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At the molecular level, man and monkey experience surprisingly similar changes during brain development

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A Skoltech-led team of scientists has peered into the brains of humans, macaques and chimpanzees to discover surprising similarities. In particular, they focused on alternative splicing during various stages of brain development in these three species. The study also provides some interesting insights into the role played by alternative splicing in the context of human evolution.

In conducting their study, the scientists focused on alternative splicing, one of the most mysterious processes that occurs in cells. It is the process by which one gene product can be combined in different ways, causing variability in the matrix RNA molecule that codes proteins. Due to this event, one gene is able to produce different types of RNA molecules and different types of proteins, respectively. It is believed that alternative splicing events take place with 95 percent of our genes, and in some cases, it results in alternative proteins.

Previous studies have shown changes in alternative splicing both during normal development and as a consequence of disease. And these changes play an important role in the overall functioning of an organism. Other studies have shown that alternative splicing changes rapidly during evolution. If we compare alternative splicing in different tissues of the same organism and in the same tissue in different organisms, then the differences in the first case, oddly enough, will be less. These two observations raise a new and interesting question: Can alternative

splicing carry out important functions if it evolves so quickly? Scientists generally accept the fact that the mechanisms responsible for the most important processes in our body evolve very slowly and extremely conservatively over the course of millions of years—they are too important to change.

In their latest study, researchers from Skoltech and the University of Shanghai analyzed alternative splicing on a batch of 168 brain samples from humans, chimpanzees and rhesus macaques. The prefrontal cortex was the focus of their study. The most mysterious part of the brain cortex, the prefrontal cortex is responsible for complex mental activities such as making decisions and drawing up action plans. The team was interested in how alternative splicing events change during individual development. Was the choice of an alternative variant of a particular protein responsible for the differences between humans and monkeys?

It turned out that the differences in splicing between individual species were much greater than the differences between different stages of development. However, although changes in the course of development do not occur very often, they are highly conservative in all three studied species. The scientists discovered mutations that explain the majority of strong interspecific splicing differences, and identify more than 20 proteins that regulate age-related changes. Notably, despite the high conservatism of alternative splicing demonstrated by scientists, humans have more age-related changes in alternative splicing than other primates

Professor Mikhail Gelfand says, "It is well known that humans, in comparison with other primates, are born prematurely. It can be assumed that the human-specific variants that we observe characterize the earlier stages in brain formation and contribute to the brain plasticity that is characteristic of man."

Skoltech research scientist Pavel Mazin, the study's lead author, said,

"Alternative splicing is considered a very important mechanism, which plays a key role in the development of the nervous system. We were wondering how much it could differ between species, as was shown in earlier studies? It seems that in fact an important part of splicing does not change as fast as we previously thought."

The results of the study have been published in the Journal RNA.

More information: Mazin, P. V., Jiang, X., Fu, N., Han, D., Guo, M., Gelfand, M. S., & Khaitovich, P. (2018). Conservation, evolution, and regulation of splicing during prefrontal cortex development in humans, chimpanzees and macaques. *Rna*. DOI: 10.1261/rna.064931.117

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