

Sea urchin genome could shed light on human disease

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Scientists have sequenced the genome of the sea urchin, an invertebrate surprisingly similar to man, a step that could help develop new treatment for human disease such as cancer, said a study released Thursday.

A group of 240 researchers from more than 70 institutions has announced the sequencing of the male California purple sea urchin. An animal frequently used in experiments, its genome has been studied intensely for years at Caltech's Kerckhoff Marine Biological Laboratory (KML), and will contribute significantly to biomedical advances of the future.

Reporting in the November 10 issue of the journal *Science*, the researchers are announcing that the high-quality "draft" sequence covers



more than 90 percent of the sea-urchin genome. In addition to the primary results in Science, 41 companion manuscripts will appear in Science and a special issue of the December 1 issue of Developmental Biology.

The project was led by Erica Sodergren and George Weinstock, a husband-and-wife team at the Baylor College of Medicine-Human Genome Sequencing Center (BCM-HGSC), along with Richard Gibbs, director of the BCM-HGSC, and Eric Davidson and Andrew Cameron of the California Institute of Technology. The National Human Genome Research Institute of the National Institutes of Health provided most of the funding for the sequencing and annotation.

According to the researchers, the sea-urchin genome contains more than 814 million letters, spelling out 23,300 genes. To date, nearly 10,000 of the genes have been scrutinized by the international consortium.

The results are the outcome of work begun at Caltech more than 30 years ago, when Davidson and Roy Britten, a scientist working at Caltech's Kerckhoff Marine Biological Laboratory, began to exploit the utility of the sea urchin as an experimental animal and decided to develop it as a model system in the then emerging field of molecular biology. In the ensuing years many advances in cell and developmental biology derived from this decision.

"Roy Britten and Eric Davidson offered a comprehensive theory of gene regulation in higher organisms, and the sea urchin has been the premier model for testing these predictions," says Gibbs. "The complete sequence is now available to further these studies."

More recently, Davidson and Cameron have coordinated efforts to have the sea-urchin genome sequenced. Starting with a special grant from the Stowers Institute for Medical Research in Kansas City, they assembled



the research materials that would be needed to sequence the genome at the Sea Urchin Genome Facility in Caltech's Beckman Institute and at the KML.

A culture system at KML in which the purple sea urchin is grown through the life cycle continues to provide the essential infrastructure. When the Human Genome Research Institute announced a way to propose additional genome sequencing to support the human genome information, the team at the BCM-HGSC was poised to take action. From these roots grew the Sea Urchin Genome Sequencing Consortium.

Sea urchins are echinoderms (Greek for spiny skin), marine animals that originated over 540 million years ago and that include starfish, brittle stars, sea lilies, and sea cucumbers. Following the great extinction of animals 250 million years ago, the modern sea urchins emerged as the dominant echinoderm species. The purple sea urchin emerged in the North Pacific Ocean during a rapid burst of speciation and diversification 15-20 million years ago.

There was great interest in the sea urchin as a target for genome sequencing because these animals share a common ancestor with humans. That ancestor lived over 540 million years ago and gave rise to the Deuterostomes, the superphylum of animals that includes phyla such as echinoderms and chordates, the phylum to which humans and other vertebrates belong. All Deuterostomes are more closely related to each other than they are to any other animals not included in the Deuterostome superphylum. For example, among sequenced genomes, the genomes of fruit flies and worms are more distant from the sea urchin genome than is the human genome. "Each genome that we sequence brings new surprises. This analysis shows that sea urchins share substantially more genes and biological pathways with humans than previously suspected," says Francis S. Collins, director of the National Human Genome Research Institute. "Comparing the genome of the sea



urchin with that of the human and other model organisms will provide scientists with novel insights into the structure and function of our own genome, deepening our understanding of the human body in health and disease." To discover how sea urchins and humans can be so different, yet be related by descent from an ancient relative, their genomes were compared. The sea urchin is an invertebrate and the first example of sequencing a Deuterostome genome outside the chordates. Most previous invertebrate genomes that were sequenced, such as insects and nematodes, were animals outside the Deuterostome superphylum, although one genome of a chordate invertebrate, the sea squirt, has been sequenced. The sea urchin lies evolutionarily in a large niche between the chordate branch of the Deuterostomes and the non-Deuterostome superphyla. "The sea urchin fills a large evolutionary gap in sequenced genomes," says Weinstock, co-director of Baylor's Human Genome Sequencing Center. "It allows us to see what went on in evolution after the split between the ancestors that gave rise to humans and insects. The sea urchin genome provided plenty of unexpected rewards and was a great choice for sequencing." The comparison of the genes of the sea urchin to the human gene list shows which human genes are likely to be recent innovations in human evolution and which are ancient. It also shows which human genes have changed slowly in the lineage from the ancestral Deuterostome animal and which genes are evolving rapidly in response to natural selection. This will make it possible one day to know the history of every human gene-and build a picture of what the extinct ancestors that gave rise to animal life ranging from worms to humans looked like. Although invertebrate sea urchins have a radically different morphology from humans and other vertebrates, their embryonic development displays basic similarities, an important shared property of Deuterostome animals. This distinguishes them from Protostomes, which have a different pattern of embryonic development. This makes the sea urchin, with its many useful properties such as transparent embryos and ease of isolation of eggs and sperm, a valuable model for studying the process of development and helping us to understand human



development. The development of the animal occurs through a complex network of genes, making the sea urchin one of the main models for systems biology, which describes how the building blocks of an animal interact in time and space. Sea urchins provide a rapid and efficient gene transfer system. By injecting DNA into the egg, researchers can determine which letters spell instructions for turning genes on and off. The series of genetic switches leading to the ordered cascade of expression of genes after fertilization in the sea urchin is among the best understood developmental systems among animal models. Now, with the genome sequence in hand, a more complete set of components of development are known, and this process can be studied exhaustively.

Because of its evolutionary position, the sea-urchin genome sequence was a sample of unknown biological territory. Some of the notable surprises and discoveries were that: -- The sea urchin has most of the same gene families found in human beings. These gene families make up the Deuterostome tool kit used to create animals in this superphylum. However, the size of gene families is often larger in humans, reflecting, in part, two whole genome duplication events during vertebrate evolution after the separation of the sea urchin and human evolutionary lines. --One unexpected exception to this size rule is the immune system. Humans have innate and acquired immune systems. The sea urchin has some of the genes of the acquired immune system, but its innate immune branch is greatly expanded with ten- to twenty times as many genes as in humans. --Innate immunity is the set of proteins that are "hard wired" to detect unique molecules within bacteria, such as their cell walls, and to signal that there is an intruder. This rich repertoire of sea urchin proteins could turn out to provide new reagents in the fight against infectious diseases. -- The sea urchin has genes for sensory proteins that are involved in human vision and hearing. Yet the sea urchin has no eyes and ears, at least as we know them. Some of the visual sensory proteins are localized within an appendage known as the tube foot, and likely function in sensory processes there. It is remarkable that the same



sensory proteins are used in organs with such different structures in sea urchins and humans. "The sea urchin reminds us of the underlying unity of all life on earth," notes Sodergren. "It is a similar set of genes and proteins being reused in different ways, different numbers, and at different times in the life cycle to create the diversity of living forms." The sea-urchin genome was one of the most challenging to sequence to date at Baylor. The genome is highly polymorphic, meaning that the two copies of the genome in the diploid organism vary from each other by about 4 percent, or one difference in spelling every 25 letters. This posed a formidable challenge in assembling the nine million separate short sequences produced by DNA sequencing. A new approach was used, emphasizing the use of BAC clones as a framework. Each BAC clone represents only one version of the genome spelling, and thus provides a consistent sequence on which to build the genome. To sequence the 8,000 BAC clones covering the genome, another new technique was used. The process, CAPSS (clone-array pooled shotgun sequencing), sequences mixtures of BAC clones, rather than individual ones, and then assigns portions of the mixture of sequences to the proper clone. This reduces the cost and time to do the genome by an order of magnitude. The sea-urchin project was thus a test bed for innovations in whole genome sequencing. The sea-urchin project is one of more than 20 projects involving animal genomes that Baylor's Human Genome Sequencing Center has undertaken, including the human genome and those of primates like the rhesus monkey, other mammals like the cow and wallaby, insects such as the honey bee, beetle, and wasp, and most recently the dolphin. In addition, numerous microbes have been sequenced, with a focus on infectious diseases. Other projects include studying the genetic basis of human disease, and this will be the major emphasis of future work.

Source: Caltech



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