NEWS

Autism genes abound in DNA regions involved in learning

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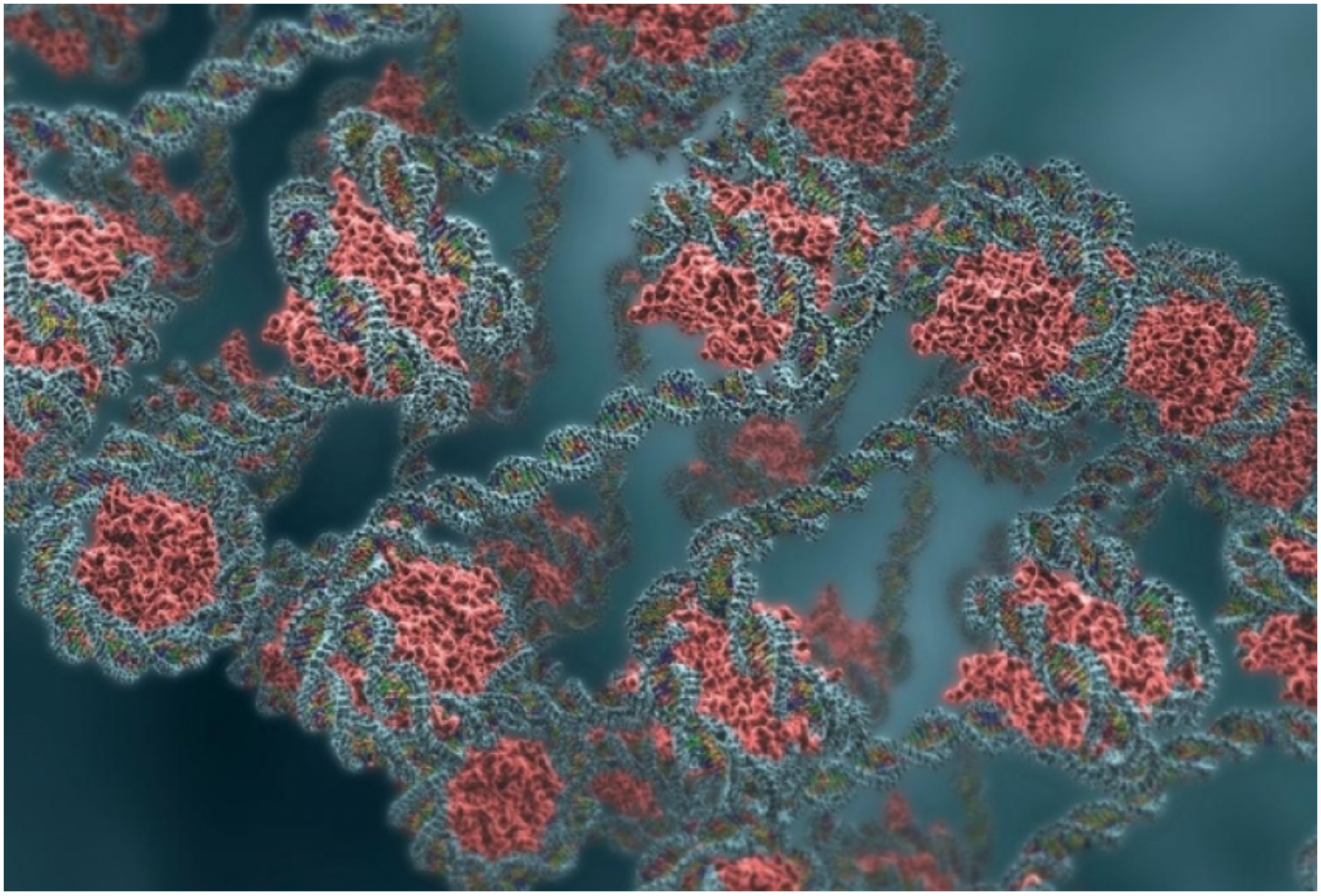

The same processes that enable the brain to store new memories may also control many autism genes, a new study suggests[1].

Candidate genes for autism are more than three times as prevalent in the genetic regions that become active after mice learn a new task as would be expected by chance, the researchers found. This connection between learning, memory and autism could explain why many children with autism have intellectual disability.

“We are trying to understand the overlap between learning and autism spectrum disorders,” says lead researcher **Lucia Peixoto**, assistant professor of biomedical sciences at Washington State University Spokane. The results appeared 16 January in *Science Signaling*.

Scientists can use this information to wade through the data from whole-genome sequences to find variants associated with autism, says **Ted Abel**, director of the Iowa Neuroscience Institute at the University of Iowa. (Peixoto began the study when she was a postdoctoral associate in Abel’s lab.)

One challenge for geneticists is figuring out which variants in a single DNA base — known as single nucleotide polymorphisms, or SNPs — found outside genes are meaningful. The new work could simplify this analysis: Instead of looking at the entire genome, researchers should focus on variants in regions known to be important to brain function, Abel says.

“[Autism] comes as the brain is developing, as the brain is being used, as there’s experience,” Abel says. “And so, looking at experience-dependent changes in gene expression is really the ticket.”

The research also underscores the importance of SNPs that fall outside genes.

“For the most part, SNPs in noncoding regions have been overlooked or dismissed,” says **Valerie Hu**, professor of biochemistry and molecular medicine at George Washington University in Washington, D.C., who was not involved in the study.

Scientists could use the same method to see whether certain genomic regions are called into action following other types of experiences, such as social contact, Hu says.

Open access:

In the new study, the mice first learn that a certain corner of their enclosure regularly yields a shock to the foot. The researchers then isolated the animals’ **hippocampus,** a brain region necessary for establishing long-term memories.

They used a method that sequences only the DNA that is loosely wrapped around proteins called histones. Tightening this wrap can turn genes off by blocking the machinery needed to express the genes; loosening it opens up access.

The researchers then designed an algorithm that identified more than 2,000 regions of the genome

that loosen up after a mouse performs the learning task. These regions overlap with genes that change their expression levels after the task, the researchers found.

Genes associated with autism are also over-represented within the open regions. They are more than three times more prevalent in those regions than would be expected by chance.

The data also suggest that the brain's response to learning is to splice together alternative versions of certain proteins: The open regions often correspond to regions between the coding portions of genes that are known to control splicing.

One of these regions is located within the autism gene **SHANK3**. After a mouse learns a task, the cell switches from making the full-length version of SHANK3 protein to a shorter version, the researchers found. They also showed that a variant in SHANK3 that overlaps with this region is statistically associated with autism.

However, the association is statistically significant only in Caucasian people. What's more, the regions with open conformation in the mouse brain may not match up to those in the human genome, says **Justin Cotney**, assistant professor of genetics and genome sciences at the University of Connecticut.

Peixoto plans to look at whole-genome sequences from people with autism to find additional variants that land within the regions involved in learning.

REFERENCES:

1. Koberstein J.N. *et al. Sci. Signaling* **11**, eaan6500 (2018) **PubMed**