NEWS

Autism risk region arose during human evolution

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H. Schaaffhausen / Wikimedia Commons Human touch: Neanderthals and other early human ancestors may not have been at risk for rearrangements at 16p11.2, which often lead to autism.

Humans may be uniquely prone to rearrangements of chromosome 16 that lead to autism, according to preliminary results presented Saturday at the **2014 American Society of Human Genetics Annual Meeting** in San Diego.

Duplications or deletions of a stretch of chromosome 16, called **16p11.2**, lead to a range of neuropsychiatric symptoms: About **one-quarter of people** with these so-called **copy number variants** (CNVs) have autism.

Most research on 16p11.2 has **focused on the 27 genes** within this 'critical' region, but its flanking regions are also important, says **Xander Nuttle**, a graduate student in **Evan Eichler**'s lab at the University of Washington in Seattle.

CNVs form when duplicated regions that flank these 27 genes bind to each other, then break and re-form at different points. Rearrangement is more likely when these regions are large, and if they are identical to each other.

To see when in evolution these flanking duplications emerged, the researchers looked at the

sequences of more than [2,359] people, [three archaic humans, a Neanderthal, a Denisovan] and 86 nonhuman primates, including chimpanzees, orangutans, gorillas and bonobos. They also created more precise versions of the reference sequence used to identify variation.

They inferred that the genetic structure that leads to CNVs in 16p11.2 arose in the past [282,000] years and is unique to humans. The 16p11.2 region is almost twice the size in humans compared with orangutans, which lack the flanking duplications. The region is also flipped in orientation in chimpanzees versus humans, which leads to different CNVs in chimps than those seen in humans.

The researchers also found that the size of the flanking regions and how well they match each other varies among people. "We predict that there's going to be vast differences in susceptibility for these duplications and deletions among the human population," says Nuttle.

To look at evolution from humans' most recent ancestors, the researchers focused in particular on one gene in the flanking regions, called BOLA2. Neanderthals and Denisovans both diverged from humans about 700,000 years ago and have two copies of BOLA2, one for each chromosome. Looking at human DNA as old as 45,000 years as well as new sequences, the researchers found that people have at least 3 copies of BOLA2, and as many as [8].

The findings suggest that duplication of BOLA2 became 'fixed' during evolution — meaning that once the gene became duplicated, it remained so. That hints that the gene is involved in a human-specific function.

“BOLA2 expanded from unique sequence to high copy number, making it the most rapidly near-fixed duplicate gene of any gene in our genome," says Nuttle. "This suggests that BOLA2 is a human-specific gene."

Researchers have suggested a similar theory for DUF1220 — certain DNA repeats that constitute the greatest increase in the genome between humans and nonhuman primates. A study published in March reported that the number of copies of a type of DUF1220 repeat **tracks with the severity of autism** symptoms.

In the new work, preliminary data from three parents of children with autism suggests that more copies of BOLA2 increase the likelihood of causing a CNV in 16p11.2. Whether BOLA2 also has a human-specific role that is involved in autism is still unclear.

The researchers are analyzing the sequences of 125 people with CNVs in the region to explore this question. "We think that all [16p11.2] deletions are not created equal," says Nuttle.

[In the study, the researchers looked at the sequences of 152 people who carry either a duplication or deletion of the 16p11.2. For 101 of them, the rearrangement begins and ends in the human-specific BOLA2 region, supporting the fact that it is driving the autism-linked variant.]

*For more reports from the 2014 American Society of Human Genetics Annual Meeting, please click **here**.*

REFERENCES:

1. Nuttle X. *et al. Nature* Epub ahead of print (2016) **PubMed**