with many firsts for the five-year-old girl: the first time walking to the car unaided and the first time she didn’t need assistance when eating, for example. “We knew that we were witnessing a miracle,” says Retta.

A few months later Noah’s right foot started to turn in and his head involuntarily tilted down. Beery and Fink recognized it as the onset of DRD and started him on levodopa as well. Not only did the drug correct his posture, but after six years of vomiting every day, “Noah stopped throwing up,” his mother recalls. Except for taking medication, the twins began living normal, active lives, playing sports and excelling in school.

But a few years later, in 2005, Alexis developed a severe night cough, and two years ago it worsened dramatically to the point that she had to inhale a synthetic adrenaline compound every day in order to breathe and sleep normally.

Desperate to get to the bottom of her children’s mysterious illness, Retta asked her husband, Joe, who had recently become the CIO of Invitrogen (now Life Technologies), to look into the possibility of having the twins’ genomes sequenced.

In the fall of 2010, the twins’ blood samples were sent to the Baylor College of Medicine’s sequencing center, where they were analyzed by a multidisciplinary team of researchers and physicians and compared to the samples from their parents and close relatives. The researchers found that the twins were compound heterozygous: each inherited a nonsense mutation from the mother and a missense mutation from the father, with both mutations occurring in different regions of the gene that codes for the enzyme sepiapterin reductase (SPR), which catalyzes the production of a cofactor—tetrahydrobiopterin (BH4)—necessary for the synthesis of the neurotransmitters dopamine and serotonin.

Not only were the twins deficient in dopamine, but they were also producing dangerously low levels of serotonin. When the doctors added 5-hydroxytryptophan (5-HTP), a serotonin precursor, to their treatment regimen, Noah’s drooling and motor skill problems vanished and Alexis’s breathing went back to normal.

Alexis, now 14, was able to run track (and place in the top three) in her spring semester, and Noah

played volleyball in this year's Junior Olympics.

"For the first time, we based a medical management treatment on a molecular diagnosis that was established through genome sequencing," says James Lupski, a geneticist at Baylor College of Medicine who led the copy number analysis of the twins' genomes. He adds, "This was no brilliant doctor, this was no new technology. This was a mom trying to figure out her child."
