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RESEARCH NEWS

OCTOBER 05, 2007

Evolution Transforms "Junk" DNA into Genetic Machinery

Evolution has mastered the art of turning trash to treasure - though, for scientists, witnessing the transformation can require a bit of patience. In new genetic research, scientists have traced the 170 million-year evolution of a piece of "junk" DNA to its modern incarnation as an important regulator of energy balance in mammals.

The discovery, they said, suggests that regions of the genome formerly presumed to be a genetic junkyard may actually be a hardware superstore, providing components that can be used to evolve new genes or new species.

The discoveries were reported by Howard Hughes Medical Institute international research scholar Marcelo Rubinstein and his colleagues October 5, 2007, in the online *PLoS Genetics*. Rubinstein is at the Institute for Research on Genetic Engineering and Molecular Biology of the National Council for Science and Technology in Argentina, and the University of Buenos Aires.

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- Marcelo Rubinstein

Researchers have long known that all genomes are prodigiously sprinkled with DNA fragments derived from mobile elements that have jumped to apparently random points in the genome. For example, the Human Genome Project revealed that about 45 percent of our genome consists of mobile element-derived sequences.

"The classical view has considered genomic sequences derived from mobile elements as "junk" DNA—a large accumulation of useless sequences," said

Rubinstein. “However, more recent work, including the findings in this paper, is producing convincing evidence that these sequences provided raw material for the evolution of novel gene functions.”

Rubinstein and his colleagues had been studying one such piece of DNA, called nPE2, which enhances the activity of a gene called POMC (proopiomelanocortin). The POMC gene is expressed in cells in the brain and produces peptides that regulate a variety of behaviors, including food intake and stress-induced analgesia.

“Our studies showed that nPE2 is highly conserved in mammals but absent in other vertebrates, so we became interested in studying its evolutionary origins,” said Rubinstein. “We then found nPE2 to be highly similar to sequences present in the genomes of the marsupials opossum and wallaby. So we thought we had found the tip of the iceberg of an evolutionary process that started around 200 million years ago, and we got really fascinated by the idea of pulling up the entire iceberg from the depths.” In fact, Rubinstein and his colleagues realized that all similar sequences originated from a superfamily of mobile elements called CORE-short interspersed elements (CORE-SINES). CORE-SINES are retroposons, meaning the genetic sequence has been copied before being inserted into new sites in the genome.

To reveal more of nPE2's evolutionary history, the researchers compared nPE2 sequences from 16 mammalian species, including human, dog, mouse, and rabbit. They found the nPE2 enhancer sequence to be highly conserved. By creating altered versions of the nPE2 sequence and testing their ability to enhance gene expression in transgenic mice, they showed that the regions that were critical to nPE2's function were most rigorously conserved over evolution. The findings, Rubinstein said, indicated that nPE2's function “contributed to the fitness of all mammals, probably by better tuning the central regulation of energy balance.”

“This paper shows, for the first time, that a retroposon of this superfamily got inserted near the *POMC* gene sometime before 170 million years ago; and after suffering a limited number of random mutations, it acquired a novel and useful function and became fixed in the genome of an ancestor to all mammals,” said Rubinstein.

The findings provide clear evidence that genes use a collection of functional sequences incorporated at different times during a very long-lasting evolutionary process, said Rubinstein. “Novel sequences that improved fitness got fixed into the genomes and continued to travel to the future together with more ancient functional sequences,” he said.

The researchers found a large number of other CORE-SINE superfamily members that had changed very little over evolutionary time, suggesting that nPE2's evolution from junk to regulatory DNA was not a unique event. In fact, Rubinstein suspects that thousands of currently functional elements are derived from ancient retroposon insertions--but their evolutionary history still needs to be untangled. “We are starting to understand how insertional elements, instead of being useless or harmful for the genomes, may be beneficial.”