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Human Brain Is Still Evolving

Howard Hughes Medical Institute researchers who have analyzed sequence variations in two genes that regulate brain size in human populations have found evidence that the human brain is still evolving.

They speculate that if the human species continues to survive, the human brain may continue to evolve, driven by the pressures of natural selection. Their data suggest that major variants in these genes arose at roughly the same times as the origin of culture in human populations as well as the advent of agriculture and written language.

The research team, which was led by Bruce T. Lahn, a Howard Hughes Medical Institute investigator at the University of Chicago, published its findings in two articles in the September 9, 2005, issue of the journal *Science*.

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- **Bruce T. Lahn**

Their analyses focused on detecting sequence changes in two genes - *Microcephalin* and "abnormal spindle-like microcephaly associated" (*ASPM*) - across different human populations. In humans, mutations in either of these genes can render the gene nonfunctional and cause microcephaly - a clinical syndrome in which the brain develops to a much smaller size than normal.

In earlier studies of non-human primates and humans, Lahn and his colleagues determined that both *Microcephalin* and *ASPM* showed significant changes under the pressure of natural selection during the making of the human species. "Our earlier studies showed that *Microcephalin* showed evidence of accelerated evolution along the entire primate lineage leading to humans, for the entire thirty to thirty-five million years that we sampled," he said. "However, it seemed to have evolved slightly slower later on. By

contrast, *ASPM* has evolved most rapidly in the last six million years of hominid evolution, after the divergence of humans and chimpanzees.”

In order to identify sequence changes that occurred in *Microcephalin* and *ASPM* in the evolutionary lineage leading to humans, Lahn and his colleagues took the following approach: They determined the DNA sequences of the two genes among a large number of primate species and searched for sequence differences between humans and nonhuman primates. By doing statistical analysis on these sequence differences, they could demonstrate that the differences were due to natural selection that drove significant sequence changes in the lineage leading to humans. These changes accumulated presumably because they conferred some competitive advantage.

The evidence that *Microcephalin* and *ASPM* were evolving under strong natural selection in the lineage leading to humans led Lahn and his colleagues to consider exploring whether these two genes are still evolving under selection in modern human populations. “In the earlier studies, we looked at differences that had already been set in the human genome,” he said. “The next logical question was to ask whether the same process is still going on today, given that these genes have been under such strong selective pressure, leading to the accumulation of advantageous changes in the human lineage. If that is the case, we reasoned we might be able to see variants within the human population that are rising in frequency due to positive selection, but haven't gone to completion yet.”

The researchers first sequenced the two genes in an ethnically diverse selection of about 90 individuals. The researchers also sequenced the genes in the chimpanzee, to determine the “ancestral” state of polymorphisms in the genes and to assess the extent of human-chimpanzee divergence.

In each gene, the researchers found distinctive sets of polymorphisms, which are sequence differences between different individuals. Blocks of linked polymorphisms are called haplotypes, whereby each haplotype is, in essence, a distinct genetic variant of the gene. They found that they could further break the haplotypes down into related variants called haplogroups. Their analysis indicated that for each of the two genes, one haplogroup occurs at a frequency far higher than that expected by chance, indicating that natural selection has driven up the frequency of the haplogroup. They referred to the high-frequency haplogroup as haplogroup D.

When the researchers compared the ethnic groups in their sample for haplogroup D of *ASPM*, they found that it occurs more frequently in European and related populations, including Iberians, Basques, Russians, North Africans, Middle Easterners and South Asians. That haplogroup was found at a lower incidence in East Asians, sub-Saharan Africans and New World Indians. For *Microcephalin*, the researchers found that haplogroup D is more abundant in populations outside of Africa than in populations from sub-Saharan Africa.

To produce more informative statistical data on the frequency of haplotype D among population groups, the researchers applied their methods to a larger population sample of more than one thousand people. That analysis also showed the same distribution of haplogroups.

Their statistical analysis indicated that the *Microcephalin* haplogroup D appeared about 37,000 years ago, and the *ASPM* haplogroup D appeared about 5,800 years ago - both well after the emergence of modern humans about 200,000 years ago. "In the case of *Microcephalin*, the origin of the new variant coincides with the emergence of culturally modern humans," said Lahn. "And the *ASPM* new variant originated at a time that coincides with the spread of agriculture, settled cities, and the first record of written language. So, a major question is whether the coincidence between the genetic evolution that we see and the cultural evolution of humans was causative, or did they synergize with each other?"

Lahn said that the geographic origin and circumstances surrounding the spread of the haplogroups can only be surmised at this point. "One can make guesses, but our study doesn't reveal how these positively selected variants arrived," he said. "They may have arisen in Europe or the Middle East and spread more readily east and west due to human migrations, as opposed to south to Africa because of geographic barriers. Or, they could have arisen in Africa, and increased in frequency once early humans migrated out of Africa."

While the roles of *Microcephalin* and *ASPM* in regulating brain size suggest that the selective pressure on the new variants may relate to cognition, Lahn emphasized that this possibility remains speculative. "What we can say is that our findings provide evidence that the human brain, the most important organ that distinguishes our species, is evolutionarily plastic," he said. Finding evidence of selection in two such genes is mutually reinforcing, he pointed out. "Finding this effect in one gene could be anecdotal, but finding it in two genes would make it a trend. Here we have two microcephaly genes that show evidence of selection in the evolutionary history of the human species and that also show evidence of ongoing selection in humans."

Lahn emphasized that it would not be correct to interpret the findings as indicating that one ethnic group is more "evolved" than another. Any differences among groups would be minor compared to the large differences in such traits as intelligence within those groups, he said. "We're talking about the average impact of such variants," he said. "We still have to treat each individual as an individual. Just because you have one gene that makes you more likely to be a little taller, doesn't mean you will be tall, given the complex effect of all your other genes and of environment." Lahn also said that a multitude of other genes likely exist that influence brain size and development, and further research could reveal far more complex effects of natural selection on such genes.

Lahn speculated that the new findings suggest that the human brain will continue to evolve under the pressure of natural selection. “Our studies indicate that the trend that is the defining characteristic of human evolution - the growth of brain size and complexity - is likely still going on. If our species survives for another million years or so, I would imagine that the brain by then would show significant structural differences from the human brain of today.”

For both *Microcephalin* and *ASPM*, Lahn and his colleagues are trying to find out the precise traits that are under natural selection. They are also performing more detailed studies of the two genes in human populations to better understand their evolutionary history. And they are searching for other brain-related genes that have changed under the pressure of natural selection. “We want to know how broad a trend these two genes represent,” said Lahn. “Did we get really lucky and hit on two rare examples of such genes? Or, are they representative of many other such genes throughout the genome. I would bet, though, that we will find evidence of selection in a lot more genes.”

Lahn and his colleagues are now working to understand how subtle changes in the sequences of these two genes can alter their function in such a way that would result in favorable selection. While there is some evidence from earlier studies that *Microcephalin* and *ASPM* code for proteins that regulate the proliferation of brain cells from immature neural stem cells, their function has not yet been determined, said Lahn.