Five new human genomes decoded, marking a transition to more personalized medicine

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It seems longer, but it was only seven years ago that the Human Genome Project deciphered the sequence of the 3 billion nucleotides that make up a single human blueprint or genome. That project cost more than $3 billion and took 13 years. But the speed of sequencing has been increasing dramatically while the cost has been dropping in a similar fashion. On Wednesday, researchers revealed the sequences of the genomes for five more people, bringing the total number of known genomes close to 20.

The new findings are a "technological tour de force," said Story Landis, director of the National Institute of Neurological Diseases and Stroke. But what makes the technology even more impressive, she said, is that these were whole genomes of people that provided "very interesting stories about rare diseases."

Dr. James Lupski of the Baylor College of Medicine in Houston was diagnosed with Charcot-Marie-Tooth disease in his teens, as were three of his seven siblings. The genetic disease, often called CMT, affects about one in every 2,500 Americans and is caused by a loss of function in nerves, impeding the transmission of electrical impulses that control movements and sensory information sent back to the brain. Because nerves to the feet have the longest distance to travel, the extremities are the first things to be affected. The disorder produces foot deformities, drop foot and other difficulties that can be corrected surgically. Lupski has so far had 10 orthopedic procedures to help overcome his problems.

There is no cure for CMT, only treatments that alleviate symptoms.

Inspired by his condition, Lupski, 53, pursued a doctorate in genetics and a medical degree, migrating to Baylor after his graduation. There, he began looking into the genetics of CMT. In 1991, his laboratory discovered that duplicate copies of a gene caused some cases of CMT, but not his own. Since then, researchers around the world have discovered 30 other genetic variants that are linked to the disorder and 10 other locations on chromosomes that appear to carry genes associated with it. Each of those genetic variations interferes with nerve transmission at a different location, but the illnesses they produce are all very similar. "But each time we would check my family, we did not find the mutation," he said.

A few years ago, Dr. Richard Gibbs, director of Baylor's Human Genome Sequencing Center, asked Lupski to participate in sequencing the genome of James Watson, co-discoverer of the structure of DNA. After that project was completed, Gibbs and Lupski were chatting at a meeting when they decided to sequence Lupski's genome. "The sequencing went very rapidly, but the analysis took a lot of time," Lupski said. "All of a sudden, you have 90 billion bases to sift through."

Ultimately, the team reported in the *New England Journal of Medicine*, they discovered two separate mutations in a gene called SH3TC2. One is a nonsense mutation that causes production of a protein to be terminated prematurely. The second is a missense mutation that causes an incorrect amino acid to be inserted into the protein, rendering it only partially functional.

Before Lupski left the East Coast, where he was raised, he banked blood samples from his grandparents, his parents and his siblings for use in future studies. When the team looked at the samples, they found that Lupski's father and his grandmother carried one of the mutations and his

mother carried the second. His three siblings who suffered from CMT all inherited both mutations, while the four unaffected siblings had only one and did not develop the disease. The team also discovered that the gene mutations had recently been discovered in a family of Spanish Gypsies. Other researchers had already produced an animal model of CMT in which the gene had been inactivated in mice and were studying its function. They found that the gene plays a role in an intracellular mechanism called endocytic recycling, which is crucial for the health of the cell. Interestingly, two other gene variants have also been linked to endocytic recycling and researchers are studying intervention with small molecules to bolster the process. Lupski hopes that work may lead to similar progress with his gene.

Surprisingly, electrophysiology studies of the family members found that people who carry only one copy of either defective gene may not develop CMT, but they are not free from nerve problems. The gene Lupski inherited from his mother confers an increased susceptibility to carpal tunnel syndrome, also known as repetitive motion syndrome. Such people suffer severe pain from compression of the medial nerve where it crosses the wrist. The gene carried by his father and grandmother produces mild neuropathy of the axons that carry nerve impulses.

"By no means do I think we will have an instant cure, but the epiphany from understanding this is quite remarkable," Lupski said. "This is a milestone in the field of CMT disease. We have gone from being totally in the dark to having enough light to see which direction to go in. But we are not in the bright light of having something" that could be a treatment.

The second report, published online in the journal *Science* by researchers from the University of Utah and the University of Washington, marks the first time in which the complete genomes of four members of a single family have been sequenced. The report does not identify the subjects, but the Salt Lake Tribune identified them as the wife and two

adopted children of researcher Lynn B. Jorde of the University of Utah and the children's biological father. The family has been active in advocating genetic research.

The mother, Debbie Jorde, and the unidentified biological father are both healthy. But the two adult children, Logan and Heather Madsen, are two of only 30 people worldwide known to suffer from Miller's syndrome, which is characterized by facial and limb malformations. The incidence is believed to be about one in 10,000 people. But in an exceptionally rare genetic double whammy, both children also suffer from primary ciliary dyskinesia or PCD, an equally rare condition in which the tiny hair-like cilia that are supposed to remove mucus from the lungs do not work properly. The odds of having both diseases are thought to be about one in a billion.

The cause of PCD was previously known. But "until now we didn't know what caused (Miller's syndrome)," Lynn Jorde told the Tribune. "We didn't even know if it was genetic. Now we have the causal gene and we understand how it is transmitted."

The gene that causes Miller's, the team found, is called DHOHD, and it is a metabolic building block, which means it could possibly be treated nutritionally, the team said.

The study also provided some other valuable information. Researchers had previously believed that each parent contributes about 75 genetic mutations -- most of them unimportant -- to each child. But by analyzing the genomes of both the parents and the children, the team found that each parent contributed less than half that number, only about 30. They were also able to identify precise locations on the chromosomes where they break apart to allow recombination of genes contributed by both the mother and father. That knowledge should prove extremely useful in future studies.

The actual sequencing of the genomes was performed by Complete Genomics Inc. of Mountain View, Calif., while the academic researchers performed the interpretation of the results.

It is now possible to sequence a complete genome for as little as $5,000, according to Landis -- still a little bit too pricey for everyone to have his genome studied. But experts think that, within a couple of years, the price will be closer to $1,000, which will make the technique much more widely available. The next big logjam, she added, will be in computer processing of the accumulated data. Researchers supported by the government have to post complete sequences online, and "the rate at which sequences will need to be archived is going to be mind-boggling. The other challenge will be developing the computational ability to sort through all the sequences and make sense of them."