

MAY 04, 2006

Mobile DNA Part of Evolution's Toolbox

The repeated copying of a small segment of DNA in the genome of a primeval fish may have been crucial to the transition of ancient animals from sea to land, or to later key evolutionary changes in land vertebrates. The discovery is tantalizing evidence that copied DNA elements known as retroposons could be an important source of evolutionary innovations, says the director of the research, Howard Hughes Medical Institute investigator David Haussler.

The big question is whether this is a special case or whether it's the tip of the iceberg, says Haussler, who is at the University of California, Santa Cruz. A report on the research is published in the May 4, 2006, issue of the journal *Nature*.

"The big question is whether this is a special case or whether it's the tip of the iceberg."

— David Haussler

Haussler and his colleagues were led to the discovery through their work on what they call ultraconserved elements—segments of DNA hundreds of nucleotides long that are almost exactly the same in a wide variety of vertebrate organisms. Haussler and postdoctoral fellow Gill Bejerano discovered the ultraconserved elements in 2003, and since then they have been trying to figure out how they arose and what function they serve.

One ultraconserved element in particular caught their eye. We were very interested in this sequence, because it had a number of copies elsewhere in the genome, says Bejerano, who is the first author of the study. Close copies of the sequence were ubiquitous in amphibians, birds, and mammals, indicating that it served an important function. We found it in every species for which we have genomes, from frogs to humans, says Bejerano.

Comparing the sequence to other species also turned up a big surprise. When the researchers compared the human ultraconserved element to all the DNA sequences in the public database GenBank, the closest match was to DNA from the coelacanth—an ancient fish thought to have gone extinct millions of years ago until a live specimen was caught in 1938 off the east coast of South Africa. The coelacanth is a descendant of the ancient marine organism that

gave rise to the terrestrial vertebrates more than 360 million years ago. Humans are therefore separated from the coelacanth by hundreds of millions of years of evolution, yet the two organisms still share critical DNA sequences.

In the coelacanth, the ultraconserved segments were produced by a retroposon known as a short interspersed repetitive element, or SINE, which is a piece of DNA that can make copies of itself and insert those copies elsewhere in an organism's genome. Haussler and his colleagues called this SINE the LF-SINE, where LF stands for lobe-finned fishes—the group of fishes that gave rise to both the coelacanth and terrestrial vertebrates.

The LF-SINE was very active in the evolutionary lineage leading to the terrestrial vertebrates, but much less active after animals moved onto land. Humans have 245 recognizable copies of the LF-SINE, most or all of which probably were in place before the origins of the mammals. But in the lineage leading to the coelacanth, the LF-SINE remained active, so that the coelacanth genome is now estimated to contain hundreds of thousands of copies of the sequence.

The close copies of the ultraconserved element scattered around vertebrate genomes have changed less than would be expected over evolutionary time, indicating that they are functionally important. But relatively few of the copies contain parts that code for proteins, which suggests they instead are helping to regulate when genes are turned on and off. Furthermore, when Bejerano analyzed the locations of the copies, he found that they tended to be near genes that control the development of the brain.

Haussler and his colleagues then looked at a particular example—a copy of the ultraconserved element that is near a gene called Islet 1 (*ISL1*). *ISL1* produces a protein that helps control the growth and differentiation of motor neurons. In the laboratory of Edward Rubin at the University of California, Berkeley, postdoctoral fellow Nadav Ahituv combined the human version of the LF-SINE sequence with a reporter gene that would produce an easily recognizable protein if the LF-SINE were serving as its on-off switch. He then injected the resulting DNA into the nuclei of fertilized mouse eggs. Eleven days later, he examined the mouse embryos to see whether and where the reporter gene was switched on. Sure enough, the gene was active in the embryos' developing nervous systems, as would be expected if the LF-SINE copy were regulating the activity of *ISL1*.

The discoverer of mobile DNA elements, Barbara McClintock, suggested in 1950 that they might play a role in the regulation of genes—a hypothesis that was more fully developed by Roy Britten and Eric Davidson in about 1970, when it was discovered that more than half of the human genome consists of remnants of mobile elements. But the mechanisms underlying this process remained obscure. Haussler's work provides direct evidence that even when they land at some distance from a gene, mobile elements like SINEs can be adapted to serve as regulatory elements that have powerful effects in their new locations. When you activate a gene in a new context, Bejerano points

out, you get processes that did not occur before.

Bejerano and Haussler's results support the hypothesis that the movement of retroposons can generate evolutionary experiments by adding new regulatory modules to genes. Most of these experiments will have no effects or will harm an organism. But every once in a while, the movement of a regulatory element will give an organism an evolutionary advantage. And to the extent that [such changes] improve the fitness of an organism, says Haussler, they eventually will become fixed in a population.

This suggests a lot of exciting evolutionary avenues, says Haussler, but we don't yet know how prevalent this kind of evolution is. Other labs have found similar examples of mobile elements that have changed the regulation of genes, and Haussler expects the number of reports to grow. It's a very exciting time to be looking at the human genome, because there's an enormous amount of DNA that we know is important, but we don't yet know what it's doing.