Neuron Cell Stickiness May Hold Key to Evolution of the Human Brain

November 2 2006

The stickiness of human neurons may have been a key factor in why the human brain evolved beyond the brains of our primate relatives. In a study comparing the genomes of humans, chimpanzees, mice and other vertebrates, researchers at the U.S. Department of Energy's Lawrence Berkeley National Laboratory and Joint Genome Institute (JGI) found a strikingly high degree of genetic differences in DNA sequences that appear to regulate genes involved in nerve cell adhesion molecules.

Cell adhesion controls many aspects of brain development including growth and structure, and enables neurons to connect with other neurons and supportive proteins. Differences in the molecular connections of human neurons compared to the neurons of chimps, mice and other animals, could help explain why the human brain is capable of far more complex cognitive functions.

In a paper published in the Nov 3, 2006 issue of the journal *Science*, a team of researchers led by Edward Rubin, MD, director of both JGI and Berkeley Lab's Genomics Division, report on a comparative genomics study of conserved noncoding sequences (CNSs) - sequences of DNA shared by many different organisms that do not code for proteins but play an important role in regulating gene expression. In their Science paper, the researchers identified 992 CNSs whose sequences were specifically modified in humans and enriched near genes involved in neuronal cell adhesion. This is the first genome-wide unbiased study to detect clear evidence of human-specific evolution in brain-related sequences. After further comparisons, the researchers concluded these

CNSs “may have contributed to the uniquely human features of brain development and function.”

The paper is entitled Accelerated evolution of conserved noncoding sequences in the human genome. Co-authoring the paper with Rubin were Shyam Prabhakar and James Noonan of Berkeley Lab, and Svante Pääbo of the Max Planck Institute for Evolutionary Anthropology in Germany.

“One of the big questions in genetics is what are the DNA sequences in the human genome responsible for the capabilities that distinguish us from the rest of the animal kingdom,” said Rubin. “We have long suspected that it would be a combination of DNA sequences coding for genes and DNA sequences that control when genes are switched on or off. In this study by comparing the entire genome of many organisms to that of humans we were able to identify a series of human-specific sequence changes that have a high likelihood of turning genes on and off.”

Homo sapiens share more than 98 percent of their genome with their chimpanzee cousins, but the final products of those genomes are quite dissimilar. Nowhere are these differences more pronounced than in the brain, where the human model is far larger and more complex than those of all other primates. Previous unbiased whole-genome studies that focused on genes have failed to find a broad pattern of human-specific evolution in brain genes. This led the Berkeley Lab researchers to suspect that the genetic basis of human-specific brain evolution might be found in the sequences that regulate genes, rather than the genes themselves.

Rubin is a leading authority on CNSs who has advanced the principle that if evolution has conserved a specific non-coding DNA sequence over many millions of years, the sequence is likely to function as a

switch turning genes on or off. In this latest study, he and his Science co-authors investigated whether CNSs also bear the signature of accelerated evolution.

Explained Prabhakar, who devised the statistical methods and performed most of the computational analysis for this study, “We started with a set of 110,549 CNSs previously identified by whole-genome multiple sequence comparisons and known to have evolved over at least the last 100 million years. We measured the average rate of evolution in the human lineage in these sequences and then identified 992 elements with a significant excess of human-specific nucleotide substitutions relative to the baseline. This is about 79-percent more than we would expect to see by chance at our assigned probability threshold.”

When Prabhakar and Noonan ran an analysis to determine whether the accelerated CNSs disproportionately occurred near genes with particular functions, they discovered that neuronal cell adhesion was the only biological process displaying a significant excess of accelerated CNSs. To determine whether this pattern of accelerated CNSs was repeated in other animals, the researchers performed similar analyses on the chimpanzee and mouse genomes. They examined 1,050 accelerated chimpanzee CNSs and 4,707 accelerated mouse CNSs.

Said Noonan, “While the accelerated chimpanzee CNSs were also significantly enriched near neuronal cell adhesion genes, there was no overlap between them and human DNA sequences, which suggests that the accelerated evolution of adhesion cell function occurred independently in humans and chimpanzees. We failed to detect any CNS enrichment near cell adhesion genes in mice.”

The actual differences in the distribution of neuronal adhesion proteins in human versus chimpanzee brains are currently not known, but the Berkeley Lab-JGI researchers are now conducting experiments to

determine the functional consequences of the accelerated CNSs they've identified.

Said Prabhakar, “On the computational side, we’re trying to identify other kinds of sequence changes that may have played a role in human evolution, such as nucleotide insertions, deletions or duplications, and chromosomal rearrangements.”

Added Rubin, “In hindsight the results of our study make sense since our cognitive abilities are clearly one of the most distinct of all human attributes and we would expect these abilities to result from human-specific aspects of neuronal development. Our results also suggest that analysis of the differences in human and chimpanzee neuronal cell adhesion gene expression is a good place to begin exploring the molecular basis of how humans became so cognitively advanced in the 5 to 6 million years since we shared a common ancestor with chimps.”

Source: Berkeley Lab