[NARRATOR:] Just before his sophomore year of college, Sam Walker decided to update his contact lens prescription. Sam’s vision has never been great, and he was having trouble seeing in low light. That routine visit to his eye doctor revealed a problem.

[SAM WALKER:] He saw these little black spots on my eye. He said I don’t 100% know what this is, but I’m pretty sure it’s RP.

[NARRATOR:] RP is short for retinitis pigmentosa. The black spots in the retina are a telltale sign of the disease. They are indicators of photoreceptor cell death. It’s the photoreceptors in our retinas that absorb light and convert it into electrical signals to the brain. RP is progressive. Over time as more photoreceptors die, a patient’s vision worsens.

Faced with the prospect of going blind, Sam visited RP expert Edwin Stone. You might call Stone a gene doctor. There are many causes of blindness, but RP is an inherited disease. It is caused by a change or a mutation in a gene.

[The first step in helping a patient like Sam is to track down which among his 20,000 or so genes is causing the vision problem. If Stone can identify the mutated gene, he may be able to design a therapy to deliver a working copy of that gene to Sam’s eyes to stop his photoreceptors from dying.

Stone began hunting for genes linked to inherited eye diseases in the 1980s. He tracked down families with a history of blindness, a strong hint that they had a genetic disease.

[EDWIN STONE:] The desire to track them down was this: genetic disease. Where’s the answer? You knew the answer was in the DNA.

[NARRATOR:] DNA is the molecule that stores instructions for building proteins. A sequence of four types of nucleotides in a particular segment of DNA, called a gene, determines the protein that gene makes.

Stone collected blood samples from family members. And he and colleagues isolated DNA from the blood cells. The goal was to find differences in the gene sequences of patients with RP compared to their family members with healthy vision. Those differences identified genes associated with RP. Today, with contributions from other research groups, many mutations have been identified and close to 100 genes are known to be associated with RP.

[STONE:] These mutations are all very well established disease-causing mutations. There’s no question that they cause RP.

[NARRATOR:] Using modern genetic techniques, Stone began scanning Sam’s DNA for one of these mutations.
We can test hundreds of the most common mutations very rapidly and very inexpensively. When we look at just a few hundred spots in the genome in a yes/no fashion, we can find mutations in about 40% or 50% of patients. So we did that in Sam and didn’t find anything.

The most likely reason they did not find anything was that Sam had a mutation in one of the genes associated with RP, but it was a rare mutation that hadn’t been discovered yet. So Stone took a more detailed look at Sam’s copies of each of the known genes linked to RP. This step identifies the problem in another 25% of RP patients, but once again, he came up empty.

So now we’re down to the last 25%, and that’s a situation in which it’s going to be a new gene. Not a gene that no one ever knew about, but a gene that no one ever knew caused retinitis pigmentosa.

Stone was determined to identify that gene.

So they looked for about a year or so, and it took them a lot longer than they expected.

In the end, their work pointed to a gene that presented a puzzle. Sam’s mutation was in a gene that is required for the proper functioning of a molecule called transfer RNA, or tRNA. Cells throughout the body rely on tRNA molecules to produce proteins.

And you’d look at that and say, well, that couldn’t possibly be it, right? tRNA synthesis is so central to biology that if you couldn’t do that, you’d be dead.

Further research showed that Sam was alive because his mutation only reduces but does not eliminate tRNA function.

So maybe there was just something about the demand for protein synthesis in the retina that made that tissue the only tissue that was really susceptible at that exact level of dysfunction.

To Stone’s knowledge, Sam was the only RP patient known to science with that particular mutation.

Sam was the only person that we had that had that genotype.

That’s not really good then to be unique in this case, unfortunately.

And I was asking myself, do I believe that enough, to the extent that you would replace that gene with a gene therapy? Probably not.

A unique instance is not strong evidence that a mutation is associated with a disease.

So what do you do to make yourself believe something like that more? So what you do is you take all of the patients that you’ve done all this screening on, but you haven’t found any mutations in yet, which number in the thousands. And now you take your specific gene that you found in this patient, and you go ask whether there’s anybody else that has that.

Stone’s painstaking research finally paid off. He identified two brothers with mutations in the same gene as Sam’s.
[STONE:] So at the moment, it’s only you and these two other guys in the whole world that we know have variations in this gene.

[WALKER:] Cool.

[STONE:] So now you’re up to a whopping three patients, right? Now are you believing it?

[NARRATOR:] Wanting still more evidence, Stone turned to another powerful tool used in genetic research: a model organism. Stone and his colleague, Diane Slursarski, genetically engineered zebrafish to have a mutation in the same gene as Sam’s to see if it caused RP in the fish. When the engineered zebrafish embryos did not respond to a visual stimulus, Stone was convinced he’d found the source of Sam’s RP.

Now, he and his team are working on a gene therapy to deliver a fully functioning copy of the mutated gene to Sam’s retinas.

[NARRATOR:] Gene therapy has already been used to treat patients with another type of blindness and other genetic diseases. The functioning gene that would be placed in Sam’s eyes would not restore lost vision but would halt further vision loss.

[WALKER:] I look forward to the day when I can go in and have the surgery done. Dr. Stone — it’s just something about him. He says he’s going to get it done, I trust that he’s going to get it done.