The evolution of human intellect: Human-specific regulation of neuronal genes

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A new study published November 20 in the open-access journal *PLOS Biology* has identified hundreds of small regions of the genome that appear to be uniquely regulated in human neurons. These regulatory differences distinguish us from other primates, including monkeys and apes, and as neurons are at the core of our unique cognitive abilities, these features may ultimately hold the key to our intellectual prowess (and also to our potential vulnerability to a wide range of 'human-specific' diseases from autism to Alzheimer's).

Exploring which features in the genome separate human neurons from their non-human counterparts has been a challenging task until recently; primate genomes comprise billions of base pairs (the basic building blocks of DNA), and comparisons between the human and chimpanzee genomes alone reveal close to 40 million differences. Most of these are thought to merely reflect random 'genetic drift' during the course of evolution, so the challenge was to identify the small set of changes that have functionally important consequences, as these might help to explain the genomic basis of the emergence of human-specific neuronal function .

The key to the present study, led by Dr Schahram Akbarian of the University of Massachusetts and the Mount Sinai School of Medicine, was not to focus on the "letters" of the DNA code, but rather on what might be called its "font" or "typeface"—the DNA strands of the genome are wrapped in protein to make a chromatin fiber, and the way in which they are wrapped, the "chromatin state", in turn reflects the

regulatory state of that region of the genome (e.g. whether a given gene is turned on or off). This is the field that biologists call "epigenetics"—the study of the "epigenome".

Dr Akbarian and colleagues set out to isolate small snippets of chromatin fibers from the frontal cortex, a brain region involved in complex cognitive operations. They were then able to analyze these snippets for the chemical signals (histone methylation) that define the regulatory state (on/off) of the chromatin. The results of their analysis identified hundreds of regions throughout the genome which showed a markedly different chromatin structure in neurons from human children and adults, compared to chimpanzees and macaques.

This treasure trove of short genomic regions is now providing researchers with interesting new leads involving the evolution of the human brain. Although some of the regions have remained unchanged during primate evolution, some more tantalizing ones have recently changed, having a DNA sequence that is unique to humans and our close extinct relatives, the Neanderthals and the Denisovans. The study also uncovered examples where several of these regulatory DNA regions appear to physically interact with each other inside the cell nucleus, despite being separated by hundreds of thousands of base pairs on the linear genome. This phenomenon of "chromatin looping" is implicated in controlling the expression of neighboring genes, including several with a critical role for human brain development.

The study, from laboratories based in the United States, Switzerland and Russia, draws further attention to the role of epigenetics and the epigenome in our biology and our evolution. As Dr Akbarian notes, "Much about human biology and disease cannot be deduced by simply sequencing the genome. Mapping the epigenome of neurons and other cells will help us to better understand the inner workings of our brain, and where we are coming from."

More information: Shulha HP, Crisci JL, Reshetov D, Tushir JS, Cheung I, et al. (2012) Human-Specific Histone Methylation Signatures at Transcription Start Sites in Prefrontal Neurons. PLoS Biol 10(11): e1001427. doi:10.1371/journal.pbio.1001427