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Different codons, same amino acid

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Melissa Phillips
Email: mlphilli@u.washington.edu

The genomes of species from bacteria to *Drosophila* show unique biases for particular synonymous codons - varying triplet base pairs that code for the same amino acids - but it has been unclear if such codon preferences exist in mammals. In a paper published in Proceedings of the National Academy of Sciences USA this week, a group led by Joshua B. Plotkin of the Bauer Center for Genomic Research at Harvard shows that cell usage of synonymous codons is systematically different between human tissues (*Proc Natl Acad Sci USA* 2004, **101:**12588-12591). In addition, the authors make a case that these codon choices result from evolutionary selection.

Plotkin and his colleagues analyzed genes expressed preferentially in six human tissues - brain, liver, uterus, testis, ovary, and vulva - and found synonymous codon biases between gene sets. In particular, they compared brain-specific genes to liver-specific genes; uterus genes to testis genes; and ovary genes to vulva genes. All three pairs differed significantly from each other in their synonymous codon usage.

"We can even predict which genes are turned on in which tissues largely on the basis of their synonymous codon usage," Plotkin told us. "These codon biases may be partly responsible for determining which genes are expressed in which tissues."

Previous studies have shown functional selection of codons in simpler organisms, Plotkin said. Mammalian genomes, however, are complicated by the presence of isochores, long stretches of homogeneous DNA sequence that are biased to be either rich or poor in GC content.

"Most mammalian genomes have huge variations in GC content from region to region, and that controls codon usage to a large degree," Plotkin said. "People haven't normally thought that codon usage could have any sort of functional importance, because it seems to be controlled by which isochore the gene happens to fall in. But the fact that we find such systematic differences between tissues is suggestive that there really is some functional reason."

One possible mechanism linking synonymous codon choice and tissue-specific gene expression is local transfer RNA abundance, Plotkin said. "The tRNA pools may differ in brain from the pools in liver, and so if the codon usage of a gene is calibrated to the tRNA pools that exist in the brain, that gene will be translated more efficiently in brain." Other mechanisms could also be at work, Plotkin said, such as mRNA modifications or secondary structure.

In a second part of the study, Plotkin and his colleagues compared codon preference in human tissue genes to orthologous genes in the mouse. Previous work has shown that base usage is similar between human and mouse not only in coding sequences, but also in untranslated regions, hinting that selection is not responsible for codon similarities. Plotkin's team found that codon usage for brain-specific genes is significantly more similar between the two species than would be expected by chance, even when controlling for sequence similarity between the two genomes.

Liver, uterus, and vulva genes also show codon usage preservation between human and mouse, Plotkin said. Synonymous codon choice is not significantly similar in ovary and testis genes, however. According to Plotkin, this result fits with studies showing that reproductive genes in primates have evolved much more rapidly than other genes.

"Codon usage in humans has been a very elusive subject," Josep Comeron of the University of Iowa told us. Isochore structure, he said, is the most important thing. Based on his own recent work as well as Plotkin's paper, however, he said, "it's clear that synonymous sites are under some selection."

Their study controls for all similarities between the two genomes, including isochore GC content and mutation rate in untranslated regions, according to Plotkin. "Given the number of mutations that have occurred between the two sequences, the codon usage would be much more diverged than it actually is, if the mutations were random," Plotkin said. "So there has been some selection to preserve the synonymous codon biases."

This work "is very suggestive and exciting," said Shannon McWeeney of Oregon Health and Science University, "but I'd like to see further analysis" of the data, including verification that the mouse orthologs of human genes are specific to the same tissue in mouse.

One possible caveat of the study, according to Stanley Sawyer of Washington University, is that Plotkin's data show "quite a few counterexamples" of tissue-specific genes that do not choose the same synonymous codons as the rest of their group. "But there's still a very strong statistical tendency," Sawyer said.

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