# Researchers crack rare disease's code with technology

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In work that offers hope to every doctor who ever refrigerated DNA from a patient with a baffling disease, government researchers have read the genes of two families afflicted with a rare illness that kills male infants and have discovered its genetic cause.

Scientists from the National Human Genome Research Institute reported this week that they examined DNA from mothers in both families. Both carried a small defect on a single gene -- a difference of just one "base" among the roughly 3 billion that form the language of the human genome.

But when the mothers passed this defect to male babies it was deadly.

"This was 100 percent lethal in these boys. Some were stillborn. Some died within a week or two of birth. The longest survivor died at 5 weeks of age," said Leslie G. Biesecker, chief of the institute's genetic disease research branch and one of the authors of a new paper published in the American Journal of Human Genetics.

Using a similar method to read the genes of a young boy, scientists from the Medical College of Wisconsin were able to diagnose his disease and recommend treatment -- a case first reported at a conference in March.

The researchers are using technologies that have come to market in the last year or so, dramatically increasing our ability to delve into the secrets of our own DNA. These products allow scientists to get answers

faster by homing in on specific parts of the genome and washing away what they don't need. They can run more samples, faster and at a lower cost.

"It's really exciting because there are all these genetic diseases that have been around and studied for a very long time and not understood," said Fred Ernani, a senior manager at Agilent Technologies Inc. in Santa Clara, Calif. Agilent supplied a sequencing system used by Biesecker's team, which works in a branch of the National Institutes of Health.

The new study joins a stream of papers in recent months that have demonstrated the value of sequencing our genes both for basic research and for diagnosing patients.

In Friday's issue of the journal Science, German scientists reported sequencing the genome of Neanderthals, our closest evolutionary relatives, and comparing the genetic profile with that of modern humans. Earlier this week scientists from the Netherlands reported in Nature Genetics that they used DNA sequencing to find the mutation that causes Schinzel-Giedion syndrome, a rare disorder that usually kills children before age 10.

Biesecker said his group had examined one of the families with TARP syndrome in 2002 and 2003 but had only been able to narrow down the list of genes that might be responsible. Fortunately the scientists kept DNA from the family.

"It was sitting in our refrigerator waiting for an opportunity, and the opportunity presented itself in this new technology," Biesecker said.

His team used a technique similar to the one employed by the Medical College of Wisconsin researchers when they sequenced the boy's genes and diagnosed an exceedingly rare illness related to inflammatory bowel

disease.

The Medical College scientists did not sequence the boy's entire genome, but opted for a less expensive and more targeted alternative. They examined only the exon, the part of each gene which contains the instructions for making different proteins. Proteins are crucial to almost every human action from breathing to thinking and many diseases result from a failure to make a protein correctly, or at all.

While our exons account for about 1 percent of the genome, they are believed responsible for 85 percent to 90 percent of the mutations that play a major role in diseases.

Howard J. Jacob, director of the Human and Molecular Genetics Center at the Medical College, called the new paper by Biesecker's team "an illustration of how the technology is evolving ... It's an example of where sequencing combined with classic genetics is helping to identify rare disease areas."

Like the Medical College team, Biesecker and his colleagues focused on the exons. However, they narrowed their search by examining only those from the X chromosome. While men have both an X and a Y chromosome, women have two X chromosomes. The families the NIH team examined were afflicted with TARP syndrome, one of a group of diseases specifically linked to the X chromosome.

Although women carry the mutation, they are not killed by it. A mother with the mutation has a 50 percent chance of passing it to her son. If she has a daughter, there is a 50 percent chance the girl will also be a carrier of the mutation.

Scientists do not know the precise role of the critical gene, RBM10, where this mutation occurs. But Biesecker said researchers examined its

role in mice and believe it may have something to do with jaw and limb development. Boys with the disease have underdeveloped jaws and severe club feet.

Although the new papers from the NIH and from the group in the Netherlands both used exon sequencing, they differ in one important respect from the project undertaken by the Medical College of Wisconsin -- the question of treatment. The Medical College researchers were able to use what they learned from sequencing the boy's genes to shape his treatment. As a result, doctors have recommended that he receive a bone marrow transplant.

So far, doctors have no such answer for children with TARP syndrome.

"Currently and for the foreseeable future we don't have any treatment technologies that allow us to undo physical birth defects that occur early in development," Biesecker said.

However, he said sequencing the X chromosomes of the disease carriers was beneficial to the families and to researchers. In such diseases, even after lives have been lost, "there is an overwhelming human need to understand what happened," Biesecker said. "We call it the diagnostic odyssey."

The scientists in the Netherlands cited a similar benefit for their discovery of the mutation responsible for Schinzel-Giedion syndrome.

Sequencing of the TARP carriers also provided a research benefit to the NIH scientists, allowing them to examine the poorly understood RBM10 gene.

"It's opened the door to understanding a gene we knew next to nothing about," Biesecker said.