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SCIENTISTS ADVOCATE GENOMIC SEQUENCING OF “LIVING FOSSIL”

STANFORD, Calif., Mon., Nov. 15, 2004 – A team of Stanford University researchers led by Dr. Richard Myers, Ph.D., in collaboration with Dr. Chris Amemiya, Ph.D. of the Benaroya Research Institute in Seattle, campaign in the December 1 issue of *Genome Research* for deciphering the genetic code of a “living fossil” fish, the coelacanth.

The genomic sequence of this large “hollow-spined” fish, which populates deep-sea volcanic caves, could hold valuable clues for biologists studying the evolution of vertebrate species. Coelacanths were believed to be long extinct before a specimen was discovered in 1938. Both of the known coelacanth species that survive today, *Latimeria chalumnae* and *Latimeria menadoensis*, are anatomically similar to their fossil relatives. Furthermore, coelacanths have exhibited little morphological change since their emergence during the Devonian period approximately 360 million years ago.

To date, complete genomic sequences for more than 200 organisms have been obtained, and hundreds more are currently in progress (www.genomesonline.org). These efforts will enable scientists to perform detailed comparisons of the complete genetic codes from multiple species, identifying the sequence changes that contributed to evolutionary adaptation and speciation. Although a wide assortment of species have been chosen for sequencing, ranging from lampreys to armadillos (www.genome.gov/12511858), Myers observed: “We’re missing an organism that could really shed light on the emergence of land vertebrates. We don’t know what genomic changes accompanied the transition from water to land, and a coelacanth genome could help identify those events.”

The coelacanth is one of only two living taxa to occupy the critical, highly informative phylogenetic position between ray-finned fishes and tetrapods. The lobe-finned ancestors of coelacanth and tetrapods underwent morphological alterations that enabled them to emerge from the sea and inhabit terrestrial environments. Fleshy, lobed fins, which are one of the defining characteristics of coelacanths, are thought to represent an intermediate evolutionary stage in the transformation of fins to limbs. Both the coelacanth and the lungfish – the only two living lobe-finned fishes – are related to important evolutionary progenitors of land vertebrates. However, the lungfish genome is very large (more than 100 billion nucleotides in length), making it technically impractical to sequence with currently available technology. The coelacanth genome, on the other hand, is estimated to be smaller than that of human or mouse, making it feasible for whole-genome sequencing.

Jim Noonan, Ph.D., a graduate student on Myers' team who did much of the work described in the *Genome Research* article, focused on a small but highly informative genomic segment from the Indonesian coelacanth (*Latimeria menadoensis*) called the protocadherin gene cluster. Protocadherin clusters are not present in invertebrates, such as fruit fly (*Drosophila melanogaster*) or roundworm (*Caenorhabditis elegans*), but they are found in more evolutionarily complex species, including all vertebrates. These genes encode proteins involved in the development and maturation of neurons and synapses in the brain. Protocadherin gene clusters are composed of a tandem array of multiple gene copies, making them particularly prone to aberrant recombination and thus, to duplication and homogenization. Because this region appears so vulnerable to evolutionary change, Noonan, Amemiya and Myers predicted that the sequence of the coelacanth protocadherin cluster would be a good indicator of the utility of the whole coelacanth genome sequence for inferring vertebrate phylogeny.

After Jane Grimwood, Jeremy Schmutz and Mark Dickson at the Stanford Human Genome Center generated more than 600,000 nucleotides of coelacanth genomic sequence spanning the protocadherin gene cluster, Noonan found that the coelacanth cluster was organized in a very similar way to the orthologous human cluster. The coelacanth genome has 49 protocadherin cluster genes organized into the same three subclusters (alpha, beta, and gamma) as the 54 protocadherin cluster genes in human. In contrast, the zebrafish (*Danio rerio*) genome contains at least 97 protocadherin genes organized into two distinct clusters, resulting from a whole-genome duplication event.

A major discovery stemming from this work is that the coelacanth genome appears to be evolving slowly relative to land vertebrates and the teleost fishes. This makes the coelacanth genome a better reference for comparative sequence analyses involving land vertebrates than teleost

genomes, which are highly derived due to the whole-genome duplication event. For these reasons, Myers and colleagues argue that the complete genomic sequence of the coelacanth would be valuable for identifying important genome modifications that occurred during the evolution of tetrapod species.

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Myers' collaborators included James Noonan (now at the Genomics Division, Lawrence Berkeley National Laboratory, Berkeley, CA) and Chris Amemiya (Benaroya Research Institute at Virginia Mason, Seattle, WA). Other authors on the study were Jane Grimwood, Jeremy Schmutz and Mark Dickson (Stanford Human Genome Center, Department of Genetics, Stanford University School of Medicine) and Joshua Danke (Benaroya Research Institute). James Noonan was the first author on the paper. A copy of the paper is available upon request.