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# DIY DNA: One Father's Attempt to Hack His Daughter's Genetic Code

By Brendan I. Koerner 01.19.09


Beatrice Rienhoff is sick. A flaw hidden deep within her genes has baffled the best doctors in the world. So her father is combing through her DNA, one nucleotide at a time.
*Photo: Ye Rin Mok*

**"Do you want to see my flashlight?"** Five-year-old Beatrice Rienhoff bounds into the foyer of her family's home, sporting a blond Prince Valiant haircut and a bashful smile. She plops down on the floor and starts unscrewing the top of her toy flashlight, eager to show off its innards. Her hazel eyes brim with curiosity. Beatrice looks like any other healthy preschooler until she leaps into her father's arms for a hug. As she does, her shorts push up a bit, exposing her legs. They are, as her dad calls them, "little bird legs," entirely lacking in visible muscle. There is no curve of calf or quadricep, just twiggy bones pressed against flesh. It's surprising that Beatrice can get around so fluidly on such gaunt limbs.

After climbing down from the embrace, Beatrice removes her sneakers, revealing soft orthopedic braces wrapped around slender, stretched-out feet. Her older brother MacCallum, perched on a nearby sofa, suggests it may be time for a new pair of braces. Hugh, whose neat gray hair and ruddy skin give him a J. Crew vibe, squats to conduct a close inspection. He quickly sees that MacCallum is right—the balls of Beatrice's feet jut beyond the edges of the braces.

This is a minor issue compared to the serious health problems that have vexed Beatrice during her brief life. She was born with a rare genetic disorder, and at one point the Rienhoffs feared she might never walk, let alone run and skip. Physical therapy has helped tremendously, but even today Beatrice struggles to climb stairs, and her muscles remain alarmingly frail. Hugh also has good reason to worry about her heart—the disease could dilate the aorta, with fatal results.

Nobody can say for sure what lies ahead for Beatrice, because no one really knows what's wrong with her. Hugh has taken her to see some of the nation's finest medical experts in hopes of finding a diagnosis, but the doctors have all been baffled by the girl's strange array of symptoms. This has left her in a sort of diagnostic purgatory, making her illness all the more fearsome and traumatic.

Families facing this kind of medical uncertainty are often paralyzed by their distress. But rather than give in to his anguish, Hugh Rienhoff made an extraordinary decision: He would dig into Beatrice's genetic code and find the answer himself. A biotechnology consultant by day, Rienhoff has been an avid student of clinical genetics since he earned his medical degree nearly 30 years ago. Now he has used this expertise to transform his Bay Area home into a makeshift genetics lab. Surrounded by his children's artwork and bookshelves loaded with his wife's political literature, Rienhoff set about sequencing a number of Beatrice's genes, preparing samples using secondhand equipment and turning to public databases to interpret the results. On the desk in his attic workspace are a pair of white binders stuffed with charts detailing 20,000 of Beatrice's base pairs; the data for nearly 1 billion can be accessed from a nearby PC. Whenever he has a spare moment, Rienhoff sequesters himself in this cluttered, carpeted room and sifts through his daughter's DNA, one nucleotide at a time. He is hunting for the single genetic quirk responsible for Beatrice's woes—an adenine in place of a guanine, perhaps, or an extra cytosine in a key location. If he can find the culprit, he figures, maybe he can find a treatment, too.

It is an overwhelming task. "The human genome," Rienhoff says, "is still a wilderness." Despite all the well-publicized advances of the past two decades, precious little is known about the genetic variants that cause even the most common maladies, to say nothing of the rare, sometimes one-of-a-kind diseases that afflict children like Beatrice. As a result, up to 40 percent of special-needs kids will never receive a precise diagnosis. "It's agonizing to have a child with a degenerative disease and not even be able to figure out what it is or what's causing it or what the course of it will be," says David Clapham, a friend of Rienhoff's and a research professor at Children's Hospital Boston, whose son Ben died of an undiagnosed neurological disorder at the age of 9. "It's like winning the lottery in reverse."

Not everyone thinks Rienhoff's quest is worthwhile. Some geneticists believe that desperation is leading him to a dead end. Rienhoff understands this view, and at times even suspects that his doubters—some of whom are good friends—may be right. But even if his odds of success are minuscule, he argues, there is nothing to be gained by standing on the sidelines. In his view, parents must be their children's greatest advocates, the people whose love keeps them pushing for answers when the medical establishment has essentially surrendered. And to Rienhoff, being the father who never relents is itself a noble goal. "In the end," he says, "this is simply about the extra ways a daddy can love his little girl."

Hugh Rienhoff with his daughter, Beatrice.
*Photo: Ye Rin Mok*

**Family life came late for Rienhoff**, after decades devoted to science. He earned an MD from Johns Hopkins University, where his mentor was Victor McKusick, arguably the greatest medical geneticist of the 20th century. After residency, Rienhoff took a post as a genetics researcher at the Fred Hutchinson Cancer Research Center in Seattle before entering the business realm. He spent most of the 1990s as a partner at New Enterprise Associates, a venture capital firm, then founded DNA Sciences, a Silicon Valley company that developed genetic screening tools. He left DNA Sciences in 2001, two years before the company filed for Chapter 11 and was sold off; today he advises biotech startups on drug-development strategies.

Rienhoff married Lisa Hane, a union organizer, in 1998. Later that year she gave birth to their first son, Colston, who was followed by a brother, MacCallum, two and a half years later. By early 2003, Hane was pregnant yet again. She was 41, her husband 50.

Because older parents (both men and women) are more likely to have children with genetic disorders, Hane's pregnancy was closely monitored. An early fetal ultrasound revealed a large nuchal translucency—a thickness at the back of the neck that indicates an increased likelihood of chromosomal abnormalities such as Down syndrome. But encouraging results from other tests, including amniocentesis and an electrocardiogram, allayed the family's fears.

Beatrice was born that December, and seconds after her birth, Rienhoff knew something was wrong. Her fingers were tightly clenched, there was a big port-wine stain splashed across her face, and her feet were abnormally long. Long feet are indicative of Marfan syndrome, a connective-tissue disorder that Rienhoff had often encountered while training at Johns Hopkins. Marfan patients grow up to be unusually tall and long-limbed, with dangerously enlarged aortas. (Historians have long debated over whether Abraham Lincoln suffered from the disease.)

Rienhoff's dread subsided, however, after receiving good news from the delivery-room staff: Beatrice had aced the Apgar test—an exam that measures a newborn's respiration and reflexes—and her height and weight were normal. Relieved, Rienhoff let himself get swept up in the elation of becoming a father for the third time.

Ten days after the birth, Rienhoff and Hane took Beatrice to an orthopedic surgeon to evaluate her contracted fingers. The doctor noted that the girl seemed to have some of the symptoms of Beals syndrome, a condition related to Marfan but far less serious and caused by a slightly different mutation—the alteration responsible for Marfan is located in the gene for fibrillin-1 (*FBN1*), whereas the Beals alteration is in the gene for fibrillin-2 (*FBN2*).

After carefully observing Beatrice over the next few days, Rienhoff wondered whether the diagnosis fit. Her fingers aside, the girl was quite flexible; such agility is never found in Beals patients, who cannot extend their long joints. Rienhoff eventually emailed the syndrome's namesake, orthopedic surgeon Rodney Beals, who concurred that Beatrice probably didn't have the disease

At around eight weeks, Beatrice's limbs and torso were still almost entirely devoid of muscle tone. By the 12-week mark, she exhibited virtually no head control when propped upright. "She was supposed to firm up by about three months, but she just stayed limp," Hane says. Worst of all, Beatrice also wasn't putting on any weight.

In April 2004, Beatrice was admitted to the hospital for "failure to thrive," a catchall condition. The medical team took the unusual step of ordering an MRI of the infant's head, to determine whether a neurological deformity was causing her muscle-tone issues. But her brain was fine.

With the doctors hopelessly bewildered, Rienhoff hit the books. "Hugh's way of dealing with the stress was to say, 'Let's figure out what's going on,'" Hane says. "He's a very action-oriented person; he's a problem solver." The family attic soon brimmed with dog-eared copies of *Science* and primers on genetic syndromes.


Rienhoff's attic doubles as a genetics lab.
*Photo: Ye Rin Mok*

For a while, Rienhoff wondered whether an intestinal parasite was gobbling up Beatrice's food before she could digest it. Later he suspected that she might have a mitochondrial disease. He started her on a regimen of coenzyme Q10, an over-the-counter treatment. There was no improvement.

Rather than visit yet another Bay Area physician, Rienhoff emailed an acquaintance from his Johns Hopkins days, David Valle, director of the Institute of Genetic Medicine at the university. Valle agreed to see Beatrice, so father and daughter flew to Baltimore in March 2005.

Beatrice was examined by Valle and a bow-tied colleague named Tyler Reimschisel. To Rienhoff's puzzlement, the two geneticists spent an inordinately long time peering down Beatrice's throat. Eventually they called for a third doctor, a Belgian named Bart Loeys, to join them.

Loeys seemed gravely concerned by what he saw in Beatrice's throat. "I have a pretty good idea what this might be," he said. "We need to do an echocardiogram right away—today, this afternoon."

Loeys explained that Beatrice was likely suffering from a disorder named after himself and Harry Dietz, yet another Johns Hopkins geneticist. Loeys-Dietz syndrome is characterized by

many of the same symptoms as Marfan and Beals syndromes, but the mutation is not found in the *FBN1* or *FBN2* genes but rather in two receptor genes for transforming growth factor beta, or *TGF-ß*. (A receptor is a structure on a cellular wall that provides a binding site for molecules.) All of these genes play vital roles in the same metabolic pathway, the *TGF-ß* signaling pathway, which regulates the growth and proliferation of cells.

One telltale sign of Loeys-Dietz is a forked uvula—the cone-shaped blob of tissue that hangs at the entry to the throat. Other examiners had noted that there was nothing peculiar about Beatrice's uvula, but the Johns Hopkins team discovered otherwise.

By coincidence, Rienhoff had already scheduled an echocardiogram back in San Francisco for later in the week. He promised to keep Loeys apprised of the results; Loeys, in turn, gave Rienhoff a paper on the syndrome that had recently appeared in the scientific journal *Nature Genetics*.

Most of the plane ride home was spent playing games with 15-month-old Beatrice, whose illness has had no effect on her intellectual development. But toward the end of the flight, Rienhoff finally managed to scan the Loeys-Dietz paper. It was a horrifying read: The syndrome, which warps the aorta and twists the arteries, is far deadlier than Marfan. The average patient dies before the age of 27. "Even though I'm not a religious guy," Rienhoff says, "I was praying that she didn't have it."

She did not. The echocardiogram showed that Beatrice's aorta was fine. Follow-up genetics tests confirmed she didn't have the specific *TGF-ß* receptor mutations characteristic of the disease, either.

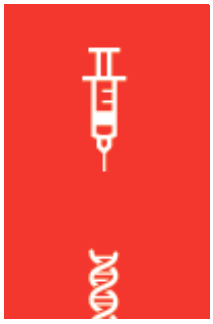
But after the Loeys-Dietz scare, Rienhoff became convinced that the *TGF-ß* signaling pathway must be involved in Beatrice's case. She now had verified symptoms from three diseases linked to abnormalities in the pathway—the Marfanoid feet, the clenched fingers from Beals, and the bifurcated uvula from Loeys-Dietz. But the problem most affecting her day-to-day quality of life was simple weakness. Rienhoff was determined to figure out whether there was any connection between skeletal muscle and *TGF-ß* signaling.

He turned his attention to myostatin, a protein that prevents muscles from growing too wildly and which is a chemical cousin of *TGF-ß*. Mice stripped of myostatin become rodent versions of Arnold Schwarzenegger circa *Pumping Iron*. Perhaps Beatrice was suffering from a genetic defect that was affecting her myostatin production.

As it happens, Rienhoff knew the man who discovered myostatin, a Johns Hopkins molecular biologist named Se-Jin Lee. The two had first crossed paths during Rienhoff's residency. "He called to describe his daughter and her circumstances," Lee says, "and told me that he was thinking about the role of myostatin in the *TGF-ß* pathway." Lee sent Rienhoff a journal article on the protein; he was amazed at Rienhoff's voracious appetite for the complex topic.

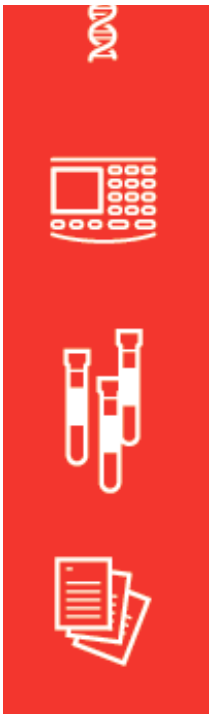
## DIY DNA

Convinced his daughter's illness was connected to the protein myostatin, Hugh Rienhoff decided to examine the genes that affect myostatin production himself.



**Step 1**
Rienhoff took vials of Beatrice's blood to a Stanford lab, where he extracted the girl's DNA by spinning the blood in centrifuges.

**Step 2**
Back home, Rienhoff ran the DNA through a polymerase chain reaction machine. It starts by heating the samples, splitting the double-stranded DNA into two



single strands.

**Step 3**
Rienhoff applied chemical primers to the split DNA. These primers, which he designed and purchased online, flagged the genes Rienhoff was targeting. The PCR machine then used a type of enzyme called a DNA polymerase to amplify just the marked segments.

**Step 4**
Rienhoff sent 50-microliter tubes of the amplified DNA to a contract lab, which posted the sequence data on a secure server.

**Step 5**
Rienhoff printed out the data—20,000 base pairs of DNA—and compared it with a reference genome stored on Ensembl, an online British database.

In the spring of 2006, the Rienhoffs made another trip to Baltimore to meet with Harry Dietz, who remained intrigued by Beatrice's case despite her normal echocardiogram and genetic tests ruling out Loeys-Dietz disease. Dietz still worried that the girl might have a fatal heart defect, and he asked Rienhoff to schedule a CT scan of her cardiovascular system.

Rienhoff balked; CT scans use x-rays, and Rienhoff was reluctant to expose Beatrice to a large dose of radiation. The two men compromised: In lieu of a CT scan, they scheduled another MRI. And they deferred the appointment until the following January.

But Rienhoff didn't like the MRI plan either—because of her age, Beatrice would have to undergo general anesthesia to ensure she remained still in the machine. He had about eight months to come up with a good reason to cancel the appointment. He focused more keenly on myostatin.

There are three receptors, known as activin receptors, that are thought to be critical to myostatin regulation: *ACVR1B*, *ACVR2*, and *ACVR2B*. Rienhoff wondered whether one of these genes was flawed in Beatrice, causing her body's myostatin system to go haywire. There was one way to find out: Examine her DNA. Activin receptors are fairly well-understood genes, so a problematic alteration would likely stand out.

Rienhoff first asked Lee to do the DNA sequencing. But Lee declined on bureaucratic grounds. Professors who wish to work with human genetic material need clearance from their university's institutional review board. This onerous approval processes can take months, and there was no guarantee Lee would get the OK.

Rienhoff was also turned down by several other doctors, including some acquaintances, who were frankly troubled by the request. They pointed out that myostatin had never been associated with human disease, so Rienhoff's hypothesis was far-fetched, bordering on foolish. The sequencing venture struck them as futile. "There were a few people who didn't want to get involved," Rienhoff says. "They think it's peripheral or wacky science."

Some skeptics were also disturbed by the notion of a father conducting, in essence, an experiment on his child: "When you start telling people it's your daughter, it weirds them out," Rienhoff says. "They're thinking that maybe you're going over the line a bit in your zealousness, maybe you're sacrificing your commitment to good science. "

By late 2006, it was clear to Rienhoff that if he wanted to get Beatrice's activin receptors

sequenced, he'd have to do it himself.

**As any fan of *CSI* knows**, polymerase chain reaction is a method for replicating a snippet of DNA, amplifying it over and over until there's enough genetic material to be sequenced. By making inquiries with local surplus brokers, Rienhoff discovered he could buy a secondhand PCR machine for less than a MacBook. He ended up purchasing a full working model for just $750.

Obtaining additional supplies, like the PCR reagents, for his experiment was tougher. Some chemical companies didn't want to ship to a private address, so Rienhoff pretended his house was the headquarters of the fictional Institute for Future Study.

Rienhoff went to friend's lab at Stanford and used the centrifuges there to extract DNA from a sample of Beatrice's blood. He then took the genetic material home and put his PCR equipment to work. The machine first blasted the genetic material with heat, splitting the double-stranded DNA into two separate strands. Then chemical primers, which Rienhoff had designed and purchased on Integrated DNA Technologies' publicly accessible PrimerQuest Web site, were added to the mix. They were coded specifically to amplify the genes that Rienhoff was focused on—the three activin receptors. This process, repeated many times over, created millions of copies of Beatrice's activin receptor genes, giving him a sample large enough for reliable sequencing.

While Rienhoff could spring for his own PCR machine, a used gene sequencer (assuming he could find one) would cost around $100,000. So he found a university lab (which he declines to identify) that would sequence the genes he had amplified, for $3.50 per 50-microliter sample. In spring 2007, Rienhoff mailed in more than 200 samples.

The sequencing results came back organized into charts resembling seismographs of a minor earthquake, with each sharp spike indicating an individual nucleotide. Rienhoff printed out everything and stored the sheets in white three-ring binders. He combed through these pages while logged on to Ensembl, a public database jointly funded by the UK's Wellcome Trust Sanger Institute and the European Bioinformatics Institute. Launched in 2000, Ensembl contains complete genomes for about 50 species, from alpacas to zebrafish. The Homo sapiens section is based on a full assembly of the genome compiled by the National Center for Biotechnology Information; this data is supplemented by annotations submitted by researchers, who identify genetic variants suspected of causing diseases. Rienhoff compared Beatrice's DNA with the information on Ensembl, looking for any base-pair variants that hadn't been previously recorded on Ensembl. He was operating on the assumption that Beatrice's genetic blip was completely unknown, which would explain why she'd been so hard to diagnose.

The job was daunting: The printouts contained data for approximately 20,000 base pairs, and there was no feasible way to automate the hunt for variants. After putting in a full day of consulting and then getting the kids to bed, Rienhoff would retire to his attic and spend hours checking Beatrice's adenines (A), thymines (T), guanines (G), and cytosines (C) against the Ensembl reference genome. Sometimes he would fall asleep on the floor, only to awaken at 1 am and go right back to work. He would imagine Beatrice sitting by his side, patiently observing as he sorted through the data that defined her.

Progress was slow, but after a decade in the boardroom, Rienhoff enjoyed doing pure science again. Mostly, though, it felt good to be an active seeker rather than an anxious parent at the mercy of an overburdened doctor. The process of combing through Beatrice's DNA printouts became a form of meditation, a way for Rienhoff to steel himself against the sadness of seeing his little girl struggle up and down the stairs each day. It began to feel quasi- spiritual—he started referring to his work as "my journey."

Confident that he was making headway, Rienhoff canceled Beatrice's MRI. Two months later, in

March 2007, he completed his study. He had identified about 20 places where the DNA for Beatrice's activin receptors didn't match the reference genome. Of those, only one, in the *ACVR1B* gene, was not mentioned anywhere in the genetic literature. As far as Rienhoff could tell, the variant was unique—an adenine on one chromosome and a guanine on the other, whereas only two adenines had ever been reported.

But the variant was far removed from the area most obviously involved with myostatin. It seemed doubtful that such an oddly placed hiccup could cause Beatrice's serious disorder. Rienhoff decided to look at his own *ACVR1B* gene to see how it compared. He later repeated the process with his blood, from centrifuge to sequencing; when the results came back, he discovered he also had an A and a G in that position. This ran contrary to Rienhoff's theory—a variant in that location couldn't cause an illness as severe as Beatrice's, if he was in perfect health.

Though his homebrew genetic analysis had been a bust so far, Rienhoff still believed that Beatrice's disorder was linked to *TGF-ß*. And there was a piece of good news: During his research, he read a study in which Marfan mice were given losartan, a common blood-pressure medication. The drug was intended to prevent aortas from dilating, but an Italian group had discovered that it might strengthen skeletal muscle, too. Rienhoff persuaded Beatrice's cardiologist to start her on losartan, figuring that they had little to lose—the potential side effects were minor; the potential upside huge.

Beatrice soon started to move with more confidence. It's difficult to say exactly why the losartan worked, or even if it was, indeed, the reason for her newfound grace. But Beatrice's physical therapist, unaware of the treatment and surprised by her improvement, pulled Rienhoff aside after one session and asked, "Has anything changed?"

**In July 2007**, a few months after wrapping up his analysis of Beatrice's activin receptors, Rienhoff attended the National Marfan Foundation's annual conference in Palo Alto. His main interest was a workshop dedicated to people like himself, parents whose children exhibited Marfanoid symptoms but did not have the disease.

The parents took turns introducing themselves and describing their various frustrations—insurance companies that wouldn't pay for genetic tests, doctors who prescribed unsuitable treatments. When Rienhoff's turn came, he spoke about his saga, from the early days of the Beals syndrome hypothesis to his sequencing of Beatrice's three activin receptors.

The attendees were both amazed and eager to hear more about Rienhoff's genetic exploration. But the doctor moderating the session, Dianna Milewicz, was apprehensive. Director of the division of medical genetics at the University of Texas Medical School at Houston, Milewicz couldn't fathom why Rienhoff would pursue such a long-shot experiment. For starters, his focus was on genes that had never been shown to play a role in Marfan-like diseases, rather than more probable culprits such as fibrillin-2. And even if he succeeded in identifying a genuinely novel variant, that was only a tiny first step in a long diagnostic process.

"Then you have to prove the variant you're seeing is truly causing the disease," Milewicz says. "Understanding how a variant relates to a disease is often very difficult. And if you're sequencing genes that we don't even know cause disease, that's where it becomes a nightmare, even for those of us who have dedicated our lives to this."

As soon as Rienhoff wrapped up his presentation, Milewicz cautioned the workshop's attendees against following his do-it-yourself lead. "I said, 'This is not a good idea to recommend to parents,'" she recalls. "They're not trained to analyze diagnostic tests."

Rienhoff bristled at Milewicz's dismissive tone. "I remember thinking, 'Who the fuck is this person?' I have never been in a situation where it was so obvious that a doctor had contempt for the curiosity of her patients. It was striking how insensitive she was to their dilemma."

Such a prickly reaction is out of character for Rienhoff, a soft-spoken man who normally exudes an easy calm. But he has developed a cynical streak about doctors, especially those who are quick to dismiss inquisitive parents as nuisances. "Medicine in general is a slightly paternalistic activity," he says. "You hear these stories about patients bringing in all sorts of information from the Internet and doctors being exasperated. And part of that is because there is so much they don't know, and they're supposed to be omniscient."

Far from taking Milewicz's warning to heart, Rienhoff was preparing to do something even more radical than his activin experiment. In summer 2008, he launched a second, more ambitious phase in his effort to diagnose Beatrice—he started sequencing her transcriptome.

The transcriptome, as Rienhoff puts it, is "the business end of the genome." In order to produce proteins, a small portion—about 1 percent—of the DNA in a particular gene is transcribed into messenger RNA. This mRNA, also known as a gene transcript, then passes along instructions to ribosomes, the cellular machines that make proteins.

Analyzing a transcriptome is essentially a low-cost alternative to sequencing a person's entire genome. It provides a glimpse at small yet vital scraps of thousands of genes. And since the transcriptome represents only a cross-section of a person's DNA, there shouldn't be too many variants to sift through. A typical human genome will have between 100 and 300 mutations that weren't present in the subject's parents; a transcriptome should have five or fewer.

Rienhoff asked a lab to extract mRNA from Beatrice's white blood cells, in which more than half of human genes are expressed. Then a reverse transcriptase enzyme was used to convert this single-stranded RNA into double-stranded DNA, suitable for sequencing. The procedure yielded fragmentary snapshots of as many as 15,000 of Beatrice's genes. (A full human genome contains 20,000 to 25,000 genes.) As a last step, Rienhoff repeated the process for himself and his wife; he figured that the mutation in Beatrice's genome must have arisen spontaneously, rather than being inherited from either parent.

"Hardcore scientists would say this is a bad experiment," Rienhoff admits. "You're sampling only a portion of the genes—you're not casting your net over whole oceans; you're just casting it over the Pacific Ocean. But from my point of view, that's a pretty damn good start."

Rienhoff is still in the midst of this project, which he dubbed his triad transcriptome experiment —the "triad" consisting of mother, father, and offspring. He has tentatively identified three genetic variants so far that Beatrice alone possesses. To his consternation, none are directly related to the *TGF-ß* signaling pathway: One is in a gene that codes transport proteins; one is in *CRNKL1*, a gene that's barely been studied in humans; and the third is in a gene so obscure that it has yet to be named.

**One of Rienhoff's heroes is Borgny Egeland**, a Norwegian mother of two mentally retarded children. In 1934, she contacted an Oslo doctor, Asbjörn Fölling, and informed him that her children's urine was emitting a powerfully musty odor. At Fölling's request, she collected urine samples from the children every other day for two months straight—more than 5 gallons in all. Fölling found that these samples contained high levels of phenylpyruvic acid, a substance that was subsequently found in the urine of many other patients suffering from retardation. It turned out that a genetic disorder was preventing these children from properly metabolizing phenylpyruvic acid, and the buildup causes brain damage. The discovery led to the most effective treatment for the disease (now called phenylketonuria)—a diet low in phenylalanine, which the body converts to phenylpyruvic acid. To Rienhoff, the story of PKU's discovery is a perfect example of how a concerned parent can press doctors to solve seemingly intractable problems. Countless afflicted children now live normal lives thanks to Egeland and Fölling's teamwork.

To encourage this kind of collaboration, Rienhoff created MyDaughtersDNA.org. The Web site,

launched in October 2007, invites parents to post the clinical histories of their undiagnosed children. The hope is that geneticists will also frequent the site, to help identify rare disorders and use the case studies to further their own research.

One of the first people to post to the site was a Bulgarian man named Stefan Petkov, who wrote about his 12-year-old daughter. The girl had weak limbs and speech problems; she also lacked the ability to shed tears. Doctors in Bulgaria were stumped, and DNA tests done in both Belgian and Bulgarian laboratories didn't point to any known genetic conditions.

Gary Gottesman, a geneticist at Saint Louis University School of Medicine in Missouri, came across Petkov's saga after reading about MyDaughtersDNA.org in the journal *Nature*. The girl's inability to cry made him think of a disorder known as Triple A syndrome. He suggested that Petkov have his daughter checked for the disease.

Less than a month later, in March 2008, Petkov wrote again. His daughter had finally been diagnosed with two of the pillars of Triple A syndrome, the most notable being Addison's disease, which limits production of the hormone cortisol. Shortly thereafter, Petkov's daughter began receiving medicine to replace the hormone, which should help build her muscle strength.

Rienhoff realizes that most parents lack the resources to operate PCR machines or jet around the country in search of a diagnosis. But he points to Petkov's story as proof that they can still play a role in their children's care by seeking answers outside traditional medical channels—embarking, in a sense, on their own Rienhoff-like journeys.

Rienhoff's personal quest has yet to produce any meaningful insight into Beatrice's condition, but his efforts have not been totally in vain. At the very least, he claims to have now conducted more work on human transcriptomes than anyone else. According to Rienhoff, there have been only two peer-reviewed papers on human transcriptome sequencing, and both have their shortcomings. "Certainly, no one has done the triad," he says, "which is the Holy Trinity of genetics." A genomics lab at UC Berkeley wants access to Rienhoff's data and is in the process of obtaining review board approval to examine Beatrice's transcriptome.

Rienhoff hopes that someone will eventually commercialize his triad transcriptome experiment, so that parents like Petkov will have a quick if crude tool for peering inside their children's genetic code. But such a diagnostic product may soon be moot: Complete Genomics, a Mountain View, California, company, recently announced that it plans to start sequencing entire human genomes for $5,000. Just a few years ago, such a massive undertaking couldn't be done for less than $1 million.

But even when labs can sequence a person's genome for less than $1,000, it will still likely be years before such tools help children suffering from complex syndromes. It's one thing to process vast amounts of DNA data; quite another to turn that data into insight about an illness—let alone use it to develop therapies. "Certainly, our science cannot help Beatrice anytime soon," says Marc Vidal, a Rienhoff confidant and director of the Center for Cancer Systems Biology at the Dana-Farber Cancer Institute.

Deep down, Hugh Rienhoff knows this. And he realizes that his DIY search for a diagnosis may never pan out. "I never pretend to know what's going on, because I don't," he says. "You can see—anybody can see if they look closely enough—that I don't have the answer to the story."

But he keeps hacking his way through Beatrice's genome, mostly because it's the only way he has of feeling some measure of control over an uncontrollable situation. Rienhoff compares his work on Beatrice's DNA to journalist Peter Matthiessen's search for the snow leopard, documented in an award-winning book. Matthiessen never found the big cat in the mountains of Nepal, but his futile quest helped him come to terms with his wife's death from cancer.

The altered nucleotide at the root of Beatrice's problems "is as elusive and mysterious as the

snow leopard," Rienhoff says. "And like Matthiessen, I may not find it. Curiously, it may not be important at all."

The journey, in other words, is its own reward. Of course, Rienhoff knows he can afford to be philosophical because Beatrice's condition isn't dire, at least not at the moment. "I am not watching my child melt away, which is the most desperate situation to be in," he says. "I can't even imagine that—I'd be working 24 hours a day."

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