NEWS

Intricate DNA flips, swaps found in people with autism

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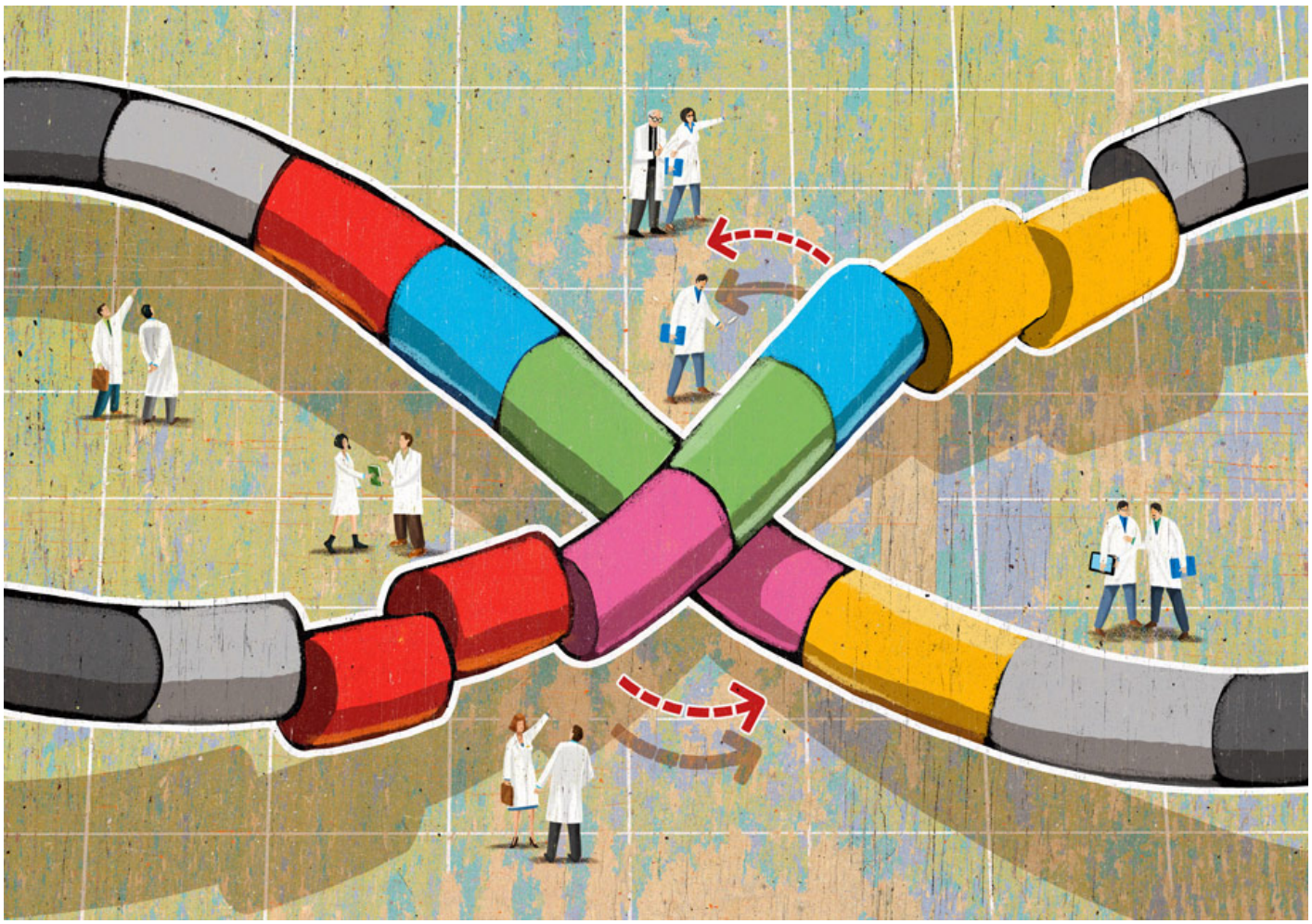

A surprisingly large proportion of people with autism have complex rearrangements of their

chromosomes that were missed by conventional genetic screening, researchers reported 2 July in the *American Journal of Human Genetics*[1].

The study does not reveal whether these aberrations are more common in people with autism than in unaffected individuals. But similar chromosomal rearrangements that either duplicate or delete stretches of DNA, called **copy number variations,** are **important contributors to autism** as well as to other neuropsychiatric disorders. These more complex variations are likely to be no different, says lead researcher **Michael Talkowsk**i, assistant professor of neurology at Harvard University.

Talkowski's team found intricate cases of molecular origami in which two duplications flank another type of structural variation, such as an inversion or deletion.

"This is going to become an important class of variation to study in autism, long term," Talkowski says.

The finding is particularly important because current methods of genetic analysis are not equipped to detect this type of chromosomal scrambling. The **go-to method for clinical testing** — which compares chopped-up fragments of an individual's DNA with a reference genome on a chip — can spot duplications or deletions. But this method cannot tell when a DNA sequence has been flipped or moved from one chromosomal location to another, for example.

Variations like this even confound genome-sequencing technologies. Last year, for example, researchers published the results of **two massive projects** that sequenced every gene in thousands of people with autism. But because these genetic jumbles often fall outside gene-coding regions, they remained unnoticed.

"The complexity of genomic variation is far beyond what current genomic sequencing can see," says **James Lupksi**, professor of molecular and human genetics at the Baylor College of Medicine in Houston, Texas, who was not involved in the study. "We don't have the analysis tools to see it, even though it's right there before our very eyes."

Complex chromosomes:

Researchers have long had hints that complex variations exist, but they had no idea how prevalent they are. In 2012, using a method that provides a rough picture of the shape of chromosomes, Talkowski and his team found **pieces of DNA swapped between chromosomes** in 38 children who have either autism or another neurodevelopmental disorder[2].

Lupski's team also found examples in which two duplications bracket a region that appears in triplicate[3]. Then last year, Talkowski and his colleagues reported one example of a chromosomal duplication that flanks a flipped, or inverted, section of DNA[4].

In the new study, the researchers looked at 259 individuals with autism and found that as many as 21, or 8 percent, harbor this type of duplication-inversion-duplication pattern. And a nearly equal number of individuals have other forms of rearrangement, such as deleted segments sandwiched between duplications.

The researchers were able to reveal these complex variants by sequencing each genome in its entirety. The traditional method chops up the genome into fragments that are about 100 bases long. When mapped back to a reference genome, however, these short fragments may miss small duplications or rearrangements.

The new method instead generates larger fragments, containing roughly 3,700 nucleotides apiece. Scientists then sequence the 100 nucleotides at the ends of each fragment. When mapped back to a reference genome, the large fragments reveal structural changes. For example, when a pair of sequenced ends brackets more DNA than is found in the reference sequence, that fragment may contain a duplication.

Because the approach generates multiple overlapping fragments, researchers also end up with about 100 pieces of sequence that include the junctions, or borders, of the rearranged fragments. The abundance of overlapping sequences provides significantly more detail than the standard method, which covers each nucleotide only a few times.

“The researchers have a found a more novel way to sequence and dug in to an insane degree — it’s work that almost no one else would want to try to attempt, because it’s so difficult,” says **Michael Ronemus**, research assistant professor at Cold Spring Harbor Laboratory in New York, who was not involved in the study. “The findings give us a sense of how common these things might be in human genomes in general.”

Whether these rearrangements are important contributors to autism and neurodevelopmental disorders is still an open question — one that Talkowski and his colleagues are gearing up to address. The genomes they sequenced came from the **Simons Simplex Collection,** a database that includes the DNA of children with autism and their unaffected parents and siblings. (The collection is funded by the Simons Foundation, SFARI.org’s parent organization.)

The researchers are using their methods to sequence the genomes of the children’s relatives. This experiment will reveal whether complex variants are more common in people with autism than in unaffected family members.

Already, there are hints that the rearrangements contribute to autism risk in some individuals. Overall, the variants in the study duplicate 27 genes, introduce 3 mutations and in one case fuse two genes together. (The particular genes involved depend on where the mix-up occurs in the

genome.) Sequencing studies have tied one of the duplicated genes, AMBP, to autism. And a regulatory gene that is disrupted by the rearrangement, **AUTS2**, also has **strong links to the disorder**.

References:

1: Brand H. *et al. Am. J. Hum. Genet.* **97**, 170-176 (2015) **PubMed**

2: Talkowski M.E. *et al. Cell* **149**, 525-537 (2012) **PubMed**

3: Carvalho C.M. *et al. Nat. Genet.* **43**, 1074-1081 (2011) **PubMed**

4: Brand H. *et al. Am. J. Hum. Genet.* **95**, 454-461 (2014) **PubMed**