Researchers focus on function to help identify genetic changes that made us human

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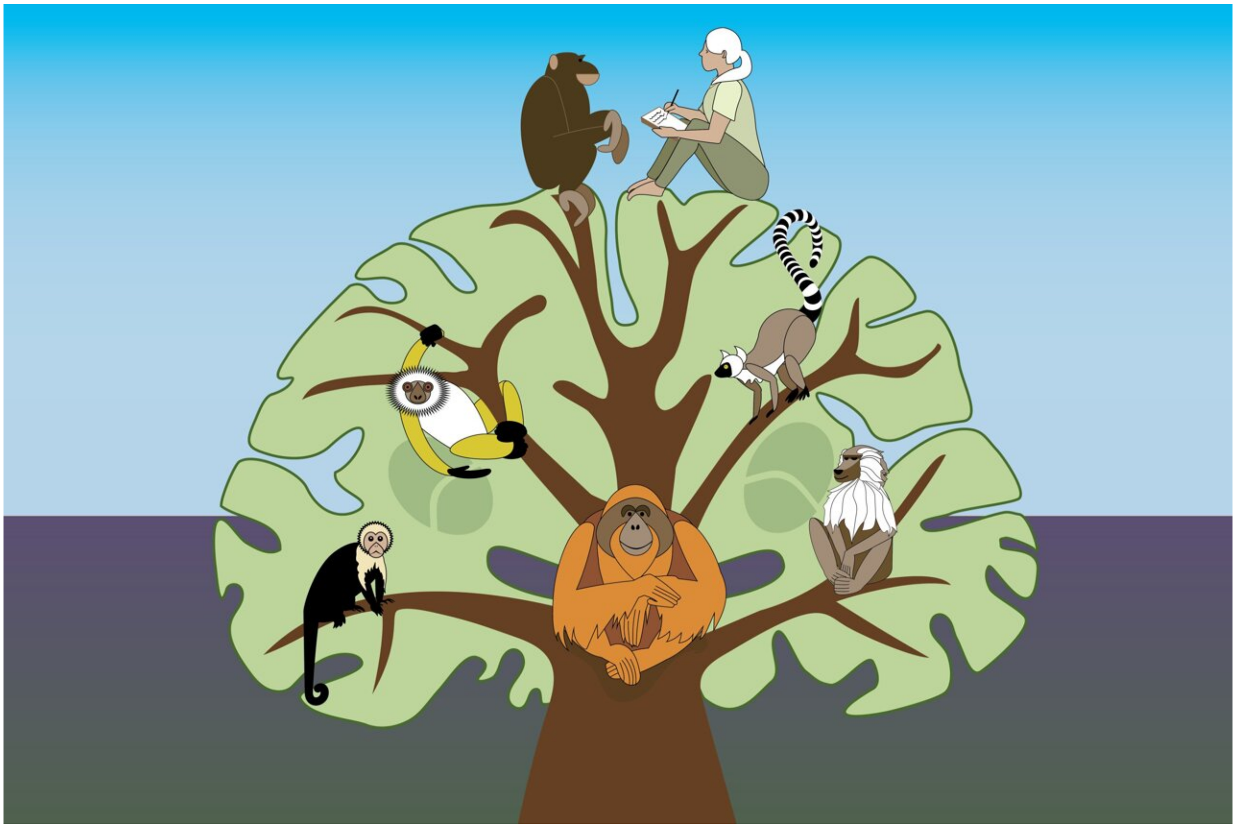

Research from Whitehead Institute Member Jonathan Weissman and colleagues sheds light on human evolution, and demonstrates an approach for identifying significant differences in how genes are used between closely-related species. Credit: Jennifer Cook-Chrysos/ Whitehead Institute

Humans split away from our closest animal relatives, chimpanzees, and formed our own branch on the evolutionary tree about seven million years ago. In the time since—brief, from an evolutionary perspective—our ancestors evolved the traits that make us human, including a much bigger brain than chimpanzees and bodies that are better suited to walking on two feet. These physical differences are underpinned by subtle changes at the level of our DNA. However, it can be hard to tell which of the many small genetic differences between us and chimps have been significant to our evolution.

New research from Whitehead Institute Member Jonathan Weissman; University of California, San Francisco Assistant Professor Alex Pollen; Weissman lab postdoc Richard She; Pollen lab graduate student Tyler Fair; and colleagues uses cutting edge tools developed in the Weissman lab to narrow in on the key differences in how humans and chimps rely on certain genes. Their findings, published in the journal *Cell* on June 20, may provide unique clues into how humans and chimps have evolved, including how humans became able to grow comparatively large brains.

Studying function rather than genetic code

Only a handful of genes are fundamentally different between humans and chimps; the rest of the two species' genes are typically nearly identical. Differences between the species often come down to when and how cells use those nearly identical genes. However, only some of the many differences in gene use between the two species underlie big changes in physical traits. The researchers developed an approach to narrow in on these impactful differences.

Their approach, using stem cells derived from human and chimp skin samples, relies on a tool called CRISPR interference (CRISPRi) that Weissman's lab developed. CRISPRi uses a modified version of the CRISPR/Cas9 gene editing system to effectively turn off individual genes. The researchers used CRISPRi to turn off each gene one at a time in a group of human stem cells and a group of chimp stem cells.

Then they looked to see whether or not the cells multiplied at their normal rate. If the cells stopped multiplying as quickly or stopped altogether, then the gene that had been turned off was considered essential: a gene that the cells need to be active—producing a protein product—in order to thrive. The researchers looked for instances in which a gene was essential in one species but not the other as a way of exploring if and how there were fundamental differences in the basic ways that human and chimp cells function.

By looking for differences in how cells function with particular genes disabled, rather than looking at differences in the DNA sequence or expression of genes, the approach ignores differences that do not appear to impact cells. If a difference in gene use between species has a large, measurable effect at the level of the cell, this likely reflects a meaningful difference between the species at a larger physical scale, and so the genes identified in this way are likely to be relevant to the distinguishing features that have emerged over human and chimp evolution.

"The problem with looking at expression changes or changes in DNA sequences is that there are many of them and their functional importance is unclear," says Weissman, who is also a professor of biology at the Massachusetts Institute of Technology and an Investigator with the Howard Hughes Medical Institute. "This approach looks at changes in how genes interact to perform key biological processes, and what we see by doing that is that, even on the short timescale of human evolution, there has been fundamental rewiring of cells."

After the CRISPRi experiments were completed, She compiled a list of the genes that appeared to be essential in one species but not the other. Then he looked for patterns.

Many of the 75 genes identified by the experiments clustered together in the same pathways, meaning the clusters were involved in the same biological processes. This is what the researchers hoped to see. Individual small changes in gene use may not have much of an effect, but when those changes accumulate in the same biological pathway or process, collectively they can cause a substantive change in the species. When the researchers' approach identified genes that cluster in the same processes, this suggested to them that their approach had worked and that the genes were likely involved in human and chimp evolution.

"Isolating the genetic changes that made us human has been compared to searching for needles in a haystack because there are millions of genetic differences, and most are likely to have negligible effects on traits," Pollen says. "However, we know that there are lots of small effect mutations that in aggregate may account for many species differences. This new approach allows us to study these aggregate effects, enabling us to weigh the impact of the haystack on cellular functions."

Researchers think bigger brains may rely on genes regulating how quickly cells divide

One cluster on the list stood out to the researchers: a group of genes essential to chimps, but not to humans, that help to control the cell cycle, which regulates when and how cells decide to divide. Cell cycle regulation has long been hypothesized to play a role in the evolution of humans' large brains. The hypothesis goes like this: Neural progenitors are the cells that will become neurons and other brain cells. Before becoming mature brain cells, neural progenitors divide multiple times to make more of themselves. The more divisions that the neural progenitors undergo, the more cells the brain will ultimately contain—and so, the bigger it will be.

Researchers think that something changed during human evolution to allow neural progenitors to spend less time in a non-dividing phase of the cell cycle and transition more quickly towards division. This simple difference would lead to additional divisions, each of which could essentially double the final number of brain cells.

Consistent with the popular hypothesis that human neural progenitors may undergo more divisions, resulting in a larger brain, the researchers found that several genes that help cells to transition more quickly through the cell cycle are essential in chimp neural progenitor cells but not in human cells.

When chimp neural progenitor cells lose these genes, they linger in a non-dividing phase, but when human cells lose them, they keep cycling and dividing. These findings suggest that human neural progenitors may be better able to withstand stresses—such as the loss of cell cycle genes—that would limit the number of divisions the cells undergo, enabling humans to produce enough cells to build a larger brain.

"This hypothesis has been around for a long time, and I think our study is among the first to show that there is in fact a species difference in how the cell cycle is regulated in neural progenitors," She says. "We had no idea going in which genes our approach would highlight, and it was really exciting when we saw that one of our strongest findings matched and expanded on this existing hypothesis."

More subjects lead to more robust results

Research comparing chimps to humans often uses samples from only one or two individuals from each species, but this study used samples from six humans and six chimps. By making sure that the patterns they observed were consistent across multiple individuals of each species, the researchers could avoid mistaking the naturally occurring genetic variation between individuals as representative of the whole species. This allowed them to be confident that the differences they identified were truly differences between species.

The researchers also compared their findings for chimps and humans to orangutans, which split from the other species earlier in our shared evolutionary history. This allowed them to figure out where on the evolutionary tree a change in gene use most likely occurred. If a gene is essential in both chimps and orangutans, then it was likely essential in the shared ancestor of all three species; it's more likely for a particular difference to have evolved once, in a common ancestor, than to have evolved independently multiple times. If the same gene is no longer essential in humans, then its role most likely shifted after humans split from chimps.

Using this system, the researchers showed that the changes in cell cycle regulation occurred during human evolution, consistent with the proposal that they contributed to the expansion of the brain in humans.

The researchers hope that their work not only improves our understanding of human and chimp evolution, but also demonstrates the strength of the CRISPRi approach for studying human evolution and other areas of human biology. Researchers in the Weissman and Pollen labs are now using the approach to better understand human diseases—looking for the subtle differences in gene use that may underlie important traits such as whether someone is at risk of developing a disease, or how they will respond to a medication.

The researchers anticipate that their approach will enable them to sort through many small genetic differences between people to narrow in on impactful ones underlying traits in health and disease, just as the approach enabled them to narrow in on the evolutionary changes that helped make us human.

More information: Alex A Pollen, Comparative landscape of genetic dependencies in human and chimpanzee stem cells, *Cell* (2023). DOI: 10.1016/j.cell.2023.05.043.
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