Living a Rare Life

A Family's Journey With Hereditary ATTR (hATTR) Amyloidosis

Living a Rare Life

A Family's Journey With Hereditary ATTR (hATTR) Amyloidosis

Sarah

A kind-looking, gray-haired woman sits in a chair, arms relaxed, legs crossed. She seems to be enjoying a beautiful fall day. There is nothing fancy about her, nothing vain. An ordinary grandma.

Sarah was anything but ordinary.

In fact, there was something rare about her, although she didn't know it at the time.

On this day in the late 1960s, when this picture was taken, Sarah only knew her hands were strangely numb. In fact, she had so little feeling that she would burn her fingers day after day on her stove without realizing it.

Mark, Sarah's grandson

I remember she loved to bake. She had an old wood fire stove that didn't have anything on there to tell you the temperature. So, she'd test it by touching it, like a hot iron in the old days. But because she had the disease — we didn't know at the time, nobody knew anything about it — she couldn't feel the heat. She burned herself so many times, a couple of fingers had to be removed.

— Mark, Sarah's grandson

Sarah had hereditary ATTR (hATTR) amyloidosis, a rare genetic disorder that today affects an estimated 50,000 people worldwide. It is an inherited disease caused by a gene change (mutation) in the TTR gene. While we know there are over 120 TTR mutations associated with amyloidosis, the mutation that runs in Sarah's family is Thr60Ala (T60A), which is often seen in people with Irish ancestry. In fact, the family can trace their heritage back to County Donegal, Ireland, where an uncommonly high number of people carry this gene mutation.

The mutation causes a protein in the blood called transthyretin (TTR) to misfold (take on an abnormal shape), which interferes with its function. When misfolded, TTR builds up and forms deposits in the nervous (nerve), cardiac (heart), and gastrointestinal (digestive) systems. These deposits cause problems, like Sarah's nerve damage.

Six generations battling a disease. Six generations helping each other cope.

A tight-knit family determined to move forward.

Sarah's sons and husband Harvey (center)

Harvey and Sarah

Henrietta, Sarah's mother

Shirley, Phyllis Ann, Margaret, Janice, Linda, and Sally

Sarah died never knowing that she had a disease that could be passed down for generations. She didn't know that if one parent carries the hATTR amyloidosis gene, each child has a 50% chance of inheriting the genetic mutation. While there are most likely other family members with the disease who have not been identified, the list of known carriers is long.

First, there were four of Sarah's eight children — *Melvin, Karl, Chandler, Margaret...*

then 16 of her grandchildren — *David, Emmeline, Rebecca, Sarah, Richard, Daryel, Cheryl, Kipper, Robin, Delores, Sean, Lynn, Lois, Wendy, Leo, Rebecca...*

nine great-grandchildren — *Leo, Dane, Lolly, Tonya, Karl, Dustin, Brian, Suzanna, Lisa...*

three great-great-grandchildren — Keith, April, Hailey...

and now her great-great-great grandchild — Samantha.

Six generations battling a disease. Six generations helping each other cope. A tight-knit family determined to move forward.

They didn't choose this rare life. But they would choose how to live it.

Angel, Sarah's great-granddaughter

When my mother's Uncle Melvin started getting sick, he pushed hard for a diagnosis.

He really did it for his brothers who were beginning to show signs of the sickness.

— **Angel,**
Sarah's great-granddaughter

Karl and Melvin, Sarah's sons

Karl, Sarah's son

Sarah's son Melvin is credited for unlocking the mystery around the sickness that was devastating the family.

Debilitating nerve pain drove the stoic World War II veteran to the hospital looking for answers.

At first, the doctors had no answers, but that was not unusual. Many hATTR amyloidosis symptoms are similar to those of other diseases, often leading doctors and patients down the wrong path to one dead end after another. Then, Melvin met a neurologist at the nearby Veterans Administration medical center.

"When my mother's Uncle Melvin started getting sick, he pushed hard for a diagnosis," explained his great-niece Angel. "He really did it for his brothers who were beginning to show signs of the sickness."

Susan, Karl's daughter and Sarah's granddaughter

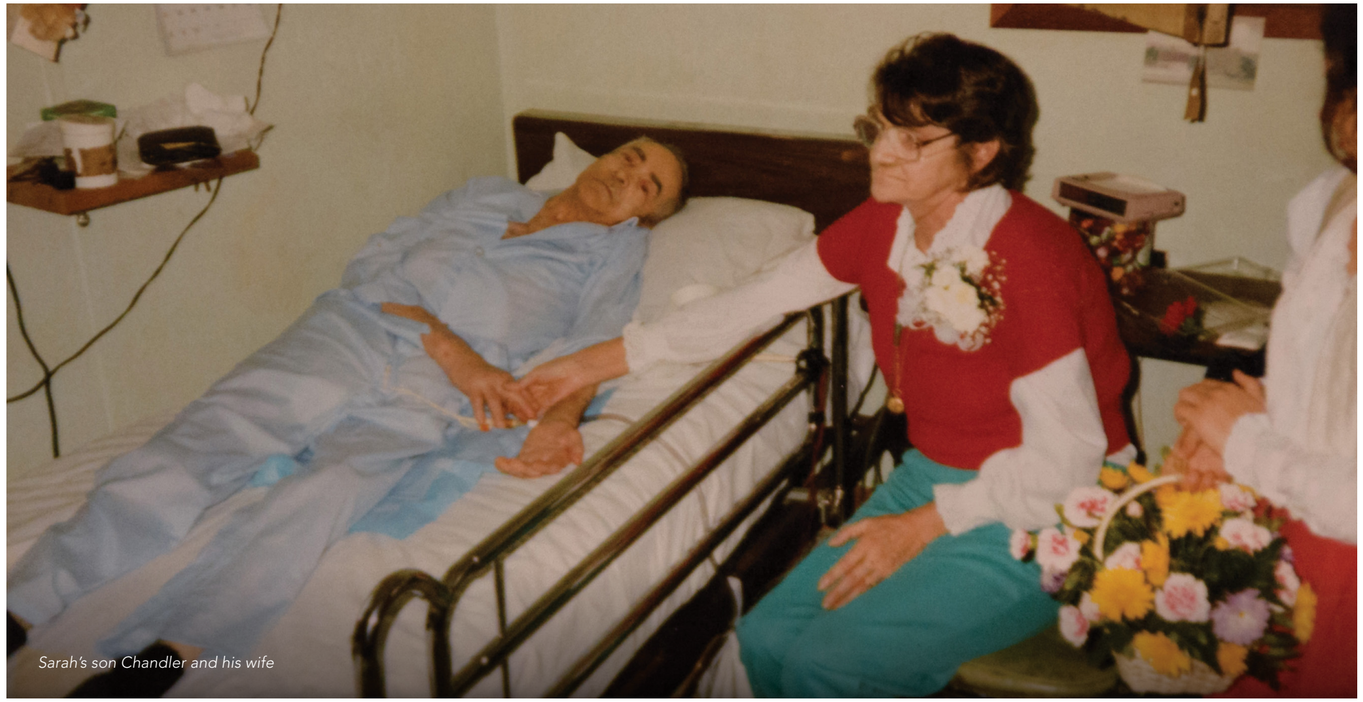
In many ways, by letting his family help him, Karl was helping them.

Melvin passed away before getting that diagnosis. But when hATTR amyloidosis was confirmed via his autopsy, it finally gave the family an answer. It also provided grim confirmation of something they already suspected… that the ones who had the disease could die from it. Faced with this knowledge, the siblings made a choice about how they would live their lives.

Residents of a lush, rural New York town along the Vermont border, they turned to the outdoors for as long as they could.

Karl's daughter Susan recalled, "They fished and hunted right up until the end." Even when Karl was in a wheelchair and had lost feeling in his fingers, his children would take him outdoors to enjoy the hunting season. It made Karl feel good just to be in the woods he loved.

It was also good for the whole family to be able to do something for Karl. In many ways, by letting his family help him, Karl was helping them. They were frustrated that they couldn't do anything to stop the disease, but helping Karl enjoy his days made them feel better.



Sarah's son Chandler and his wife

Chandler, Sarah's son

Cha, Chandler's son

Karl's brother Chandler suffered greatly, not only from the nerve pain but also uncontrolled diarrhea. His son Chandler, called Cha by his family, lived with his dad in the final years to help care for him. It was difficult, and yet, he was grateful for the experience.

Cha's voice broke when describing his father's courage and love of family. He began by revealing that, although he and his siblings didn't know it, their parents had never married. Cha's sister Sarah picked up the story.

"One day, he called me on the phone. He said, 'Want to go to a wedding?' And I said 'Whose?' And he said, 'Your mother and me.'"

Shortly after, the family gathered at Chandler's bedside and watched the couple marry after being together for over 30 years. A few days later, Chandler died. He was 60 years old.

The brothers' attitude had a profound impact on the extended family. They showed a rare courage that has become part of the family's character. "My father [Karl], my uncles [Melvin, Chandler, and Robert], they never gave up. We're a family like that. We don't give up. You hold your head and keep going. Absolutely keep going," Karl's daughter Daryel said.

Daryel, Sarah's granddaughter

Daryel is the third generation to carry both the pride and the risk of being a member of this family.

For her, that risk turned into reality. She tested positive for the gene mutation as a teenager.

There was a chance that she would never develop the disease. The hATTR amyloidosis mutation has "variable penetrance." That means some people carry a mutation all their lives but do not develop amyloid deposits. But Daryel did, and is now facing the same challenges as her father before her.

Her daughter Tonya described what life is like for Daryel. "I really didn't know how bad she was until she moved in with me. She sleeps constantly due to the medication for the pain. She can sleep 10 hours a day and still be tired. She has a hard time walking sometimes because the pain between her knee and her hip is so severe. I have to write things out for her because her hands hurt so bad that she can't write or they go numb."

Daryel, a petite grandmother with a ready smile despite being in constant pain, spoke candidly about coming to terms with hATTR amyloidosis. "There have been times when I have looked at people, even in my own family, that don't have this disease and I say, 'Why me? Why us? Why do we have to take this?' It's anger and confusion and everything rolled into one… you just want to lash out… But then, in the same moments, I look at my fantastic role models. They were proud men and they just kept going forward no matter what the outlook or outcome was. I wouldn't want to let them down."

Her brother Kipper shared Daryel's feelings. "It's a curse. Gone through all our family," he said quietly, resigned but unbowed. Kipper also lived for decades knowing that hATTR amyloidosis could strike because he tested positive for the gene mutation when he was just 18.[a]

Their father Karl insisted his children get tested. "Yeah, there was no question about it. You did what you were told. You didn't back talk. You just did it."

When Kipper's symptoms began about 10 years ago, they quickly became severe. "Once I was using the grinder and burnt my finger, had to have it cut off. My legs hurt all the time. I can't walk very far. It's just hard, hard to move around and get around. But you just keep on going. Nothing else to do."

He glanced away, then added, "If you sit around, you're just going to fall apart."

[a]Kipper's interview was conducted prior to his death in early 2019.

Linda, Sarah's granddaughter

Despite an initial push, the drive to know dropped off and the family settled into a sort of "dormant" period.

hATTR amyloidosis has been particularly devastating to Sarah's grandchildren, (almost a third of them have the condition).

Some were tested because Chandler and Karl insisted that they get diagnosed as soon as possible. They saw value in knowing.

Their neurologist helped them reach out to other family members. In a 1985 letter to Linda, Sarah's granddaughter, the doctor acknowledged that "the psychological impact of a positive result is large and possibly upsetting." But he concluded, "The benefit of knowing ahead of time, however, is also substantial. Proper planning for the future and first steps toward therapy will be made possible by an early diagnosis."

Despite this initial push, the drive to know dropped off and the family settled into a sort of "dormant" period. Decades passed between the time that Karl's daughter Daryel and her affected siblings were diagnosed and when they started to develop symptoms. "It kind of dropped off the radar because nobody was actively sick. They knew it was there, for some people it was coming, but it was always in the future. But then they started to get sick," said Daryel's daughter Angel.

Dane, Sarah's great-grandson

> **When I first [started having] symptoms, I tried to find other reasons why it wasn't [hATTR amyloidosis].**
>
> **— Dane,**
> ***Sarah's great-grandson***

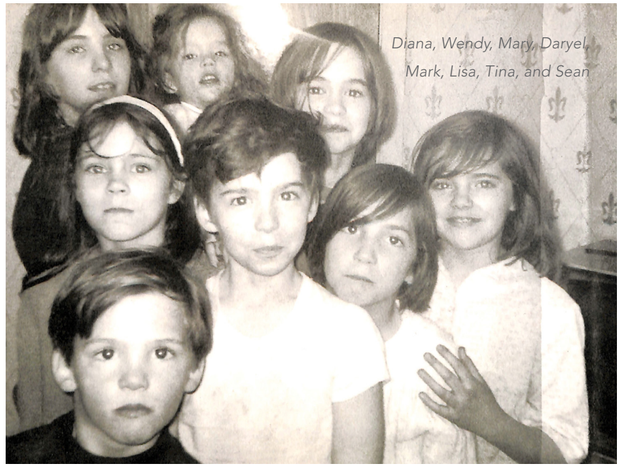
Even as Sarah's grandchildren began to suffer from the effects of the disease, many in the family chose not to be tested, believing that with no treatment available for the disease, there was no point in knowing. Angel's sister Tonya described hATTR amyloidosis as a "black cloud." She said, "You have it or you don't. It's either you're just lucky or you know what you're going to die from."

Some family members didn't get tested because of a lack of good information. Melvin's daughter Delores, or "Sissy," who had the disease, didn't fully explain how it is inherited to her son, Dane. Now Dane, who recently tested positive for the gene mutation, is dealing with his symptoms and learning about hATTR amyloidosis. "A lot of it was kept from me. [My mother] said it could skip generations, but now I understand that she was just protecting me. Just hoping that I wouldn't [develop] it as well, I'm guessing," Dane said gently. He is not angry with his mom, but he is struggling to reconcile long-held beliefs and the facts he is now understanding. "It's just so confusing because I keep going back to what I was told as a kid."

Mark, Sarah's grandson, and his wife Dee

Dane is learning a great deal from his cousin Leo, Karl's grandson. Leo was tested in 2014 and was positive for the genetic mutation. Even faced with what they saw previous generations go through, the first impulse for Dane was to try to find any other possible explanation. "When I first came down with symptoms, I tried to find other reasons why it wasn't," said Dane.

Since receiving his own test results, Leo has become a strong advocate for testing in the family. His cousin, Mark, is convinced of its value as well. Mark tested negative for the gene mutation, so he will not develop the disease; however, in an ironic twist, degenerative disc disease in his neck caused four discs to herniate and push against his spinal cord, leading to symptoms similar to hATTR amyloidosis. "I can definitely relate to those who are suffering from the disease because I have so many common symptoms with them. Now I understand that my dad had a lot of pain in his legs, particularly in his calves. They're sore and hard as rocks all the time. So, yeah, it's tough for them. I can feel that."



Diana, Wendy, Mary, Daryel, Mark, Lisa, Tina, and Sean

Leo, Sarah's great-grandson

Sarah's great-granddaughter, Tonya, with her daughter

Tonya tested positive for the gene and feels strongly about testing and educating the next generation. Many of her cousins do not openly discuss the disease. "They feel like there's nothing they can do about it so they're just not going to worry about it," she said.

"When I received the results of my test, my sense of security melted away. I fell into a depression. I'm scared for what an hATTR diagnosis means for myself and my children. Some days we feel so alone in this journey," Tonya recalled.

Tonya has made it a point to educate her children. "I think it's important for [my family] to know about it," she explained.

Angel, Sarah's great-granddaughter, with her family

Tonya's sister Angel and her children will not develop hATTR amyloidosis. They tested negative for a mutated form of the gene that causes the disease.

Angel continues to help, by raising awareness on behalf of her family. This has become her mission. She has done so much already, and doesn't plan on stopping anytime soon. Her sister Tonya shared, "When Angel's results were negative, she could've just stopped there. But she has been trying to get information to my mother and my cousins [about research and trials]. She's just networking everywhere to get people aware, to get our family help."

One critical challenge has been getting primary care for the family.

Even doctors with whom they had a long-established relationship would turn them away. Daryel shook her head as she shared a story about her doctor of 18 years, still stunned at his response to her increasing neuropathic pain. "When I started showing signs of the disease, he looked at me and said, 'I don't know about it. I don't want to know about it. Find yourself another doctor.'"

Wendy, Karl, and Sarah

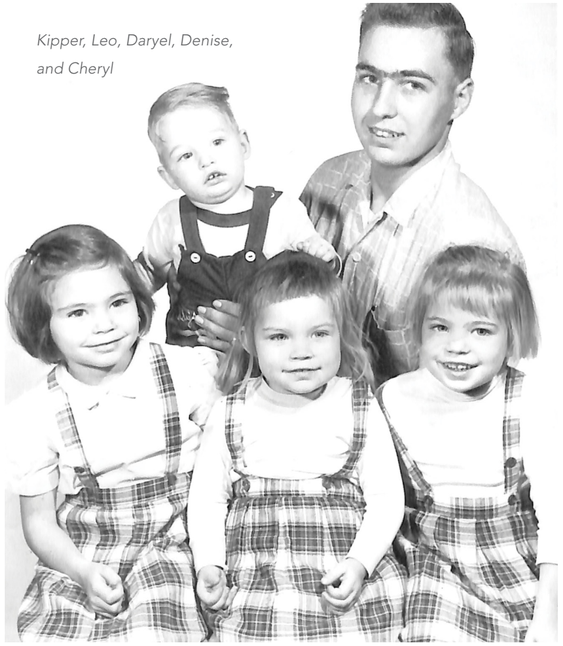
Because they don't live in a metropolitan area, it has been difficult to find a medical team willing not only to learn about the disease but also take on an entire family. "That's a big hurdle," said Angel. "I've found doctors willing to jump in, but then they're like, 'Whoa, this is just way too many people, too much information. And we don't even know where to start.'" But true to the family's character, she kept trying. "There is somebody out there that will help you. You may go through four or five doctors, but there is somebody that will listen."

After months of searching, Angel found a medical practice that has agreed to take on her mother, uncle, and cousins as patients. "It's important to make sure that we try to alleviate some of their symptoms so they don't go through the same things that the generation before them did."

Small town communications — a letter mailed to Chandler and his wife

"There is somebody out there that will help you. You may go through four or five doctors, but there is somebody that will listen."

— Angel,
Sarah's great-granddaughter



Kipper, Leo, Daryel, Denise, and Cheryl

Sarah's great-granddaughter Angel and Sarah's great-grandson Leo

Daryel and Angel, along with Daryel's nephew Leo, have become active in the rare disease community.

They travel to meetings where they can learn about pharmaceutical research and clinical trials.

"We get to talk to other families that have it, which is good, because then we hear things that they're going through. We [spoke at] a meeting in Albany for new people just diagnosed. They walked away after we were done talking with a better knowledge of it. I helped somebody and it made me feel good. That's what I want. I want to be able to help someone. I want them to understand what we are dealing with, but also that I'm not letting this disease take over my life," said Daryel.

Karl, Sarah's son

Wendy

Angel, Sarah's great-granddaughter and her family

Support group meetings are an important pipeline of information and hope for the rest of the family.

Angel, Tonya's daughter, Paige, and Daryel

Those meetings are an important pipeline of information and hope for the rest of the family. As Dane explained, "With my cousin Leo giving me updates, it's shown me that a positive thing can come out of this research on helping future generations. The progress I see is... giving hope."

The meetings also inspire new connections.

While at one support group gathering, Angel met a man who had been diagnosed with hATTR amyloidosis but didn't know any other family members with the disease. He came to the meeting alone, but left an honorary member of the family.

The name of the town the family has called home for over 100 years means:

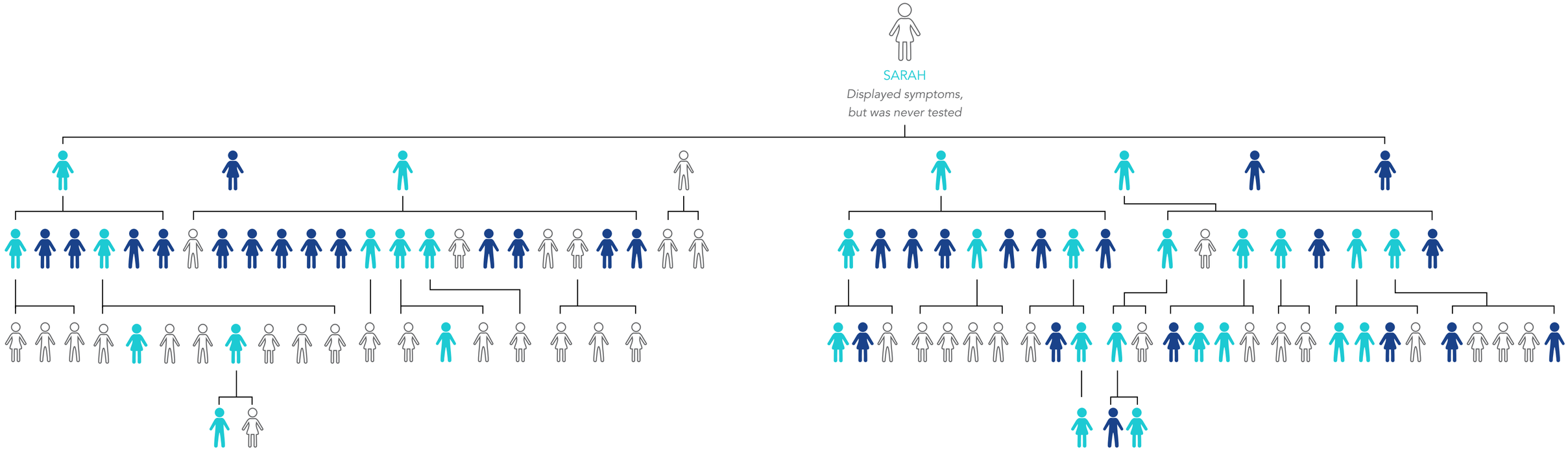
“It is at the junction of two waterways.”

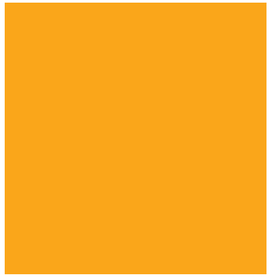
That feels very appropriate.

For generations, there have been two sides to the family — those with hATTR amyloidosis and those without. But just like the waterways, they come together. And together, they form something mightier — a family that takes care of each other. “These are my people,” said Angel with intense affection and fierce pride. “And I will fight for them forever.” That might sound rare in these transient times, but it’s the way the family has chosen to live. And it’s safe to say, Sarah would be proud.

How hATTR amyloidosis was inherited in Sarah's family

A family tree can help family members understand how a genetic mutation is passed from one generation to the next.





A Special Thanks to the Family

We would like to thank Sarah's entire family for so generously sharing their story. They are an inspiration and a testament to the power of community. They encourage everyone to find out more about hATTR amyloidosis.

In Loving Memory of Kipper

AlnylamAct®

Alnylam Pharmaceuticals is sponsoring no-charge, third-party genetic testing and counseling for individuals who may carry gene mutations known to be associated with hATTR amyloidosis.

Genetic testing and counseling may help to:

- Identify risk of disease for patients and their family members
- Shorten the time to diagnosis and prevent misdiagnoses
- Help patients consider clinical trials
- Provide information about support resources such as patient advocacy organizations

While Alnylam provides financial support for this program, tests and services are performed by independent third parties. Healthcare professionals must confirm that patients meet certain criteria to use the program. Alnylam receives de-identified patient data from this program, but at no time does Alnylam receive patient identifiable information. Alnylam receives contact information for healthcare professionals who use this program. Genetic testing is available in the U.S. and Canada. Genetic counseling is only available in the U.S. Healthcare professionals who use this program have no obligation to recommend, purchase, order, prescribe, promote, administer, use or support any Alnylam product.

For more information about the Alnlyam Act® Program, please visit www.alnylamact.com.

the BRIDGE® hATTR amyloidosis

The Bridge® program, developed by Alnylam Pharmaceuticals, promotes education, awareness, and conversation about hATTR amyloidosis among affected individuals, their families, and caregivers. The program includes a website, an educational kit, and other resources.

Visit www.hATTRbridge.com to learn more.

Alnylam® PHARMACEUTICALS

Alnylam is committed to advancing awareness of hereditary ATTR amyloidosis. In that spirit, we are proud to support "Living a Rare Life — A Family's Journey With Hereditary ATTR (hATTR) Amyloidosis". The story, the experiences, and the information related to diagnosis and family tree are based solely on information and recollections provided by members of the family highlighted in this book.