Transcription factors guide differences in human and chimp brain function

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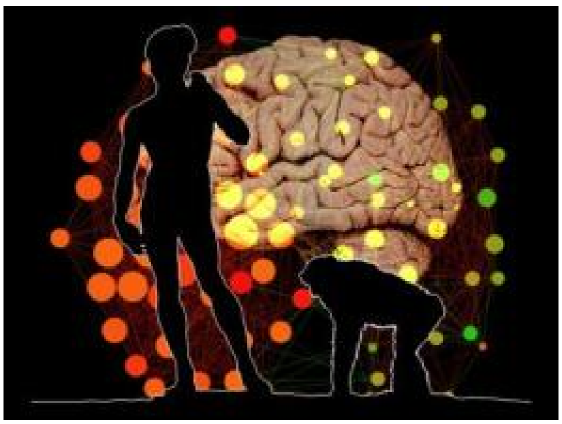


Gene regulatory networks differ between human and chimp brains, the researchers found. Credit: Image: Edwin Hadley, University of Illinois.

Humans share at least 97 percent of their genes with chimpanzees, but, as a new study of transcription factors makes clear, what you have in your genome may be less important than how you use it.

The study, in Proceedings of the National Academy of Sciences, found that broad differences in the gene activity of humans and of chimpanzees, affecting nearly 1,000 genes, appear to be linked to the action of about 90 transcription factors.

Transcription factors are proteins that bind to specific regions of the DNA to promote or repress the activity of many genes. A single transcription factor can spur the transcription of dozens of genes into messenger RNA (mRNA), which is then translated into proteins that do the work of the cell. This allows specific organs or tissues to quickly ramp up a response to an environmental change or internal need.

Previous studies have found differences in gene expression between humans and chimps, particularly in the brain. Genes involved in metabolism or protein transport, for example, are translated into mRNAs at a much higher level in human brains than in the smaller brains of chimpanzees.

This makes sense, said University of Illinois cell and developmental biology professor Lisa Stubbs, who led the new analysis with postdoctoral researcher Katja Nowick.

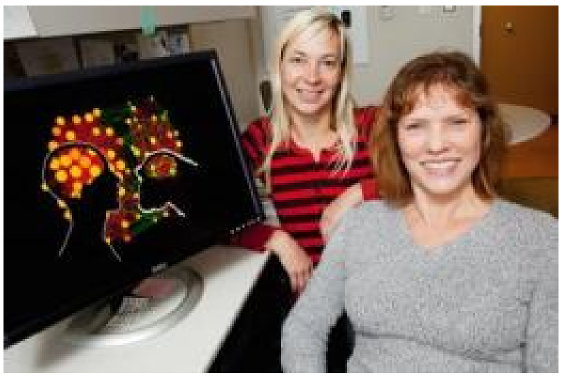
"These differences fit what we know because the human brain is so much larger and proteins need to be shuttled a long way out to the synapses," Stubbs said. "A higher requirement for metabolic energy has also been demonstrated independently for human brains."

What wasn't clear from previous studies was how this upsurge in gene activity was coordinated, she said.

Stubbs has had a longtime interest in the evolutionary role of transcription factors and other regulatory agents in the genome. She is particularly interested in the largest family of transcription factors in mammals, the KRAB zinc finger (KRAB-ZNF) genes, which on average have accumulated more differences in sequence between humans and chimps than other genes.

"There are a lot of unique new transcription factors that arise in this family," Stubbs said. "And they arise by duplication of older genes. So the genes make a new copy of themselves and then that new copy takes on a slightly different or even dramatically different function."

"Our very strong bias is to believe that these transcription factors are involved in speciation and traits that make species unique," she said.



Cell and developmental biology professor Lisa Stubbs (right) and postdoctoral researcher Katja Nowick found distinct differences in gene activity between humans and chimps. These differences are associated with about 90 transcription factors, they found. Credit: Photo by L. Brian Stauffer, U. of I. News Bureau.

Nowick, who studies human and primate evolution, was part of a team (at the Max Planck Institute for Evolutionary Anthropology, in Leipzig, Germany) that analyzed differences in gene expression between humans and chimps.

In the new study, Nowick and computer scientist Tim Gernat, a co-author, took a new look at data from that study, which tracked gene expression - including genes coding for transcription factors - in tissues from six humans and five chimpanzees.

"Katja and Tim came up with a strategy for cleaning up the data and looking at these genes more uniquely," Stubbs said. "It hadn't been done before."

The analysis revealed a broad pattern of activity in 90 transcription factors that paralleled the activity of about 1,000 genes in humans and chimps.

The KRAB-ZNF genes were the most common members of this group, but many other transcription factors were also involved. Some were activators and some were repressors, but their activity coincided with a general upsurge of these genes in human brains.

Eivind Almaas, a researcher at the Norwegian University of Science and Technology and a co-author on the study, developed a gene regulatory network diagram of the transcription factors in relation to the genes that rise or fall with them. The proximity of one transcription factor to another in the network depended on the degree of overlap of the lists of genes that correlate with each. Almaas created one network diagram for humans and another for chimps, and uncovered some interesting differences.

"The chimp network looks very much like the human one except there are a few transcription factors in different positions and with different connectivity," Stubbs said. "Those are of interest from the point of view that they signal a major gene regulatory shift between species, and this shift may help us explain some of the biological differences."

The new findings indicate that certain transcription factors are working together in a coordinated way to regulate the changes in seen in gene expression between humans and chimps, the researchers said.

"Once this network of transcription factors is established, changes in the network can be amplified because transcription factors control other genes," Nowick said. "Even a small change in transcription factor expression can therefore produce a large effect on overall gene expression differences between chimpanzees and humans."

Source: University of Illinois at Urbana-Champaign (news : web)