NEWS

Repeats of certain DNA segments may align with autism severity

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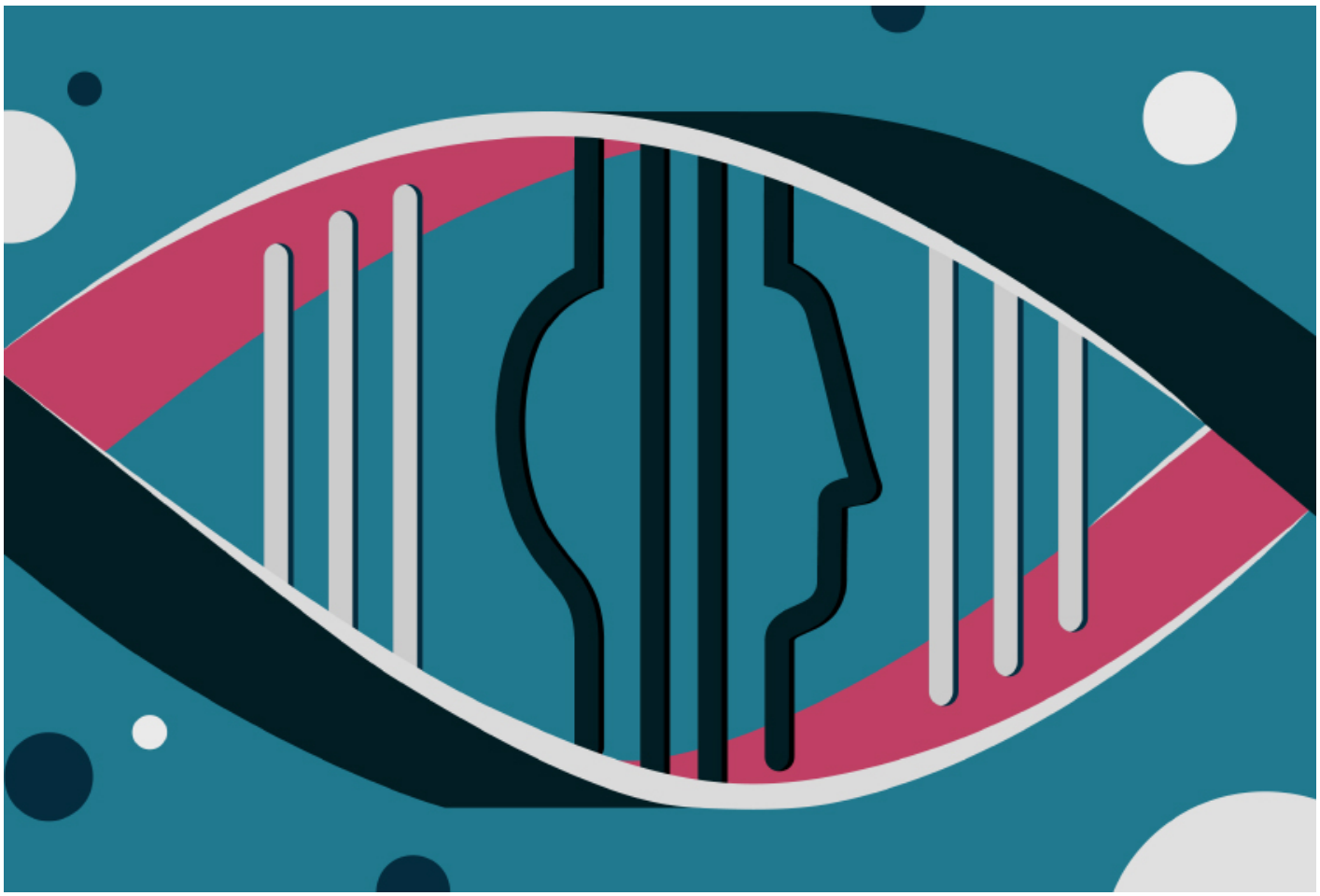

Certain repeated stretches of DNA that are linked to the expansion of the primate brain may also enhance autism traits, according to a new study[1].

There are six main types of these repeats, called Olduvai and formerly known as **DUF1220**; one of the types was previously linked to autism. The sequence of the repeats varies, but each encodes a piece of protein with 65 amino acids. The function of these protein fragments is uncertain, but they may **play a role in generating neurons**.

People carry 250 to 350 Olduvai repeats; nonhuman primates have about 100; apes have about 100, and monkeys have 30 to 40. This trend suggests that the repeats helped to drive an increase in brain size over the course of primate evolution, says lead researcher **James Sikela**, professor of biochemistry and molecular genetics at the University of Colorado in Aurora.

The new study is the third to link the number of Olduvai repeats to autism severity; all three are from Sikela's team.

"These sequences are so complex that they are not being examined by virtually all studies," Sikela says.

The results hint that sequencing studies miss some types of inherited risk for autism.

"How many more such genomic elements exist, and how much 'missing' heritability of risk can be found there?" says **Bernard Crespi**, professor of evolutionary biology at Simon Fraser University in British Columbia, Canada, who was not involved in the work.

Repeat effect:

Olduvai repeats are defined by their sequence similarity. In 2014, Sikela's team linked one of the repeat types, called CON1, to autism severity[2].

The repeats all crop up in a set of 23 genes, most of which cluster in a region of chromosome 1 called 1q21.1. A duplication of this region — which doubles the number of repeats — often leads to autism.

In the new study, Sikela's team looked at whole-genome sequences from 215 individuals with autism — 165 male and 50 female. These people each carry between 61 and 84 copies of CON1, which is in the typical range.

However, men with the most copies tend to have the greatest trouble with social interactions and communication, based on scores derived from the Autism Diagnostic Interview-Revised, the new study found.

The researchers saw the same effect when they combined results from these participants and 309 others from their previous two studies. Here, too, the number of repeats predicted social and communication ability.

“[The finding] warrants further targeted investigations of this dynamic region of the genome,” says **Anne Goriely**, associate professor of human genetics at the University of Oxford in the United Kingdom, who was not involved with the study.

The whole-genome analysis allowed the researchers to implicate the repeats in two specific genes: NBPF1 and NBPF14. NBPF1 contains several CON1 repeats. NBPF14, which is located within the 1q21.1 region, carries a type of Olduvai repeat called HLS1, and this is also linked to autism severity. The results appeared in February in the *American Journal of Psychiatry*.

The findings raise the intriguing possibility that regions that drive the evolution of the brain predispose people to autism.

“[The work] connects human brain evolution, in the context of brain size and measures of intelligence, with neurodevelopmental disorders,” Crespi says.

Olduvai repeats seem to be linked to autism severity in families that have multiple members with autism, but not in those with only one affected individual — a finding that has implications for inherited risk. More detailed information may also reveal differences in Olduvai repeats between autistic and typical people, Sikela says.

“We don’t know exactly what’s happening with these sequences,” Sikela says. “It’s which, when, where and how the copies change that can determine whether they are harmful or beneficial.”

REFERENCES:

1. Davis J. *et al. Am. J. Psychiatry* Epub ahead of print (2019) **PubMed**
2. Davis J.M. *et al. PLOS Genet.* **10**, e1004241 (2014) **PubMed**