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A rare disease killed her mother. Can this scientist save herself?

By Karen Weintraub

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Sonia Vallabh and Eric Minikel both changed careers to study the prion disease that could kill Vallabh. *Courtesy Maria Nemchuk / Broad Institute*

CAMBRIDGE, Mass. — Five years ago, after watching her 51-year-old mother descend quickly into dementia, disability, and then death, Sonia Vallabh learned she was destined for the same fate. They both shared an extremely rare genetic mutation that leads a protein in the brain to turn toxic.

Vallabh, then a recent Harvard Law School graduate working as a consultant, decided to quit her job to spend time learning more about the mutation and nascent efforts to understand and treat it.

Now, she and her husband, Eric Minikel, a former transportation planner, are first authors on a paper about so-called prion diseases. Published Wednesday in [Science Translational Medicine](#)¹, the paper found that not all prion gene mutations are an early death sentence — though Vallabh's variation is.

The husband-and-wife team, now both PhD students working in the same lab at the Broad Institute, also found that people can survive with only one copy of the prion gene, suggesting that a treatment to block

the mutated version can be delivered safely.

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Lots of patients have become advocates to raise money to research a disease that affects their family. And some researchers have redirected their expertise to help loved ones who fall ill. But Vallabh's and Minikel's story is quite unusual: Both traded other fields for careers in science.

Their hope is to find a cure before the disease attacks Vallabh. If they're lucky — and they have been so far — they have a few decades. Vallabh is now 31. Prion disease can strike at any age, but the average is 49, Minikel said.

Prion diseases were made famous by “mad cow disease,” outbreaks of which have led to mass killings of cattle. Eating sick cows can cause the fatal neurodegenerative illness known as Creutzfeldt-Jakob disease. But there are genetic versions of prion diseases that account for about 15 percent of cases. They come from mutations to the prion protein gene PRNP, which causes a protein in the brain to fold the wrong way, forming toxic clumps.

Once these proteins get a foothold in the brain, they can cause extremely rapid damage.

Vallabh's mother, who seemed completely normal at Christmastime in 2009, showed the first symptoms of disease in January 2010 and was demented and unable to speak clearly by March. She last recognized her daughter in May, Vallabh said, and died two days before Christmas that year, shortly after doctors finally identified the cause of her bizarre symptoms.

Vallabh, Minikel, and their coauthors compared a data set — painstakingly collected over decades — of gene sequences from 16,000 prion disease patients from all over the world, with two data sets of sequences from healthy people: more than 60,000 collected by the Broad-led [Exome Aggregation Consortium](#) ³ and 530,000 from 23andMe, a consumer genetics company that invites clients to volunteer their gene sequences for research.

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The size of the data sets allowed the researchers to draw conclusions even with a condition as rare as prion disease. Doctors had previously only known about 63 possible mutations in people with disease, so they had thought that all the mutations necessarily caused problems. But the researchers found 141 healthy people in the 23andMe dataset who had mutations to the PRNP gene — a rate far higher than the incidence of prion disease. That means some of the mutations must be harmless or at least not always cause disease, said J. Fah Sathirapongsasuti, a computational biologist at 23andMe and a study coauthor.

Out of 16 mutations for which there was evidence in the larger populations, they concluded that three were likely benign, three caused somewhat increased risk of disease, and four others, including Vallabh's mutation, definitely do cause the fatal illness, they found.

They also discovered three older, healthy people who carried only one functional copy of the PRNP gene. That means that knocking out the mutated version of PRNP with gene therapy, or tamping down its activity with drugs, should be an effective way to eliminate the risk of disease without causing life-threatening problems.

Sathirapongsasuti said that based on their track record, he's pretty confident that Vallabh and Minikel will succeed in finding a treatment in time. "I think within the next five to 10 years, we're definitely going to see some magical event," he said.

Their paper has already helped at least one person, according to Dr. Robert Green, a medical geneticist at Brigham and Women's Hospital, who cowrote an [opinion piece](#)⁵ published alongside the new study.

One of Green's patients, whose mother died of prion disease, had been told her mom's mutation — which she didn't inherit, but her sister did — was always fatal. After seeing the new study, Green was able to inform the sister that her mutation was most likely harmless.

"I was very pleased to be able to tell someone who was living with this kind of concern that they could let go of that," he said.

Green said he was also impressed by the amount of collaboration involved in the current study, with so many patients and doctors willing to share data, and by the power of knowledge. Often in his field, Green said, experts worry about telling patients that their future probably includes a terrible illness, especially when there's no way to prevent or treat it. But Green said the example of Vallabh and Minikel shows that, for some people, knowledge really is power.

"Here is yet another extraordinary example of unforeseen actionability," he said.

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For her part, Vallabh said the worst time for her was the six to eight weeks after she finally learned what caused her mother's fate, but before she got results from her own genetic testing. Once she had the results, she said, she could start doing something, even if it was just gathering information.

"After maybe a week or so, I could already feel that as much as you never want to adapt to terrible new information, it's kind of remarkable that we do and we can," she said Wednesday morning, speaking in a fifth-floor conference room in the Broad's new Cambridge offices.

Both she and Minikel said their current goal is to look for possible treatments for her disease. And unlike most PhD students, they're in no rush to defend their theses and move on.

“We're here, we're working on developing methods for screening drugs against the prion protein — all the things we think are most likely to lead to a drug,” Minikel said. “We'll stay until they kick us out.”

About the Author

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Karen Weintraub is an independent health/science journalist, journalism teacher, and book author.

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