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When two of his sons developed an untreatable genetic disease, the head of a shrimp processing company took a crash course in molecular biology, raised millions of dollars and sought out a distinguished Stanford geneticist as part of an all-out war.

## A father's mission



PHOTOGRAPHS BY RICHARD GRAULICH - SPECIAL TO THE MERCURY NEWS

Brad Margus plays with sons Jarrett, 11, and Quinn, 10, outside their home in Boca Raton, Fla. When Margus learned that the two boys had a fatal genetic disease, he began a search for a cure.

**FATHER'S EFFORTS HELP IDENTIFY THE CAUSE OF A RARE DISEASE, BUT THAT TRIUMPH ISN'T ENOUGH TO SPARE HIS TWO SONS**



**BY PAUL JACOBS**  
*Mercury News*

As toddlers, Brad Margus' sons developed difficulty walking; their newfound speech became slurred.

When the Florida business executive learned that the two boys had an extremely rare, untreatable and fatal genetic disease, he began a search for a cure.

Over the next seven years, Margus helped raise \$7 million, money that helped identify the mutated gene that causes ataxia-telangiectasia, or A-T, a disease that afflicts only 500 or so youngsters in the United States. That triumph

of biological research wasn't enough to spare his two sons, Quinn and Jarrett, now wheelchair-bound at ages 10 and 11.

"Every time I see them, I know we haven't done anything, because we haven't stopped the progression," he said recently. "My kids are slipping away."

So what does a well-educated, hard-driving businessman do?

He signs on as chief executive of a new biotechnology company in Santa Clara, not to focus on a rare disease with an almost unpronounceable name but to push an innovative technology that could advance the whole field of genetic research.

Margus' new company, Perlegen Sciences Inc., is a spinoff of Affymetrix Inc. of Santa Clara, which makes DNA microchips — half-inch squares of glass that can be used to detect microscopic pieces of genes. In the next 12 months, Perlegen intends to adapt the Affymetrix technology to decipher 50 different versions of the human genetic code, a task that would have been impossible just a year ago and that promises to open up new avenues of research into a host of diseases.

How Margus made the journey from boss of a \$100 million-a-year shrimp processing company to biotech executive, and how a new generation of DNA chips can add to the understanding of a host of diseases, including A-T, is a personal, deeply human story.

It is also a cautionary tale in an age of miraculous discovery, a time when most of the human genetic code has been deciphered and once baffling diseases are being understood for the first time. But it is a time when knowledge of the genetic compo-

nent of disease often runs far ahead of the ability to correct the defects.

Margus and his wife, Vicki, first learned that two of their boys had A-T in 1993. Their oldest child, Colton, was healthy, so it came as a shock when the younger ones, Jarrett and Quinn, slowly developed troubling symptoms -- a wobbliness when walking and a subtle slurring of speech.

This loss of muscular coordination is called ataxia. Telangiectasia is the medical term for little blood vessels that pop up on the skin and eyes of many of these youngsters. As the children grow, their failing immune systems make them susceptible to infection; 40 percent develop cancer. Few live past their 20s.

In 1993, when the Marguses first heard of A-T, it was already known that the disease was caused by a mutated gene transmitted from parent to child.

Like the parents of all A-T children, Brad and Vicki Margus are carriers — each carries a copy of the defective gene as well as an unaffected gene. Individuals with a single copy of the defective gene have no apparent symptoms, except they do have an increased risk of certain cancers.

As long as the child gets at least one healthy version of the gene from one of his parents, he will be disease-free, which is the case for Colton. But, as chance would have it, Jarrett and Quinn got an A-T gene from each parent and so they have full-blown cases of the disorder.



Brad Margus goes for a walk with three of his four sons, left to right, Colton 12, Quinn, 10, and Jarrett, 11.

Seven years ago, scientists knew that the responsible gene could be found somewhere on chromosome 11 — one of the 23 pairs of chromosomes found in almost every human cell.

But researchers still had not found the gene itself; doing so was a logical first step toward finding a way to treat the disease.

Margus isn't a scientist — he's a Harvard MBA,



Brad Margus' son, Quinn, plays with his family's new puppy, Riley, as brother Jarrett watches. The boys have a disease that afflicts only 500 or so youngsters in the United States.

whose Florida firm, Kitchens of the Oceans, sells frozen shrimp to restaurant chains, cruise lines, hotels and some supermarkets.

### Problem solving

His business school training taught him to break down any problem into smaller pieces, to bring some order out of seemingly uncontrollable events. To learn the science he needed to persuade scientists to study the disease, he hired a tutor to give him a crash course in molecular biology. He and his wife studied the intricacies of raising money for rare diseases, and started the non-profit A-T Children's Project. They learned how to lobby Congress and the National Institutes of Health to win support for research funding.

As Margus describes it, fighting a rare genetic disease is like waging a multi-front war — in this case, outgunned by competing groups that represent much larger numbers of patients or that are backed by celebrity sponsors.

Early on, Margus sought out Dr. David R. Cox, a distinguished Stanford University geneticist and pediatrician, hoping to persuade him to head the A-T Children's Project's scientific advisory board.

Cox is co-director of Stanford's human genome center and is an accomplished gene hunter. His group developed one of the basic tools that helped scientists complete a rough draft of the human genetic code earlier this year.

At a meeting in his campus office in 1993, Cox told Margus that he was too busy to advise the parents' group on how best to spend the money it was raising for research or to help them organize scientific conferences.

Imagining how difficult it would be to tell his wife that Cox had turned him down, Margus kept talking.

Cox was impressed with how well prepared Margus was. "I knew if I spent time with this man, together we would get things done," the scientist said in a recent interview.

### Breakthrough in Tel Aviv

Two years later a group at Tel Aviv University, headed by Dr. Yosef Shiloh and backed by A-T Children's Project funding, identified the mutated gene.

The discovery led to a burst of publicity for the disease and for the Marguses, who were interviewed by Barbara Walters on an ABC News magazine. (The birth of the couple's fourth child, Caden, a healthy boy, was recorded for the broadcast.)

And because the defective gene was linked to other diseases, including cancer and Parkinson's disease, scientific interest soared. The A-T Children's Project even organized a trial of a drug normally used to treat Parkinson's, but the medication proved disappointing in A-T.

Still, Brad Margus had plenty of reason for self-congratulation, after accomplishing so much in so short a time.

"The accolades are great, but what have I done?" Margus asks.

Early this year, he was still leading what he calls a "schizophrenic life" while running his Florida-based company.

"One call would be from the president of a restaurant chain," he said, "the next one from a molecular biologist looking into funding, and another from the Capitol, or from a parent whose kid was just diagnosed with the disease." Then, in February, Cox invited Margus out to California to meet with the chairman and CEO of Affymetrix, Stephen Fodor.

On sabbatical from Stanford, Cox believed it was possible to use Affymetrix technology and the detailed information from the Human Genome Project to decipher, quickly and cheaply, 50 different genetic codes or genomes — taken from cells donated by volunteers to the publicly funded effort.

The idea is to pack probes for every possible variation of the code onto 300, 5-inch by 5-inch glass plates. A modified version of an Affymetrix scanner could determine all the ways that any individual's genetic code varies from the standard draft genome completed this summer.

The information should help scientists understand how differences in genetic makeup explain the different ways that individuals react to the same disease or the same medication. And that knowledge should lead to new treatments.

Fodor and Cox wanted Margus to lead the new company.

It was not hard to persuade him.

"I showed him the science," said Cox, who is now Perlegen's scientific director. "It's pretty unusual for a shrimp guy to look at the genetic science and know what it means. He's not your average shrimp guy."

The company expects to complete a \$100 million round of private financing next month.

Margus and Cox hope that Perlegen will supply the new technology needed to understand many of the most common diseases. That will be the focus of the company. But they agree there could be benefits to A-T children like Jarrett and Quinn as well.

"Everyone who gets A-T gets the same gene, but not everyone gets the disease to the same severity," Cox said. "Almost certainly there are effects from the outside as well as variations in other genes in the genome that contribute. . . . If you could find those and find out how they work, you might come up with new treatments."

### Real world reminder

In addition to running the business, Cox said, Brad Margus is a daily reminder to everyone at Perlegen about the need for practical results.

"We'd like to see more genomics companies apply their work to real things rather than just hope," Cox said. "With Brad as CEO, not many hours go by each day without being reminded of that."

Meanwhile, the A-T Children's Project continues to fund research specific to the disease. "Breakthroughs happen in unexpected places," Margus said. "The best way to orchestrate that is to provide scientists with the resources they need and get people working. A solution may come tomorrow."

### Contacts:

*A-T Children's Project*

Tel: 954-481-6611 E-mail: [info@atcp.org](mailto:info@atcp.org)

*Perlegen Sciences, Inc.*

Tel: 408-731-8000 E-mail: [info@perlegen.com](mailto:info@perlegen.com)

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