Study suggests catalyst for human brain evolution

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Researchers from Gladstone Institutes Katie Pollard (right) and Kathleen Keough (left) led a study that found large structural changes to the genomes of our ancestors likely set off a cascade of other rapid changes in human DNA that may underlie uniquely human features, particularly the brain. Credit: Michael Short/Gladstone Institutes

More than a million years ago, large chunks of the human genome were rearranged—a chance event during egg or sperm formation that led to

the deletion, duplication, or reversal of sections of DNA. Those structural variants, researchers have now discovered, likely set off a cascade of other rapid changes in human DNA that may underlie uniquely human features, particularly the brain.

The new finding, published today in *Science* by researchers at Gladstone Institutes, came out of a study analyzing how stretches of DNA called human accelerated regions (HARs) differ between humans and chimpanzees. HARs are nearly identical among all humans, but differ between humans and all other mammals. Researchers have long wondered why these sequences—many of which control brain development—changed so rapidly in early human evolution.

"What we found is that many HARs are in regions of DNA where structural variants caused the genome to fold differently in humans compared to other primates," says Katie Pollard, Ph.D., director of the Gladstone Institute of Data Science and Biotechnology and lead author of the new study. "This gave us an idea how HARs could have arisen in the first place."

Folding like origami

When comparing human and chimpanzee genomes nearly two decades ago, Pollard discovered regions of DNA—now called HARs—that were stable in mammals for millennia, but suddenly changed in early humans. Her lab has since shown that most HARs are enhancers, short stretches of DNA that regulate the activity of genes related to brain development. But researchers still have many questions about how HARs came about and the role they play in making humans distinct from other primates.

Pollard and her colleagues wondered whether other changes to the DNA surrounding HARs might help explain their origin. In collaboration with The Zoonomia Project, an international collaboration to study

mammalian genomes, the researchers analyzed HARs and their surroundings in 241 mammalian genomes. They concluded that HARs tend to be located in areas of the human genome that have large structural differences when compared to other mammals.

So, the scientists next probed whether the structural variations around HARs might have changed the way the DNA folded.

"The way the genome folds up in three-dimensional space like origami is particularly important for enhancers," explains Pollard, who is also a professor at UC San Francisco and a Chan Zuckerberg Biohub investigator. "That's because enhancers can impact the activity of any gene that ends up close by, which can vary depending on how DNA is folded."

To study the relationship between HARs and DNA folding, Pollard's team used a machine learning model they previously developed to predict DNA folding patterns, and applied it to human and chimpanzee DNA sequences. Then, they identified the regions of the genome that folded differently in humans. The computer predicted that nearly 30 percent of HARs were in areas of the genome that folded differently in humans compared to chimpanzees.

"We realized that these human-specific structural changes may have created the right environment for HARs to evolve fast in the human ancestor, after remaining almost the same over millions of years of mammal evolution," said Kathleen Keough, Ph.D., first author of the study and former postdoctoral scholar in the Pollard lab at Gladstone.

Piecing together the past

If DNA near HARs folded differently in humans and brought different genes in proximity to HARs, this could have had drastic consequences

for our ancestors.

"Imagine you're an enhancer controlling blood hormone levels, and then the DNA folds in a new way and suddenly, you're sitting next to a neurotransmitter gene and need to regulate chemical levels in the brain instead of in the blood," says Pollard. "Your instructions are now out-of-date and need to be changed."

The predictions from the machine learning model suggested that large structural changes had occurred near HARs, but did not demonstrate which genes had fallen under their control. To address that question, Pollard and her colleagues carried out lab experiments that let them determine, in human and chimpanzee brain cells they derived from stem cells, what stretches of DNA were closest to hundreds of different HARs.

In many cases, they found, the human HARs were close to genes known to play a role in brain development; in some instances, the nearby genes were also associated with neurodevelopmental or psychiatric diseases.

Pollard's team recently reported that the variations that rapidly appeared in HARs during early human evolution often opposed each other, first turning up the activity of an enhancer and then turning it down, or vice versa. The new results, she says, fit in well with the model proposed in that study.

"Something big happens like this massive change in genome folding, and our cells have to quickly fix it to avoid an evolutionary disadvantage," said Pollard. "But the fix might kind of overdo it and need to be refined over time."

While the new paper helps answer how HARs may have emerged in the beginning, Pollard's team still has questions they plan to follow up on

about why the massive structural changes survived the test of time and how HARs impact human brain development.

More information: Kathleen C. Keough et al, Three-dimensional genome re-wiring in loci with human accelerated regions, *Science* (2023). DOI: 10.1126/science.abm1696.
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