Quest for a cure: Gene therapy offers hope for children with rare form of Charcot-Marie-Tooth disease

Jocelyn Duff calls her daughter Talia's trisomy 21 "the first big surprise," discovered at birth on November 9, 2005.

"We thought our world had turned upside down, but quickly we fell head-over-heels in love with her. Never did we imagine that just ten years later we would receive a truly devastating diagnosis of CMT4J. The part of Talia that is Down syndrome has brought us joy more than anything else. CMT has brought us nothing but heartache and grief," says Jocelyn, who is a physician assistant. Her husband John Duff is a dean at a community college.

Charcot-Marie-Tooth (CMT) disease causes muscle weakness and wasting, starting typically with the feet and hands and moving inward. Jean Martin Charcot and his student Pierre Marie published the first description in 1886, as did Howard Henry Tooth in a dissertation.

[Editor's note: This story, written for Rare Disease Day on February 28, looks at a couple's efforts to help their daughter, and others like her, born with an extremely rare form of CMT.]

The first signs of CMT – low muscle tone, delayed gross motor milestones – would likely not have been missed in a child who didn't also have Down syndrome. Jocelyn describes what happened. "When Talia was about 3½, she got very sick with a flu-like illness. She recovered, but we noticed after that she was starting to lose milestones. Things she could do before, like getting up from sitting on the floor to standing, and crawling up the stairs — instead of using her arms and knees, she started using her chin like a tripod to help the rest of her body. She stopped using her arms over her head, and she was not as curious, no longer trying to reach up onto the tables and countertops."

The detour

The Duffs had been to Boston Children's Hospital early on to evaluate the Down syndrome, but in March 2010 they returned to check out Talia's weak muscles and loose joints. Tests for the most common CMT mutations were negative. Instead, doctors diagnosed chronic inflammatory demyelinating polyneuropathy (CIDP).

Initially that was good news, because intravenous antibodies and steroids can treat CIDP. They helped Talia a bit, but she plateaued and then whenever the steroids were withdrawn, she'd get weaker. "At her strongest, she was able to walk in a halting gait for about 10 steps. Mostly she got around holding onto a hand or push toys, and then later a little walker," Jocelyn told me. Still the doctors attributed her persistently poor muscle tone to the CIDP and Down syndrome. They were reluctant to try other immunosuppressants because the drugs have a slight risk of causing leukemia or lymphoma, and Down syndrome already raised those risks.

The diagnosis

In April 2015, a neurologist at Children's Hospital of Philadelphia revisited the possibility of CMT, suggesting tests for the rare forms – mutations in at least 30 genes cause the condition. Jocelyn and John realized that Boston Children's had suggested further genetic testing too. So Talia was tested in June, and in September came the bad news: CMT4J. Only a few dozen cases were known in the world.

And so began the nightmare, the shock and then the tumbling into the abyss of terror yet at the same time, facing a barrage of scientific information.

"I was devastated at first. I was almost fearful of my medical background, that I knew too much. The more research I did, the more I didn't sleep. But within a week we decided to find the people in the world who knew this disease better than anyone else," Jocelyn recalls.

They quickly found CMT expert Michael Shy, MD, attending neurologist at the Carver College of Medicine at the University of Iowa, and Jun Li, MD, PhD, who specializes in the 4J form at Vanderbilt University. Both book appointments 6 months out or longer, so the family visited the University of Iowa in January of 2016, and Vanderbilt in May.

Rare among the rare

Overall, CMT isn't that rare — in the US, 1 in 2500 (2.8 million) people has a form of it. It can be disabling but doesn't usually shorten life. My dentist developed it in his fifties and had to retire, as had his father. For some people, a CMT diagnosis comes almost as a relief that symptoms aren't due to ALS.

talia

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Most forms of CMT are dominant, inherited from an affected parent or a new mutation, and with adult onset. But most children who have the condition inherited recessive mutations, one from each carrier parent. The weakness in CMT4J is unusual in that it begins proximally, and is first noticeable as abnormal gait when a child attempts to toddle. Later sensory symptoms include inability to feel light touch or vibrations.

CMT4J accounts for only about a fifth of the 4% of CMT cases that are recessive. Trauma can hasten it. "Talia fell and fractured her leg in August 2015, and that's what really set things in motion. She's never really gotten back out of the wheelchair," Jocelyn says. Osteoporosis from the steroids used to treat CIDP

could have weakened her bones.

Drs. Li and Shy and their colleagues discovered CMT4J in 2007 in 4 patients with CMT among 95 who didn't have known mutations. The gene encodes a protein called FIG4, and is fascinating.

The patients, and others since identified, share a missense mutation (which substitutes one amino acid in the FIG4 protein for another) plus a truncating mutation (which shortens the protein). Yet not only do nearly all of them have the exact same missense mutation, in which a single DNA base change alters an isoleucine to a threonine, but the same sequence in that part of chromosome 6. The fact that the patients are unrelated means that this isn't a simple case of inheriting a chromosome chunk from a shared ancestor. A more likely explanation is that individuals with other *FIG4* genotypes either are never born, or do not have CMT symptoms so are never detected.

The mutation also shows up in other species – chimp, dog, zebrafish, mouse, fly, and worm — and in yeast FIG4 protein is involved in signaling. Such evolutionary conservation suggests importance.

Cells with abnormal FIG4 protein become riddled with fleets of expanding bubbles (vesicles) and then die. Specifically, the protein encodes an enzyme that removes a phosphate from a signaling molecule that dots the series of vesicles that ferry debris to the lysosomes, which are like cellular garbage disposals. The cell without functional FIG4 protein becomes like a city without cabs and trash collectors. It shuts down.

In CMT4J, certain neurons in the brain and spinal cord that control movement, as well as the glial cells that spool out the myelin sheath necessary for neurotransmission, fill with bubbles and die. As nerve cells are stripped of their fatty coats and their axons shrivel, signals to muscles fail, weakness spreads, and a little girl can no longer walk unaided.

A study from 2011 added 11 patients to the roster of those with CMT4J and calculated a carrier rate among northern Europeans of 1 in 1,000. That's rare, but not as rare as a "private" mutation in a single extended family. And the disease is surprisingly variable – in age of onset, pace, and severity – suggesting interactions with other genes. CureCMT4J is working with genetic testing labs to find more patients, and 10 families have found them though social media (@CureCMT4J for Facebook, Instagram, and Twitter).

A path forward

The last thing that Jocelyn and John expected when they traveled to Vanderbilt University to meet Dr. Li in May of 2016 was hope. "He said there's a possibility for a cure, and we were completely flabbergasted," Jocelyn recalls.

Dr. Li told the Duffs about Lori and Matt Sames, whose daughter Hannah had gene therapy for giant axonal neuropathy (GAN) last summer following 8 years of fundraising and planning the clinical trial. The doctor said he thought CMT4J would be treatable too. Lori is the Kevin Bacon of the rare disease community who has helped many panicked parents along the journey.

Jocelyn and John quickly discovered the world of parent advocates that began back in the 1990s with

They invented an oil to treat their son Lorenzo's adrenoleukodystrophy.
Odone's and Sames' stories.)

Jocelyn got right on it. "I emailed Lori when we were still in Tennessee and heard back the first day we returned. In late May 2016 we formed our organization and identified people and friends in the community who we knew had skills who could help us reach our goal of a small clinical trail with gene therapy. It all moved fast and yet glacially slowly at the same time."

Lori told the Duffs about my gene therapy book, and they contacted me. We met midsummer on Martha's Vineyard. And my husband Larry and I fell in love with Talia and Teaghan. The sisters are extraordinary – charming, polite, and articulate beyond their years. As Jocelyn and I discussed how to balance publicity and privacy, we were oblivious to Talia, who was playing with an iPhone. After, she showed us the film of our conversation about privacy – acknowledging the irony with a little half-smile. I gave her one of my beloved stuffed hippos, formerly known as brown hippo, whom she immediately renamed Cynthia.

Assembling the research team

The first meeting of Cure CMT4J: Advancing Gene Therapy for Rare Diseases was held September 24, 2016 in Bethesda, and spanned expertise from basic researchers to physicians to the designer of Hannah's gene therapy, Steve Gray, PhD, from the University of North Carolina. Another critical member of the fledgling team is Guy Lenk, PhD, a geneticist at the University of Michigan whom Jocelyn contacted after discovering that he had been studying *FIG4* mutations in the "pale tremor" mouse model for years.

The animal folds up like a “child’s pose” in yoga.

“Dr. Lenk was in his lab when I called and said “oh, I’d love to hear more but I have to be at lab on other side of campus, so send me an email about what you’re doing,” Jocelyn recalls. “I never expected to hear back, but in 24 hours I got a very long email letting me know how excited he was to finally know about someone who had this disease that he had been working on for so many years. He has 3 kids and that’s a part of the reason he feels so invested. He can’t imagine having to go through this with one of his children.”

That’s what drew Steve Gray to the GAN project and now to CMT4J – he’s a dad. The night before the September meeting, he said to Jocelyn, *“You do know you are hosting the world’s first ever symposium on CMT4J, don’t you?”*

Cathleen Lutz, PhD, is working on the mouse model that has human *FIG4* mutations at Jackson labs, thanks to National Institute of Neurological Disorders and Stroke funding announced last August for inherited peripheral neuropathies, including CMT. Increasing *FIG4* expression helps the mice, so demonstrating proof-of-concept for gene therapy should come fairly quickly.

Next will be toxicity testing and then a small clinical trial, within a year. But cost is an issue.

“The $1-3 million price tag that parent-driven rare disease foundations have to shoulder to get to a small clinical trial–to save their child’s life and other children’s lives–is by far the greatest obstacle. Ultra-rare diseases affect so few people that it’s difficult to attract pharma and biotech. But gene therapy is translatable to countless other rare diseases, and the beauty is the possibility of a one-time fix. We’re striving to make the path shorter, easier, and cheaper for the rare diseases to follow,” Jocelyn says. To help click here.

CureCMT4J has made astonishing progress, rounding up experts and devising a plan in under a year. And Steve Gray is ready to go. “ I was impressed by the organization and tenacity of the Duff family. What they’ve accomplished in a short amount of time is amazing, and it is inspiring for me to begin this journey with them towards a treatment.”

talia

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Meanwhile, Talia has lost the strength in her upper arms, and her parents are concerned about her breathing muscles. “The hardest thing is this is starting to affect her emotionally and we’re trying to find the right words to explain that we’re working hard to try to fix it,”

Jocelyn says.

And fix it they will. Hannah, 7 months post-gene therapy, can now sit unassisted, while Eliza O'Neill, who received gene therapy for Sanfilippo syndrome last spring, is working with therapists in an effort to regain skills and speech. She's training for a 5k run, zipping around her back yard!

Gene therapy's time has come, and these brave families and the researchers behind them are leading the way.

This article originally appeared on the PLOS DNA Science blog under the title Rare Disease Day 2017: Talia's Story and has been republished with permission from the author.

Ricki Lewis is a long-time science writer with a PhD in genetics. She writes the DNA Science blog at PLOS and contributes regularly to Rare Disease Report and Medscape Medical News. Ricki is the author of the textbook *Human Genetics: Concepts and Applications* (McGraw-Hill, 12th edition out late summer); *The Forever Fix: Gene Therapy and the Boy Who Saved It* (St. Martin's Press, 2013) and the just-published second edition of *Human Genetics: The Basics* (Routledge Press, 2017). She teaches Genethics online for the Alden March Bioethics Institute at Albany Medical College and is a genetic counselor at CareNet Medical Group in Schenectady, NY. You can find her at her website or on Twitter at @rickilewis