Researchers discovered that humans are a 'privileged' evolutionary lineage

December 30 2004

The genes that regulate brain development and function evolved much more rapidly in humans than in nonhuman primates and other mammals because of natural selection processes unique to the human lineage. Researchers reported their findings in the cover article of the Dec. 29, 2004, issue of the journal *Cell*.

"Humans evolved their cognitive abilities not due to a few accidental mutations, but rather, from an enormous number of mutations acquired though exceptionally intense selection favoring more complex cognitive abilities," said lead scientist Bruce Lahn, an assistant professor of human genetics at the University of Chicago and an investigator at the Howard Hughes Medical Institute.

"We tend to think of our own species as categorically different – being on the top of the food chain," Lahn said. "There is some justification for that."

From a genetic point of view, some scientists thought that human evolution might be a recapitulation of the typical molecular evolutionary process, he said. For example, the evolution of the larger brain might be due to the same processes that led to the evolution of a larger antler or a longer tusk. It's just a particular feature that is exaggerated in the human species.

"We've proven that there is a big distinction. Human evolution is, in fact, a privileged process because it involves a large number of mutations in a large number of genes," Lahn said. "To accomplish so much in so little

evolutionary time – a few tens of millions of years – requires a selective process that is perhaps categorically different from the typical processes of acquiring new biological traits."

Generally speaking, the higher up the evolutionary tree, the bigger and more complex the brain becomes (after scaling to body size). But this moderate trend became a huge leap during human evolution. The human brain is exceptionally larger and more complex than the brains of nonhuman primates, including man's closest relative, the chimpanzee.

One way to study evolution at the molecular level is to examine changes of when and where proteins are expressed in the body. "But there are many challenges to study the evolution of protein expression. Instead, we chose to track structural changes in proteins," said graduate student Eric Vallender, lead author of the article along with former graduate student Steve Dorus, both of Lahn's laboratory.

Researchers examined the DNA of 214 genes involved in brain development and function in four species: humans, macaques (an Old World monkey), rats and mice. (Primates split from rodents about 80 million years ago; humans split from macaques 20 million to 25 million years ago; and rats split from mice 16 million to 23 million years ago.)

For each of these brain-related genes, they identified changes 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 selection, 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, known as the gene's molecular clock. The ratio of the two types of changes gives a measure of the pressure of natural selection driving the evolution of the gene.

Researchers found that brain-related genes evolved much faster in humans and macaques than in rats and mice. Additionally, the human lineage has a higher rate of protein changes than the macaque lineage. Similarly, the human lineage has a higher rate than the chimpanzee lineage.

"For brain-related genes, the amount of evolution in the lineage leading to humans is far greater than the other species we have examined," Lahn said. "This is based on an extensive set of genes."

They argue that a significant fraction of genes in the human genome were impacted by this selective process. The researchers estimate there may have been thousands of mutations in thousands of genes that contributed to the evolution of the human brain. This "staggering" number of mutations suggests that the human lineage was driven by intense selection process.

To further investigate the role of selection on brain development, the researchers compared the evolutionary rate of brain-related genes against a control group of 95 genes, which are involved in basic functions necessary for each cell in the body to survive.

"If there is something inherently different about humans in the evolution of their genes – not related to selection – the control genes should reveal it too. These basic, conserved genes are the last to change," Vallender said.

The control genes looked the same. The researchers did not find an excess of changes in these genes during human evolution. This provides a sharp contrast to the tremendous excess of changes in the brain-related genes.

The study also revealed two dozen "outliers" – those genes with the

fastest evolutionary rates in the human lineage. Of these, 17 are involved in controlling brain size and behavior, arguing that genes that affect brain size and behavior are preferential targets of selection during human evolution. Lahn and his colleagues now are focusing on these outlier genes, which may reveal more about how the human brain became bigger and better.

For two of these outliers, ASPM and Microcephalin, previous work from Lahn's group already has implicated them in the evolutionary enlargement of the human brain. Loss-of-function mutations in either ASPM or Microcephalin cause microcephaly in humans – a severe reduction in the size of the cerebral cortex, the part of the brain responsible for planning, abstract reasoning and other higher cognitive function.

The researchers found that both the ASPM and Microcephalin genes showed clear evidence of accelerated changes due to intensified evolutionary pressure in the lineage leading to humans. For ASPM, the acceleration is particularly prominent in recent human evolution after humans parted way from chimpanzees. By contrast, the researchers' analyses of ASPM and Microcephalin in the more primitive monkeys and in cows, sheep, cats, dogs, mice and rats, showed no evidence of accelerated evolutionary changes.

Lahn also is considering the wider impact of this research. "Are the genes involved in the evolution of the human brain more likely to be linked to diseases of the human brain? What happens when something goes wrong in these genes? Does it create neurological and psychiatric problems such as mental retardation or addiction? Could these genes contribute to IQ differences in humans? Do people with a particular mutation in one of these genes study better?"

According to Lahn, data from the Cell paper secures humans' privileged

position in the evolutionary tree. "Human brain evolution required a major overhaul of the genetic blueprint -- perhaps much more so than the evolution of other biological traits," he said.

But how did human ancestors encounter an environment where selection for better brains suddenly became such a prominent force? Lahn suggests that because humans have become a progressively more social species, greater cognitive abilities have become more of an advantage.

"As humans become more social, differences in intelligence will translate into much greater differences in fitness," he said, "because you can manipulate your social structure to your advantage.

"Even devoid of the social context, as humans become more intelligent, it might create a situation where being a little smarter matters a lot.

"The making of the large human brain is not just the neurological equivalent of making a large antler. Rather, it required a level of selection that's unprecedented," Lahn said. "Our study offers the first genetic evidence that humans occupy a unique position in the tree of life. Simply put, evolution has been working very hard to produce us humans."

Source: University of Chicago Medical Center