

Animal's Genetic Program Decoded, in a Science First

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Biologists have for the first time deciphered the full genetic programming of an animal, a landmark achievement both in its own right and as a milestone toward understanding the human genome.

The animal is a microscopic roundworm known as *Caenorhabditis elegans* and used in laboratories throughout the world as a means to explore biology at the genetic level. Its genome, or full DNA, has now been found to consist of 97 million chemical units and is expected to contain 19,099 genes. If printed in ordinary type, the DNA sequence would take up 2,748 pages of this newspaper.

The genome, deciphered by two teams of biologists headed by John E. Sulston of the Sanger Center near Cambridge, England, and Robert H. Waterston of Washington University in St. Louis, gives biologists their first sight of the information needed to develop, operate and maintain a multicellular animal. They are announcing their effective completion of the genome in today's issue of the journal *Science*.

The worm genome has paved the way technically for decoding the human genome and will also help to interpret it. Understanding the human genome is expected to lead to profound changes in treating the many diseases that have a genetic basis.

The only genomes sequenced up until now have belonged to single-celled organisms like bacteria and yeast. Because worms and humans have turned out to have many genes in common, the worm genome is regarded by biologists as an essential basis for understanding how the human genome works.

"In the last 10 years we have come to realize humans are more like worms than we ever imagined," said Dr. Bruce Alberts, president of the National Academy of Sciences and editor of a leading textbook on molecular biology.

Seeing the worm's complete genome is humbling, Dr. Alberts said, because it makes biologists realize how much there is yet to understand. "We always underestimate the complexity of life, even of the simplest processes," he said. "So this is really only the beginning of unraveling the mystery of life."

Dr. Eric Lander, director of a human genome sequencing center at the Whitehead Institute in Boston, said: "This is really a landmark achievement. It is the first time we've had a picture of the gene set needed to run a multicellular organism."

Referring to the evolution of animals from single-cell precursors, Dr. Lander added, "This is a brilliant innovation of half a billion years ago that we are getting a look at for the first time."

Completion of the worm's genome, a 10-year project that was finished on schedule, also gives credibility to the Federal human genome project, which is locked in an undeclared race with a formidable new rival, a private enterprise, Celera, in Rockville, Md. Celera is owned by the Perkin-Elmer Corporation, the concern that makes the leading brand of DNA sequencing machines.

Dr. Sulston's work was financed by Britain's Medical Research Council and the Wellcome Trust of London, and Dr. Waterston's by the National Institutes of Health. The two teams worked in close cooperation, although they were an ocean apart.

The two laboratories are also the leading production centers of the human genome project. When the two researchers first decided to sequence the worm's genome in 1988, each was advised by colleagues that the task was a lunatic venture. The longest stretches of DNA that had been sequenced at the time were just a few thousand units in length.

"Several people told me I was nuts and was throwing away my career," Dr. Waterston said. "But I have a lot of faith in John," he said, referring to his colleague's ability to solve difficult problems.

When James Watson, then director of the human genome project, first told the two researchers he would advance money for a pilot project, they realized a long commitment lay ahead of them. Dr. Sulston recalls standing on the platform of the Long Island Rail Road station at Syosset, near Dr. Watson's laboratory at Cold Spring Harbor, with Dr. Waterston: "I said to Bob, 'The prison door has just closed behind us -- I heard it clang.' "

The two researchers first met in Cambridge, England, in the laboratory of Sydney Brenner, the biologist who selected the *C. elegans* worm as a model animal for scientific study. Dr. Sulston was completing a study of how the worm grows from a single egg to the 959 cells of the adult animal. He moved on to mapping the worm's six chromosomes, the packages in which the DNA is stored. Dr. Waterston, a physician interested in muscle disease, had been persuaded by Dr. Brenner to study muscle disorders first in the worm.

The task of sequencing the worm's genome was not the usual kind of academic research project. Both Dr. Waterston at the Washington University School of Medicine and Dr. Sulston in Cambridge had to transform their laboratories into semi-industrial plants employing more than 200 people each in almost round-the-clock operations.

One major problem in sequencing a genome is that the machines that analyze DNA can read segments of only 500 units or so in length. The full genome must be reconstituted from an inordinate number of small overlapping pieces.

Another complexity is that the DNA must be amplified, or copied many times, so as to furnish the machines with a sufficient amount to analyze. Many regions of the worm genome, however, resist the usual amplification processes. Even now the genome, though effectively complete, has a few small gaps that remain to be filled in.

From early on in the project, Dr. Sulston and Dr. Waterston posted the DNA sequences they obtained on the Internet, as a free gift for other scientists to analyze. "As the Internet evolved, a mechanism developed for us to provide data to people in a practical way," Dr. Waterston said. Biologists throughout the world soon learned that at the touch of a button they could compare any gene they were working on with the growing set of genes available from the worm project.

The worm genome proved to be of broad interest because of the unexpected degree of overlap between worm and human genes. A researcher who finds some gene is involved in human disease can compare its DNA sequence with those in the worm genome database. A match with a worm gene of known function will often reveal the role of the human gene. The worm genome is thus providing an essential platform from which to understand how the human genome is put together.

Yet it will take years of work to understand even the worm genome. Unlike computer programming, in which programmers usually insert explanatory remarks to describe what function each segment of code performs, biological programming comes unannotated, with no explicit hint of evolution's intentions. Biologists know or can guess the role of about half of the worm's genes; they have no idea what the rest may do.

At first glance the worm genome seems just a thicket of puzzles. Dr. Francis Collins, director of the human genome project at the National Institutes of Health, said geneticists had believed humans have about 10 different genes for making varieties of collagen, the main structural protein of skin. Yet the worm turns out to have 170 collagen genes. Biologists have no idea why it would need so many but they say they trust in evolution's wisdom that it does..

For many genes that exist in one copy in the worm, humans have four versions, confirming the long-held suspicion that the genome of backbone animals has twice been duplicated in the course of evolution. The spare copies were presumably free to evolve new and useful functions. The *C. elegans* worm would have split off on a separate evolutionary path before the first of the two duplications occurred.

An intriguing pattern already discernible in the general organization of the worm's genome is that its genes fall into two broad classes that are arranged differently on the chromosomes. One set of genes performs basic housekeeping functions for the cell. These genes have many counterparts in yeast and must have been highly conserved through evolution for two such different organisms to carry matching sets.

The other set of genes is special to the worm and seems to be evolving at a much brisker pace.

Dr. Sulston and Dr. Waterston report that the two sets of genes have different sites on the worm's chromosomes, with the older, conserved genes lying in the central region of chromosomes and the more variable genes being positioned toward the two ends. "It really does look as if the genome has found a way to hide its more important genes from the vicissitudes of the evolution that is going on more rapidly in the arms," Dr. Waterston said.

Many of the worm's genes occur in clusters, as if one important gene had been duplicated many times to perform variations of the original function. "One of the things I found surprising was that there are so many gene clusters -- 402 -- yet many are of genes about whose function we know nothing," said Dr. Robert Horvitz, a worm biologist at the Massachusetts Institute of Technology.

Dr. Sulston believes that only a small fraction of the worm genome's value is yet apparent. "The genome is not an open sesame in itself," he said. "It just provides this marvelous tool kit with all the basic information for making an animal, if biologists can just figure it out. The value it will deliver over time is much greater than the value you get on first analysis."

Biologists have already found the worm genome of great value. "I can't tell you how indebted those of us who do molecular genetics are to the people who did the genome sequence," said Dr. Gary Ruvkun of the Massachusetts General Hospital.

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