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Translations

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When Gabi was born, the hospital kept her in the NICU for three weeks because they couldn't quite figure out what she had. She looked a little different from your average infant, her eyes were spread further apart than usual and slanted slightly downwards. She had long fingers, and low muscle tone kept her hands slightly open instead of the familiar clenched fists of newborns. She had a dislocated hip and left leg, for which she got a minute cast at just three days of life. They did echocardiograms, X-rays, CT scans, and an MRI. Doctors agreed she had a syndrome, but they couldn't agree on which one. Something called Shprintzen-Goldberg syndrome was their best guess.

A week after coming home from the hospital, we had our first appointment with Dr. Rosenbaum, a geneticist at Children's National Hospital in Washington, D.C. Dr. Rosenbaum personally opened the door for us at the Children's outpatient center in Rockville where he was in clinic that morning, seeing us for an early appointment before the building even opened. I pushed Gabi, tucked in her

stroller, alongside my then-husband, Carlos, and my Mom, the four of us following Dr. Rosenbaum through the quiet hallways to an exam room.

Dr. Rosenbaum was serious, articulate, and soft-spoken as he examined Gabi. Thankfully, he was just as thoughtful in helping me chart a course of action with what became a growing list of subspecialists—cardiology, neurology, neurosurgery, ophthalmology, gastroenterology, orthopedic surgery, and ENT. He even helped me get organized, suggesting I start one of those thick three-ring binders with dividers for each specialist.

Other advice I cherished from Dr. Rosenbaum came during one of our early consults. "It's frustrating that we know so little about Shprintzen-Goldberg," I vented. His response: "You know, there are some syndromes we understand very well, but about which we can do very little. In Gabi's case, we may not have all the answers, but everything she has is manageable."

Everything is manageable. That's what I kept repeating to myself. It's what I told friends who asked.

Thus, Carlos and I embarked on parenthood. As most other first-time parents, we lived with that sense of elated exhaustion, awed by the miracle of having Gabi in our lives while also adjusting to sleeplessness and what seemed like the endless cycle of feeding-burping-changing. We also managed mounting appointments and tried weaving insights across subspecialists; this in an era before electronic medical records.

Having only a tentative underlying diagnosis for Gabi, we consulted other geneticists, making

our rounds through Johns Hopkins Hospital in Baltimore, Children's Hospital of Philadelphia, and Boston Children's Hospital. At Hopkins, we met Dr. Hal Dietz who, like the others, methodically analyzed our medical records and examined Gabi. This was 2004, when Gabi was two.

A year later, Dr. Dietz called me. "I have some news for you," he said. "I don't think your daughter has Shprintzen-Goldberg. I think she has this new syndrome called Loeys-Dietz."

A week later, Carlos, Gabi, and I were back in his clinic. Dr. Dietz and Dr. Loeys were there, both of them personally drawing blood samples from the three of us to look for the mutation associated with Loeys-Dietz. The results for Carlos and me came back negative. They were positive for Gabi, a one in a million "spontaneous mutation."

That same month, Dr. Dietz, Dr. Loeys, and their team published their first article on Loeys-Dietz in *Nature Genetics* (2005):

> We report heterozygous mutations in the genes encoding either type I or type II transforming growth factor b receptor in ten families with a newly described human phenotype … (p. 275)

Translation: Researchers identified ten families with similar physical traits (phenotypes) that didn't fit under previously existing diagnoses. In trying to figure out the genetic mutations associated with these traits, they found something odd about the genes affecting the behavior of the substance that

shapes how cells grow, differentiate, and develop (transforming growth factor b receptor).

> We describe ten families with a new aortic aneurysm syndrome characterized by widely spaced eyes (hypertelorism), bifid uvula and/or cleft palate, and generalized arterial tortuosity with ascending aortic aneurysm and dissection. (p. 275)

Translation: In common, these families exhibited aortic aneurysms. That's when the large blood vessel (aorta) that distributes blood from the heart to the rest of the body weakens and stretches for some reason, creating a balloon-like bulge (aneurysm). This stretching can lead to a sudden tearing of the layers of the aorta (dissection). In addition to this frail structure, images of arteries in these families showed jumbled twists and turns instead of flowing vessels (arterial tortuosity). These families also looked a little different. They tended to have widely spaced eyes and, if they opened their mouths, you'd see a split in the soft flap of tissue that hangs from the back of the mouth (bifid uvula) and a slight opening in the roof of the mouth (cleft palate).

> This syndrome shows autosomal dominant inheritance and variable clinical expression. (p. 275)

Translation: If one parent is affected by the genetic mutation associated with Loeys-Dietz, their children have a fifty percent chance of also being affected. And like other syndromes, Loeys-Dietz has a spectrum of implications for patients.

Okay. We weren't the only ones. There were at least ten other families out there with this syndrome and here was an article explaining what no other geneticist had managed to figure out. Though the genetics of Loeys-Dietz read like a foreign language, the different physical features associated with the syndrome were by now familiar.

Loeys-Dietz affected Gabi from head to toe. She had an aneurysm at her aortic root, right where the aorta joins the heart. That's why we had been seeing a cardiologist every six months for imaging and had started Gabi on propranolol, believed to slow the growth of the aneurysm. Gabi's beautiful brown eyes were also widely spaced and she had a bifid uvula. She didn't have a cleft palate, but rather a submucus cleft, which always seemed inconsequential.

"Variable clinical expression" meant a lot more for Gabi. In addition to the standard features, Gabi also had a premature fusion of the skull bones (craniosynostosis), abnormal accumulation of cerebral-spinal fluid in her brain (hydrocephalus), a lazy eye (strasbismus), chronic inflammation of the lining of her large intestine (indeterminate colitis that morphed into ulcerative colitis), and low muscle tone.

Despite the countless appointments, stressful surgeries and procedures, and a growing medicine cabinet, Gabi was this joyful and engaging toddler. One of my favorite pictures from this period is one that Carlos took of the two of us in front of our home on a crisp fall afternoon, laughing as we ran to grab the leaves dancing on their way to the

ground. Gabi's wearing her matching red hoodie and pants, her hair is flowing with the wind, her arms reaching to grab a leaf. I can still hear her laughter. Another picture is of the two of us sitting on a pier near Chincoteague Island, where we went for a long weekend. We're sitting right next to each other, our legs swinging off the pier, both of us barefoot. We're both looking down to something in the water, I think some tiny fish.

Gabi thrived and we took comfort in knowing we were in the best possible hands. With Dr. Dietz at Johns Hopkins, it soon became the world's premier center for patients with Loeys-Dietz, with an expanding cadre of doctors advancing our understanding of the syndrome in the lab and in the clinic.

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A year after that seminal article, Gabi now four, Dr. Dietz and his team published their findings in *The New England Journal of Medicine* (2006). Now they drew from a cohort of 40 affected families.

> We found a mutation in TGFBR1 or TGFBR2 in all probands with typical Loeys–Dietz syndrome (type I) and in 12 probands presenting with vascular Ehlers–Danlos syndrome (Loeys–Dietz syndrome type II). The natural history of both types was characterized by aggressive arterial aneurysms (mean age at death, 26.0 years) … . (p. 788)

Translation: There's more than one type of Loeys-Dietz syndrome, but they're both as deadly, with patients dying on average as young adults. They continued,

> There were 59 vascular surgeries in the cohort, with one death during the procedure. This low rate of intraoperative mortality distinguishes the Loeys–Dietz syndrome from vascular Ehlers–Danlos syndrome. (p. 788)

Translation: Most patients with Loeys-Dietz have vascular surgery, but they rarely die from surgery itself.

> The craniofacial severity index was used to determine the severity of symptoms of the Loeys–Dietz syndrome. … The scores can range from 0 to 11, with higher scores indicating more severe abnormalities. Patients were given a score of 2 for marked hypertelorism … a score of 6 if both [cleft palate and craniosynostosis] were present. For malformations of the uvula, a bifid uvula was given a score of 3 … . (p. 789)

Translation: Though all patients with Loeys-Dietz live with the risk of having aneurysms and dissections, those risks are higher for patients who have more of its outward features.

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Twenty-six years. That's what stayed with me from this article. That and the fact that Gabi had the highest possible score on the craniofacial severity index.

No, that can't be right, I told myself as I sat at my desk, pencil in hand, studying each line of the article. Even though researchers now had a larger sample size, these patients probably represented extreme manifestations of Loeys-Dietz since it's the most severe cases that make it to hospitals like Hopkins. Moreover, these young adults dying from Loeys-Dietz had been misdiagnosed all their lives. Outcomes would surely be different for newer generations of patients being effectively managed from a younger age. Gabi would live much, much longer.

Carlos didn't understand why I read these articles. "They just make you worry about stuff that may never happen," he'd say. "These articles don't tell us anything about how to care for Gabi. That I'd understand."

He was right. I stopped reading these articles. We now counted on the expert guidance of Dr. Dietz and other leading doctors at Hopkins. Towards the end of our follow-ups, after discussing their latest assessment of Gabi and suggestions on management and meds, we asked about their latest research on Loeys-Dietz. We often couldn't follow the medical jargon, but we got the gist. More importantly, bright minds were hard at work searching for ways of improving the lives of people with Loeys-Dietz.

And Gabi's symptoms were all manageable. A simple eye muscle surgery when she was an infant

corrected her strabismus. Cranial reconstruction when she was a toddler addressed her craniosynostosis. Open heart surgery when she was four fixed her aortic aneurysm. She was on the indicated combination of meds that would helpfully keep other aneurysms from developing.

Gabi somehow just skipped through it all. I remember this day at Hopkins, Gabi five or six, the two of us walking hand in hand along the corridor by the cafeteria, the one with the nice internal garden where they house the turtles every year for the Turtle Derby. We must've been there for an MRI since we were walking from the Meyer building back to the outpatient center. We were chatting when she turned to me and asked, "When will I be a guest here again?"

Not anytime soon, I thought to myself.

She wasn't thinking about the post-operative recovery, the discomfort of removing the breathing tube, the hourly bright light shone in her eyes. What came to mind as she asked me that innocent question were the silly clowns that visited her room and made her laugh hysterically as they bumped into the doors, the nurses who painted her nails, the child life specialists who came by with crafts and toys, the countless movies we watched, the ride on the red wagon to the play room as she was recovering.

I also stopped reading those articles because, most importantly, Gabi was thriving. Yes, we had the morning and evening meds, the follow-up consults, the yearly MRIs, but those became mundane parts of our lives.

From kindergarten through elementary school, most days were so normal that we'd sometimes even forget about Loeys-Dietz. Every year, she'd be nervous about the first day of school, only to come home excited about her new teacher, her classmates, the possibility of singing in the choir, running for student government, or auditioning for the musical. She had her school friends, with the usual giddiness and drama that I learned started much earlier than in my day. She embraced each and every holiday, our home somehow decorated continuously from Halloween through Epiphany, then again for Easter. Summers she'd explore arts, dance, and drama at her favorite camp at Norwood in Potomac. We traveled to visit family in Hawaii and Brazil, we traveled to explore Boston, New York City, Philadelphia, the Disney parks in Orlando, Historic Williamsburg, and the Von Trapp Family Lodge in Vermont.

Life was easy, precious.

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The winds changed about the time Gabi entered middle school. During our annual cardiology appointment in early 2014, Gabi now almost 12, doctors realized that the synthetic graft they had placed over her aortic aneurysm when she was four had somehow "migrated"; the aneurysm, more aggressive than they had imagined, was bulging beneath the graft. Gabi had another open-heart surgery two months later.

During a routine checkup a year later, they found something called a pseudo-aneurysm at the

site of one of her earlier sutures. Imagine a garden hose with a pinpoint hole where, instead of the water squirting out, the outer layer of the hose expands out at that orifice like a tiny balloon. Left unchecked, the wall of that balloon eventually bursts. This time, we went from the cardiology clinic, Gabi still in her school uniform, directly to the ICU where days later she had her third open heart surgery.

Gabi never fully recovered from those back-to-back heart surgeries.

"I've never been able to run again like I used to, you know, even just at recess, like running out to hang out by the jungle gym," she shared one day as we were having our usual chat before bedtime, me sitting at the edge of her bed caressing her hair.

In early April of 2016, Gabi developed a terrible backache that took us back to Hopkins (just to be sure). She had the beginnings of what turned out be a descending dissection. She survived surgery, but not the subsequent hemorrhage, the cascading organ failure, and sepsis. Gabi was 13. She had just been accepted with merit scholarships to her two top high schools and was excited about her upcoming eighth grade graduation, fourteenth birthday sleepover party, and plans for the summer.

Yes, Loeys-Dietz was very manageable.

Until it wasn't.

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I recently decided to do a quick search on Loeys-Dietz just to see what came up. Four hundred and eighty articles. I picked one published in 2017 in *The Journal of Thoracic and Cardiovascular Surgery* (2017) on intermediate outcomes of cardiovascular surgery authored by a team from Hopkins, including the four surgeons who had operated on Gabi over the years.

> Growing experience with Loeys-Dietz syndrome has confirmed the early impressions of its aggressive nature and proclivity toward aortic catastrophe. Surgical outcomes are favorable, but reintervention rates are high. (p. 406)

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Aortic catastrophe. No translation needed.

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