The Surprising Legacy of a Genetic Disorder; Research on fragile X syndrome shows that even people who don't have the disease can be shaped by it in deeply personal ways

Skomorowsky, Anne . Wall Street Journal (Online) ; New York, N.Y. [New York, N.Y]. 05 May 2022.

FULL TEXT

Genetic diseases like sickle cell anemia or cystic fibrosis occur when a section of a chromosome or a single gene is defective or missing, and their effects are unmistakable. But in recent years researchers have found that other genetic conditions are more subtle, affecting things like temper and the ability to learn, which are often thought of as simply part of an individual's personality. Even more surprising, researchers are starting to understand how these traits can appear in carriers of a genetic disease who don't have the full-blown disease themselves.

That was the case for Carol, now in her 70s. (I have changed her name and those of her family members to protect their privacy.) For most of her life, she assumed that everything wrong with her family was just the way families were. Growing up in a Chicago suburb in the 1950s, she was scorned by her father, Lewis, who expressed his contempt for her and his wife in one blow: "You're stupid like your mother." When Carol grew up and had children of her own, her daughter Amy was introverted and a poor student. Counselors at school told Carol that Amy's problem was that she couldn't measure up to her mother's expectations.

Then a surprising development shed new light on the role that genes might play in the family's woes. When Amy was 12, her cousin Ben was diagnosed with fragile X syndrome, the most common known inherited form of autism and intellectual disability. Ben's diagnosis set off a cascade of genetic tests, which showed that Amy had fragile X syndrome too, providing an explanation for her social anxiety and learning disabilities. But the unusual mechanism behind fragile X meant that not only Carol but even her father, who didn't have the syndrome, could still have been affected by it.

Fragile X syndrome is named after a defect in the X chromosome that causes it to pinch so that it looks like a little piece is about to break off. As a result, the body is unable to produce an important protein, preventing the brain from developing normally. With classic genetic diseases, people are affected when they inherit two copies of a defective gene, one from each of their parents. The parents themselves each have only one copy of the gene, having inherited it from one of their own parents and not the other.

This makes them carriers of the disease: They are able to pass it down to their children, but they don't suffer from it themselves. Fragile X belongs to a set of diseases in which the mutation is on the X chromosome. Typical X-linked diseases, like hemophilia, only affect men, and only women can be unaffected carriers. That is because women have two X chromosomes, and men one X and one Y.

But fragile X is not typical of X-linked diseases either. In one of the early scientific conferences about the disease, in 1986, population geneticist Stephanie Sherman showed that in a family affected by fragile X, each generation has more members with the syndrome than the one before. A man is more likely to have a grandson with fragile X than a brother who has it. This seemed paradoxical at first, since it was so unlike typical genetic diseases, and it came to be known as the Sherman paradox.

A few years later, researchers discovered the explanation. It turned out that there is a minor form of the fragile X mutation known as a premutation. In the carrier state, the X chromosome appears normal. But with each

generation the premutation becomes more significant, a rare phenomenon known in genetics as anticipation. At a certain point a threshold is crossed, and the apparently unaffected carrier gives birth to a child with fragile X syndrome.

The discovery of the premutation also clarified several mysteries about fragile X disorders. In contrast with other X-linked diseases, both men and women can be carriers, and girls and boys can be born with full mutation fragile X syndrome. Fragile X is a rare disease; according to the CDC, it is diagnosed in approximately one in 7,000 men and one in 11,000 women. The fragile X carrier state is much more common, affecting up to one in 150 women and one in 450 men in the U.S.

Until the late 1980s, premutation carriers were believed to have no symptoms. Since then, however, premutation symptoms have been found to be widespread and even life-defining. The premutation isn't a mild form of fragile X syndrome, but it has its own means of wreaking havoc in the carrier's body and brain. It causes mutated, toxic RNA to build up in the ovaries, where it can lead to infertility and early menopause, and the neurons, where it ties up useful proteins so they can't do their jobs. Brain cells called astrocytes may die young. About 70% of elderly carrier men and a smaller percentage of women develop a constellation of tremor, ataxia or gait disturbance, and personality change.

This last symptom raises the intriguing possibility that a hidden genetic mutation may account for an array of character traits that people might not think of as hereditary. Carol learned from genetic testing that she had passed on the fragile X mutation to her daughter Amy from her father Lewis, whose meanness and irritability had been considered just an unfortunate part of his personality. Upon his death, however, neuropathological examination of Lewis's brain confirmed that he had the tremor/ataxia syndrome.

Looking back, Carol now believes that her father's behavior was influenced by changes throughout his brain. His executive function was severely impaired, as was his capacity for empathy. His poor impulse control and inability to stay on task made him lash out at his wife and two daughters. Research in the past few years has shown that the fragile X premutation is associated with a broad array of psychiatric and medical problems, including anxiety, depression, phobias, sleep disorders, fibromyalgia, migraines and other forms of chronic pain. Most of these aren't traditionally thought to be caused by a tiny alteration in a single gene.

Lewis, Carol and Amy represent three generations of a fragile X family. Amy, with full-mutation fragile X syndrome, can't make change or drive on a highway. Carol, a carrier, suffers from anxiety, depression and chronic pain. Lewis, a carrier too, appeared healthy until he reached old age but was a punitive, even cruel father and husband. Today it's not a mystery when a genetic mutation produces a defective protein that causes disease. But premutation carriers like Carol and Lewis, once thought to be unaffected, raise questions about previously unrecognized ways that genes can affect the way we think, act and feel.

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DETAILS

Subject:	Daughters; Families &family life; Womens health; Anxieties; Genes; Disease; Genetic disorders; Brain research; Ataxia; Personality; Mutation; X chromosomes
Publication title:	Wall Street Journal (Online); New York, N.Y.
Publication year:	2022

Publication date:	May 5, 2022
column:	Essay
Section:	Life
Publisher:	Dow Jones &Company Inc
Place of publication:	New York, N.Y.
Country of publication:	United States, New York, N.Y.
Publication subject:	Business And Economics
e-ISSN:	25749579
Source type:	Newspaper
Language of publication:	English
Document type:	News
ProQuest document ID:	2659667835
Document URL:	http://proxy.library.stonybrook.edu/login?url=https://www.proquest.com/newspapers/surprising-legacy-genetic-disorder-research-on/docview/2659667835/se-2?accountid=14172
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Last updated:	2022-05-07
Database:	The Wall Street Journal

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