

BEING HUMAN

The Genes That Could Cancel Out a Fatal Diagnosis

The key to treating genetic disease might be hidden in other “modifier” genes.

By Roxanne Khamisi

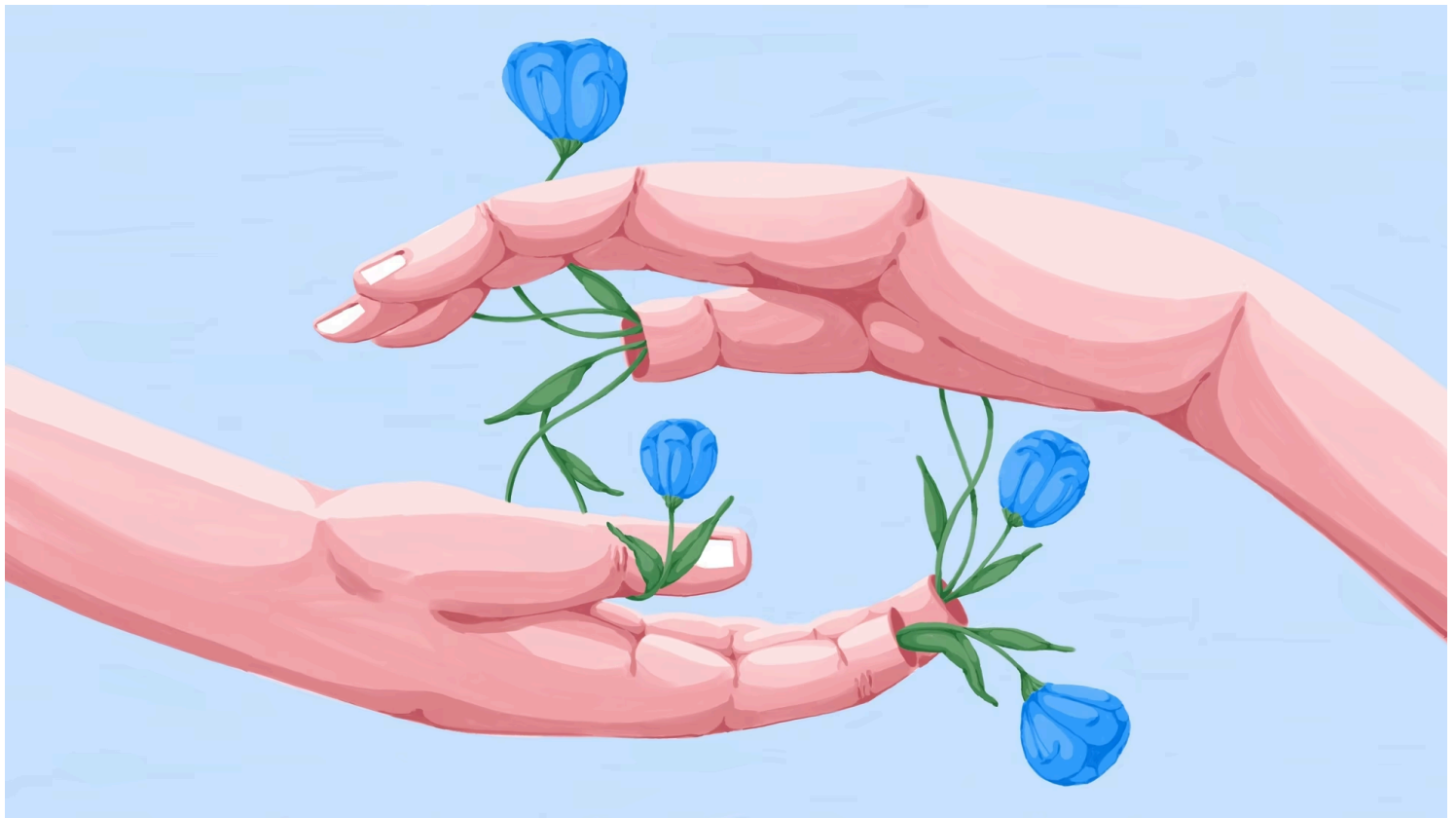


Illustration by Flo Meissner

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When Ludvine Verboogen and Romain Alderweireldt’s third child was born in Belgium in late 2015, they marveled at his long fingers. Perhaps one day he will be a famous pianist, they thought. But soon Ludvine grew worried that her son was not developing as well as his two older sisters had. His muscles seemed weak, and the physiotherapy appointments she was taking him to three times a week didn’t seem to be helping. “A lot of doctors were telling us that he was fine, nothing was wrong with him,” Romain recalled to me.

Ludivine persisted, and shortly before their son was a year old, she and Romain found out that his long fingers and lack of muscle tone had a devastating explanation. He was diagnosed with a disease called Marfan syndrome, which generally involves mutations in a gene that helps build connective tissue in the body. Many people with Marfan are exceptionally tall—Abraham Lincoln, for one, may have had the syndrome—and are at very high risk of a kind of fatal rupture in the heart. Ludivine and Romain learned that their son had the neonatal form of the condition, and they were told that he probably would not live past 16 months.

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When Romain got the news, he lay down on his office floor, overwhelmed with emotions. His boss found him there and encouraged him to get back up and start working on a solution. Before long, Romain and Ludivine came across a new paper describing how scientists had combed through genetic data from more than 500,000 people and identified 13 adults who defied their genetic destinies—who were alive and healthy despite having multiple or dominant genetic mutations that normally cause grave illness beginning in childhood. The hope of such studies, they learned, is to identify “modifier” genes within the human genome that can be manipulated to mitigate or cancel out genetic conditions.

“I had a look to see if something like that had been done in the field of Marfan, and it had not,” Romain said. Marfan syndrome is particularly mysterious because members of a family who carry the same exact mutation can have wildly different health trajectories, Catherine Boileau, a geneticist at the French health research institution INSERM, told me. Within a given family, she said, the disease can appear at very different ages and with starkly different severity. Some people might experience a fatal tear in their aorta early in life; their relatives might have only mild symptoms and not require surgery.

Romain began combing through databases of genetic information to see if he could find people with Marfan mutations who did not appear to have symptoms of the disease. He found 122 of them, including 24 who had errors in the gene thought to

cause the neonatal version of Marfan. Perhaps one of these people, or someone like them, held in their genes the possibility of a different life for his son.

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Boileau knows from experience that finding modifier genes can pave the way to lifesaving therapies. She was involved in early research into a gene called *PCSK9*: Mutations that lower the gene's activity, it turns out, can avert sky-high cholesterol levels usually caused by inherited errors in another gene. That discovery helped create a class of drugs that mimic the effects of disabling *PCSK9*.

Modifier genes also have a role in sickle cell disease, one of the most common inherited disorders in the world. In the disease, the body produces an abnormal form of the oxygen-carrying molecule hemoglobin. Scientists identified genetic mutations causing sickle cell disease decades ago, but around the mid-2000s, they began discovering modifier genes, including one that could help jump-start hemoglobin production. Normally, this modifier gene suppresses the creation of a second kind of hemoglobin, typically made only during fetal development; repressing the gene prompts cells to start making the fetal form of hemoglobin again, which acts as a backup. One of the very first gene-editing therapies that the FDA approved for sickle cell disease works precisely by shutting down this modifier gene.

In recent years, more scientific groups have been identifying genetic outliers who might possess helpful variants of modifier genes. A study published in March from researchers in Singapore and Australia, for example, examined the genomes of almost 10,000 healthy people and looked for errors in more than 1,600 genes associated with severe pediatric disease. They found nine individuals ranging in age from 12 to 62 years old who showed no signs of illness despite having DNA profiles presumed to cause grave health issues in childhood. Last month, researchers presented new data at the European Human Genetics Conference in which they searched for 15 genetic conditions in about 900,000 individuals and found that, for some illnesses, the degree of severity is more variable than previously believed.

The research that first inspired Ludivine and Romain's was part of an effort called the Resilience Project, which was led by scientists at the Icahn School of Medicine at Mount Sinai and has been paused for a number of years. Stephen Friend, a physician-scientist who helped spearhead the original project, told me that, a decade ago, confirming the beneficial effects of suspected modifier genes was difficult, but the advent of techniques such as CRISPR editing has made running such tests far easier. Now the scientists behind the project are looking to reboot it. In the new iteration, the project will apply AI tools to scan more than 2 million genomes for more than 500 rare and ultra-rare diseases, Eric Schadt, a computational biologist at the Icahn School of Medicine, told me. Schadt is working with Friend, and they have assembled a team that spans multiple institutions; their goal is to identify the modifying genes in outliers and develop drugs that replicate their beneficial effects. In a paper published last week, Friend and other scientists note that modifier genes that suppress symptoms have so far been found in around 100 different human diseases.

The mystery of why some people who carry a deadly gene variant might not have symptoms traces back a century, to when biologists were trying to understand how traits were passed from one generation to the next. In fruit flies, they noticed, the expected mutations sometimes caused only partial changes in the insects' anatomy. Some other factor, or factors, helped determine the flies' fate.

In the intervening years, scientists have identified modifier genes and other forces that can influence whether a particular trait manifests. Environmental factors can play a huge role. For example, people with phenylketonuria, an inherited metabolic disorder, usually develop severe cognitive impairment, but won't if they follow a diet that omits foods with specific proteins. Scientists also now know that chemical tags on DNA known as epigenetic markers can switch genes on and off, affecting the degree to which genetic traits produce symptoms.

Identifying the factors that influence the intensity of symptoms caused by inherited mutations is getting easier—and really “has only recently become possible to study systematically,” according to Caroline Wright, a geneticist at the University of Exeter Medical School, in England. Wright, who was involved in the report on 900,000 people, told me that looking at large populations has made it more possible to identify people with other changes in their genomes that mitigate congenital diseases. These large studies have also shown that the symptoms caused by pathogenic mutations are commonly milder than doctors had believed. Focusing scrutiny on the DNA of people who were unwell—a reasonable choice when genetic analysis tools were neither cheap nor fast—might have introduced a bias toward believing that the mutations were always extremely harmful.

And better understanding the flip side—the ways in which worrisome gene mutations might not always cause severe illness—is the key to knowing “if and when to start treatment for those that carry the mutation but still don't have the disease,” Dusan Bogunovic, the director of the Center for Genetic Errors of Immunity at Columbia University Irving Medical Center, told me.

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Bogunovic published a paper in March that highlighted how much we don't understand about these phenomena. Each of us inherits a set of genes from each of our parents, but recent studies have suggested that the copy from one parent is four times as active as the other version. So if a person's healthy copy is more active than the mutated one, they might have far fewer symptoms than expected. This kind of skewing has become much easier for scientists to track with new sequencing technology. For as many as half of the genes we carry, one copy might be at least 50 percent more active than the other, Bogunovic estimated.

Gene skewing might even influence outcomes of Marfan syndrome: A small number of case reports have hinted that skewed gene activity might happen with the fibrillin-1 gene. One study, in which 80 people with Marfan were compared with 80 healthy volunteers, found a roughly fourfold difference in fibrillin-1 gene activity in both groups, suggesting that it might be prone to skewing. This skewing has been hypothesized as a contributor to the variability in symptoms of Marfan in families with the same mutation.

Romain and Ludivine's son has not yet needed heart surgery, but they are still eager to identify outliers with Marfan and learn which factors are helping those people. They started the 101 Genomes Foundation in an attempt to create a database of complete, "whole genome" data from that many people with Marfan mutations. In the past decade, the effort has amassed more than 230 genomes, and it continues to add more each month. (Boileau, the geneticist in France, is an adviser to the project.) The puzzle of why some people with neonatal forms of Marfan's succumb within months and others live with mild effects weighs on Ludivine and Romain: They have met countless patients and parents like themselves, and although their son is doing relatively well, they know children who have died from the condition in infancy.

They now have a glimmer of insight into genetic variation outside the fibrillin-1 gene that determines whether Marfan patients get sick early in life or remain relatively healthy. At the European Conference on Rare Diseases in June, the 101 Genomes team presented what their years of research had uncovered: five potential modifier genes that had a chance of explaining some of those wild variations. And in as-yet-unpublished data, they have identified a variant of an additional modifier gene that affects the heart's ability to contract and has a strong protective effect against Marfan mutations, according to Bart Loeys, a clinical geneticist at the University of Antwerp who is helping to lead the research supported by the 101 Genomes Foundation. "If nature has the means of correcting or buffering the effects of a pathogenic variant in one gene, we can learn from that," he told me. "Maybe we can try to mimic that in other patients."

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ABOUT THE AUTHOR

Roxanne Khamisi



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Roxanne Khamisi is a contributing writer to *The Atlantic* and the author of the forthcoming book *Beyond Inheritance: Our Ever-Mutating Cells and a New Understanding of Health*.

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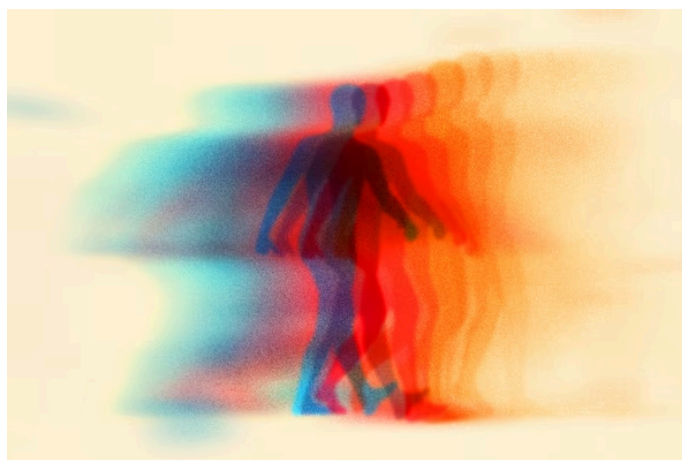


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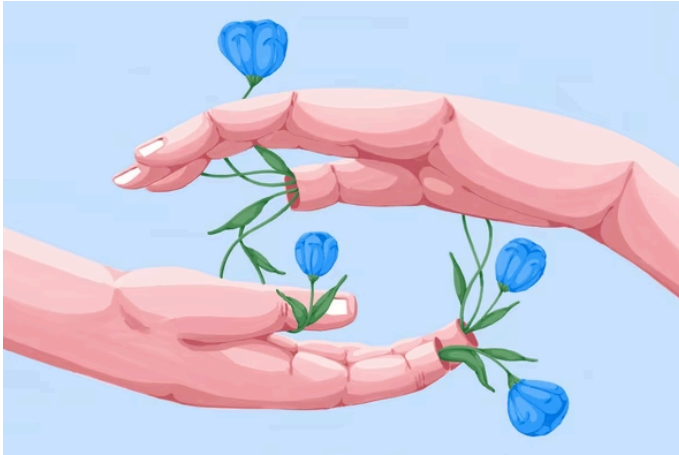


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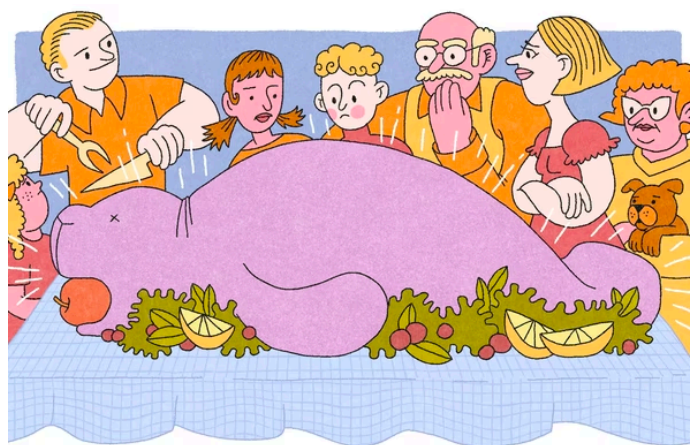


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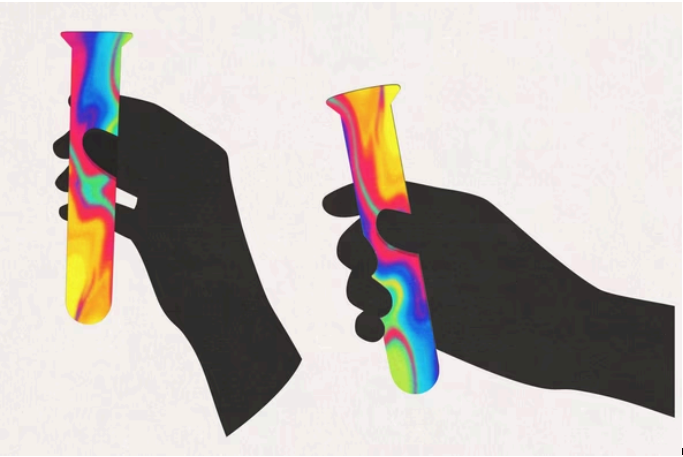


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