MedicalXpress

More 'functional' DNA in genome than previously thought

December 11 2007

Surrounding the small islands of genes within the human genome is a vast sea of mysterious DNA. While most of this non-coding DNA is junk, some of it is used to help genes turn on and off. As reported online this week in *Genome Research*, Hopkins researchers have now found that this latter portion, which is known as regulatory DNA and contributes to inherited diseases like Parkinson's or mental disorders, may be more abundant than we realize.

By conducting an exhaustive analysis of the DNA sequence around a gene required for neuronal development, Andrew McCallion, Ph.D., an assistant professor in the McKusick-Nathans Institute of Genetic Medicine, and his team found that current computer programs that scan the genome looking for regulatory DNA can miss more than 60 percent of these important DNA regions.

The current methods find regulatory sequences by comparing DNA from distantly related species, under the theory that functionally important regions will appear more similar in sequence than non-functional regions. "The problem with this approach, we have discovered," says McCallion, "is that it's often throwing the baby out with the bath water. So while we believe sequence conservation is a good method to begin finding regulatory elements, to fully understand our genome we need other approaches to find the missing regulatory elements."

McCallion had suspected that using sequence conservation would overlook some regulatory DNA, but to see how much, he set up a small

pilot project looking at the phox2b gene; he chose this gene both because of its small size and his interest in nerve development (phox2b is involved in forming part of the brain associated with stress response as well as nerves that control the digestive system).

The researchers created what they call a “tiled path,” cutting up the DNA sequence around the phox2b gene into small pieces, then inserted each piece into zebrafish embryos along with a gene for a fluorescent protein. If a phox2b fragment was a regulatory element, then it would cause the protein to glow. By watching the growing fish embryos - which have the advantage of being transparent - the researchers could see which pieces were regulators.

They uncovered a total of 17 discrete DNA segments that had the ability to make fish glow in the right cells. The team then analyzed the entire region around the phox2b gene using the five commonly used computer programs that compute sequence conservation; these established methods picked up only 29 percent to 61 percent of the phox2b regulators McCallion identified in the zebrafish experiments.

“Our data supports the recent NIH encyclopedia of DNA elements project, which suggests that many DNA sequences that bind to regulatory proteins are in fact not conserved,” says McCallion. “I hope this pilot shows that these types of analyses can be worthwhile, especially now that they can be done quickly and easily in zebrafish.”

McCallion is now planning a larger study of other neuronal genes. “I think we are only starting to realize the importance and abundance of regulatory elements; by regulating the gene activity in each cell they help create the diverse range of cell types in our body.”

Source: Johns Hopkins Medical Institutions