What Defines a “Carrier”?

In my role as a genetic counselor, I frequently meet with women who have Fragile X pre- or full mutations. Most of these women are typically functioning mothers who found out about their own Fragile X mutations only after they had a child affected by Fragile X syndrome. Whether they have a premutation or full mutation, we generally refer to such mothers as “carriers.”

The term carrier is problematic, however, since in genetics, it generally refers to someone with a gene mutation without showing any symptoms. We now know that some women with premutations have infertility or Fragile X-associated tremor/ataxia syndrome, known as FXTAS, while those with full mutations may have learning or psychiatric issues.

I know many women with Fragile X full mutations who have average or above average intelligence with only mild manifestations of the gene expansion, such as excessive shyness or a lifelong difficulty with math.



We also use carrier for men who have Fragile X premutations, even though many of them will eventually go on to develop symptoms of FXTAS. Although carrier is not technically correct for people who have symptoms, in the Fragile X world, we generally use it to describe individuals with unimpaired intellectual functioning, regardless of whether they have pre- or full mutations.

Why So Much Variability?

Why is there so much variability among male and female Fragile X carriers? There are a number of factors involved. Because the Fragile X gene is X-linked, gender plays a big role in determining who might show symptoms. Male premutation carriers, because they have only one X chromosome, are much more commonly affected by FXTAS than are female carriers.

Females have two X chromosomes, so even when they carry a Fragile X

premutation on one of them, they have a second copy that can significantly reduce their risk of developing FXTAS.

On the other hand, because men don't have ovaries, they're not at risk for developing Fragile X-associated primary ovarian insufficiency, known as FXPOI, a condition that affects only women and is associated with hormonal symptoms such as irregular periods, infertility, and early menopause.

Only premutation carriers are at risk for developing FXTAS and FXPOI; these conditions do not affect males or females with full mutations.

Another factor influencing carrier symptoms is the amount of FMRP (Fragile X protein) a gene produces. Typically, male and female premutation carriers have normal amounts of FMRP and do not have intellectual symptoms. A Fragile X gene with a full mutation usually does not produce FMRP, and this leads to Fragile X syndrome in almost all males and many females who have full mutations.

However, in some females with full mutations, their second X chromosome does a good job of compensating for the missing protein, and they show minimal to no intellectual symptoms. Such females are carriers who can pass the gene mutation to their children, but who themselves show few effects.

Fragile X Inheritance is Complicated

Fragile X inheritance is particularly complicated compared to other genetic disorders, so it's no surprise that families often have difficulty understanding where one draws the line in defining who's a carrier. Even the scientific community has marveled at the way the Fragile X story has unfolded, going from a straightforward X-linked cause of intellectual disability in boys to a highly complex adult-onset condition.

Twenty years ago, no one would have guessed that a single gene disorder could manifest itself in so many different ways, from autism and learning issues to infertility and balance problems. Different symptoms present themselves in different ways and to varying degrees over the lifespan. As one carrier mother once said, "Fragile X is the gift that keeps on giving."

Fragile X isn't the only condition with genetic counselors questioning the definition

of carrier. With the completion of the Human Genome Project in 2003 and the many advances in genetic testing that followed, we now know about many genes that have subtle effects or that predispose individuals to developing problems later on. Actress Angelina Jolie made news when she decided to undergo a double mastectomy because she carried a gene that caused breast cancer in her mother and other family members. Other genes have been found that predispose carriers to behavioral differences, such as ADHD and mental illness.

It is estimated that every human carries anywhere from a handful to dozens of mutations or other genetic differences that have the potential to cause medical, developmental, or psychiatric disabilities in themselves or their children. Most people go through life never knowing which genes they carry unless they happen to develop a hereditary health problem or have a child with a genetic condition. It may be that Fragile X carriers have no greater number of gene mutations than anyone else in the population, but for various reasons, they come to discover that one of their genes is a Fragile X mutation. With knowledge comes power, and in that sense, carriers have a unique window into their genetic destiny.



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Brenda Finucane, MS, CGC, has been actively involved with the Fragile X community for many years and is currently a National Fragile X Foundation genetic counseling consultant. She is a long-time member of the NFXF's Scientific and Clinical Advisory Committee and has served two terms on our board of directors. In her day job, Ms. Finucane is a professor and licensed genetic counselor at Geisinger's Autism and Developmental Medicine Institute in Lewisburg, Pa.