END PAIN FOREVER HOW A SINGLE GENE COULD BECOME A VOLUME

KNOB FOR HUMAN SUFFERIN G

by Erika Hayasaki | art by Sean Freeman 04.18.17

ON A SCALE of 1 to 10, how would you rate your pain? Would you say it aches, or would you say it stabs? Does it burn, or does it pinch? How long would you say you've been hurting? And are you taking anything for it?

Steven Pete has no idea how you feel. Sitting in Cassava, a café in Longview, Washington, next to a bulletin board crammed with flyers and promises—your pain-free tomorrow starts today; remember: you're not alone in your battle against

peripheral neuropathy!—he tells me he cannot fathom aches or pinches or the searing scourge of peripheral neuropathy that keep millions of people awake at night or hooked on pills. He was born with a rare neurological condition called congenital insensitivity to pain, and for 36 years he has hovered at or near a 1 on the pain scale. He's 5′ 8″, with glasses and thinning brown hair, and he has a road map of scars across his body, mostly hidden beneath a T-shirt bearing the partial crests of Batman, Green Lantern, Flash, and Superman. Because he never learned to avoid injury, which is the one thing pain is really good for, he gets injured a lot. When I ask how many bones he's broken, he lets out a quick laugh.

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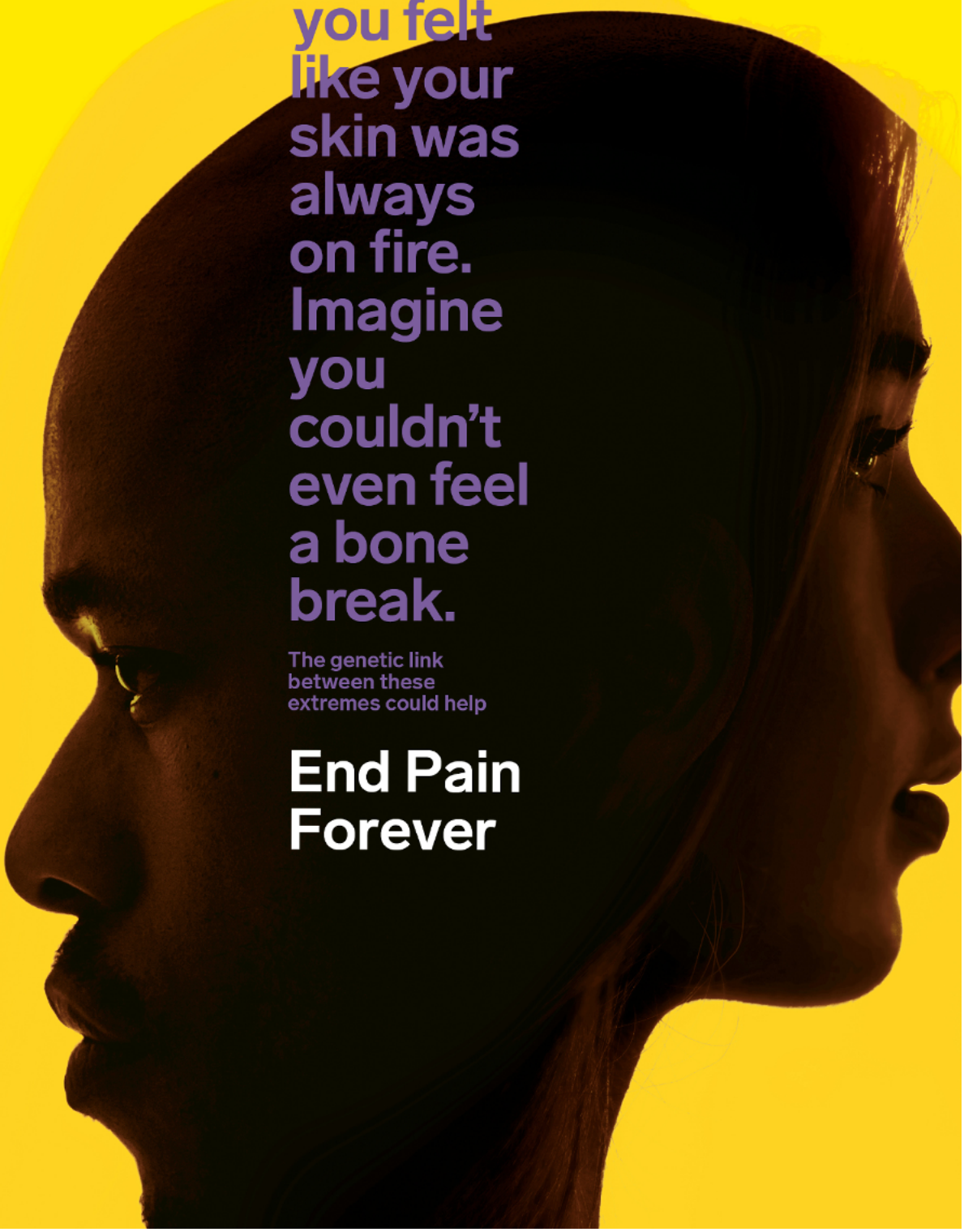

Imagine you felt like your skin was always on fire. Imagine you couldn't even feel a bone break.

The genetic link between these extremes could help

End Pain Forever

“Oh gosh. I haven’t actually done the count yet,” he says. “But somewhere probably around 70 or 80.” With each fracture, he didn’t feel much of anything—or even notice his injury at all. Whether he saw a doctor depended on how bad the break appeared to be. “A toe or a finger, I’d just take care of that myself,” he says, wagging a slightly bent index finger. “Duct tape.”

What about something more serious? Pete pauses for a moment and recalls a white Washington day a few years ago. “We had thick snow, and we went inner-tubing down a hill. Well, I did a scorpion, where you take a running start and jump on the tube. You’re supposed to land on your stomach, but I hit it at the wrong angle. I face-planted on the hill, and my back legs just went straight up over my head.” Pete got up and returned to tubing, and for the next eight months he went on as usual, until he started noticing the movement in his left arm and shoulder felt off. His back felt funny too. He ended up getting an MRI. “The doctor looked at my MRI results, and he was like, ‘Have you been in a car accident? About six months ago? Were you skydiving?’ ”

“I haven’t done either,” Pete replied.

The doctor stared at his patient in disbelief. “You’ve got three fractured vertebrae.” Pete had broken his back.

Throughout his body today, Pete has a strange feeling: “a weird radiating sensation,” as he

describes it, an overall discomfort but not quite pain as you and I know it. He and others born with his condition have been compared to superheroes—indomitable, unbreakable. In his basement, where the shelves are lined with videogames about biologically and technologically enhanced soldiers, there is even a framed sketch of a character in full body armor, with the words painless pete. But Pete knows better. "There's no way I could live a normal life right now if I could actually feel pain," he says. He would probably be constrained to a bed or wheelchair from all the damage his body has sustained.

His wife, Jessica, joins us at the café. She is petite and shy, with ice-blue eyes traced in black eyeliner. When I ask her what it's like to live with a man who feels no pain, she sighs. "I worry about him all the time." She worries about him working with his power tools in the basement. She worries about him cooking over a grill. She worries about bigger things too. "If he has a heart attack, he won't be able to feel it," she says. "He'll rub his arm sometimes, and I freak out: 'Are you OK?' " She looks over at Pete, who chuckles. "He thinks it's funny," she says. "I don't think it's funny."

PAM COSTA LIVES an hour and a half from Pete, outside Tacoma, Washington, and she occupies the other end of the pain scale. Costa is 51 and girlish, with shoulder-length auburn hair and a wide smile. At first glance, she has the rosy flush of someone

who has spent time in the sun. But if you look closer at her cheeks, her feet, and her legs, they bear traces of a deeper shade of plum. Everywhere there is plum, there is pain. She was born with a rare neurological condition called erythromelalgia, otherwise known as man on fire syndrome, in which inflamed blood vessels throughout her body are constant sources of pain. Because the inflammation is exacerbated by physical contact, stress, and even the smallest elevation in surrounding temperature, Costa lives her life with great care. She wears loose-fitting clothes because fabric feels like a blowtorch against her skin. She sleeps with chilled pillows because the slightest heat makes her limbs feel like they are crackling. "Have you ever been out in the bitter, bitter cold, where your feet were ice?" she asks me. "Almost frostbite? Then you warm them up and it burns? That burning sensation: That is what it feels like all the time."

Costa begins and ends every day with a 50-milligram dose of morphine, just as she has for the past 35 years. And there are other pills. "I pop a lot of these," Costa, barefoot, tells me as she opens her medicine cabinet and twists open a jumbo bottle of Aleve. The directions say not to exceed three pills a day, and though it is early afternoon and this is her fourth such pill in the past five hours, she expects to take a couple more before the day's over. She is an instructor of psychology at a

local college and the mother of a teenage daughter, and she agonizes over her morphine dependency. “I have a drive to stop—to just not be dependent on opiates,” she says. But without her medication, her pain becomes unbearable.

A year ago she went to Las Vegas for a work conference, and the plane home got stuck on the tarmac with a mechanical issue. There was no air-conditioning, and the temperature started to rise. “An hour and a half in, people are taking off their clothes, fanning themselves,” she says. With the plane 20 feet from the gate and her skin throbbing, Costa persuaded a flight attendant to let her off. “I was so afraid I was going to pass out or throw up or get to where I was immobilized.” When the doors finally opened, she fled the plane, and she sat in the airport dousing herself with Smartwater.

Costa and Pete have never met. Their daily negotiations with the world could not be more different. Yet scientists have uncovered a genetic link that binds their mirror-image conditions together, and pharmaceutical researchers are now deep into clinical trials on a new type of drug that seeks to mimic Pete’s condition to treat Costa and others living with chronic pain. Such a drug would not merely dull inflammation the way ibuprofen does or alter our neurochemistry the way opioids do: It would block the transmission of pain signals from cell to cell without ruinous side effects on the brain or body.

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The scale of the problem that this breakthrough could help solve is so vast that it's difficult to take in. Pain has always been the price of being alive, but according to the National Institutes of Health, more than one in 10 American adults say that some part of their body hurts some or all of the time. That's more than 25 million people. In study after study, more middle-aged Americans than ever before say they suffer from chronic pain. Because of that pain, more of them than ever before say they have trouble walking a quarter mile or climbing stairs. More say they have trouble spending time with friends. More say they can no longer work.

To get through the day, many of these people turn to pills, and nearly 2 million Americans say they're addicted to painkillers. If the pills stop working, many people try something else—80 percent of heroin users previously abused prescriptions—or they simply up (and up, and up) their dosage. Opioid overdoses led to 33,000 deaths in 2015, an all-time high and four times as many as in 2000. They now kill as many Americans every year as car accidents or guns do, and the crisis, it seems, is only getting worse.

Pam Costa sleeps with chilled pillows because the slightest heat makes her limbs feel like they are crackling.CAIT OPPERMANN

IF YOU BURN yourself on a stove, it hurts. More specifically, the nerve cells in your hand sense the heat and send pain signals to your spinal cord. The signal then travels up to the brain, which instructs you to howl with pain or issue the appropriate profanity. This is what's known as acute pain. It can stab or pinch or shock, hurting like hell and telling us to stop doing what we are doing, take care of ourselves, get medicine, get help. The medical community knows how to treat most acute pain. Temporary prescriptions for opioids dull the sting from surgical incisions; anti-inflammatories can mask the discomfort of a sprain. Acute pain persists, but it also goes away. Acute pain is also easier to empathize with: Show someone an image of a pair of scissors cutting a hand, and the observer's brain will react as much as if their own hand were being pinched.

Chronic pain, on the other hand, is a phantom: an enduring ache, a tenderness that does not turn off. It can be inflammatory (brought on by diseases like arthritis) or neuropathic (affecting the nerves, as in some cases of shingles, diabetes, or chemotherapy treatments). Some chronic pain never even traces back to a coherent cause, which makes it that much harder to understand. Give us broken bones, burn marks, blood—in the absence of proof (or personal experience), the hidden pain of others is easy to dismiss.

As a child, Costa would dawdle in the deep gutters lining the streets near her home, the cool, mucky water providing her momentary pain relief. In classrooms she would wrap her hands and feet around the poles of a desk, like a koala, to feel the coolness. And she'd sneak off to water fountains to wipe down her limbs with cold water.

Doctors didn't know how to diagnose her. Some adults thought she had behavioral issues or depression. One physician said her symptoms were psychosomatic. The plum color was the only visible evidence that she might have any medical disorder at all. Then, in 1977, when Costa was 11, a letter arrived from the Mayo Clinic. A cousin had been referred to the medical center after complaining of constant pain, and the doctors there, intrigued by her mysterious condition, had begun interviewing members of Costa's extended family. They discovered that many of them had the same symptoms (redness, irritation, swelling), and they found that 29 members of Costa's family, spanning five generations, appeared to have man on fire syndrome. After corresponding with Costa's parents and learning more about her symptoms, a Mayo researcher told them that their daughter had apparently inherited the same problem.

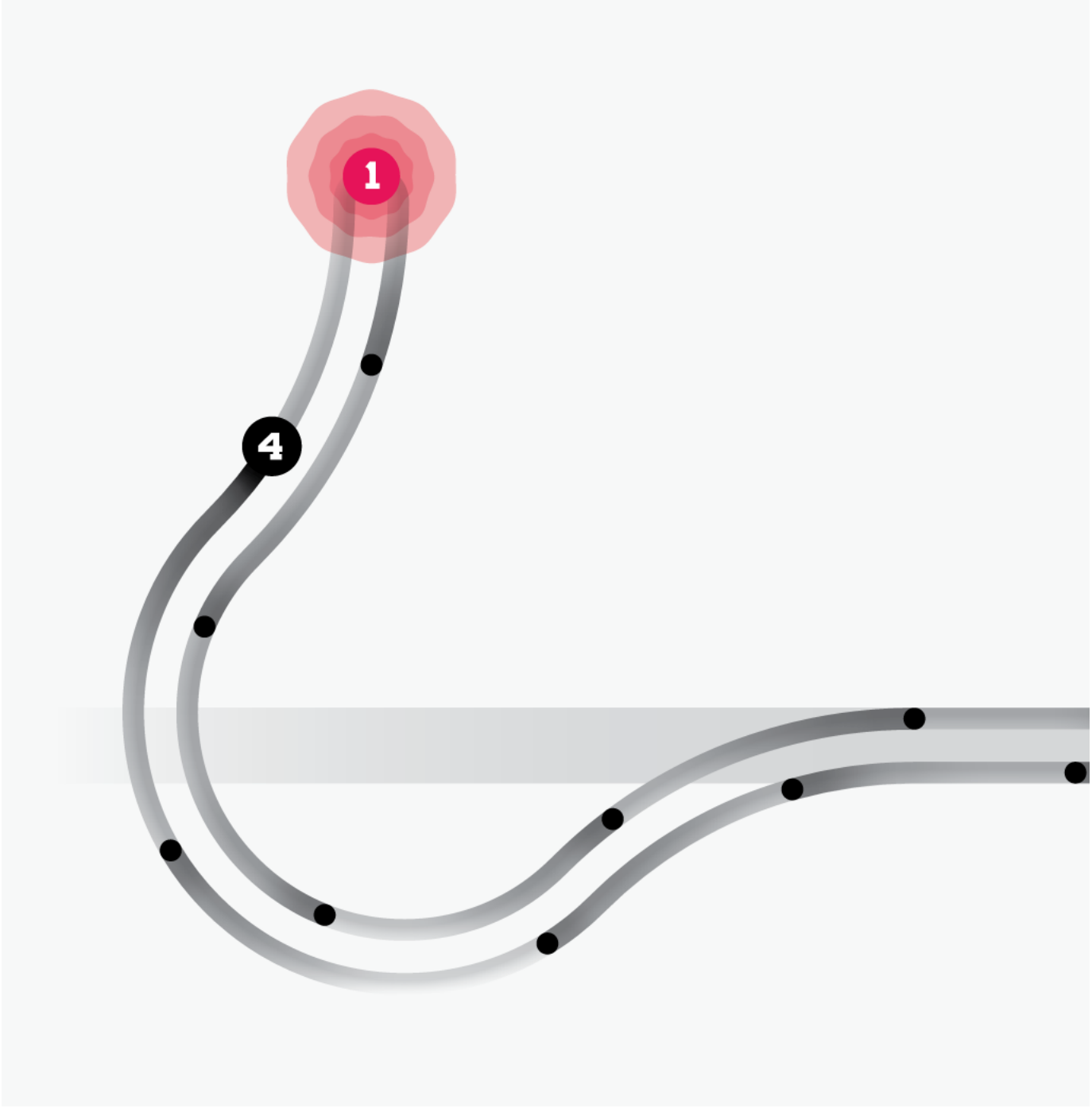
But a diagnosis didn't mean that anyone understood why it happened or how it could be treated. The researchers created a family tree for

the Costas, identifying every relative with erythromelalgia. For Costa, it was stunning to see the clean, clinical diagram of hereditary hurt. And though she realized there was a chance she wouldn't pass on her condition to any children she might have, she wasn't going to take the risk. "I had my tubes tied right after my 18th birthday," she tells me, a hint of grief filling her voice. "Always, since I was a little girl, I wanted to be a mother more than anything in the world." When dating, she'd tell her suitors that she couldn't have biological children. "That was a deal breaker for many guys," she says. Costa eventually did get married, and in 2000 she and her husband adopted a daughter.

For most of her life, the underlying cause of her condition remained a mystery, both to her and to the global scientific community. But that began to change in 2004 with a discovery in a Beijing lab. Scientists there had studied a family in which three generations had been afflicted with man on fire. They found that, of the 20,000-plus genes that make up the recently mapped human genome, mutations in a single gene, SCN9A, were somehow linked to erythromelalgia. It was the first evidence of a specific genetic cause of man on fire, and for people like Costa it was a sign of hope.

HOW PAIN WORKS

From onset to agony. —-Gregory Barber



1 Detection

Acute pain begins with nociceptors—long neurons that originate in the spinal cord and end as thin fibers in the skin. Those fibers are tipped with receptors that respond to pain-inducing stimuli. When a stimulus is strong enough, these receptors generate an electrical current—the pain signal.

2 Transmission

The pain signal travels along the neurons through a series of channels that allow sodium ions back and forth across cell membranes. These channels, like Nav1.7, allow those charged particles across a membrane if the pain signal is strong enough. (If it isn't, the person feels no pain.)

3 Perception

When a pain signal reaches the spinal cord, it continues up to the brain, where the somatosensory cortex is primarily responsible for translating information about the intensity of the pain signal. The brain's motor cortex then generates the body's response—a shout of surprise, a jerk of a hand.

4 Aftermath

After an injury, even an innocuous stimulus—like a warm bath or a pat on the back—can generate a pain signal at the site of the original injury.

WHEN STEPHEN WAXMAN was a student at the Albert Einstein College of Medicine in the early 1970s, he became interested in pain—how people feel it, how the body transmits it, and how, as a future neurologist, he could learn to control it. Later in his career, after his father was in the final stages of agonizing diabetic neuropathy, he became obsessed with helping patients like his dad, who could find no relief from their pain. "We simply had to do better," he says.

Today Waxman is the director of the Center for Neuroscience and Regeneration Research at the Yale University School of Medicine. He is 71, with oval-shaped glasses that rest on the ridge of his nose when he reads and eyebrows that arch toward each other like upward-facing arrows. He's spent nearly half a century trying to chart the molecular and cellular pathways involving pain, and for much of this time Waxman was interested in the sodium channels found in the membranes of neurons—portals that allow charged particles to

flow in and out of the nerve cells. In particular, he believed that one of those sodium channels, Nav1.7, played an especially powerful role in how we experience pain. In his theory, a stimulus triggers the Nav1.7 channel to open just long enough to allow the necessary amount of sodium ions to pass through, which then enables messages of stinging, soreness, or scalding to register in the brain. When the trigger subsides, Nav1.7 closes. In those with faulty Nav1.7 channels, sensations that typically wouldn't register with the brain are instead translated into extreme pain.

That was his theory, anyway. As the Chinese researchers were finalizing their results, Waxman's team was searching for human subjects with some form of inherited pain, so they could sequence their sodium-channel genes and test the Nav1.7 hypothesis. Among the genes they wanted to sequence was SCN9A, which encodes Nav1.7 and determines whether it works. When Waxman learned that the Chinese scientists had discovered a link between SCN9A and erythromelalgia, he thought, "My God, we've been scooped." The Chinese scientists seemed to have solved a mystery he'd spent much of his career examining. As Waxman dug deeper into the report, though, his mood lifted. The Beijing group had linked SCN9A mutations to man on fire, but they didn't explain or uncover how they were linked. For Waxman and his team, there was still an opportunity to connect

the biochemical dots between faulty SCN9A genes, dysfunctional Nav1.7 channels, and man on fire. To do that, they needed to show how cells with mutant Nav1.7 channels would react to pain. Thanks to the Beijing group, they knew just where to look: families with erythromelalgia.

This is how Waxman first encountered Pam Costa's family. He reached out and began gathering DNA from 16 of her cousins, aunts, and uncles who suffer from erythromelalgia. He sequenced their genes and used them to create faulty Nav1.7 channels, which he added to cells; he then tracked how these channels responded to stimuli. The results not only demonstrated that SCN9A mutations made Nav1.7 channels more likely to open (meaning harmless stimuli often triggered feelings of pain) but also showed that when those channels opened, they did so for longer, amplifying the feeling of discomfort. It was the breakthrough Waxman had spent his life working toward: "We now had a fully convincing link from Nav1.7 to pain." This meant that if his team could somehow regulate or even turn off the Nav1.7 channel, they could regulate or even turn off how we experience certain kinds of pain.

STEVEN PETE WAS born in 1981 in the 2,200-person town of Castle Rock, Washington, near Mount Saint Helens. At around 6 months old, when Pete started teething, he chewed off part of his tongue. As he got older he would bang his head

against walls, not even stopping when it became swollen or indented. His parents made him wear a helmet, and they wrapped his arms and legs in long socks, securing them with duct tape, to prevent him from chewing away at his own limbs. His younger brother, Chris, had many of the same symptoms and all the same fearlessness. A day rarely passed when one of them didn't bleed or bruise.

When his parents took Pete to a local pediatrician, they explained that they did not think he felt any pain. Maybe neither son did. The pediatrician hadn't heard of a condition that prevented someone from experiencing pain, but after weeks of research, he found over 40 similar cases, including four siblings in Birmingham, England. The Pete boys were eventually diagnosed with congenital insensitivity to pain, and though the condition was likely passed down from one generation to another, there was no known cause, much less a cure.

Pete went on to live what appeared to be an ordinary life. In 2003, while working a security job at a mall, Pete met Jessica online. "We talked on the phone for hours," Jessica remembers. Pete told her about his painlessness, and at the time she didn't think much of it. "I guess I was like, 'That's pretty cool,' " she says now with a shrug. They married in 2005, and he started working at the Cowlitz Indian Tribe Health and Human Services

Department. All that time, he was unaware that just a few hundred miles north, outside Vancouver, British Columbia, a small company was inching toward a breakthrough in understanding his condition.

For years that company, which is now called Xenon Pharmaceuticals, had been working to understand rare single-gene disorders such as familial exudative vitreoretinopathy (which causes vision loss) in order to create drugs that could be used to treat more common disorders with similar symptoms (like other conditions involving vision loss). In 2001 the company heard about a family in Newfoundland in which four members could not feel pain. One of the sons "actually stood on a nail and it had gone through his foot," says Robin Sherrington, then senior director of biological sciences at Xenon. "He had no idea that it had happened until he got home and his parents saw it." No gene had yet been linked with their condition, but given the familial links in the Newfoundland case, Xenon researchers suspected it was genetic. They started hunting for more subjects.

Following news reports and word of mouth, Xenon tracked down and studied 12 families from around the world with insensitivity to pain. (The Petes were not among them. Outside their immediate community, few people knew about the brothers' condition.) For Sherrington, it was incredible that

these individuals and their genomes existed. Evolution should have weeded out most of their ancestors. “Feeling pain is protective,” Sherrington says. “They would not have felt certain noxious stimuli. They should not have survived.” By studying those 12 families’ genomes throughout 2001 and 2002, Xenon found a common trait among those with insensitivity to pain: mutations in a single gene, SCN9A, and the non-functioning sodium channel it encodes, Nav1.7.

“This single channel, when it is nonfunctioning in a human being, renders them unable to understand or feel any form of pain,” Sherrington says, summarizing the team’s initial findings. And if Xenon could develop a new drug that could somehow mimic this condition—“to inhibit the Nav1.7 channel to partially replicate that absence of pain,” he explains—then it could relieve people’s pain without any of the side effects of opioids.

It is rare for biology to deliver such a seamless positive-negative effect within a single gene. In man on fire patients, one SCN9A mutation leads to a hyperactive Nav1.7 channel, which causes extreme discomfort. In those with insensitivity to pain, another SCN9A mutation leads to an inactive Nav1.7 channel, which results in total numbness. Given that the teams at Xenon and Yale were working on opposite coasts, and on conditions that fell on opposite sides of the pain spectrum, they

only learned of each other's discoveries through published reports and journal articles. (Sherrington first learned about Waxman's study at Yale in 2004; Waxman only read about Sherrington's work at Xenon after the company published its results in 2007.) Both teams arrived at the same clinical destination from a totally different direction, surprised as anyone that people like Pam Costa and Steven Pete had anything in common. "I was overwhelmed when we saw both sides of the genetic coin," Waxman remembers. "SCN9A really is a master gene for pain."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When Steven Pete was 6 months old, he chewed off part of his tongue. Today he has a road map of scars across his body.CAIT OPPERMANN

NOT LONG AFTER their discovery, technicians at Xenon set to work putting Nav1.7 channels into tissue cultures, then testing each with a compound from their vast library of molecules. They were looking for a blocker that would shut off or at least turn down the faucet on Nav1.7 without affecting the body's other eight sodium channels. If you block Nav1.4, for -example, you might block muscle movement. Blocking Nav1.5 can inhibit the heart. Blocking Nav1.6 might impact the brain, causing double vision, confusion, balance problems, or even seizures. One by one, they experimented with thousands of combinations until they got a hit—a compound that plugs up Nav1.7 without major side effects. From that, researchers then created a drug called TV-45070 and conducted pilot tests on four erythromelalgia patients. In three of the four, "these individuals' pain responses were markedly blunted, and in one case we couldn't elicit pain at all," says Simon Pimstone, president and CEO of Xenon. Now TV-45070 is being used in a phase 2 clinical trial on 330 patients who suffer from nerve pain.

As for Waxman, he and his researchers at Yale helped Pfizer test five erythromelalgia patients with another Nav1.7 blocker. Scientists triggered the subjects' pain with heating blankets and asked them to rate their feelings before and after taking the drug. Last year Pfizer and Waxman's team

reported that three of the five patients described a decrease in pain with the blockers.

There are other, less conventional approaches under way too. At Amgen, a pharmaceutical company in Thousand Oaks, California, scientists test up to 10,000 molecules against Nav1.7 each week. In 2012 they discovered that the toxin of a Chilean tarantula can target Nav1.7 with minimal impact on other sodium channels. They've since engineered a synthetic version of the spider's toxin that's more potent than the original.

These findings, while significant, are still small steps forward. Over the next few years, with larger pools of patients suffering from arthritis, sciatica, shingles, and many other kinds of pain, researchers will continue to test the practical applications of these discoveries. "At least a half dozen companies are trying to develop sodium-channel blockers that preferentially or selectively block 1.7," Waxman says. And while obstacles remain—ensuring that only the Nav1.7 channel is affected; creating compounds that will allow some pain to register without cutting it off altogether; surviving the rigors of FDA approval—he and many others see a way forward.

WHICHEVER COMPANY GETS a prescription drug to market first, no progress would have been made without people like Costa and Pete, both of whom have taken part in studies for years.

Costa still remembers the day in 2011 when she

first visited Yale and met Waxman in person, after corresponding with him by email and phone for six years. She got a tour of the labs, meeting more than a dozen scientists from around the world who have been working to fix Nav1.7. While walking through the lab, Costa saw a row of computers. Waxman asked, “Do you want to see what happens with your sodium channels?” She did.

Waxman pulled up an image of a normal person’s sodium channel on the screen, the strings of amino acids that form it neatly folded. Then he pulled up another image: The protein here was a tangled clump, amino acids zigzagging almost off the screen. “This is you,” he said.

“I’ll never forget,” Costa says. Her entire life, she could only tell others how she felt—she could never show them. To see the medical proof of her pain for the first time, Costa says, “was the most validating experience in my entire life.”

At the end of my visit to her home, Costa rushes outside barefoot to catch me before I leave. As she stands on the grass in the 60-degree weather, her legs are already turning purplish with aggravation, and she pulls out a handwritten letter that she’s just found, from her cousin Helaine, who sent it in 1986. Helaine lived in Alabama and also had erythromelalgia. She was one of Costa’s favorite cousins. They looked alike. Helaine was divorced, living in a trailer. She never had access to the kind of medical treatment that Costa has received.

When Costa and her cousin talked, it was often about their mutual state of hurt. In 2015, Helaine died. Costa doesn't know how, exactly. She just knows her cousin never woke up.

Today when Costa resurrects memories of her own pain, they come with specific details and anecdotes—like that terrible day on the delayed plane, with the Smartwater bottles, or dunking her feet in gutter water as a child. Neurologists believe that, in the brain, pain is associated with memory-making processes, which explains the specificity of her stories. You don't remember every time you've gone running, but you remember the day you slipped on ice and broke your knee. Pain also leaves an imprint on our cellular memory—the experiences our bodies hold on to and may pass on to our children and grand-children—which some scientists believe may one day help explain why chronic pain can persist even after an injury has healed. We live with the echo of pain inside us, constantly reminding us to watch our step, back away from the stove, slow down. Someone could get hurt.

For Pete, recalling details of his injuries does not come easily, and his memories of growing up with his younger brother, Chris, are often vague too. Pete wishes Chris could help refresh his memory. "I relied on my brother a lot for retelling my stories and holding on to my memories," Pete says, breaking into tears. A lifetime of injuries caused so

much damage to Chris' body that a doctor told him he would likely end up in a wheelchair before he turned 30. Living the rest of his life incapacitated like that was too much for Chris to bear. Eight years ago, he hung himself in the barn on their parents' property. He was only 26. "It felt like losing … my life," Pete says.

He wipes his tears away and takes a deep breath. "I hope that one day parents will be able to make a choice for their children who don't feel pain, to activate that sodium channel so that their children can live a normal life." The work under way to target the Nav1.7 channel won't help Pete or others with congenital insensitivity to pain—there's no point blocking a portal that's permanently closed. Instead, the condition remains the most frustrating of mysteries: one with a known cause but no cure, passed down from one generation to the next.

When his daughter was born in 2008, Pete asked the doctor in the delivery room, "Does she feel pain?"

"They pricked her," his wife remembers. "And she cried." It felt something like relief.

Erika Hayasaki (@ErikaHayasaki) wrote about the mystery of a woman's missing memories in issue 24.04.

This article appears in the May issue. Subscribe now.

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peripheral neuropathy!—he tells me he cannot fathom aches or pinches or the searing scourge of peripheral neuropathy that keep millions of people awake at night or hooked on pills. He was born with a rare neurological condition called congenital insensitivity to pain, and for 36 years he has hovered at or near a 1 on the pain scale. He's 5′ 8″, with glasses and thinning brown hair, and he has a road map of scars across his body, mostly hidden beneath a T-shirt bearing the partial crests of Batman, Green Lantern, Flash, and Superman. Because he never learned to avoid injury, which is the one thing pain is really good for, he gets injured a lot. When I ask how many bones he's broken, he lets out a quick laugh.

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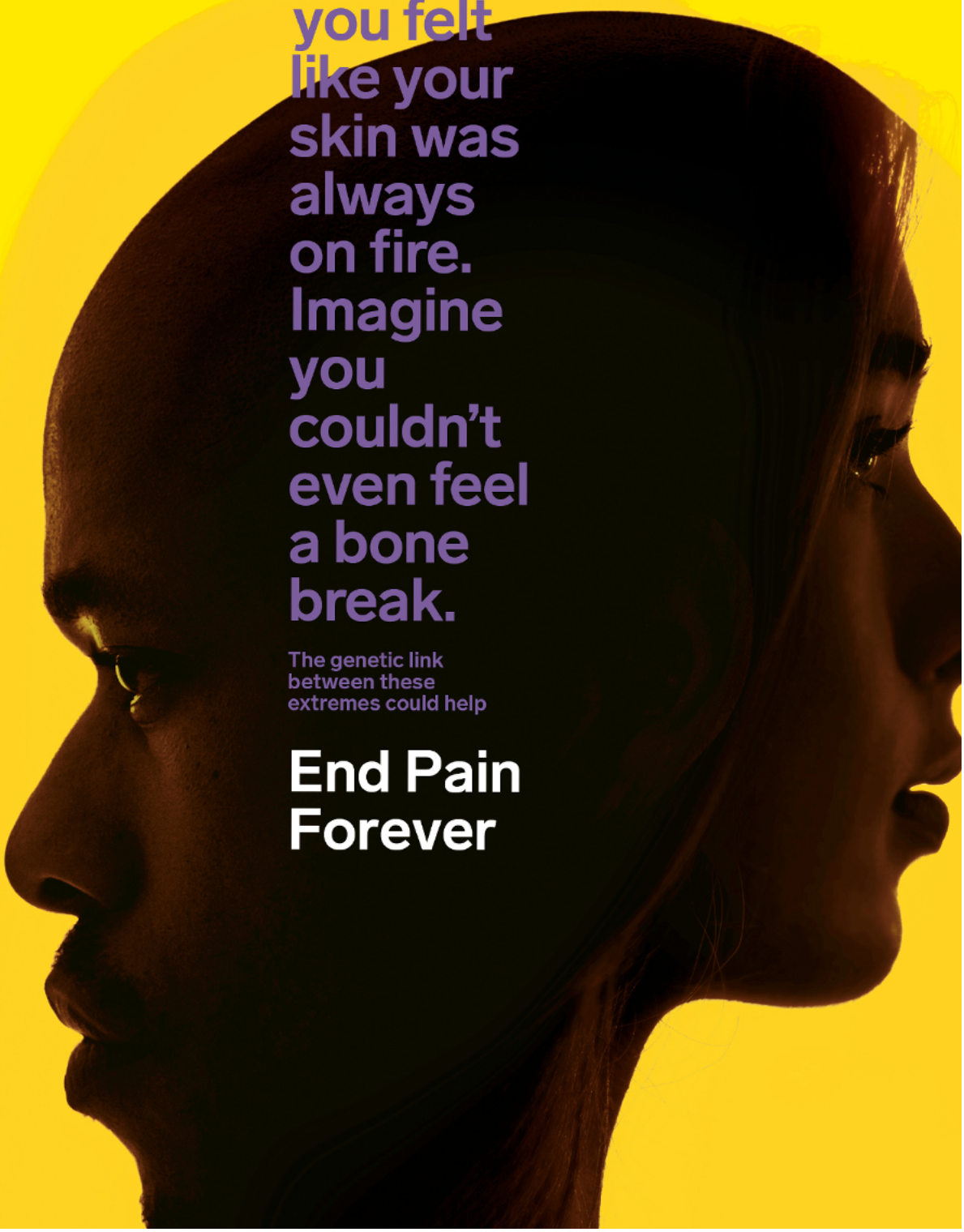

Imagine you felt like your skin was always on fire. Imagine you couldn't even feel a bone break.

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“Oh gosh. I haven’t actually done the count yet,” he says. “But somewhere probably around 70 or 80.” With each fracture, he didn’t feel much of anything—or even notice his injury at all. Whether he saw a doctor depended on how bad the break appeared to be. “A toe or a finger, I’d just take care of that myself,” he says, wagging a slightly bent index finger. “Duct tape.”

What about something more serious? Pete pauses for a moment and recalls a white Washington day a few years ago. “We had thick snow, and we went inner-tubing down a hill. Well, I did a scorpion, where you take a running start and jump on the tube. You’re supposed to land on your stomach, but I hit it at the wrong angle. I face-planted on the hill, and my back legs just went straight up over my head.” Pete got up and returned to tubing, and for the next eight months he went on as usual, until he started noticing the movement in his left arm and shoulder felt off. His back felt funny too. He ended up getting an MRI. “The doctor looked at my MRI results, and he was like, ‘Have you been in a car accident? About six months ago? Were you skydiving?’ ”

“I haven’t done either,” Pete replied.

The doctor stared at his patient in disbelief. “You’ve got three fractured vertebrae.” Pete had broken his back.

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His wife, Jessica, joins us at the café. She is petite and shy, with ice-blue eyes traced in black eyeliner. When I ask her what it's like to live with a man who feels no pain, she sighs. "I worry about him all the time." She worries about him working with his power tools in the basement. She worries about him cooking over a grill. She worries about bigger things too. "If he has a heart attack, he won't be able to feel it," she says. "He'll rub his arm sometimes, and I freak out: 'Are you OK?' " She looks over at Pete, who chuckles. "He thinks it's funny," she says. "I don't think it's funny."

PAM COSTA LIVES an hour and a half from Pete, outside Tacoma, Washington, and she occupies the other end of the pain scale. Costa is 51 and girlish, with shoulder-length auburn hair and a wide smile. At first glance, she has the rosy flush of someone

who has spent time in the sun. But if you look closer at her cheeks, her feet, and her legs, they bear traces of a deeper shade of plum. Everywhere there is plum, there is pain. She was born with a rare neurological condition called erythromelalgia, otherwise known as man on fire syndrome, in which inflamed blood vessels throughout her body are constant sources of pain. Because the inflammation is exacerbated by physical contact, stress, and even the smallest elevation in surrounding temperature, Costa lives her life with great care. She wears loose-fitting clothes because fabric feels like a blowtorch against her skin. She sleeps with chilled pillows because the slightest heat makes her limbs feel like they are crackling. "Have you ever been out in the bitter, bitter cold, where your feet were ice?" she asks me. "Almost frostbite? Then you warm them up and it burns? That burning sensation: That is what it feels like all the time."

Costa begins and ends every day with a 50-milligram dose of morphine, just as she has for the past 35 years. And there are other pills. "I pop a lot of these," Costa, barefoot, tells me as she opens her medicine cabinet and twists open a jumbo bottle of Aleve. The directions say not to exceed three pills a day, and though it is early afternoon and this is her fourth such pill in the past five hours, she expects to take a couple more before the day's over. She is an instructor of psychology at a

local college and the mother of a teenage daughter, and she agonizes over her morphine dependency. “I have a drive to stop—to just not be dependent on opiates,” she says. But without her medication, her pain becomes unbearable.

A year ago she went to Las Vegas for a work conference, and the plane home got stuck on the tarmac with a mechanical issue. There was no air-conditioning, and the temperature started to rise. “An hour and a half in, people are taking off their clothes, fanning themselves,” she says. With the plane 20 feet from the gate and her skin throbbing, Costa persuaded a flight attendant to let her off. “I was so afraid I was going to pass out or throw up or get to where I was immobilized.” When the doors finally opened, she fled the plane, and she sat in the airport dousing herself with Smartwater.

Costa and Pete have never met. Their daily negotiations with the world could not be more different. Yet scientists have uncovered a genetic link that binds their mirror-image conditions together, and pharmaceutical researchers are now deep into clinical trials on a new type of drug that seeks to mimic Pete’s condition to treat Costa and others living with chronic pain. Such a drug would not merely dull inflammation the way ibuprofen does or alter our neurochemistry the way opioids do: It would block the transmission of pain signals from cell to cell without ruinous side effects on the brain or body.

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The scale of the problem that this breakthrough could help solve is so vast that it's difficult to take in. Pain has always been the price of being alive, but according to the National Institutes of Health, more than one in 10 American adults say that some part of their body hurts some or all of the time. That's more than 25 million people. In study after study, more middle-aged Americans than ever before say they suffer from chronic pain. Because of that pain, more of them than ever before say they have trouble walking a quarter mile or climbing stairs. More say they have trouble spending time with friends. More say they can no longer work.

To get through the day, many of these people turn to pills, and nearly 2 million Americans say they're addicted to painkillers. If the pills stop working, many people try something else—80 percent of heroin users previously abused prescriptions—or they simply up (and up, and up) their dosage. Opioid overdoses led to 33,000 deaths in 2015, an all-time high and four times as many as in 2000. They now kill as many Americans every year as car accidents or guns do, and the crisis, it seems, is only getting worse.

Pam Costa sleeps with chilled pillows because the slightest heat makes her limbs feel like they are crackling.CAIT OPPERMANN

IF YOU BURN yourself on a stove, it hurts. More specifically, the nerve cells in your hand sense the heat and send pain signals to your spinal cord. The signal then travels up to the brain, which instructs you to howl with pain or issue the appropriate profanity. This is what's known as acute pain. It can stab or pinch or shock, hurting like hell and telling us to stop doing what we are doing, take care of ourselves, get medicine, get help. The medical community knows how to treat most acute pain. Temporary prescriptions for opioids dull the sting from surgical incisions; anti-inflammatories can mask the discomfort of a sprain. Acute pain persists, but it also goes away. Acute pain is also easier to empathize with: Show someone an image of a pair of scissors cutting a hand, and the observer's brain will react as much as if their own hand were being pinched.

Chronic pain, on the other hand, is a phantom: an enduring ache, a tenderness that does not turn off. It can be inflammatory (brought on by diseases like arthritis) or neuropathic (affecting the nerves, as in some cases of shingles, diabetes, or chemotherapy treatments). Some chronic pain never even traces back to a coherent cause, which makes it that much harder to understand. Give us broken bones, burn marks, blood—in the absence of proof (or personal experience), the hidden pain of others is easy to dismiss.

As a child, Costa would dawdle in the deep gutters lining the streets near her home, the cool, mucky water providing her momentary pain relief. In classrooms she would wrap her hands and feet around the poles of a desk, like a koala, to feel the coolness. And she'd sneak off to water fountains to wipe down her limbs with cold water.

Doctors didn't know how to diagnose her. Some adults thought she had behavioral issues or depression. One physician said her symptoms were psychosomatic. The plum color was the only visible evidence that she might have any medical disorder at all. Then, in 1977, when Costa was 11, a letter arrived from the Mayo Clinic. A cousin had been referred to the medical center after complaining of constant pain, and the doctors there, intrigued by her mysterious condition, had begun interviewing members of Costa's extended family. They discovered that many of them had the same symptoms (redness, irritation, swelling), and they found that 29 members of Costa's family, spanning five generations, appeared to have man on fire syndrome. After corresponding with Costa's parents and learning more about her symptoms, a Mayo researcher told them that their daughter had apparently inherited the same problem.

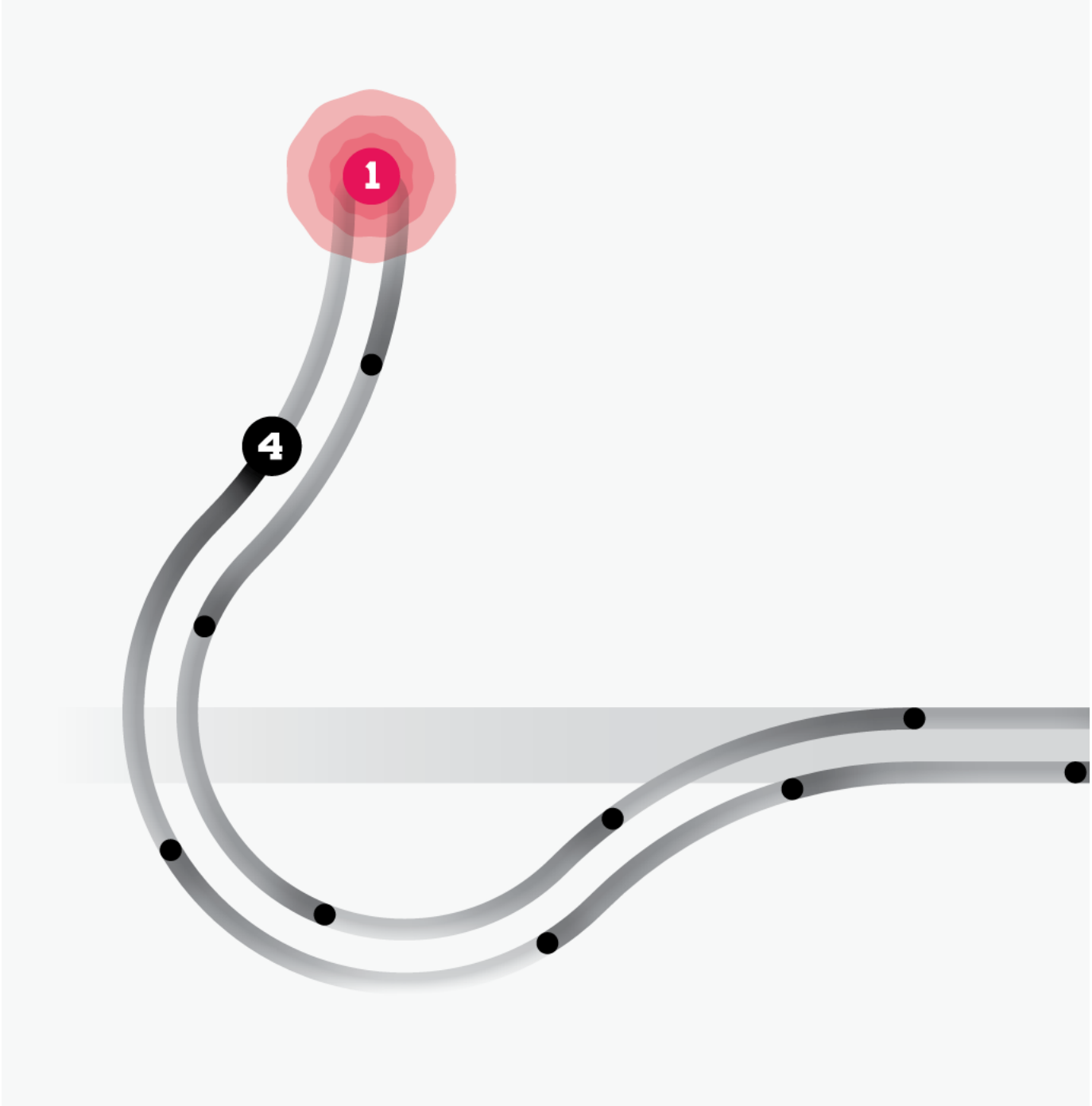
But a diagnosis didn't mean that anyone understood why it happened or how it could be treated. The researchers created a family tree for

the Costas, identifying every relative with erythromelalgia. For Costa, it was stunning to see the clean, clinical diagram of hereditary hurt. And though she realized there was a chance she wouldn't pass on her condition to any children she might have, she wasn't going to take the risk. "I had my tubes tied right after my 18th birthday," she tells me, a hint of grief filling her voice. "Always, since I was a little girl, I wanted to be a mother more than anything in the world." When dating, she'd tell her suitors that she couldn't have biological children. "That was a deal breaker for many guys," she says. Costa eventually did get married, and in 2000 she and her husband adopted a daughter.

For most of her life, the underlying cause of her condition remained a mystery, both to her and to the global scientific community. But that began to change in 2004 with a discovery in a Beijing lab. Scientists there had studied a family in which three generations had been afflicted with man on fire. They found that, of the 20,000-plus genes that make up the recently mapped human genome, mutations in a single gene, SCN9A, were somehow linked to erythromelalgia. It was the first evidence of a specific genetic cause of man on fire, and for people like Costa it was a sign of hope.

HOW PAIN WORKS

From onset to agony. —-Gregory Barber



1 Detection

Acute pain begins with nociceptors—long neurons that originate in the spinal cord and end as thin fibers in the skin. Those fibers are tipped with receptors that respond to pain-inducing stimuli. When a stimulus is strong enough, these receptors generate an electrical current—the pain signal.

2 Transmission

The pain signal travels along the neurons through a series of channels that allow sodium ions back and forth across cell membranes. These channels, like Nav1.7, allow those charged particles across a membrane if the pain signal is strong enough. (If it isn't, the person feels no pain.)

3 Perception

When a pain signal reaches the spinal cord, it continues up to the brain, where the somatosensory cortex is primarily responsible for translating information about the intensity of the pain signal. The brain's motor cortex then generates the body's response—a shout of surprise, a jerk of a hand.

4 Aftermath

After an injury, even an innocuous stimulus—like a warm bath or a pat on the back—can generate a pain signal at the site of the original injury.

WHEN STEPHEN WAXMAN was a student at the Albert Einstein College of Medicine in the early 1970s, he became interested in pain—how people feel it, how the body transmits it, and how, as a future neurologist, he could learn to control it. Later in his career, after his father was in the final stages of agonizing diabetic neuropathy, he became obsessed with helping patients like his dad, who could find no relief from their pain. "We simply had to do better," he says.

Today Waxman is the director of the Center for Neuroscience and Regeneration Research at the Yale University School of Medicine. He is 71, with oval-shaped glasses that rest on the ridge of his nose when he reads and eyebrows that arch toward each other like upward-facing arrows. He's spent nearly half a century trying to chart the molecular and cellular pathways involving pain, and for much of this time Waxman was interested in the sodium channels found in the membranes of neurons—portals that allow charged particles to

flow in and out of the nerve cells. In particular, he believed that one of those sodium channels, Nav1.7, played an especially powerful role in how we experience pain. In his theory, a stimulus triggers the Nav1.7 channel to open just long enough to allow the necessary amount of sodium ions to pass through, which then enables messages of stinging, soreness, or scalding to register in the brain. When the trigger subsides, Nav1.7 closes. In those with faulty Nav1.7 channels, sensations that typically wouldn't register with the brain are instead translated into extreme pain.

That was his theory, anyway. As the Chinese researchers were finalizing their results, Waxman's team was searching for human subjects with some form of inherited pain, so they could sequence their sodium-channel genes and test the Nav1.7 hypothesis. Among the genes they wanted to sequence was SCN9A, which encodes Nav1.7 and determines whether it works. When Waxman learned that the Chinese scientists had discovered a link between SCN9A and erythromelalgia, he thought, "My God, we've been scooped." The Chinese scientists seemed to have solved a mystery he'd spent much of his career examining. As Waxman dug deeper into the report, though, his mood lifted. The Beijing group had linked SCN9A mutations to man on fire, but they didn't explain or uncover how they were linked. For Waxman and his team, there was still an opportunity to connect

the biochemical dots between faulty SCN9A genes, dysfunctional Nav1.7 channels, and man on fire. To do that, they needed to show how cells with mutant Nav1.7 channels would react to pain. Thanks to the Beijing group, they knew just where to look: families with erythromelalgia.

This is how Waxman first encountered Pam Costa's family. He reached out and began gathering DNA from 16 of her cousins, aunts, and uncles who suffer from erythromelalgia. He sequenced their genes and used them to create faulty Nav1.7 channels, which he added to cells; he then tracked how these channels responded to stimuli. The results not only demonstrated that SCN9A mutations made Nav1.7 channels more likely to open (meaning harmless stimuli often triggered feelings of pain) but also showed that when those channels opened, they did so for longer, amplifying the feeling of discomfort. It was the breakthrough Waxman had spent his life working toward: "We now had a fully convincing link from Nav1.7 to pain." This meant that if his team could somehow regulate or even turn off the Nav1.7 channel, they could regulate or even turn off how we experience certain kinds of pain.

STEVEN PETE WAS born in 1981 in the 2,200-person town of Castle Rock, Washington, near Mount Saint Helens. At around 6 months old, when Pete started teething, he chewed off part of his tongue. As he got older he would bang his head

against walls, not even stopping when it became swollen or indented. His parents made him wear a helmet, and they wrapped his arms and legs in long socks, securing them with duct tape, to prevent him from chewing away at his own limbs. His younger brother, Chris, had many of the same symptoms and all the same fearlessness. A day rarely passed when one of them didn't bleed or bruise.

When his parents took Pete to a local pediatrician, they explained that they did not think he felt any pain. Maybe neither son did. The pediatrician hadn't heard of a condition that prevented someone from experiencing pain, but after weeks of research, he found over 40 similar cases, including four siblings in Birmingham, England. The Pete boys were eventually diagnosed with congenital insensitivity to pain, and though the condition was likely passed down from one generation to another, there was no known cause, much less a cure.

Pete went on to live what appeared to be an ordinary life. In 2003, while working a security job at a mall, Pete met Jessica online. "We talked on the phone for hours," Jessica remembers. Pete told her about his painlessness, and at the time she didn't think much of it. "I guess I was like, 'That's pretty cool,' " she says now with a shrug. They married in 2005, and he started working at the Cowlitz Indian Tribe Health and Human Services

Department. All that time, he was unaware that just a few hundred miles north, outside Vancouver, British Columbia, a small company was inching toward a breakthrough in understanding his condition.

For years that company, which is now called Xenon Pharmaceuticals, had been working to understand rare single-gene disorders such as familial exudative vitreoretinopathy (which causes vision loss) in order to create drugs that could be used to treat more common disorders with similar symptoms (like other conditions involving vision loss). In 2001 the company heard about a family in Newfoundland in which four members could not feel pain. One of the sons "actually stood on a nail and it had gone through his foot," says Robin Sherrington, then senior director of biological sciences at Xenon. "He had no idea that it had happened until he got home and his parents saw it." No gene had yet been linked with their condition, but given the familial links in the Newfoundland case, Xenon researchers suspected it was genetic. They started hunting for more subjects.

Following news reports and word of mouth, Xenon tracked down and studied 12 families from around the world with insensitivity to pain. (The Petes were not among them. Outside their immediate community, few people knew about the brothers' condition.) For Sherrington, it was incredible that

these individuals and their genomes existed. Evolution should have weeded out most of their ancestors. “Feeling pain is protective,” Sherrington says. “They would not have felt certain noxious stimuli. They should not have survived.” By studying those 12 families’ genomes throughout 2001 and 2002, Xenon found a common trait among those with insensitivity to pain: mutations in a single gene, SCN9A, and the non-functioning sodium channel it encodes, Nav1.7.

“This single channel, when it is nonfunctioning in a human being, renders them unable to understand or feel any form of pain,” Sherrington says, summarizing the team’s initial findings. And if Xenon could develop a new drug that could somehow mimic this condition—“to inhibit the Nav1.7 channel to partially replicate that absence of pain,” he explains—then it could relieve people’s pain without any of the side effects of opioids.

It is rare for biology to deliver such a seamless positive-negative effect within a single gene. In man on fire patients, one SCN9A mutation leads to a hyperactive Nav1.7 channel, which causes extreme discomfort. In those with insensitivity to pain, another SCN9A mutation leads to an inactive Nav1.7 channel, which results in total numbness. Given that the teams at Xenon and Yale were working on opposite coasts, and on conditions that fell on opposite sides of the pain spectrum, they

only learned of each other's discoveries through published reports and journal articles. (Sherrington first learned about Waxman's study at Yale in 2004; Waxman only read about Sherrington's work at Xenon after the company published its results in 2007.) Both teams arrived at the same clinical destination from a totally different direction, surprised as anyone that people like Pam Costa and Steven Pete had anything in common. "I was overwhelmed when we saw both sides of the genetic coin," Waxman remembers. "SCN9A really is a master gene for pain."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When Steven Pete was 6 months old, he chewed off part of his tongue. Today he has a road map of scars across his body.CAIT OPPERMANN

NOT LONG AFTER their discovery, technicians at Xenon set to work putting Nav1.7 channels into tissue cultures, then testing each with a compound from their vast library of molecules. They were looking for a blocker that would shut off or at least turn down the faucet on Nav1.7 without affecting the body's other eight sodium channels. If you block Nav1.4, for -example, you might block muscle movement. Blocking Nav1.5 can inhibit the heart. Blocking Nav1.6 might impact the brain, causing double vision, confusion, balance problems, or even seizures. One by one, they experimented with thousands of combinations until they got a hit—a compound that plugs up Nav1.7 without major side effects. From that, researchers then created a drug called TV-45070 and conducted pilot tests on four erythromelalgia patients. In three of the four, "these individuals' pain responses were markedly blunted, and in one case we couldn't elicit pain at all," says Simon Pimstone, president and CEO of Xenon. Now TV-45070 is being used in a phase 2 clinical trial on 330 patients who suffer from nerve pain.

As for Waxman, he and his researchers at Yale helped Pfizer test five erythromelalgia patients with another Nav1.7 blocker. Scientists triggered the subjects' pain with heating blankets and asked them to rate their feelings before and after taking the drug. Last year Pfizer and Waxman's team

reported that three of the five patients described a decrease in pain with the blockers.

There are other, less conventional approaches under way too. At Amgen, a pharmaceutical company in Thousand Oaks, California, scientists test up to 10,000 molecules against Nav1.7 each week. In 2012 they discovered that the toxin of a Chilean tarantula can target Nav1.7 with minimal impact on other sodium channels. They've since engineered a synthetic version of the spider's toxin that's more potent than the original.

These findings, while significant, are still small steps forward. Over the next few years, with larger pools of patients suffering from arthritis, sciatica, shingles, and many other kinds of pain, researchers will continue to test the practical applications of these discoveries. "At least a half dozen companies are trying to develop sodium-channel blockers that preferentially or selectively block 1.7," Waxman says. And while obstacles remain—ensuring that only the Nav1.7 channel is affected; creating compounds that will allow some pain to register without cutting it off altogether; surviving the rigors of FDA approval—he and many others see a way forward.

WHICHEVER COMPANY GETS a prescription drug to market first, no progress would have been made without people like Costa and Pete, both of whom have taken part in studies for years.

Costa still remembers the day in 2011 when she

first visited Yale and met Waxman in person, after corresponding with him by email and phone for six years. She got a tour of the labs, meeting more than a dozen scientists from around the world who have been working to fix Nav1.7. While walking through the lab, Costa saw a row of computers. Waxman asked, “Do you want to see what happens with your sodium channels?” She did.

Waxman pulled up an image of a normal person’s sodium channel on the screen, the strings of amino acids that form it neatly folded. Then he pulled up another image: The protein here was a tangled clump, amino acids zigzagging almost off the screen. “This is you,” he said.

“I’ll never forget,” Costa says. Her entire life, she could only tell others how she felt—she could never show them. To see the medical proof of her pain for the first time, Costa says, “was the most validating experience in my entire life.”

At the end of my visit to her home, Costa rushes outside barefoot to catch me before I leave. As she stands on the grass in the 60-degree weather, her legs are already turning purplish with aggravation, and she pulls out a handwritten letter that she’s just found, from her cousin Helaine, who sent it in 1986. Helaine lived in Alabama and also had erythromelalgia. She was one of Costa’s favorite cousins. They looked alike. Helaine was divorced, living in a trailer. She never had access to the kind of medical treatment that Costa has received.

When Costa and her cousin talked, it was often about their mutual state of hurt. In 2015, Helaine died. Costa doesn't know how, exactly. She just knows her cousin never woke up.

Today when Costa resurrects memories of her own pain, they come with specific details and anecdotes—like that terrible day on the delayed plane, with the Smartwater bottles, or dunking her feet in gutter water as a child. Neurologists believe that, in the brain, pain is associated with memory-making processes, which explains the specificity of her stories. You don't remember every time you've gone running, but you remember the day you slipped on ice and broke your knee. Pain also leaves an imprint on our cellular memory—the experiences our bodies hold on to and may pass on to our children and grand-children—which some scientists believe may one day help explain why chronic pain can persist even after an injury has healed. We live with the echo of pain inside us, constantly reminding us to watch our step, back away from the stove, slow down. Someone could get hurt.

For Pete, recalling details of his injuries does not come easily, and his memories of growing up with his younger brother, Chris, are often vague too. Pete wishes Chris could help refresh his memory. "I relied on my brother a lot for retelling my stories and holding on to my memories," Pete says, breaking into tears. A lifetime of injuries caused so

much damage to Chris' body that a doctor told him he would likely end up in a wheelchair before he turned 30. Living the rest of his life incapacitated like that was too much for Chris to bear. Eight years ago, he hung himself in the barn on their parents' property. He was only 26. "It felt like losing … my life," Pete says.

He wipes his tears away and takes a deep breath. "I hope that one day parents will be able to make a choice for their children who don't feel pain, to activate that sodium channel so that their children can live a normal life." The work under way to target the Nav1.7 channel won't help Pete or others with congenital insensitivity to pain—there's no point blocking a portal that's permanently closed. Instead, the condition remains the most frustrating of mysteries: one with a known cause but no cure, passed down from one generation to the next.

When his daughter was born in 2008, Pete asked the doctor in the delivery room, "Does she feel pain?"

"They pricked her," his wife remembers. "And she cried." It felt something like relief.

Erika Hayasaki (@ErikaHayasaki) wrote about the mystery of a woman's missing memories in issue 24.04.

This article appears in the May issue. Subscribe now.