# Evolution of brain active gene promoters in human lineage towards the increased plasticity of gene regulation

Konstantin V. Gunbin[1,2,3]

[1]*Center of Brain Neurobiology and Neurogenetics, Institute of Cytology and Genetics SB RAS, Lavrentyeva ave. 10, 630090, Novosibirsk, Russia;*

[2]*Systems Biology Department, Institute of Cytology and Genetics SB RAS, Lavrentyeva ave. 10, 630090, Novosibirsk, Russia;*

[3]*Novosibirsk State University, Pirogova str., 2, 630090, Novosibirsk, Russia;*

genkvg@gmail.com

Mikhail P. Ponomarenko[2,3], Valentin V. Suslov[2,3], Fedor Gusev[1,4,5], Gennady G. Fedonin[1,4] and Evgeny I. Rogaev[1,4,5]

[4] *Vavilov Institute of General Genetics RAS, Gubkina str., 3, 119333, Moscow, Russia;*

[5] *University of Massachusetts Medical School, Brudnick Neuropsychiatric Research Institute, 55,*

evgeny.rogaev@umassmed.edu

Comparative genomic analysis demonstrated ~98-99% of the identity of protein-coding gene sequences of humans and chimpanzees or gorillas, which is in sharp contrast with the significant morphological, physiological and ecological differences between these species. Therefore, it would reasonable to anticipate the elevated rate of alterations in evolution of certain neuorogenes in the human-specific lineage. However, to date a very few genes have been found showing prominent brain-specific expression along with a signature of an adaptive evolution of protein-coding sequences in humans, but not in other anthropoids. Missense- or loss-of-function mutations in genes showing accelerated evolution in human lineage may lead to severe pathologies and can be deleterious in human and animal populations. It is conceivable that the selection acting on compensatory genetic variants interfering with deleterious mutations may also contribute to the process of adaptive evolution. Modern humans possess at least one feature that makes them be strongly different from anthropoids (chimpanzee and gorilla): the broad tolerances to the environment or, as Th. Dobzhansky spoke– “man is genetically specialized to be unspecialized”. As a result, humans

can live in a broad spectrum of habitats and landscapes, spreading across the continents. This broad tolerance to the environment is associated with a widening norm-of-reaction of the genotype. Consequently, the sought-for hominoid-specific vector of selection may have been directed at widening the norm-of-reaction, that is, being associated not so much with the reduced or increased level of expression of the specific genes as with the enhanced regulatory plasticity of the genes or ability to vary the gene expression level within a broad range. To our knowledge, no search for evidence of such selection using whole-genome data has been performed as yet.

In this study [1], we focused on the structural and functional evolution of the core promoters of human genes. At present, the location of a gene promoter is considered to be clearly determined if more than one independent experimental approaches identifies the same position. In this study, the positions of promoters were inferred from two independent sources of experimental information: (1) CAGE data obtained from a large number of tissue-specific experiments, and (2) ChIP-seq data revealing the presence of transcriptionally active promoters in certain genomic regions marked by trimethylated histones H3K4 (H3K4me3), a chromatin protein associated with transcriptional start sites (TSS). According to modern views, transcription does not proceed continuously, but by jerks called “transcriptional bursts”, the magnitude of which “is a promoter-specific property that is relatively robust to sequence mutations but is strongly dependent on the interaction between the TATA box and promoter nucleosomes”, which, in turn, is dependent on the abundance of CG dinucleotides in the promoter. Moreover, there are a plenty of papers arguing whether increasing CpG sites (DNA regions enriched with CG dinucleotides) in a promoter can increase the range of transcriptional levels. Earlier, analysis of ChIP-seq data revealed presence of non-canonical TATA-like sites for binding TBP in the case of TATA-less promoters in mouse. Additionally, in vitro experiments suggested that primary initiation of transcription requires evolutionary conservative TBP, whereas transcription-re-initiation can occur in “TBP-free” assay. That is why the TBP/TATA complex is considered to be necessary anchor on DNA molecule for binding with RNA Pol II and the transcription preinitiation complex. Considering this view, we have performed an analysis of the evolution of three features of the upstream region of core promoter (-600; -1): (1) appearance or disappearance of CG

dinucleotides, (2) predicted nucleosomal packing levels (nucleosome/DNA affinity), and (3) predicted affinity for TATA-binding protein (TBP/DNA affinity). We used a comprehensive set of currently annotated promoters active in neural and non-neural human brain cells.

We used the original set of the data for promoters active in human and ape brain neurons using original ChIP-seq data. Using the computational approaches, we provided the comprehensive evidence for accumulation of mutations leading to increased flexibility of gene promoters functioning specifically in human lineage (Fig. 1). In contrast, after splitting with ancestral lineages of Homo sapiens, the evolution of ape species is characterized by reduced flexibility of promoters functioning (Fig. 1). Widening of the flexibility of gene promoters functioning in human lineage can be connected to the well-known Morris Goodman's hominoid rate slowdown.

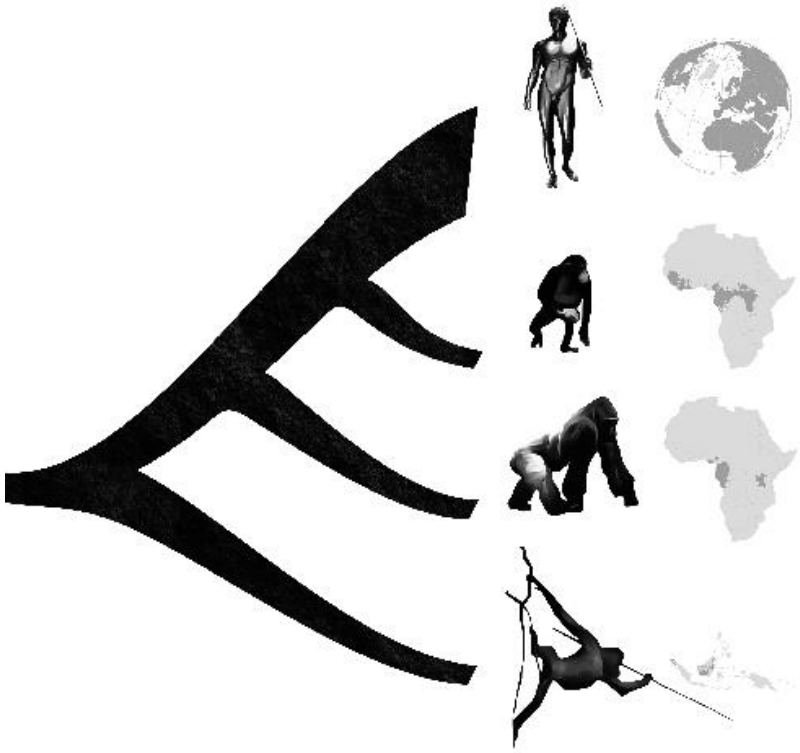

Fig. 1. Plasticity of brain active gene promoters is increased in human lineage and decreased in great ape evolution.

The work supported by grant 14.B25.31.0033 from the government of the Russian Federation (Resolution No.220) and by Russian Science Foundation grant № 14-44-00077 (Alzheimer's disease gene characteristics). MPP was partly supported by grant 17-04-00501 from the Russian Foundation for Basic Research. VVS was partly supported by the project VI.61.1.2 from the Russian State Budget. EIR was supported, in part, by NIH/NIA AG029360.

1. Gunbin KV, Ponomarenko MP, Suslov VV, Gusev F, Fedonin GG, Rogaev EI. Evolution of Brain Active Gene Promoters in Human Lineage Towards the Increased Plasticity of Gene Regulation. Mol Neurobiol. 2017 Feb 24. doi: 10.1007/s12035-017-0427-4.