

MEDICAL DISPATCH JULY 21, 2014 ISSUE

## ONE OF A KIND

*What do you do if your child has a condition that is new to science?*

**By Seth Mnookin**



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*Until recently, Bertrand Might was the only known patient with a certain genetic disorder. His parents began searching for others.*

**M**att Might and Cristina Casanova met in the spring of 2002, as twenty-year-old undergraduates at the Georgia Institute of Technology. Cristina was an industrial-design major with an interest in philosophy; Matt was a shy computer geek obsessed with “Star Trek.” At first, Cristina took no notice of him, but the two soon became friends, and that fall they began dating. Within a year, they were married.

The couple had their first child, a son, on December 9, 2007, not long after Matt completed his Ph.D. in computer science and Cristina earned her M.B.A. They named him Bertrand, in honor of the British philosopher and mathematician

Bertrand Russell. After a few blissful weeks, the new parents began to worry. Matt and Cristina described Bertrand to friends as being “jiggly”; his body appeared always to be in motion, as if he were lying on a bed of Jell-O. He also seemed to be in near-constant distress, and Matt’s efforts to comfort him “just enraged him,” Matt says. “I felt like a failure as a father.” When the Mightys raised their concerns with Bertrand’s doctor, they were assured that his development was within normal variations. Not until Bertrand’s six-month checkup did his pediatrician agree that there was cause for concern.

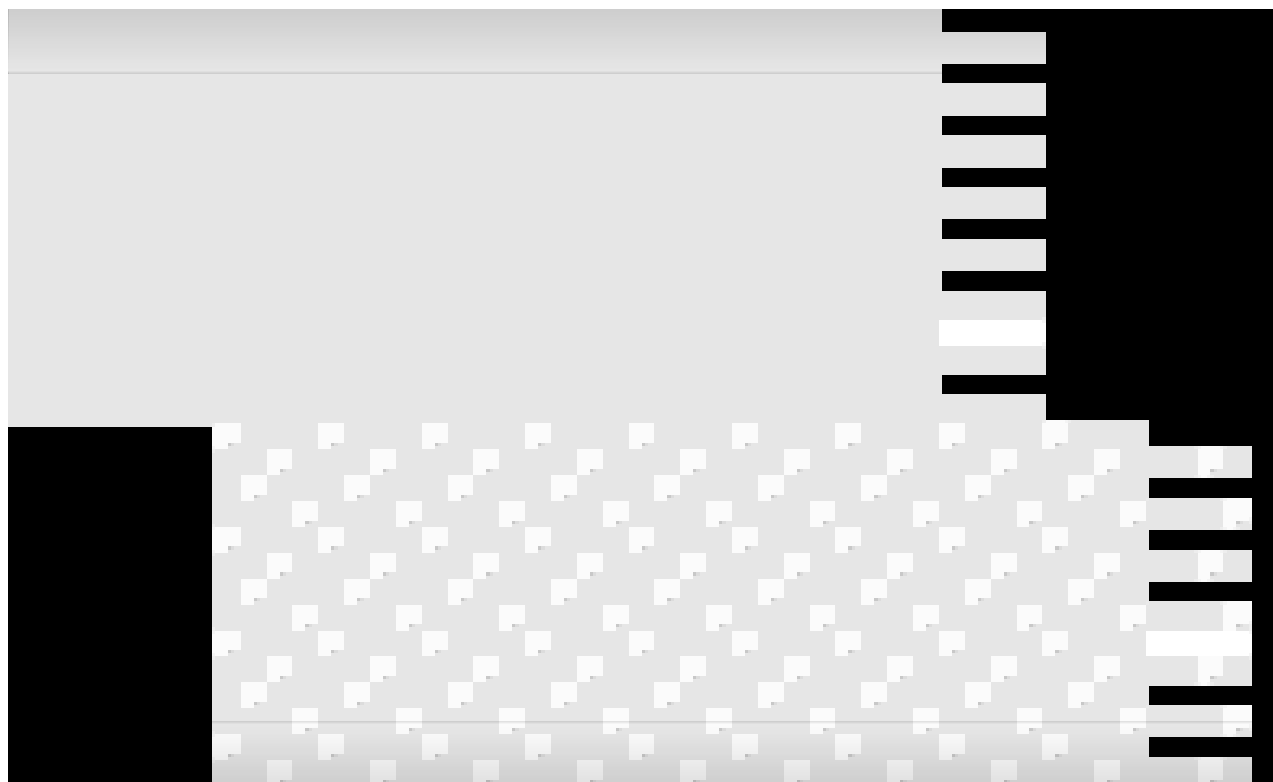
By then, Matt had a new job, as an assistant professor at the University of Utah’s School of Computing. It took two months to get Bertrand on the schedule of a developmental specialist in Salt Lake City, and the first available appointment fell on the same day as a mandatory faculty retreat. That afternoon, when Matt was able to check his phone, he saw that Cristina had left several messages. “I didn’t listen to them,” he told me in an e-mail. “I didn’t have to. The number of them told me this was really bad.”

Bertrand had brain damage—or, at least, that was the diagnosis until an MRI revealed that his brain was perfectly normal. After a new round of lab work was done, Bertrand’s doctors concluded that he likely had a rare, inherited movement disorder called ataxia-telangiectasia. A subsequent genetic screen ruled out that diagnosis. When Bertrand was fifteen months old, the Mightys were told that urine screening suggested that he suffered from one of a suite of rare, often fatal diseases known as inborn errors of metabolism. During the next three months, additional tests ruled out most of those ailments as well.

As Matt tried to get a foothold in his new job, Cristina struggled to care for a wheelchair-bound child whose condition seemed to worsen by the day. When Bertrand was hospitalized, she would stay by his bedside, often neglecting to eat; the constant stress contributed to osteoarthritis so severe that her doctor told her she’d need to have her right knee replaced. In April of 2009, the Mightys flew to Duke University, in Durham, North Carolina, to meet with a range of specialists,

including a geneticist named Vandana Shashi, whose clinical practice focusses on children with birth defects, intellectual disabilities, and developmental delays. After five days of tests and consultations, the Duke team told the Mightys that there was widespread damage to Bertrand's nervous system and that some of his odd behavior—wringing his hands, grinding his teeth, staring into space—was likely due to the fact that his brain appeared to be suffering from spikes of seizure-like activity.

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When Bertrand was a newborn, Matt joked to friends that he would be so relaxed as a parent that he wouldn't care which technical field his son chose to pursue for his Ph.D. In May of 2009, the Mightys closed Bertrand's college savings accounts so that they could use the money for medical care. That fall, Bertrand was rushed to the emergency room after suffering a series of life-threatening seizures. When the technicians tried to start an I.V., they found Bertrand's veins so scarred from months of blood draws that they were unable to insert a needle. Later that evening, when Cristina was alone with Matt, she broke down in tears. "What have we done to our child?" she said. "How many things can we put him

through?” As one obscure genetic condition after another was ruled out, the Mightys began to wonder whether they would ever learn the cause of their son’s agony. What if Bertrand was suffering from a disorder that was not just extremely rare but entirely unknown to science?

**I**n September of 2012, I visited the Mightys in Salt Lake City, where they lived in a two-story brick Craftsman bungalow. Matt wore a striped Brooks Brothers polo shirt and jeans; with a neatly trimmed beard and shoulder-length brownish-blond hair, he brought to mind Björn Borg of the late nineteen-seventies. Cristina, who is five feet ten, with porcelain skin and long black hair, greeted me with a hug and a wry smile.

In early 2010, the couple had decided to try to have a second child. This was a gamble: if Bertrand’s condition was indeed new to science, there was a chance that it was caused by a spontaneous, or *de novo*, mutation in the egg or sperm cell, and was not in Matt’s or Cristina’s DNA. On the other hand, if the condition had a genetic history, the Mightys could pass it on to other children. That summer, Cristina learned that she was pregnant, and on April 14, 2011, she gave birth to a girl, Victoria. Within minutes of the delivery, Matt and Cristina knew that their daughter was healthy; she moved with a fluidity that Bertrand never had. When I arrived at the Mightys’ house, Victoria was bouncing around and grabbing at her mother’s sleeve. “Victoria, you need to wait for Mommy to say hello,” Cristina said. To me, she added, “I had no idea how easy we had it with Bertrand.”

Bertrand, who was four at the time, was on the floor in the playroom, around the corner from the kitchen. He had round cheeks and a mop of brown hair. As with many children with genetic disorders, he also had some mild facial abnormalities: his eyelids drooped, and his nose was smaller than is typical, with an indentation on the bridge and slightly upturned nostrils. Two years earlier, the Mightys had noticed that Bertrand didn’t produce tears; every time he blinked it was as if sandpaper were scraping against his corneas. To keep the resulting scar tissue from causing permanent blindness, Matt and Cristina put medicated drops and

lubricating ointment in Bertrand's eyes every few hours, which made the skin around his eyes look as if it had been rubbed with Vaseline. Because Bertrand doesn't reflexively align his head with his body, his face was often pointed away from where he was trying to look, and he ground his teeth with such force that it sounded as though he were chewing on rocks. Yet the Mightys told me that, for all of his medical issues and his many hospitalizations, he seemed oddly immune to more ordinary ailments, such as colds and allergies.

I had brought each of the kids a small plush doll; when I placed Curious George on Bertrand's stomach, Victoria grabbed hold of Harry the Dirty Dog. When Cristina went to get something in the kitchen, she warned me not to let Victoria bite her brother. "She doesn't understand that Bertrand just can't interact with her the way everybody else can," she said. "So she gets frustrated and does everything she can to get his attention." Later, when I was lying on the floor with Bertrand and Victoria teetered into view, he seemed to flinch.

That evening, over pizza in their dining room, the Mightys told me about a pattern they had noticed when Bertrand was a year old. At first, they said, he seemed to represent a challenging problem for each new specialist to solve. But, as one conjecture after another was proved wrong, the specialists lost interest; many then insisted that the cause of Bertrand's illness lay in someone else's area of expertise. "There was a lot of finger-pointing," Cristina said. "It was really frustrating for us—our child hot-potatoed back and forth, nothing getting done, nothing being found out, nobody even telling us what the next step should be."

Then, in the summer of 2010, Vandana Shashi, the Duke geneticist, contacted the Mightys about a new research project that was exploring whether genetic sequencing could be used to diagnose unknown conditions. There was a chance, Shashi said, that by looking for places where Bertrand's genome differed from Matt's and Cristina's, Shashi and her colleagues would be able to pinpoint the cause of Bertrand's problems. The Mightys enrolled Bertrand in the study.

Genetic testing has been a part of regular medical practice since the nineteen-seventies; it enables doctors to search for mutations that cause known disorders, such as Tay-Sachs disease and sickle-cell anemia. Genetic sequencing, which entered the popular lexicon with the launch of the Human Genome Project, in 1990, allows for the opposite type of search: comparing the entire genomes of people who suffer from an unknown disorder, to see if they have genetic mutations in common. Sequencing also allows researchers to compare people who share genetic mutations, to see if they also share any previously unidentified disorders.

For years, sequencing was too expensive for common use—in 2001, the cost of sequencing a single human genome was around a hundred million dollars. But by 2010, with the advent of new technologies, that figure had dropped by more than ninety-nine per cent, to roughly fifty thousand dollars. To reduce costs further, the Duke researchers, including Shashi and a geneticist named David Goldstein, planned to sequence only the exome—the less than two per cent of the genome that codes for proteins and gives rise to the vast majority of known genetic disorders. In a handful of isolated cases, exome sequencing had been successfully used by doctors desperate to identify the causes of mysterious, life-threatening conditions. If the technique could be shown to be more broadly effective, the Duke team might help usher in a new approach to disease discovery.

For their study, Shashi, Goldstein, and their colleagues assembled a dozen test subjects, all suffering from various undiagnosed disorders. There were nine children, two teen-agers, and one adult; their symptoms included everything from spine abnormalities to severe intellectual disabilities. The researchers began by sequencing each patient and both biological parents—what's known as a parent-child trio. There are between thirty and fifty million base pairs in the human exome; the average child's exome differs from each of his parents' in roughly fifteen thousand spots. The researchers could dismiss most of those variations—either they corresponded to already known conditions, or they occurred frequently enough in the general population to rule out their being the cause of a rare

disease, or they were involved in biological processes that were unrelated to the patient's symptoms. That left a short list of about a dozen genes for each patient.

The next step was to search through databases to see if any of those candidate genes were already associated with a rare disorder; if so, the patient was probably suffering from an unusual form of a known disease. In three of the twelve subjects, that's exactly what the researchers found. Two others had de-novo mutations on the same gene, which meant that the Duke team had likely discovered the genetic basis of a new disorder. As a diagnostic tool, sequencing seemed to work. In several of the remaining cases, the technique helped identify genetic mutations that accounted for some, but not all, of a patient's symptoms; in others it simply determined that none of the identified candidate genes were involved in the patient's illness.

Then there was Bertrand. The Duke team thought it was likely that mutations on one of his candidate genes, known as NGLY1, were responsible for his problems. Normally, NGLY1 produces an enzyme that plays a crucial role in recycling cellular waste, by removing sugar molecules from damaged proteins, effectively decommissioning them. Diseases that affect the way proteins and sugar molecules interact, known as congenital disorders of glycosylation, or CDGs, are extremely rare—there are fewer than five hundred cases in the United States. Since the NGLY1 gene operates in cells throughout the body, its malfunction could conceivably cause problems in a wide range of biological systems.

*“Where? Where?”*

In September of 2011, Goldstein sent an e-mail to Hudson Freeze, a glycobiologist at Sanford-Burnham Medical Research Institute, in La Jolla, California, and the foremost authority on CDGs. Goldstein told Freeze that he believed he'd found a child suffering from a glycosylation disorder that had never before been seen. That November, Goldstein shipped Freeze a supply of Bertrand's cells. Freeze was unable to find evidence of a functioning NGLY1

gene. He soon reported back: Goldstein's hypothesis—that Bertrand suffered from a new glycosylation disorder caused by NGLY1 mutations—was almost certainly correct.

On May 3, 2012, nearly two years after the sequencing study began, the Might's met with the Duke team in an examination room of a children's hospital in Durham. Shashi explained that Bertrand's condition was probably not caused by a de-novo mutation, as the Might's had thought; rather, Matt and Cristina each had a different NGLY1 mutation, and Bertrand had inherited both. Matt and Cristina had only to look at their daughter playing on the floor to realize how lucky they'd been: Victoria had had a twenty-five-per-cent chance of being born with the same disorder as Bertrand. (Later testing showed that she had not inherited either parent's NGLY1 mutation.)

Goldstein, who was meeting the Might's for the first time, spoke next. He explained that, until other patients with the same condition were found, there was a chance, however remote, that Bertrand's disorder was caused by something else. Moreover, without additional cases, there was virtually no possibility of getting a pharmaceutical company to investigate the disorder, no chance of drug trials, no way even to persuade the F.D.A. to allow Bertrand to try off-label drugs that might be beneficial. The Duke researchers estimated that there might be between ten and fifty other patients in the country with Bertrand's condition, which would make it one of the rarest diseases in the world. "That's basically what they left us with—'You need more patients,' " Matt told me. "And I said, 'All right, we'll get more.' "

**A**s recently as a decade ago, researchers could spend years trying to find a second case of a newly discovered disease. When a paper describing two or more cases finally appeared in one of hundreds of medical journals, it still had to be read and remembered by clinicians in order for awareness of the disorder to spread. Genetic sequencing has dramatically sped up the process, theoretically enabling a child like Bertrand to receive a tentative diagnosis in just weeks or



months.

But a number of factors prevent sequencing from reaching its full diagnostic potential. As a matter of protocol, researchers typically avoid sharing test results with subjects until the research is published; the Mightys didn't learn that NGLY1 was the likely cause of Bertrand's condition until months after the Duke team reached that conclusion.

Researchers also hesitate to share data with potential competitors, both to protect their funding and to insure that they get credit for their work. In their attempt to confirm Bertrand's condition, the Duke team searched for NGLY1 mutations in everyone who had been sequenced at Duke, and also combed through an exome database maintained by the National Heart, Lung, and Blood Institute. This gave them access to the genetic data of more than six thousand people—a small fraction of those around the country who have been sequenced. Isaac Kohane, a pediatric endocrinologist at Boston Children's Hospital, told me that many researchers believe, incorrectly, that patient-privacy laws prohibit sharing useful information.

“If you want to be charitable, you can say there's just a lack of awareness” about what kind of sharing is permissible, Kohane said. “If you want to be uncharitable, you can say that researchers use that concern about privacy as a shield by which they can actually hide their more selfish motivations.”

If a team hunting for a new disease were to find a second case with the help of researchers from a competing lab, it could claim to have “solved” a new disease. But it would also have to share credit with competitors who may have done nothing more than grant access to existing data. When I asked Shashi if she could imagine a scenario that would result in one research team's publishing a paper with data from a different research group working on a similar project, she said, “Not that I can think of.”

David Goldstein added, “It’s not an overstatement to say that there are inherent conflicts of interest at work.” Daniel MacArthur, a genetics researcher at Massachusetts General Hospital, is even more blunt. “It’s an enormous deal,” he told me. “And it’s a big criticism of all of us, but it’s a criticism we all need to hear. The current academic publication system does patients an enormous disservice.”

The National Institutes of Health is taking steps to promote the sharing of genomic data about rare diseases. In January, the agency awarded nine million dollars to researchers at Harvard Medical School to coordinate a nationwide network of centers for rare diseases. Each center will mirror the type of work being done by the N.I.H.’s Undiagnosed Diseases Program, in Bethesda, Maryland, and each will be required to share its data with the others. Kohane, who develops software to make it easier for institutions to share information, will organize the initiative. “It’s creating an ecosystem that I think represents the medicine of the future,” he said.

**T**he Mightys couldn’t wait for the culture of scientific research to change: they had been told that Bertrand could have as little as a few months left to live. The same day that they learned about NGLY1, they began plotting ways to find more patients on their own. Several years earlier, Matt had written a blog post, called “The Illustrated Guide to a Ph.D.,” that became a worldwide phenomenon; it was eventually translated into dozens of languages, including Serbian, Urdu, and Vietnamese. The popularity of the post, combined with Matt’s rising profile among computer programmers, meant that almost anything he put online was quickly re-posted to Hacker News, the main social news site for computer scientists and entrepreneurs. He decided to use his online presence to create what he referred to as a “Google dragnet” for new patients.

For the next three weeks, Matt worked on an essay that described Bertrand’s medical history in clinical detail. Matt called the result, which was more than five thousand words long, “Hunting Down My Son’s Killer,” and on May 29, 2012, he posted it to his personal Web site. It began: “I found my son’s killer. It took three

years. But we did it. I should clarify one point: my son is very much alive. Yet, my wife Cristina and I have been found responsible for his death.”

Half an hour after Matt hit “publish,” Twitter began to light up. By the end of the day, “Hunting Down My Son’s Killer” was the top story on Reddit. The next morning, an editor from Gizmodo, a tech blog owned by Gawker Media, asked Matt for permission to republish the essay. In less than twenty-four hours, the post had gone viral. The more it was shared and linked to, the higher it rose in search engines’ rankings, and the easier it would be for parents of other children to find.

Eight days later, the co-founder of a commercial genetic-testing company in San Francisco e-mailed the piece to a friend, Matt Wilsey. The Wilseys are one of the most prominent families in San Francisco, famous both for their philanthropic generosity and for the complicated marital life of Alfred Wilsey, Matt’s grandfather, who died in 2002. Matt Wilsey, who is thirty-six, graduated from Stanford in 2000. After working on George W. Bush’s election campaign and spending five months as an aide in the Pentagon, he returned to Northern California to work as a tech entrepreneur. In the fall of 2007, he married a former classmate at Stanford. Two years later, Matt and Kristen Wilsey had their first child, a girl they named Grace.

Last fall, I met Matt Wilsey at the annual conference of the Society of Glycobiology, in St. Petersburg, Florida. He has a wide smile and black hair that is flecked with gray. Over lunch at an outdoor café, he told me that Grace’s problems began before she was born: she was delivered by emergency Cesarean section after her heartbeat dipped dangerously low. Almost immediately after Grace’s birth, he and Kristen began to worry. “She just seemed out of it,” Matt said. Within days, Grace was admitted to the neonatal I.C.U. Her doctors collected a number of samples, including cerebrospinal fluid from a lumbar puncture. Three weeks later, when she was discharged from intensive care, the Wilseys still did not know what was causing their daughter’s problems.

In the months to come, the Wilseys received one piece of bad news after another. They were told that Grace was not growing sufficiently, that she had low muscle tone, and that there were signs that she was suffering from developmental delays. “It was a continuous grief process,” Kristen told me last December. When Grace was around six months old, the Wilseys met Gregory Enns, the director of the biochemical-genetics program at Stanford’s Lucile Packard Children’s Hospital. Before long, Enns, whose research focusses on mitochondrial disorders, was functioning as Grace’s de-facto pediatrician. (Mitochondria are the so-called “power plants” within cells that generate most of the body’s energy.)

During the next two years, Matt Wilsey used his networking skills to set up meetings with specialists at institutions around the country, including Baylor College of Medicine, in Houston; the Broad Institute of M.I.T. and Harvard; Johns Hopkins; Columbia; and the University of California, San Francisco. “We’d talk to one great doctor and say, ‘Who’s the best liver person in the country?’ ” he told me. “And then that would lead us to one person and then that person would lead us to two more. That’s just kind of how we did it.”

When the Wilseys first read Matt Might’s blog post, it didn’t occur to them that Grace and Bertrand might be suffering from the same disease. “Their phenotypes were too different,” Matt Wilsey said. Grace could crawl and pull herself up to a standing position, while, at age four, Bertrand wasn’t even able to roll over. She also had a vocabulary of more than two dozen words, and was able to follow one-step directions, while Bertrand could only make indistinguishable grunts. The most striking difference, Kristen said, had to do with Bertrand’s seizures. “At the time, we didn’t think Grace was having seizures,” she said. “And so we thought, Oh, no, no—she’s completely different from Bertrand. So we just ruled it out.” (Later testing showed some abnormal activity in Grace’s brain.)

By the spring of 2012, Grace’s genome had already been sequenced twice: once at Baylor and once at Stanford. As it happened, Stanford geneticists had identified NGLY1 as a candidate gene, but they set it aside because Enns believed that

Grace was suffering from an unidentified mitochondrial disorder. By the time Grace turned three, that October, the Wilseys had consulted more than a hundred researchers around the world, yet they were still without a diagnosis. Around this time, Kristen said, “I told Matt, ‘I don’t want to do this anymore. I’m just exhausted.’ ”

Matt asked Kristen if they could make one final trip to Baylor, and in February of 2013 the Wilseys took Grace back to Houston. They were introduced there to a young geneticist named Matthew Bainbridge. When he looked through Grace’s genome, he ignored mitochondrial genes entirely—“I figured Stanford had that covered,” he told me—and soon narrowed his search to three genes: one known to cause intellectual disability, one associated with a movement disorder, and NGLY1. “NGLY1 stuck out, because I’d never seen it before,” Bainbridge said. When he searched a Baylor database of more than seven thousand people, he found that a handful of them had a single NGLY1 mutation, but none had two.

Bainbridge next looked online for information about the gene. He quickly found “Hunting Down My Son’s Killer.” After reading about one of Bertrand’s more unusual symptoms, Bainbridge e-mailed the Wilseys a question: Did Grace produce tears? Kristen replied almost immediately: Grace could produce tears but not very often. Then, four and a half hours later, Kristen wrote back, “After thinking about it this afternoon, it is actually very rare that Grace will make a tear. I have only seen it a handful of times in her three years.” As soon as Bainbridge read that, he told me, he thought, “Oh, we fucking got it.”

*“And for an extra fourteen hundred dollars I’ll stop touching your arm.”*

On March 19, 2013, Bainbridge sent the Mightys an e-mail. He told them that he believed he had identified a second case of Bertrand’s disorder, and that Matt’s blog post had been instrumental in his finding it. The next day, the Mightys received an e-mail from Matt Wilsey. “I wanted to connect with you directly as you have heard about my daughter, Grace,” Wilsey wrote. “We are so thankful to find you.”

As it happened, Grace Wilsey was not the first new NGLY1 case that the Mightys had uncovered. On June 3, 2012, five days after “Hunting Down My Son’s Killer” was published, Joseph Gleeson, a neurogeneticist at the University of California, San Diego, e-mailed Hudson Freeze, the Sanford-Burnham glycobiochemist that the Duke team had consulted on Bertrand’s case, to ask him if he’d seen the post. Gleeson told Freeze about Murat Günel, a Yale neurosurgeon and geneticist who had sequenced a pair of severely disabled siblings from Turkey, each of whom had two NGLY1 mutations. In August, Freeze confirmed that the siblings were suffering from the same condition as Bertrand.

Then, the following March, nine days before the Mightys learned of Grace Wilsey, they were contacted by a researcher working with an Israeli medical geneticist named Tzipora Falik-Zaccari, who said that their group had also identified siblings with NGLY1 mutations. In May, the Mightys received an e-mail from Pam Stinchcomb, a woman in Georgia who had just learned that two of her daughters had NGLY1 mutations: Jordan, sixteen, who had been thought to have cerebral palsy, and Jessie, who was two. Later that month, the Mightys heard from a doctor in Delaware with a twenty-year-old patient in whom sequencing had just revealed two NGLY1 mutations.

The most remarkable discovery came in June. Cristina Might received an e-mail from a German woman who was living in India with her husband and their severely disabled two-year-old son. (She asked that her name be withheld.) The woman had been looking online for information about how better to control her son’s seizures when she came upon a blog post that Cristina Might had written about Bertrand when he was two. Within weeks, the woman had sent her son’s cells to Freeze, who confirmed that the boy was, in all likelihood, an NGLY1 patient—the first person to be identified before he had even been sequenced. Freeze told me that if someone had predicted a year earlier that the Mightys would identify new patients through blog posts alone, “I’d have said, ‘Ah, come on, you can’t do that.’ ”

Thirteen months after Bertrand Might became the first NGLY1 patient in the world, the Might family had helped identify nine more cases. “There were more kids—it wasn’t just our son,” Cristina told me one afternoon in her kitchen. “There are parents like us, who have been lost and confused and jerked around.” Matt nodded. “Even if Bertrand dies, there are kids out there that are just like him,” he said.

Last November, the Might family moved to a new home, in Federal Heights, an upscale Salt Lake City neighborhood at the foot of the Wasatch Range. Bertrand was about to turn six, and soon it would be difficult to carry him up and down stairs. The new house had several amenities for a family with a handicapped child, including an entrance at street level, wider hallways, and an elevator.

I visited the Might family three days after they moved. When I arrived, Cristina told me that she was two months pregnant. (Six weeks later, prenatal testing showed that the fetus had not inherited either parent’s NGLY1 mutation.) Most of the family’s possessions were still in boxes, but a small alcove off the kitchen had been set up as Bertrand’s playroom, where, six days a week, he would spend up to three hours with a physical therapist. The room resembled an infant’s nursery, with a stock of diapers, changing pads, and an assortment of soft toys. Bertrand seemed different from the way he’d been during my last visit, fourteen months earlier. He had become much more expressive: he furrowed his eyebrows and scrunched his nose and, when he was pleased, grinned broadly and let out what the Might family called a “happy hoot.” He was also much more coordinated, and, with considerable effort, he could roll over and push himself up to a sitting position. To everyone’s surprise, he had even learned to communicate preferences between objects by pointing or leaning toward the one he wanted to play with.

The Might family attribute their son’s improvement to several factors. Because his diagnosis revealed that Bertrand was not suffering from a seizure disorder, he was no longer on a severely restrictive diet or receiving painful, sometimes dangerous

treatments such as steroids. Two over-the-counter supplements seemed to be helping, as well. The first was a highly concentrated cocoa extract. “It sounds like a scam, except there’s research showing that cocoa actually improves cells’ energy production,” Matt told me. The second was N-acetylcysteine, or NAC, an amino acid that helps produce a naturally occurring antioxidant. Bertrand hadn’t been admitted to the hospital since he’d had his tonsils removed, nearly a year and a half earlier—a stark contrast to 2010 and 2011, when he’d been rushed to the hospital more than a dozen times.

In the past year, the Mightys and the Wilseys have formed a coalition dedicated to researching their children’s condition. Patient-advocacy groups have been around for decades, but it’s extremely unusual for one or two families to single-handedly direct an international research agenda. It helps that both the Mightys and the Wilseys have family money. (Matt Might’s father is the president and C.E.O. of Cable One, the cable-television division of the former Washington Post Company.) Since 2012, the Mightys have devoted more than a hundred thousand dollars a year to NGLY1-related research in Hudson Freeze’s lab, while the Wilseys have spent two million dollars funding researchers around the world.

Still, one of the Mightys’ and the Wilseys’ biggest accomplishments to date required no money at all: they successfully pushed for the clinicians and researchers with whom they were working to collaborate on a single, all-encompassing clinical report on the disease. The paper, written by Gregory Enns, contained contributions from thirty-three authors, including Matthew Bainbridge, Hudson Freeze, David Goldstein, and Vandana Shashi. Eighteen departments from eleven institutions in the U.S., Canada, Germany, and the U.K. were represented. After the paper was all but completed, one of the challenges in getting it published was agreeing on the order in which the authors’ names would appear.

Neither Murat Günel, at Yale, nor Tzipora Falik-Zaccai, in Israel, joined in the publication. Günel had been invited but his research team had already submitted



a paper elsewhere. (It was later rejected.) Freeze told me that Falik-Zaccai had stopped responding to his e-mails, and that when he inquired about the specific NGLY1 mutations of Falik-Zaccai's patients she had all but told him that he would find out what he wanted to know when he read about it in a journal. (When I contacted Falik-Zaccai, in March, she denied this account and said that she would be delighted to work with the other researchers.)

The Might and Wilsey collaboration has also prompted the N.I.H. to study the condition. This past spring, the agency began inviting NGLY1 patients to come to Bethesda for a week of tests and examinations. Bertrand was the first child to take part, and his participation has already yielded a potentially important insight. As Bertrand and the other NGLY1 patients illustrated, the inability to get rid of malfunctioning glycoproteins has devastating consequences, especially for developing infants. But Sergio Rosenzweig, an N.I.H. immunologist who met with Bertrand, thinks it might confer one advantage, as well.

Rosenzweig recently published a paper describing two siblings who rarely got viral infections, despite being severely lacking in antibodies. Rosenzweig and his colleagues discovered that the siblings suffer from an ultra-rare congenital disorder of glycosylation known as CDG-IIb. The puzzle began to make sense. Since CDG-IIb patients have trouble making glycoproteins, it is possible that the siblings had some protection from a class of viruses that are known to depend on those molecules to spread within the body. (There have been only two other known CDG-IIb patients. One is now deceased and the other does not seem to be able to ward off infection.)

When Rosenzweig learned that Bertrand rarely caught colds, he couldn't hide his excitement: perhaps Bertrand was able to avoid infections because viruses got stuck after attaching themselves to his defective glycoproteins. Rosenzweig is quick to emphasize that until he can test other NGLY1 patients he won't know if his hypothesis warrants further exploration. But if it bears out, he says, it could point to a way to treat acute infections ranging from influenza to Ebola

hemorrhagic fever.

“We try to help these patients with rare diseases,” he told me. “Sometimes we are able to, and sometimes we’re not—but these children are teaching us a lot we didn’t know about ourselves. And we can use what they are teaching us to help other people.”

**O**n a Thursday night this past February, the families of five NGLY1 patients met at the restaurant of the Estancia La Jolla Hotel and Spa, outside San Diego. They were in town for the annual Rare Disease Symposium at Sanford-Burnham, which Freeze had organized. This year’s meeting was devoted entirely to NGLY1. Kristen Wilsey and Grace were the first to arrive at dinner. A few minutes later, the German woman, her husband, and their son, all of whom had travelled from India, entered. Next came the Mightys, followed by Kaylee Mayes, a four-year-old from Washington state who had received a diagnosis of NGLY1 disorder the previous month, and her parents, Kelsey and Daniel. Pam and Tony Stinchcomb and their youngest daughter, Jessie, arrived last. (The Stinchcombs’ older daughter, Jordan, was too sick to travel.) The trip from Atlanta was just the second time that Tony Stinchcomb had been on a plane. “I’m not much into flying,” Tony, a large, affable man with a gray goatee, told me. “But this seemed worth it.”

That night marked the first time that two unrelated NGLY1 children were in the same room at the same time. For several hours, over ahi sliders, fish tacos, and empanadas, the families shared stories about what it had been like to care for children who were severely ill for reasons their doctors didn’t understand. Just before everyone went back to their hotel rooms for the night, the German woman, fighting back tears, told me, “It feels like we’ve come home, but to a home we didn’t know we had.”

The next morning, five researchers presented their work on NGLY1 to around ninety people, a group that included the families, a handful of their friends, and

scientists from as far away as Japan. Both Matt Might's and Matt Wilsey's parents were there, as were Michael Gambello, an Emory University geneticist who had sequenced the Stinchcombs, and Gregory Enns. Cristina Might, who was five and a half months pregnant at the time, looked on from the front row. (In June, she gave birth to a healthy boy.) Bertrand, who was the most severely disabled of all the children there, sat nearby in his wheelchair, humming to himself, as Kaylee amused herself on the floor.

That afternoon, Matt Might gave a talk titled "Accelerating Rare Disease." After describing the effects of his blog post, he told the crowd that it was inevitable that parents of children with other newly discovered diseases would form proactive communities, much as he, Cristina, and the Wilseys had done. Vandana Shashi believes that such communities represent a new paradigm for conducting medical research. "It's kind of a shift in the scientific world that we have to recognize—that, in this day of social media, dedicated, educated, and well-informed families have the ability to make a huge impact," she told me. "Gone are the days when we could just say, 'We're a cloistered community of researchers, and we alone know how to do this.'" ♦

*Seth Mnookin is an assistant professor of science writing at M.I.T. His most recent book is "The Panic Virus: The True Story Behind the Vaccine-Autism Controversy."*

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