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Alternative Ways of Reading DNA Have Spurred Evolution

Humans are substantially more complex than the tiny worm *Caenorhabditis elegans*, yet both organisms have about the same number of genes. Why is human DNA so much more versatile?

One reason is that many mammalian genes come in more than one form. Now research by Howard Hughes Medical Institute researcher Philip Green and his colleagues at the University of Washington has revealed key characteristics of a genetic tool, known as an alternative promoter, that can produce protein variants and thereby increase genetic diversity. Their studies are published in the February 2007 issue of the journal *Genome Research*.

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— Philip Green

A promoter in DNA is analogous to a chapter title in a book. It tells specialized enzymes where to start reading the DNA message that is used to produce a protein. Having alternative promoters is like having separate titles for the same chapter of a book. Sometimes alternative promoters produce the same protein. But those promoters might be active in different tissues or at different times in an organism's life. In other cases, alternative promoters tell the enzymes to begin reading DNA at different starting points, ultimately resulting in different proteins with different functions. Even if you know the genes encoded in DNA, you don't know everything encoded in those genes unless you know whether there are multiple promoters, said Green.

Previous studies had suggested that a larger than expected percentage of mammalian genes have alternative promoters. By comparing promoters in the human genome to those in the mouse genome and by using a new statistical tool to identify alternative promoters, Green and his colleagues confirmed these suggestions. In the article published in the journal *Genome Research*, Green and his colleagues conclude that roughly 40-50 percent of human and mouse genes have alternative promoters. The data suggest that alternative promoters are critically important to the functioning of higher organisms, Green said.

Comparing alternative promoters across species also allowed the group to estimate whether a given promoter is more or less likely to change over evolutionary time. Surprisingly, alternative promoters, which would seem to give a cell greater flexibility, are more stable than single promoters. That was a surprising result, said Dixie L. Mager, senior scientist at the Terry Fox Laboratory of the BC Cancer Research Centre in Vancouver, British Columbia, who studies the influence of mobile genetic elements on gene regulation.

There's a reason why so many genes have alternative promoters, said Mager. There is great potential to modify expression patterns of single genes through the use of distinct promoter elements. People haven't paid enough attention to differential regulation of genes through the operation of promoters and this article should help spur research in that field.

According to Green, the tighter regulation of alternative promoters underscores their importance in cellular function. "If you have more than one promoter, you have to be able to regulate which promoter to use," he said. "So presumably the higher conservation reflects the higher density of functional elements involved in regulating promoter choice."

All promoters can be divided into two broad categories. One category includes promoters that have CpG islands — stretches of DNA containing multiple copies of the dinucleotide CpG, which consists of the nucleotide cytosine (C) followed by guanine (G). The other category consists of promoters that lack these CpG islands.

Alternative promoters in both of these categories tend to be more active during embryonic development, Green and his colleagues found. In addition, alternative promoters with CpG islands are more often involved in the regulation of genes and in the development of the brain and lung, while alternative promoters without CpG islands tend to be associated with the development of the heart and liver.

Single promoters with CpG islands tend to be linked to the everyday housekeeping functions of cells. Single promoters without CpG islands are also more active in the adult organism than during development. However, they are more often associated with highly regulated biological systems such as the immune and digestive systems.

Green's studies of promoter function suggest intriguing hypotheses about evolutionary patterns. The way *C. elegans* and a lot of other organisms increase their flexibility is simply to make a duplicate copy of a gene and have different regulation for the duplicate, said Green. With mammals, one way in which evolution has generated more diversity is to produce different versions of the same gene and allow the cell to regulate expression in multiple tissues. This is a way that evolution gets more bang for its buck, because it gets additional functions for the same gene.