Young human-specific genes correlated with human brain evolution

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Young genes that appeared since the primate branch split from other mammal species are expressed in unique structures of the developing human brain, a new analysis finds.

The correlation suggests that scientists studying the evolution of the human brain should look to genes considered recent by evolutionary standards and early stages of brain development.

"There is a correlation between the new gene origination and the evolution of the brain," said Manyuan Long, PhD, Professor of Ecology & Evolution at the University of Chicago and senior author of the study in *PLoS Biology*. "We're not talking about one or two genes, we're talking about many genes. This is a process that is continually moving and changing our brain."

Scientists have long sought to solve how the brain evolved to have the anatomical features and functional ability that separate humans from their primate ancestors. With the completion of the Human Genome Project in 2003 and the growing availability of genome sequences for primates and other species, researchers have looked to genetics for answers on brain evolution.

From these studies, many scientists have hypothesized that differential regulation of conserved genes shared across species, rather than the arrival of new species-specific protein-encoding genes, was responsible for the dramatically different human brain. But in a 2010 study, Long's

laboratory discovered that the younger species-specific genes could be just as important as older conserved genes to an organism's development.

For the PLoS Biology paper, researchers merged a database of gene age with transcription data from humans and mice to look for when and where young genes specific to each species were expressed.

The researchers found that a higher percentage of primate-specific young genes were expressed in the brain compared to mouse-specific young genes. Human-specific young genes also were more likely to be expressed in the recently expanded human brain structures, such as the neocortex and prefrontal cortex.

"Newer genes are found in newer parts of the human brain," said Yong Zhang, PhD, postdoctoral researcher and first author on the study. "We know the brain is the most remarkable difference between humans and other mammals and primates. These new genes are a candidate for future studies, as they are more likely to underlie this difference."

The timing of when the young human-specific genes are expressed in the brain also intrigued the researchers. Inspired by an ultrasound appointment with his pregnant wife, Zhang calculated when young genes were expressed in the human brain, discovering that they were more likely to appear during fetal or infant development.

The early activity of these genes suggests scientists should be looking at earlier developmental stages for genetic activity that ultimately shapes the complexity of the human brain.

"What's really surprising is that the evolutionary newest genes on the block act early," said co-author Patrick Landback, a graduate student in Long's laboratory. "The primate-specific genes act before birth, even when a human embryo doesn't look very different from a mouse

embryo. But the actual differences are laid out early."

Thus far, researchers comparing adult brains between species have focused on regulatory differences as the primary driver of evolutionary changes. But the new research suggests that new genes with novel functions may have also played an important, previously overlooked role in the evolution of the human brain.

"Traditionally, people don't believe that a new protein or a new gene can play any role in an important process. Most people pay attention to only the regulation of genes," Long said. "But out of a total of about 1,300 new genes, only 13 percent were involved in new regulation. The rest, some 1,100 genes, are new genes that bring a whole new type of function."

Future research will look at the function of these genes and the role they may have played in building the unique human brain.

"People tend to study genes that are old functions present in organisms, and not those from new genes," said Maria Vibranovski, PhD, study co-author and research assistant professor. "This work will open a window such that people will start working in these new genes to try to figure out what exactly the functions are."

For now, the authors stress that their finding is only a correlation between the appearance of young human-specific genes and the evolutionary appearance of advanced brain structures. More data will need to be collected on the timing and location of gene expression in non-human primates to determine precisely which new genes and biological functions contributed to the evolution of the human brain.

"We don't know if this observation has any causation biologically, and there is a long way to go from there, but this correlation can predict

some future work to do," Long said.

More information: Zhang YE, Landback P, Vibranovski MD, Long M (2011) Accelerated Recruitment of New Brain Development Genes into the Human Genome. *PLoS Biol* 9(10): e1001179. doi:10.1371/journal.pbio.1001179

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