The Atlantic

HEALTH

Insomnia That Kills

A woman and her husband are racing to find a treatment for her deadly genetic sleep disorder before symptoms set in.

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AIMEE SWARTZ | FEB 5, 2015

Almost everyone has had at least one night where it's been impossible to fall asleep. But Sonia Vallabh dreads those nights more than most. For her, insomnia is more than an inconvenience—it's the first sign of the deadly disease that she and her husband, Eric Minikel, have dedicated their lives to studying.

Called fatal familial insomnia, or FFI, it's an extremely rare genetic disease that

causes progressively worsening sleeplessness. Difficulty sleeping soon turns into total insomnia, causing rapid physical and mental deterioration and, inevitably, death—within a year, usually sooner.

“It’s an unbelievably swift and brutal way to die,” said Vallabh said.

Four years ago, she watched helplessly as her mother hovered in a twilight state—stuck somewhere between wakefulness and sleep—before dying at age 52.

“She was just lucid enough to know something horrible was happening to her,” Vallabh said. At the time, neither Vallabh nor the doctors—who were unable to come up with a diagnosis—knew much more.

Just months before her death, she said, her mother had been seemingly healthy, helping Vallabh and Minikel plan the details of their wedding. Shortly after the ceremony, though, Vallabh began to notice that “something was just off.”

"It’s an unbelievably swift and brutal way to die."

“In the beginning, my mom’s symptoms were vague: speech disturbances, memory problems, small errors in judgment. She was losing weight without trying.” Vallabh recalled.

Over the next few months, Vallabh said, her mother deteriorated rapidly: “She couldn’t walk or talk or feed herself. She became deeply paranoid and fell into a profound dementia. She went on life support, and died a few weeks later.”

Vallabh’s mother’s illness remained a mystery for several months after her death,

until a piece of tissue taken from her brain tested positive for a mutation in a gene called *PRNP* that is known to cause FFI. Results from an autopsy had also concluded that FFI was a possible cause of death.

"Nobody even for one second suspected fatal familial insomnia, because there's no sign of neurodegenerative disease in the family," Vallabh said. There are 28 families worldwide who have the gene for FFI in their bloodlines. Most of them have pedigrees marred by inexplicably premature deaths.

FFI is what's known as a prion disease, a family of rare progressive neurodegenerative disorders that also includes bovine spongiform encephalopathy, or Mad Cow Disease. In people with FFI and similar diseases, mutated proteins called prions trigger normal proteins in the brain to fold abnormally, destroying brain cells and leaving the brain filled with sponge-like holes. But unlike Mad Cow, which can be acquired by ingesting contaminated beef, FFI is genetic. Children of a parent with FFI have a one in two chance of inheriting a mutated *PRNP* gene.

Just months after her losing her mother to the disease, Vallabh decided to get herself screened. "Once I knew I was at risk, there was no turning back from the knowledge," she said.

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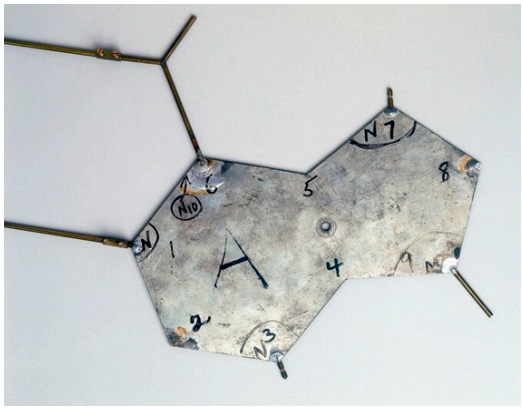


How One Woman Deciphered Her Own

She, too, harbors the gene, and will almost certainly develop and die from FFI unless treatments are developed that slow or stave off the disease's progression—and soon. The average age of onset for FFI is 50; Vallabh is 30.

"We didn't seem to be in a position to do anything about it. The fact that my mom died undiagnosed seemed, to us, the final

word on the disease," Vallabh said. To prepare themselves for what lay ahead, she and her husband began to research the condition.

But as the couple started learning more about FFI and other prion diseases, they slowly became more hopeful. Scientists were looking into treatments, they discovered—which meant that maybe, just maybe, it was possible to change Vallabh's fate.

"We read everything we could about it, from Wikipedia to scientific papers. We badgered our friends who were scientists. We stayed up discussing what we had learned about the disease that day," Minikel said. "There was much more research going on, and much more known about prions, than Sonia or I had assumed."

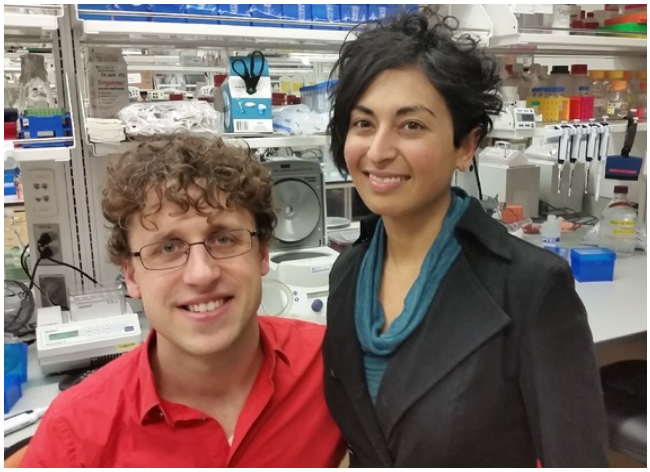
Vallabh, a Harvard-trained lawyer, began sitting in on science classes at the Massachusetts Institute of Technology. Soon, she left her job in consulting and took a job as a lab technician at the Massachusetts General Hospital's Center for Human Genetic Research. Minikel, an MIT-educated urban planner, followed soon after. He quit his job as a software engineer and took a job in the same division of Mass. General, analyzing genetic data from people with Huntington's disease. In September 2014, the couple enrolled in a doctoral program in Biological and Biomedical Sciences at Harvard Medical School.

"To really help move the field forward, it was obvious to us both that we had to commit to being the best scientists we could be, to really immerse ourselves in research," Minikel said. "There just aren't enough hours in the day to work full-time and then come home and study prion diseases all night."

"In the beginning a lot of people asked us, 'Are you guys sure you want to change careers? Are you sure you want to think about this all the time?'" Vallabh added.

“As we started doing science as our day jobs, it became clear that thinking about this disease at the molecular level or the research level is very different from thinking about your mortality 24/7.”

Joel Watts, an assistant professor of biochemistry who oversees a prion disease-research lab at the University of Toronto, met the couple back in 2012 at a conference for prion researchers. Their story, he says, has also been a powerful motivator.



Eric Minikel and Sonia Vallabh (Jeff Minikel)

“We study molecules and mice, and not a lot of us get a chance to experience dealing with patients, or potential patients as in Sonia’s case. As scientists, sometimes we get a little bit detached from the big picture,” he said. “They’ve been very successful in rallying the field as a whole to get with it and work together. FFI is a huge tragedy for Sonia and Eric, but their involvement with this disease in certainly a blessing to prion research.”

Minikel has already made an important contribution to the scientific literature on prion disease: He developed a computational method that disproved the widely held belief that in a family with genetic prion disease, each successive generation will fall ill about seven to 14 years earlier than the last. (The phenomenon, which geneticists call “anticipation,” is common in other genetic disorders.) The analysis was published in October 2014 in the *American Journal of Human Genetics*.

“It might not have been a pressing research question for most scientists, but it was an important distinction and, quite honestly, a huge relief for us,” Minikel said.

The couple is far more interested, though, in research that will lead to the development of new treatments that could potentially save Vallabh's life.

In 2013, through Prion Alliance, the research organization that Vallabh and Minikel founded, the pair successfully crowdsourced funds to study in mice the effects of an experimental compound in inhibiting prion activity in mice, thus delaying the onset of genetic prion disease.

"We can't afford to be wedded to any one idea. If it isn't working, we have to move on."

"We want to know how relevant this compound will be to human genetic prion diseases. If the answer is 'very,' then we hope that the data from our study will help to speed [the compound's] advancement," Minikel said.

But he and Vallabh aren't limiting themselves to just one possible treatment. They periodically make month-long visits to the prion-research labs at the Rocky Mountain Laboratories in Hamilton, Montana, and the University Hospital of Zurich, Switzerland, where they work as guest researchers to discover new approaches to treating prion diseases—from drugs to gene therapies to better ways of monitoring treatment efficacy in patients.

"All interest us to the extent that they are promising. But we want to make sure there are lots of horses in the race. We can't afford to be wedded to any one idea. If it isn't working, we have to move on," Vallabh said.

Watts at the University of Toronto says a treatment for FFI is "far more likely to

be discovered through the dedication and perseverance of people like Eric and Sonia." As is the case for most rare diseases, he says, "big pharma isn't exactly looking to invest money into a disease that affects so few people."

Still, Vallabh and Minikel know that progress depends on scientists' willingness to openly share data and methodologies. That's why they've made it a priority to build partnerships across government labs, private-sector companies, hospitals, and universities in the U.S. and abroad. They also speak regularly before audiences of hundreds at major medical meetings, encouraging scientists of various specialties, patients, advocates, and policymakers to join them in their quest.

"It's absolutely possible that a treatment will be developed in the next 10 to 20 years."

"A treatment for prion disease will require contributions from many—scientists with a range of expertise, who build on the shoulders of those who went before us; funders, both conventional and unconventional; doctors, who help identify patients and develop better diagnostics and way to measure disease progression," Vallabh said. "And someday, helping hands on the policy side to quickly get a new treatment approved."

In the meantime, Vallabh remains hopeful that a breakthrough will happen in the years before her symptoms set in.

"It's absolutely possible that a treatment will be developed in the next 10 to 20 years. And yet day-to-day, it's impossible to say which experiment, chance

insight, or encounter that happens today will become the project that becomes the solution," Vallabh said.

"Our story is unfolding in real time. And while we're optimists, we have no idea how it ends," she added.

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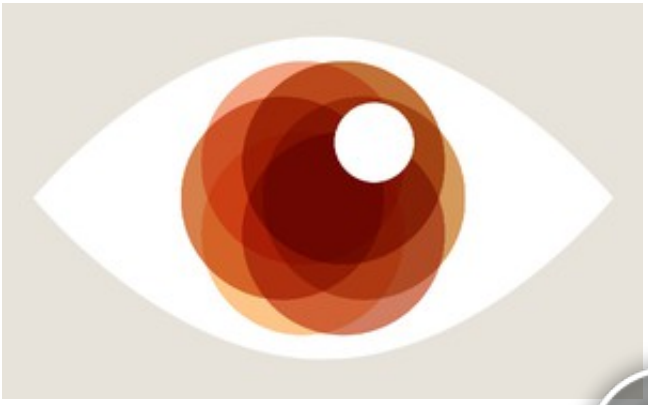

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ABOUT THE AUTHOR

AIMEE SWARTZ is a freelance writer based in Washington, D.C. Her work has appeared in *The Washington Post* and *The Scientist.*

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