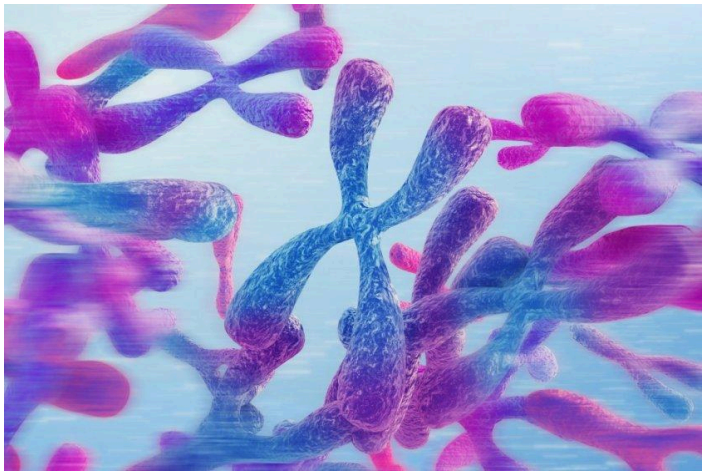
X chromosome gene may reduce autism rates in women and girls

A gene called ZFX exerts powerful effects on an entire network of genes linked to autism, which may help explain why the condition is less common in females

By Michael Marshall on November 9, 2026



The X chromosome seems to help reduce the chances of developing autism and we may be closer to understanding how. nopparit/Getty Images

A single gene on the X chromosome may help explain why autism is less common in women and girls. The gene, *ZFX*, has powerful effects on a set of genes that contribute to the risk of autism, and is expressed more in women than in men.

“It’s about the fact that *ZFX* has a relationship with these other autism-associated genes,” says Rebecca Andersen, a neurogeneticist at Boston Children’s Hospital in Massachusetts. This one gene can keep other genes turned on when they might otherwise be deactivated, she says, reducing the chances that girls will develop autism.

Autism is a developmental condition. Autistic people have a variety of traits that can include difficulties with socialising and communicating, unusually high sensory sensitivity that can cause them to become overwhelmed, and restricted behaviours and interests.

Many studies have found that autism is more common in males than in females: up to four times as common. “That specific number is contested,” says Andersen, partly because we now know that autism presents differently in females, including subtler effects on socialising.

Furthermore, women and girls with autism often "mask" or "camouflage" their autistic traits, enabling them to pass as neurotypical at the cost of their mental health. This means females often go undiagnosed, or are diagnosed later in life, skewing the figures.

Nevertheless, many autism researchers believe there is a "female protective effect": something about being female makes people less likely to be autistic. Notably, women diagnosed with autism tend to have more autism-linked mutations than men diagnosed with autism. This suggests there is a requirement for a "greater genetic load in females in order to manifest with autism at all, or to manifest to a degree that would be diagnosed", says Andersen.

Understanding this requires understanding the genetics of autism. "We've long known that there's a very strong genetic component to autism," says Andersen. "There have been a lot of large-scale sequencing studies that have identified hundreds of different genes that are implicated in autism," she says. "It's been really perplexing to understand how so many different genes could all be relevant for autism."

To figure out how these genes work together, Andersen and her colleagues grew neural progenitor cells – which develop into neurons – in culture. They then targeted each of 20 genes, all known to be associated with autism. Rather than deleting or mutating the genes, they used a version of the CRISPR gene-editing technology to break down the RNA produced when the genes were expressed. Reduced expression of these genes is thought to increase the chances of developing autism. "We could target the RNA for degradation and have very rapid changes in expression levels of those genes," says Andersen.

To their surprise, the researchers found that reducing the expression of any one of these genes tended to also significantly reduce the expression of most of the others. "Across almost all of our perturbations, they just looked very similar to one another, and in particular, how much they affected the other autism-associated genes," says Andersen. "It seemed to make sense that they would have to converge in some way, in order to be related to autism, but we didn't necessarily expect to find such a strong degree of convergence."

The researchers then built a model of the interactions between the genes. This enabled them to identify a core of 70 genes, all of which strongly regulate the 20 autism-associated genes, and also regulate each other. Andersen calls these genes the "central hub".

"This provides strong evidence that apparently distinct genetic causes of autism may converge on common pathways," says Louise Gallagher at the Hospital for Sick Children in Toronto, who wasn't involved in the study.

Having identified these core genes, the team then identified a set of 82 genes that were expressed less when the autism-related genes were suppressed, and which are known to be more heavily expressed in female brains compared with male. This led the researchers to *ZFX*, which is found on the X chromosome. Females have two X chromosomes, but males have one X

and a smaller Y chromosome. This means females have two copies of *ZFX* – and unusually for genes on the X chromosomes, both copies are expressed.

“We found that *ZFX* was very related to many of these different autism-associated genes,” says Andersen. This means *ZFX* could act as a buffer. A girl could have a lot of mutations that reduce the expression of autism-associated genes and thus increase her probability of autism – only for the *ZFX* to increase the expression of those genes and reduce her chances of autism.

“That’s very interesting and biologically plausible,” says Gallagher. However, the claim rests on the team’s model of the interactions between the genes. “The paper doesn’t show that increasing *ZFX* expression rescues the consequences of the variants.” That would require additional experiments.

“It’s also unlikely that something as complex as the female protective effect will be attributable to a single gene,” says Gallagher. “It could be related to other sex-linked genetic mechanisms, hormonal influences and broader differences in developmental biology.”

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