MORGAN GRACE: I think I kind of always knew that I had something different than other kids.

[Morgan Grace, High School Student]

I have danced since I can remember, like whenever I hear any kind of music, I can't just sit still. I loved being on stage. It started to, like, get worse as I was going through puberty. But I just remember like just a wave of pain washed over my body. When I go through a bad pain crisis, they come out of nowhere. I had to quit dancing because of being in the hospital. It just made, like, a lot of things in my life have to stop.

MORGAN'S MOM: Morgan!

NARRATOR: Morgan has sickle cell disease, an inherited condition that affects her red blood cells. Before modern medicine, many people with this disease didn't survive into adulthood.

The theory of evolution by natural selection predicts that harmful traits should be rare. But what's so puzzling about sickle cell is that it's relatively common, especially in people with ancestry from certain parts of the world. Figuring out why this harmful trait is so common will take us on a remarkable journey of scientific discovery.

NURSE: Dr. Archer will see you now.

[Natasha Archer, Pediatric Hematologist, Boston Children's Hospital/Harvard]

DR. NATASHA ARCHER: Hematology is the study of blood disorders. A pediatric hematologist takes care of children with those blood disorders.

Hi, how are you?

MORGAN: I'm good.

DR. ARCHER: You start school already?

MORGAN: Yeah, I started last week.

DR. ARCHER: I really got interested in hematology when I started to meet patients who had sickle cell disease.

NARRATOR: Sickle cell disease is caused by a change or mutation in a single gene. The gene codes for a subunit of the protein hemoglobin, the protein in red blood cells that binds oxygen. A mutation in a single nucleotide in the gene causes a single amino acid change in each subunit, which in turn causes the hemoglobin molecules to stick together and change the shape of the red blood cells.

DR. ARCHER: Typically, red blood cells have this disc shape to them that enable them to move throughout the body with ease. Sickle cell disease makes the red blood cells a little bit more rigid — so changes the shape and makes it like a crescent moon or sickle shape. That rigidity of the red blood cell causes them to block blood vessels, not allowing blood to get to different parts of the body, causing severe and debilitating pain.

DR. ARCHER: For a pain crisis, my patients typically describe it as a pain that won't go away. Thinking of your worst pain and not being able to do anything about it, really.

You're doing great. Keep up the good work, keep taking your medicine. And I'll see you in three months.

MORGAN: In kindergarten, we had this book. It's about this young girl with sickle cell, but she didn't really know what it was. She just ended up in the hospital quite often. And I could kind of remember, like, having that feeling, like, I'm in the hospital but I don't really know why. It was really just a lot.

NARRATOR: American researchers first began to study sickle cell diseases in the early 20th century.

DR. ARCHER: In the US, it was most common among individuals of African ancestry. So they assumed that it was a condition from Africa.

NARRATOR: But no one could explain why sickle cell would be more common in Africa. Then, in the early 1950s, a Kenyan medical student named Tony Allison made a surprising discovery while conducting research on different blood type groups in East Africa.

[Anthony Allison (1925–2014), Geneticist, Medical Scientist]

TONY ALLISON: And I actually learned, just before going out and about, this sickle cell condition. And nobody really knew the frequencies of sickle cells in East Africa.

NARRATOR: Allison wanted to measure the frequencies of the sickle cell allele. He knew that we inherit two copies of most of our genes, one from each of our biological parents. These copies, called alleles, can be the same or different.

People with two copies of the allele without the sickle cell mutation are homozygous, which means their alleles are the same. They have round red blood cells and they don't have sickle cell disease. People with two copies of the allele with the mutation are also homozygous, but for the sickle cell allele. Many of their red blood cells are sickled and they have sickle cell disease. People with one allele with the sickle cell mutation and one allele without are heterozygous and have what scientists call "sickle cell trait." Under most circumstances, their red blood cells are round and they don't have any symptoms of the disease.

At the time Tony Allison did his research, there was no genetic test for sickle cell mutation. All he could do was look at the blood cells of individuals.

DR. ARCHER: Tony Allison's major challenge was really trying to identify who were the heterozygotes. It's only in prolonged low-oxygen environments that their blood cells actually become sickled. So here's the blood of a patient with sickle cell trait. They have only one sickle cell allele copy. If you look at this patient's blood under the microscope, it looks completely normal under normal conditions.

NARRATOR: Researchers can mix a chemical agent to that drop of blood, which creates a low-oxygen environment. After a few hours, the red blood cells start to sickle. This allows researchers to distinguish between someone with no sickle cell alleles and someone with sickle cell trait. Allison used this simple test to measure the frequency of sickle cell traits in some parts of Kenya.

TONY ALLISON: You could do it in the field, and I did. I had a little traveling microscope, run off a small bulb that came from a car battery.

NARRATOR: After analyzing hundreds of samples, an interesting geographic pattern started to emerge.

TONY ALLISON: But what was striking was that you had high frequencies of people carrying the sickle cell character in the coast and near Lake Victoria, and very low frequencies in the high country in between, in Nairobi.

NARRATOR: In the lowlands, the sickle cell trait frequencies were over 20%, whereas in the highlands, the frequencies were less than 1%. What could explain such dramatic differences between these regions?

A childhood memory helped Tony make the connection. Allison had caught malaria, a deadly infectious disease, on a family vacation to the Kenyan coast. So he knew very well that the humid lowlands around Lake Victoria are breeding grounds for the *Anopheles* mosquito, which spread the malaria parasite. Allison also knew that these mosquitoes, and the malaria they spread, are not common in the drier highlands. Could sickle cell and malaria somehow be connected?

TONY ALLISON: And if that's the case, you predict that you have high frequencies of sickle cells only in areas where malaria is endemic.

NARRATOR: To test this hypothesis, Allison needed data from more people and a larger area. He visited markets in villages throughout Uganda, Kenya, and Tanzania offering checkups and medicine to the people in those markets. During these checkups, he collected about 5,000 blood samples. The research of Allison and others confirmed that there is a strong correlation between the frequency of sickle cell trait and malaria. Tony wondered if having a sickle cell allele offered an advantage to people living in areas with malaria. How could he test this hypothesis?

TONY ALLISON: You look at malaria in children of the appropriate age and find out whether they are in fact protected against malaria.

NARRATOR: He collected blood samples from children aged 5 months to 5 years and analyzed them under a microscope. In each sample, he counted the number of parasites that cause malaria. He then compared the parasite counts in children with sickle cell trait to those without.

TONY ALLISON: The sickle cell trait would have lower parasite counts.

NARRATOR: This was the strongest evidence yet that the sickle cell trait gave heterozygotes an advantage where malaria was present. People with no sickle cell allele were less likely to survive and reproduce due to malaria. People with two sickle cell alleles were less likely to survive and reproduce due to sickle cell disease. But people with one sickle cell allele were more likely to survive and reproduce. Tony Allison had discovered the first clear example of natural selection in humans. But how did the sickle cell allele protect people from malaria?

TONY ALLISON: I have to say I left that part of the story to others, because it's quite a complex story.

NARRATOR: The parasite that causes malaria feeds on hemoglobin inside red blood cells. Natasha Archer studies how the sickle cell trait affects this process.

DR. ARCHER: When a mosquito bites you, the parasite makes its way into the red blood cells. Eventually, it releases these proteins that attach to blood vessels and force the red blood cell to stay in one location. What's unique about the blood vessels that it sticks to is that those environments typically have low oxygen. If you remember, individuals with sickle cell trait, their red blood cells sickle if they are in prolonged low-oxygen environments. And the malaria parasite now will not have hemoglobin that's as easily digestible.

NARRATOR: Without hemoglobin to feed on, malaria parasites can't grow or reproduce as quickly.

DR. ARCHER: Our research takes us one step further in understanding how sickle cell trait is protective against malaria.

NARRATOR: Malaria occurred in many regions around the world. Does the pattern Tony Allison observed in East Africa also occur in these other regions?

[Mathew Glarum, Musician & Nurse]

MATHEW GLARUM: What I love about playing music is that when I am up there playing, there's nothing but that. That's my therapy.

[singing song]

According to my grandma, I was begging her for guitar lessons at five years old. So it's always been around in my life — instruments and stuff.

[music playing]

When I was born, my mom knew to look out for us potentially having sickle cell because my brother, he was born with it. When you're a kid and all you want to do is have fun with your friends, we could get pain, get taken to the hospital. We couldn't participate in holidays, family vacations, and we couldn't go to school. That gets in the way a little bit. Now, as an adult, I've had experiences where my sickle cell and getting into a crisis has messed up important stuff. My mom's part of the family comes from the Mediterranean area in Sicily. Then my dad's from Norway, and then Belize.

DR. ARCHER: When we look at the people who carry the sickle cell allele, they share recent ancestry with regions that have historically experienced high rates of malaria, like sub-Saharan Africa, Greece, Italy.

NARRATOR: Several studies have shown that throughout the world, the frequency of the sickle cell allele tends to be lower in areas with little to no malaria, and higher in areas with a lot of malaria, similar to what Tony Allison and other researchers observed in Africa. Scientists have observed similar patterns with other inherited conditions that affect red blood cells.

DR. ARCHER: I also treat patients who have mutations in other genes, which cause diseases like ovalocytosis, thalassemia, G6PD enzyme deficiency, and others.

NARRATOR: Mutations in these genes also make it harder for the malaria parasite to infect, survive, or reproduce in red blood cells.

DR. ARCHER: Just like the sickle cell allele, all of the alleles causing these other disorders are found in high frequencies in people with ancestors from parts of the world that have historically had high rates of malaria, but are extremely rare among people without ancestry from those areas.

NARRATOR: In evolutionary terms, these differences in allele frequencies reflect that specific mutations in these genes confer a net advantage in areas with high incidence of malaria and are favored by natural selection over generations in a population, whereas they confer a disadvantage and are disfavored by natural selection in environments without malaria.

DR. ARCHER: It's clear that malaria has had a profound effect on human biology.

[Southern Technical College]

MATHEW: Right now I'm in nursing school, so I'll be graduating as a nurse at the end of this year. I think it will be beneficial for me, especially as a nurse, knowing what it's like to be in that hospital bed.

DR. ARCHER: Hey Morgan, I'm ready for ya.

MORGAN: I don't let having sickle cell stop me at all. I'm still gonna do the things that I want to do. I might just do it with extra precaution. I think it's made me a more determined person. It doesn't matter, like, if I have a weeklong hospital stay, I just need to get it done and do the best that I can.

DR. ARCHER: So tell me how you're feeling?

MORGAN: I'm feeling pretty good.

DR. ARCHER: When I talk to my patients, I start by discussing the biology. They inherited these genes, and that they are part of fighting this global threat, which was malaria. Science has helped us understand sickle cell disease, and it's the only thing that's going to help us cure it. I am very confident that we will eventually tackle this problem.

I'll see you in a couple of months, don't forget to schedule your visit, and call me if you need me, okay? Alright, bye!

[music]