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Gene regulation differences between humans and chimpanzees more complex than thought

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Changes in gene regulation have been used to study the evolutionary chasm that exists between humans and chimpanzees despite their largely identical DNA. However, scientists from the University of Chicago have discovered that mRNA expression levels, long considered a barometer for differences in gene regulation, often do not reflect differences in protein expression—and, therefore, biological function—between humans and chimpanzees. The work was published Oct. 17 in *Science*.

"We thought that we knew how to identify patterns of mRNA expression level differences between humans and chimpanzees that would be good candidates to be of functional importance," said Yoav Gilad, PhD, Professor of Human Genetics at the University of Chicago. "Now we see that even such mRNA patterns are not translated to the protein level. Which means that it is unlikely that they can affect a functional phenotypic difference."

For genes to be expressed, DNA must be transcribed into messenger RNA (mRNA), which then code for proteins, the biological building blocks and engines that drive cellular function. Although humans and chimpanzees share highly similar genomes, previous studies have shown that the species evolved major differences in mRNA expression levels. Many of these differences were thought to indicate areas of evolutionary divergence, thus pointing to genes important for human-specific traits.

To test this, Gilad, Jonathan Pritchard, PhD, currently at Stanford University, and their team, spearheaded by postdoctoral fellow Zia

Khan, PhD, used high-resolution mass spectrometry to compare the expression levels of thousands of proteins with corresponding mRNA expression data in human and chimpanzee cell lines.

The team found 815 genes with differing mRNA expression levels but only 571 genes that differed in protein expression. In total, they identified an estimated 266 genes with mRNA differences that did not lead to changes in protein levels. They found similar results in rhesus macaque cell lines when compared to both chimpanzees and humans, confirming the trend.

"Some of these patterns of mRNA regulation have previously been thought of as evidence of natural selection for important genes in humans, but this can no longer be assumed," Gilad said.

The study raises questions over why mRNA expression levels differ between species if they do not necessarily cause protein differences. Although further study is needed, Gilad believes this study suggests that protein expression levels evolve under greater evolutionary constraint than mRNA levels, via a yet-uncharacterized compensation or buffering mechanism.

For now, research that uses mRNA expression levels as a measure of the functional importance of a gene requires reassessment, and not just in studies on evolution.

"We've gained insight into complex diseases by studying mRNA transcripts, but we also have a lot of gaping holes in our knowledge. Perhaps some of them are because of this disparity," Gilad said.

More information: Primate Transcript and Protein Expression Levels Evolve under Compensatory Selection Pressures, *Science*, 2013.

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