Splicing sites evolution in primates prefrontal cortex

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Human and chimpanzee brains are very similar in its structure and development, but there are significant differences between them, genetic basis of which is poorly understood. In addition to a larger volume of the human brain, human has higher dendrite, spine, axon density and higher glia to neuron ratio. At the same time, there are only small differences in the amino acid sequence between human and chimpanzee, so regulation of the processes of transcription and translation may play a decisive role in the evolution of the brain. Recently, was shown that genes involved in processes of synapse formation and neuronal development showed significant differences in expression levels between humans and chimpanzee. Alternative splicing is the process that allows single gene to produce several mRNAs. Alternative splicing plays an important role in the regulation of the work and development of the brain. Conserved sequences at intron ends, called splicing sites, are required for splicing, and involved in the regulation of the alternative splicing.

Here we used RNA-seq data of human, chimpanzee and macaque brains (119 samples) to create unbiased, not-human-based annotation for all three genomes to get lineages-specific splicing sites of human and chimpanzee. We used very sensitive methods for identification of gained and lost splicing sites in the human and chimpanzee lineages using macaque as outgroup. Comparison of number of the gained and lost sites have shown a significant excess of the gained sites in both human and chimpanzee lineages. We have not found any difference in the lineage-specific sites abundance between human and chimpanzee. Most of the new gained lineage-specific sites appearing in a few samples. Analysis of the single nucleotide polymorphism of new gained human splicing sites has shown a significantly higher level of polymorphism in the human population as compared to control sites. These observations point to the contribution of the nucleotide polymorphism to the new human splicing sites polymorphism. The number of single nucleotide substitutions between the genomes increased in new

human-specific splice sites. We have found prominent strengthen of novel human-specific splice sites compared with ancestral state. We have shown that proteins involved in synaptic transmission and brain development enriched in human proteins with human-specific splicing. Genes with human-specific splicing participate in the signal path of long-term potentiation, long-term potentiation widely considered one of the major cellular mechanisms that underlies learning and memory.

Thus, we have shown that splicing sites used in brain are accumulated under recent evolution of human and chimpanzee. Functional analysis reveals that genes with human-, but not chimpanzee specific splicing are involved in numerous processes linked to brain development.