A mother's determination, next-generation sequencing provide solutions for twins

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When Noah and Alexis Beery were diagnosed with cerebral palsy at age 2, their parents thought they at last had an answer to the problems that had plagued their twin infants from birth. However, that proved only a way station on a journey to find an answer to the children's problems that combined their mother's determination, the high tech world of next-generation sequencing in the Baylor Human Genome Sequencing Center (HGSC) and the efforts of talented physicians from across the country.

In a report in the current issue of Science Translational Medicine, researchers from Baylor College of Medicine, experts in San Diego and at the University of Michigan in Ann Arbor describe how the sequencing of the children's whole genome along with that of their older brother and their parents zeroed in on the gene that caused the children's genetic disorder, which enabled physicians to fine-tune the treatment of their disorder.

More than that, it also took human genome sequencing to a new level – that of improving treatment for an individual. The Baylor Genome Sequencing Center has pioneered whole genome sequencing of individuals, beginning when they presented Nobel Laureate Dr. James Watson with his full genome sequence on May 31, 2007. It was followed up in 2010, when Dr. Richard Gibbs, director of the Baylor Human Genome Sequencing Center, and Dr. James Lupski, vice chair of molecular and human genetics at BCM, published information on Lupski's whole genome sequence, identifying the gene mutation that caused his form of Charcot-Marie-Tooth (CMT) Syndrome, an inherited

disorder.

"When the Baylor HGSC sequenced Watson's genome, it showed we could do a whole genome sequence," said Lupski. "When we sequenced my genome, it showed that whole genome sequencing was robust enough to find a disease gene among the millions of genetic variations. Now, not only have we found the variation that caused the disease, it enabled us to change therapy to improve their outcome."

"This is a giant step forward in our ability to use whole genome sequencing to benefit patients," said Gibbs.

"This work is a pivotal example of how genomics will revolutionize medicine by improving diagnostics and ultimately helping physicians optimize care for their patients", said Dr. Matthew Bainbridge, the first author on the report who was a graduate student during much of the work.

Lupski was one of the physicians who consulted on the case of the Beery children at Texas Children's Hospital, and he credits their mother Retta Beery with fighting for her children's future and her absolute determination to find an answer.

"Because of this mother, the children have a diagnosis and whole genome sequence that changed their diagnosis. Now they have additional therapy that works," he said.

When the twins reached age 4, it became apparent to their parents that the diagnosis of cerebral palsy did not match the problems their children were facing. Their mother did Internet research and found a description of a disease that fit her daughter's diagnosis better – dopa-responsive dystonia. The muscles of people with dystonia contract and spasm involuntarily. In this case, the disease was responsive to a drug called L-

dopa, which substituted for the neurotransmitter dopamine that they lacked. Neurotransmitters are critical to proper functioning of nerves that, in this case, control muscle fibers.

Dr. John Fink, professor of neurology at the University of Michigan, diagnosed first Alexis and then Noah with the disorder and started them on small doses of the drug, which alleviated many of their symptoms, at age 6. They went to school and began to function as normal children.

"It's completely changed their lives," said Retta Beery. Then, about 18 months ago, Alexis Beery began to have breathing problems so severe that eventually they forced her to stop the athletics she loved. Twice, paramedics came to the Beery house because her breathing problem became acute. Her ability to breathe was decreasing and her mother began another desperate search for an answer.

That is when their mother brought up the issue of whole genome sequencing to her husband Joe, who is the chief information officer of Life Technologies, Inc., a company pioneering new methods and manufacturing the research equipment for next-generation sequencing. That brought them to Baylor College of Medicine and Gibbs at the Baylor Human Genome Sequencing Center.

There, a team began the search for the mutated gene that was causing the twins' problems. Existing single-gene tests for the two genes known to cause the dopa-responsive dystonia were negative. When the Baylor team sequenced the whole genome of each twin (and studied their parents and brother for comparison), they found the twins had three genes with mutations that might be causative.

Two of the genes had no known purpose, but one – sepiapterin reductase (SPR) – had also been associated previously with dopa-responsive dystonia. The twins each inherited two mutated copies of that gene. One

of the copies came from their mother and the other from their father. The mother had a nonsense mutation and the father had a missense mutation. (A nonsense mutation stops the reading of messenger RNA, resulting in a truncated protein that does not work. A missense mutation is a change that results in the production of a different amino acid that causes an alteration in the protein associated with the gene.)

When SPR is mutated, it disrupts a cellular pathway that is responsible for not only the production of dopamine but also two other neurotransmitters – serotonin and noradrenalin. Both dopamine and serotonin act at the synapse, the junction at which one neuron passes electrical or chemical signals to the next.

The result meant that the twins were not only deficient in dopamine, they were also deficient in serotonin. In consultation with the twins' California pediatric neurologist, Dr. Jennifer Friedman of Rady Children's Hospital in San Diego, the Baylor doctors at Texas Children's Hospital advised adding a small dose of a supplement called 5-HTP to their medications. Friedman, a neurologist, had actually treated another child with the disorder.

"A month after adding the new therapy, Alexis's breathing improved dramatically," said Retta Beery. "She's been running track again."

Noah has also benefited, she said. His handwriting has improved and he was able to focus more in school.

The Beery case also has important general implications for studying human genetics as the genome sequencing resulted in a better understanding of what happens when a person has only one copy of the mutated gene. Each of the Beery parents has one of the gene mutations that affected their children. While the two mutated genes caused profound disease in the children, at least one mutation appeared to be

potentially associated with Retta Beery's susceptibility to fibromyalgia, which also affected other members of her family.

In other words, two mutated copies of the gene (even when the mutations are different) cause the profound disease. A single mutated copy of the gene may confer susceptibility to a more common ailment.

The additional information in the Beery family is like the story in the Lupski family, where some people on one side of his family who had just one copy of the mutated genes had carpal tunnel syndrome and some on the other side of the family who had another mutated gene copy had axonal neuropathy (a disorder that affects the axon, the part of the neuron that extends away from the main body and carries messages to peripheral parts of the body). Only family members, like Lupski himself, who inherited both mutated copies were affected by the full Charcot-Marie-Tooth disease

"I think we may find more examples of genes with mutations that cause disease, and when you look at family members who have only one of the mutated alleles, you may find other variations that result in milder common disease," said Gibbs.

"This is an important finding," said Lupski. "We found evidence that sometimes, when you have a heterozygous state (only one of the mutated genes), you might be more susceptible to more common diseases."

"The key is that the children were correctly diagnosed clinically, but the molecular diagnosis offered a refinement that enabled better medical management which could further alleviate symptoms and improve quality of life for these terrific twins," said Lupski. "It answers the question of why do the genome sequence. I believe it also shows what we can all learn from a mother's persistence!"

More information: *Science Translational Medicine*: http://stm.sciencemag.org/