Against the Clock

charles river

Against the Clock

Award recognizes a couple's race to cure her rare prion disease

In recognition of their courage and initiative in pursuing treatments for fatal familial insomnia and other prion diseases, **Sonia Vallabh** and **Eric Minikel** will receive the Charles River Research Models in Discovery Award. The prize will benefit their nonprofit Prion Alliance, which supports their research.

Their scientific career began with a single, devastating data point.

In December 2011, a genetic test revealed to Sonia Vallabh and Eric Minikel that she had inherited a mutation for a rare neurological disease called fatal familial insomnia.

Instantly, the young couple's life was transformed. Sonia's mother had died of the disease a year earlier, at age 52, after rapidly declining into dementia. The young couple now knew that in about 25 years Sonia would face a similar fate.

It was heartbreaking news. But Eric and Sonia also saw opportunity.

> Not everyone is given 20 years notice as to their cause of death," Sonia says. "We started to see that knowledge as power, and we started to put it to use."

Neither of them were scientists—Sonia had just graduated from Harvard Law School, and Eric worked in transportation planning as a software engineer. But they were both fast learners who threw themselves into researching this strange ailment.

What they learned at first was discouraging. Fatal familial insomnia is one of several genetic prion diseases, a handful of closely related inherited conditions that cause a misfolded protein to accumulate in the brain. These diseases are progressive, untreatable and always fatal.[1] But as Sonia and Eric's knowledge grew, they began to realize that in time scientific progress might transform that dire outlook.

"There's actually quite a wealth of basic science knowledge about prions," Sonia says. "There are also groups thinking about therapeutics. It was really this discovery that led us to push the envelope and ask, 'What can we do?' "

Back to School

Sonia started taking classes at MIT, and landed a job in a neurogenetics lab at Massachusetts General Hospital. Eric took night classes in bioinformatics and molecular biology, then left his job for a position in the same lab where Sonia worked. In 2014, they started a PhD program in biological and biomedical sciences at Harvard Medical School. The next year they were invited to join the Broad Institute lab of Stuart Schreiber, which specializes in the development of therapeutic molecules.

"The amount that they've done to make it possible for us to do our research here in terms of mentorship and resources is incredible," Eric says of their Broad colleagues.

The pair has no illusions that they will be able to find a cure for genetic prion disease on their own. Their main goal is to create tools and resources that will advance research across the field of prion research. It is a pragmatic, goal-oriented approach that often sets them apart from their more academically oriented peers.

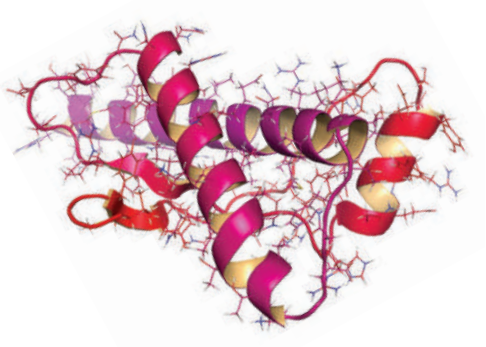
"It definitely orients us differently," Sonia says. "Whatever comes up that's most on mission, we just have to do it. It's not a question of whether it's within our expertise at that given moment, is it something we've done before, are we the best people to do it, is it interesting to do? Whatever comes up, we just have to do it."

One Thing

Human data suggest that early intervention to prevent or reduce the production of the prion protein would be a safe and effective treatment. In a study that surveyed more than 60,000 human genomes, Eric and Sonia found three individuals who have mutations in one copy of the prion gene that completely inactivate its protein.[2] Yet even with half the normal amount of the protein, these three people appear to suffer no major deleterious effects. Neither do knockout mice that produce no prion protein at all.

> If you wait until the patient has dementia, it's a very uphill battle to try to reverse that. One thing we know from prion mouse models is that the earlier you intervene, the more good you can do."

Any effort to develop a therapy that reduced prion protein production would need to demonstrate its effectiveness by measuring levels of the protein in the brain. So one of Eric and Sonia's current projects involves measuring the protein in cerebrospinal fluid to determine if its concentration there can serve as a proxy for brain levels. Such a marker would allow the drug's effect to be measured in presymptomatic people, who would be much more likely to benefit from treatment.



"If you wait until the patient has dementia, it's a very uphill battle to try to reverse that. One thing we know from prion mouse models is that the earlier you intervene the more good you can do," Eric says.

The question is, how to do it? In principle, CRISPR or some other strategy could be used to delete the prion gene or suppress its expression. But in practice, such a treatment would have to reach every cell in the brain without causing any unintended side effects.

"The big challenge that we face is delivery. That makes a lot of things that are theoretically elegant solutions not very feasible in the immediate term," Sonia says. "But in the end, we need one thing to work and we need to keep our eyes on the prize."

There are times when that can be tough to do. On those days when progress is hard to come by, Eric says, he and Sonia focus on how far they have already come.

"In science, 90 percent of things fail. It's inevitable that if you look at what you accomplished today, or this week or this month you'll feel sad," he says. "But having chances to zoom out and reflect on where we've come in the last five years, and where we maybe could get five years from now, makes me very optimistic."

References

1. Pocchiari, M. et al. Predictors of survival in sporadic Creutzfeldt–Jakob disease and other human transmissible spongiform encephalopathies. *Brain* 127: 2348-2359 (2004)

2. Minikel, E.V. et al. Quantifying penetrance in a dominant disease gene using large population control cohorts. *Science Translational Medicine* 8: 322ra9 (2016)

3. Lek, M. et al. Analysis of protein-coding genetic variation in 60,706 humans. *Nature* 536:285-291 (2016)

Do-it-yourself science

When doctors told Sonia Vallabh and Eric Minikel that she carried a mutation linked to a rare prion disease, one of the questions the couple asked was how certain the connection was. Did everyone with this mutation eventually develop the disease?

"The doctors told us this is a mutation where you're very likely to develop this disease, maybe guaranteed to develop this disease, at some point in your life," Eric says.

At the time, he and Sonia had no way of evaluating the validity of that statement. But a few years later, with a much better understanding of the genetics of rare diseases, they were ready to find out for themselves if Sonia's situation was as dire as they'd been told.

Working with Broad Institute geneticist Daniel MacArthur, they launched a project to look at the frequency of various mutations in the prion protein gene, *PRNP*, in the human population. If there were more mutations than would be expected given the frequency of prion disease, it would suggest that not all people who inherit defects in *PRNP* develop the condition.

Eric and Sonia started with a database of genetic sequences for 60,706 people.[3] Knowing that prion diseases strike about two people in a million during a given year, they expected to see about 1.7 *PRNP* mutations.

When they looked, however, they found 52 people with *PRNP* mutations.[2] One mutation, M232R, was so common that it couldn't possibly be linked to prion disease. If it were, the disease would show up much more frequently than it does. Another mutation, V2101, was found in two out of the 60,706 people.At that frequency, it might confer a slight increase in prion disease risk, but would have no effect in most or maybe even all people who have it. And then there were mutations like D178N, the one that Sonia has. She and Eric did not find a single example of it in the database. That simple observation suggests that whenever the D178N mutation does arise, it almost always leads to disease.

"Unfortunately, Sonia's mutation really is rare," Eric says. "But we now know a handful of patients who had been told news as bad as we had gotten, and they now know that they are at low or no risk."