NEWS

Repeats in human DNA may aggravate autism symptoms

BY **JESSICA WRIGHT**

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Bee Johnson

Certain DNA repeats that increased exponentially during human evolution are directly related to the severity of autism symptoms, according to a preliminary study published 20 March in *PLoS Genetics*[1].

The repeats each span 65 amino acids and are collectively referred to as DUF1220, for ‘domain of unknown function.’ There are six types of these repeats, each with a slightly different sequence and all of which diverged from a common ancestor.

The repeats mostly cluster in a set of 22 genes on a section of chromosome 1 called **1q21.1**, which **is linked to autism**. This region, and the repeats themselves, are also both linked to **a large head size**, a **characteristic feature** in some children with autism[2].

Researchers first hit upon the significance of the repeats when searching for genomic regions that

arose during the evolution from primates to humans[3]. They found these repeats to be the most significant increase in the genome that distinguishes people from primates .

People carry as many as 271 of these sequences across all six types, but as one travels along the evolutionary tree, the number drops dramatically: Apes, including chimps and gorillas, have about 100 copies, monkeys have about 30, dolphins have 4, cats have 3 and mice have 1.

DUF1220 may be responsible for the boost in brain power that drove human evolution, the researchers say.

“All of this data together is pointing to DUF somehow being an advantageous new addition that promotes brain size and neuron number,” says lead researcher **James Sikela**, professor of molecular genetics at the University of Colorado, Denver.

This may explain why the 1q21.1 region persisted through evolution, even though its duplication may increase risk of autism. Deletion of the same region is linked to small head size, schizophrenia and heart disease.

Dose count:

The study looked at only one subfamily of DUF1220 repeats, called CON1. The 170 people with autism in the study have between 56 and 88 copies of these repeats, researchers found — about the same range as in the general population.

But those who have more CON1 repeats struggle with communication and social interactions and have more **repetitive behaviors** than those who have fewer of the repeats, the study found.

The researchers found that with each additional copy of this repeat, the participants have more severe symptoms, as rated on three diagnostic questionnaires: the Social Diagnostic Score, the Communicative Diagnostic Score and the Repetitive Behavior Diagnostic Score. These tests assess social deficits, communication and repetitive behaviors, core symptoms of autism.

“I don’t think anything like this has been found before, where there’s a dosage effect that relates to severity,” says Sikela.

This link to autism severity is intriguing but must be confirmed in much larger groups of people, experts say.

“It would be an endlessly fascinating result if it were true,” says **Jonathan Sebat**, chief of the Beyster Center for Molecular Genomics of Neuropsychiatric Diseases at the University of California, San Diego, who was not involved in the study. “But we can’t draw these conclusions from the strength of the data. They absolutely must replicate this.”

The study also falls short of describing the role of the repeats, which cluster in genes of unknown function.

“We still are left with it being a correlation as opposed to some kind of a causation,” says **James Lupski,** professor of molecular and human genetics at Baylor College of Medicine, in Houston, who was not involved in the study.

Lupski also notes that it is challenging to **accurately assess autism severity**. The next step, he says, is to determine how the repeats may drive a large head size and autism symptoms.

Sikela and his team plan to address this question and to look at the five other types of DUF1220 repeats. Because there are more copies of the other subtypes than there are of CON1, they are more challenging to sequence. They may turn out to be more prevalent in people with autism than in controls, he says.

Meanwhile, the human genome may harbor other such families of repeats, undiscovered in reams of sequencing data. Traditional sequencing studies are not able to detect repeated sequences, and as a result, most sequencing studies of autism have “ignored” DUF1220, Sikela says.

“Our study shows that there are parts of the genome that are very important to human disease that have been understudied,” he says. “There could be other, similar things in the genome that are quite important to autism.”

References:

1: Davis J.M. *et al. PLoS Genet.* **10**, e1004241 (2014) **PubMed**

2: Dumas L.J. *et al. Am. J. Hum. Genet.* **91**, 444-454 (2012) **PubMed**

3: Popesco M.C. *et al. Science* **313**, 1304-1307 (2006) **PubMed**