

DECEMBER 29, 2004

Human Brain Evolution Was a 'Special Event'

Genes that control the size and complexity of the brain have undergone much more rapid evolution in humans than in non-human primates or other mammals, according to a new study by Howard Hughes Medical Institute researchers.

The accelerated evolution of these genes in the human lineage was apparently driven by strong selection. In the ancestors of humans, having bigger and more complex brains appears to have carried a particularly large advantage, much more so than for other mammals. These traits allowed individuals with “better brains” to leave behind more descendants. As a result, genetic mutations that produced bigger and more complex brains spread in the population very quickly. This led ultimately to a dramatic “speeding up” of evolution in genes controlling brain size and complexity.

“People in many fields, including evolutionary biology, anthropology and sociology, have long debated whether the evolution of the human brain was a special event,” said senior author Bruce Lahn of the Howard Hughes Medical Institute at the University of Chicago. “I believe that our study settles this question by showing that it was.”

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Lahn and his colleagues reported their data in a research article published in the December 29, 2004, issue of the journal *Cell*.

The researchers focused their study on 214 brain-related genes, that is, genes involved in controlling brain development and function. They examined how the DNA sequences of these genes changed over evolutionary time in four species: humans, macaque monkeys, rats, and mice. Humans and macaques shared a common ancestor 20-25 million years ago, whereas rats and mice are separated by 16-23 million years of evolution. All four species shared a common ancestor about 80 million years ago.

Humans have extraordinarily large and complex brains, even when compared with macaques and other non-human primates. The human brain is several times larger than that of the macaque—even after correcting for body size—and “it is far more complicated in terms of structure,” said Lahn.

For each gene, Lahn and his colleagues counted the number of changes in the DNA sequence that altered the protein produced by the gene. They then obtained the rate of evolution for that gene by scaling the number of DNA changes to the amount of evolutionary time taken to make those changes.

By this measure, brain-related genes evolved much faster in humans and macaques than in mice and rats. In addition, the rate of evolution has been far greater in the lineage leading to humans than in the lineage leading to macaques.

This accelerated rate of evolution is consistent with the presence of selective forces in the human lineage that strongly favored larger and more complex brains. “The human lineage appears to have been subjected to very different selective regimes compared to most other lineages,” said Lahn. “Selection for greater intelligence and hence larger and more complex brains is far more intense during human evolution than during the evolution of other mammals.”

To further examine the role of selection in the evolution of brain-related genes, Lahn and his colleagues divided these genes into two groups. One group contained genes involved in the development of the brain during embryonic, fetal and infancy stages. The other group consisted of genes involved in “housekeeping” functions of the brain necessary for neural cells to live and function. If intensified selection indeed drove the dramatic changes in the size and organization of the brain, the developmental genes would be expected to change faster than the housekeeping genes during human evolution. Sure enough, Lahn's group found that the developmental genes showed much higher rates of change than the housekeeping genes.

In addition to uncovering the overall trend that brain-related genes—particularly those involved in brain development—evolved significantly faster in the human lineage, the study also uncovered two dozen “outlier” genes that might have made important contributions to the evolution of the human brain. These outlier genes were identified by virtue of the fact that their rate of change is especially accelerated in the human lineage, far

more so than the other genes examined in the study. Strikingly, most of these outlier genes are involved in controlling either the overall size or the behavioral output of the brain—aspects of the brain that have changed the most during human evolution.

According to graduate student Eric Vallender, a coauthor of the article, it is entirely possible by chance that two or three of these outlier genes might be involved in controlling brain size or behavior. “But we see a lot more than a couple—more like 17 out of the two dozen outliers,” he said. Thus, according to Lahn, genes controlling the overall size and behavioral output of the brain are perhaps places of the genome where nature has done the most amount of tinkering in the process of creating the powerful brain that humans possess today.

There is “no question” that Lahn's group has uncovered evidence of selection, said Ajit Varki of the University of California, San Diego. Furthermore, by choosing to look at specific genes, Lahn and his colleagues have demonstrated “that the candidate gene approach is alive and well,” said Varki. “They have found lots of interesting things.”

One of the study's major surprises is the relatively large number of genes that have contributed to human brain evolution. “For a long time, people have debated about the genetic underpinning of human brain evolution,” said Lahn. “Is it a few mutations in a few genes, a lot of mutations in a few genes, or a lot of mutations in a lot of genes? The answer appears to be a lot of mutations in a lot of genes. We've done a rough calculation that the evolution of the human brain probably involves hundreds if not thousands of mutations in perhaps hundreds or thousands of genes—and even that is a conservative estimate.”

It is nothing short of spectacular that so many mutations in so many genes were acquired during the mere 20-25 million years of time in the evolutionary lineage leading to humans, according to Lahn. This means that selection has worked “extra-hard” during human evolution to create the powerful brain that exists in humans.

Varki points out that several major events in recent human evolution may reflect the action of strong selective forces, including the appearance of the genus *Homo* about 2 million years ago, a major expansion of the brain beginning about a half million years ago, and the appearance of anatomically modern humans about 150,000 years ago. “It's clear that human evolution did not occur in one fell swoop,” he said, “which makes sense, given that the brain is such a complex organ.”

Lahn further speculated that the strong selection for better brains may still be ongoing in the present-day human populations. Why the human lineage experienced such intensified selection for better brains but not other species is an open question. Lahn believes that answers to this important question

will come not just from the biological sciences but from the social sciences as well. It is perhaps the complex social structures and cultural behaviors unique in human ancestors that fueled the rapid evolution of the brain.

“This paper is going to open up lots of discussion,” Lahn said. “We have to start thinking about how social structures and cultural behaviors in the lineage leading to humans differed from that in other lineages, and how such differences have powered human evolution in a unique manner. To me, that is the most exciting part of this paper.”