NEWS

Girls protected from autism, study suggests

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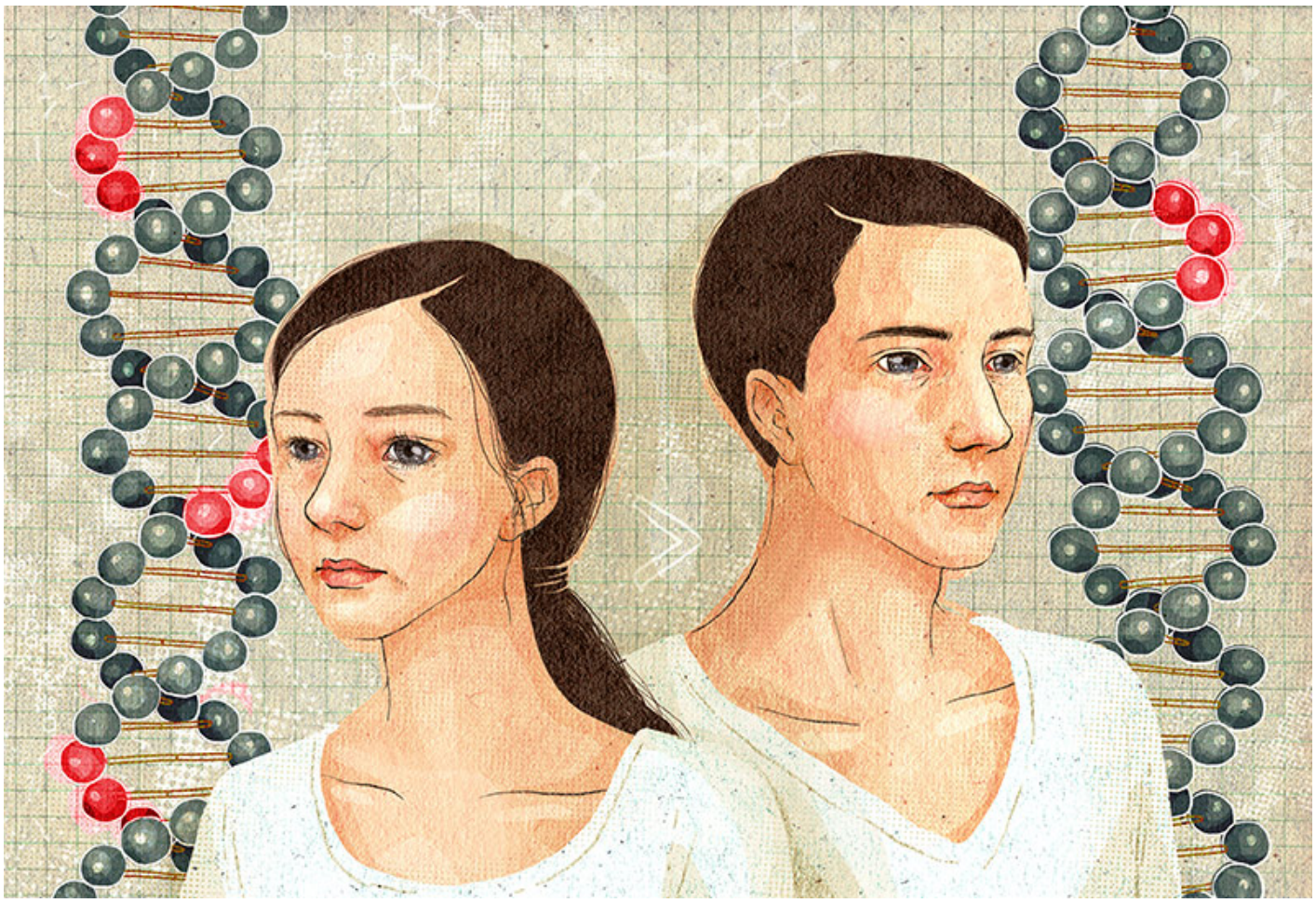
10 MARCH 2014



It takes more mutations to trigger autism in women than in men, which may explain why men are

four times more likely to have the disorder, according to a study published 26 February in the *American Journal of Human Genetics*[1].

The study found that women with autism or developmental delay tend to have more large disruptions in their genomes than do men with the disorder. Inherited mutations are also more likely to be passed down from unaffected mothers than from fathers.

Together, the results suggest that women are resistant to mutations that contribute to autism.

“This strongly argues that females are protected from autism and developmental delay and require more mutational load, or more mutational hits that are severe, in order to push them over the threshold,” says lead researcher **Evan Eichler**, professor of genome sciences at the University of Washington in Seattle. “Males on the other hand are kind of the canary in the mineshaft, so to speak, and they are much less robust.”

The findings bolster those from previous studies, but don't explain what confers protection against autism in women. The fact that **autism is difficult to diagnose in girls** may mean that studies enroll only those girls who are severely affected and who may therefore have the most mutations, researchers note.

“The authors are geneticists, and the genetics is terrific,” says **David Skuse**, professor of behavioral and brain sciences at University College London, who was not involved in the study. “But the questions about ascertainment are not addressed adequately.”

Genetic burden:

The new study draws from the **Simons Simplex Collection** (SSC), a database of families that have one child with autism and unaffected parents and siblings. (This project is funded by the Simons Foundation, SFARI.org’s parent organization.) In a 2011 study, researchers found that girls with autism in the SSC tend to have more large duplications or deletions of regions of the genome, called **copy number variants** (CNVs), than do boys with the disorder, although this disparity does not reach statistical significance[2].

For the new study, Eichler and his colleagues cataloged the number of CNVs in 109 girls and 653 boys with autism from the SSC. They found that females are twice as likely as males to carry CNVs that are at least 400 kilobases long. (The larger the CNV, the more likely it is to disrupt important genes.)

When the researchers analyzed only CNVs that encompass risk genes for neurodevelopmental disorders, they found that females with autism are three times as likely as males with the disorder to carry CNVs that encompass these genes.

Females with autism also carry slightly more rare mutations that change a single DNA nucleotide than the men do. These are the “nastiest of nasty mutations,” says Eichler, because they interfere with the protein’s function.

The researchers saw a similar but smaller effect for CNVs in a larger group of 9,206 males and 6,379 females referred for genetic testing: 75 percent of this group turned out to have developmental delay, intellectual disability or autism.

Women in this group are 1.28 times more likely than men to carry large CNVs that include risk factors for these disorders.

Many autism-linked mutations **arise spontaneously**, or *de novo*, and about 80 percent of these **come from the father**.

Eichler and his colleagues found that women are far more likely than men to transmit the inherited mutations that confer autism risk.

Of the 27 large CNVs the researchers identified in the SSC group, 70 percent, or 19,were inherited from the mother. Mothers had similarly passed down about 57 percent of the 3,561 CNVs detected in the neurodevelopmental group.

Eichler intends to extend this work in a bigger study to assess whether certain mutations are more likely than others to be inherited.

“I think it’s really critical to identify these inherited components,” he says. “We know they’re there, but we need to really focus on identifying the specific genes so we can advise [parents] a little more about recurrence.”

However, it’s unclear whether this gender bias is the result of genetics or reflects differences in diagnosis or the way females manifest symptoms of the disorder. Girls with autism tend to actively compensate for their symptoms in ways that boys don’t, which may account for the discrepancy, says Skuse.

As a result, the females enrolled in studies may tend to be severely affected and carry multiple mutations. “There is some suggestion that higher-functioning females are out there in the general population, but they're not being referred,” he says.

The study also does not address why women with autism transmit more mutations, or how they are protected from autism.

“We need to ask what it is about brain development that makes it such that females are protected — because ultimately that is what we want know,” says **Aravinda Chakravarti**, director of

theCenter for Complex Disease Genomics at the Johns Hopkins University School of Medicine in Baltimore. “We need to re-create that developmental environment.”

The most obvious explanation for autism’s gender bias is that because men have only one X chromosome, they are hypersensitive to mutations in this chromosome. In line with this theory, several autism-linked genes are located **on the X chromosome**. However, most of the mutations that show a gender bias in the new study are not on the X chromosome, suggesting that other factors must be involved.

***Correction**: This article has been modified from the original. An earlier version incorrectly stated that 80 percent of the genetic risk factors for autism arise spontaneously. The exact contribution of spontaneous genetic variants to autism is not known.*

References:

1: Jacquemont S. *et al. Am. J. Hum. Genet.* Epub ahead of print (2014) **PubMed**

2: Levy D. *et al. Neuron* **70**, 886-897 (2011) **PubMed**