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Gene May Be Key to Evolution of Larger Human Brain

Howard Hughes Medical Institute researchers have identified a gene that appears to have played a role in the expansion of the human brain's cerebral cortex—a hallmark of the evolution of humans from other primates.

By comparing the gene's sequence in a range of primates, including humans, as well as non-primate mammals, the scientists found evidence that the pressure of natural selection accelerated changes in the gene, particularly in the primate lineage leading to humans.

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— **Bruce T. Lahn**

The researchers, led by Howard Hughes Medical Institute (HHMI) investigator Bruce Lahn at the University of Chicago, reported their findings in an advance access article published on January 13, 2004, in the journal *Human Molecular Genetics*. Patrick Evans and Jeffrey Anderson in Lahn's laboratory were joint lead authors of the article.

"People have studied the evolution of the brain for a long time, but they have traditionally focused on the comparative anatomy and physiology of brain evolution," said Lahn. "I would venture, however, that there really hasn't been any convincing evidence until now of any gene whose changes might have contributed to the evolution of the brain."

In this study, the researchers focused on a gene called the Abnormal Spindle-Like Microcephaly Associated (*ASPM*) gene. Loss of function of the *ASPM* gene is linked to human microcephaly - a severe reduction in the size of the cerebral cortex, the part of the brain responsible for planning, abstract reasoning and other higher brain function. The discovery of this association by HHMI investigator Christopher A. Walsh and colleagues at Beth Israel Deaconess Medical Center is what prompted Lahn to launch an evolutionary study of the gene.

Lahn and his colleagues compared the sequence of the human *ASPM* gene to that from six other primate species shown genetically to represent key positions in the evolutionary hierarchy leading to *Homo sapiens*. Those species were chimpanzee, gorilla, orangutan, gibbon, macaque and owl monkey.

“We chose these species because they were progressively more closely related to humans,” said Lahn. “For example, the closest relatives to humans are chimpanzees, the next closest are gorillas, and the rest go down the ladder to the most primitive.”

For each species, the researchers identified changes in the *ASPM* gene that altered the structure of the resulting protein, as well as those that did not affect protein structure. Only those genetic changes that alter protein structure are likely to be subject to evolutionary pressure, Lahn said. Changes in the gene that do not alter the protein indicate the overall mutation rate - the background of random mutations from which evolutionary changes arise. Thus, the ratio of the two types of changes gives a measure of the evolution of the gene under the pressure of natural selection.

Lahn and his colleagues found that the *ASPM* gene showed clear evidence of changes accelerated by evolutionary pressure in the lineage leading to humans, and the acceleration is most prominent in recent human evolution after humans parted way from chimpanzees.

“In our work, we have looked at evolution of a large number of genes, and in the vast number of cases, we see only weak signatures of adaptive changes,” said Lahn. “So, I was quite surprised to see that this one gene shows such strong and unambiguous signatures of adaptive evolution—more so than most other genes we’ve studied.”

By contrast, the researchers' analyses of the *ASPM* gene in the more primitive monkeys and in cows, sheep, cats, dogs, mice and rats, showed no accelerated evolutionary change. “The fact that we see this accelerated evolution of *ASPM* specifically in the primate lineage leading to humans, and not in these other mammals, makes a good case that the human lineage is special,” said Lahn.

According to Lahn, among the next steps in his research will be to understand how *ASPM* functions in the brain. Studies by Walsh and others hint that the protein produced by the gene might regulate the number of neurons produced by cell division in the cerebral cortex. Lahn and his colleagues plan functional comparisons of the *ASPM* protein among different species, to understand how this gene's function or regulation changes with evolution.