

Two-step Process Filters Evolution of Genes of Human and Chimpanzee

Although the human and chimpanzee genomes are distinguished by 35 million differences in individual DNA "letters," only about 50,000 of those differences alter the sequences of proteins. Of those 50,000 differences, an estimated 5,000 may have adaptive consequences in the evolutionary divergence between these two species, according to a study published in the March 6, 2007, issue of the *Proceedings of the National Academy of Sciences*.

Before such a new and beneficial mutation can take its place in the human genome it has to pass through a rigorous two-step—negative and positive—screening process, say the study authors, evolutionary geneticists from the University of Chicago, the University of Tokyo and the University of Washington. Both steps focus on the most radical changes.

In step one, mutations, the genetic equivalent of typographical errors, are randomly introduced. When these mutations are still rare in the population, only strongly deleterious ones get weeded out through negative selection. The more radical mutations are more likely to be harmful and quickly removed. For those that are only slightly harmful, neutral or beneficial, the selective forces are weak and luck determines their fates.

In step two, a new mutation that has been fortunate enough to survive the initial elimination process, and confers some benefit, can then spread quickly through positive selection. The more radical the mutation, at this point, the faster it is likely to spread.

"We found that the same genetic changes that are unlikely to survive early negative selection are the ones that spread most quickly once they gain a foothold," said the study's senior author Chung-I Wu, Ph.D., professor of ecology and evolution at the University of Chicago. "To reach that conclusion, we needed to decouple the two steps of evolution and classify mutations into many different kinds."

The researchers used the very large survey of human genetic variation called HapMap for their analysis, which compared human variations with the chimpanzee genome. They focused their analysis on the simplest and most common mutations, those that alter just one letter, a single base pair, of DNA.

DNA uses a three-letter code to designate the 20 types of amino acids that are strung together in specific order to create a protein. Some mutations alter just one letter of the code, replacing one link in a protein's amino-acid chain with a different amino acid. While some of those substitutions make only a moderate difference in a protein's structure or function, others have radical impact on its shape and performance.

Radical amino acid changes alter protein function. Most of those are deleterious and get removed, but "when a mutation is beneficial, we do not know whether they tend to be the radical or moderate kind of amino acid changes," Wu said. "Since beneficial changes are the ones that fuel evolution, we wanted to find out if these improvements are smooth or jerky."

When Wu and colleagues sorted these changes according to their evolutionary success, they found that radical changes were more harshly screened—negatively and positively—by the forces of evolution.

When radical changes occurred, those mutations were far more likely to be eliminated by negative selection. But in rare cases, radical mutations escaped elimination by negative selection. Once they had established a beach head, occurring in as little as five percent of a population, these radical mutations tended to spread quickly throughout the species, their survival or reproductive advantage allowing them to gain ground over multiple generations.

"We found that both positive and negative selection are more effective on the same subset of radical amino acid changes," Wu said. "If changes from amino acid one to amino acid two are more likely to be deleterious, then some fraction of those very same changes is also more likely to be advantageous. In short, radical amino acid changes have trouble going through the first phase of evolution to reach even five percent in the population, but once they do, they have an easier time going through the second phase to prevail in the population."

Although the physical or chemical differences between the various amino acids should provide a straightforward measure of the "radicalness" of amino-acid substitutions, those measures did not correlate well with how these changes fared in evolution.

"This tells us that we need new measures for how conservative or radical an amino acid change might be," Wu said. "We need to base that on evolutionary dynamics in addition to biochemical structure."

Using these results, the researchers measured how many of the amino acid changes within functioning genes were adaptive—able to survive rigorous negative selection and then spread rapidly throughout a population. They estimated "the proportion of adaptive changes between human and chimpanzee to be 10.4 to 12.8 percent," similar to previous estimates using entirely different approaches.

When they multiplied that result times current estimates of the number of functional genes, it came to about 3,000 to 7,000.

"These are the genetic changes that are possibly adaptive," said Wu. "Out of those differences, we suspect that some, and perhaps most, are responsible for the most significant changes between human and chimpanzee."

Source: University of Chicago Medical Center

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