Worm Offers the First Animal Genome

Pity poor *Caenorhabditis briggsae*. Like most nematodes, this worm lives an uncelebrated life. Three decades ago, however, the millimeter-long worm had its big shot at fame—and came up short.

At that time, biologists were picking a worm species on which to concentrate their genetic and developmental studies. Sydney Brenner, who led the effort, had his eye on *C. briggsae*. But when the dust settled, a relative, *Caenorhabditis elegans*, had stolen the part.

Testifying to its subsequent rise to biological stardom, *C. elegans'* sinuous body graces the cover of the Dec. 11 SCIENCE. In the journal, investigators announce that they have essentially finished sequencing the worm's genome, making it the first multicellular organism whose full set of genes is known.

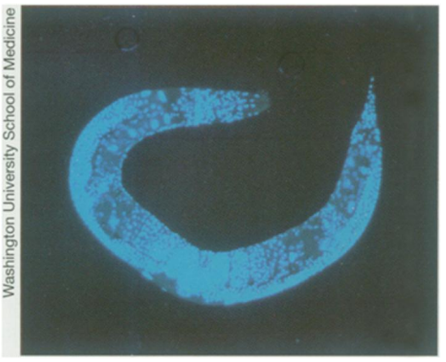
That feat thrusts *C. elegans* and the small, tightly knit community that studies it into the scientific spotlight. "It's fun," says nematode biologist Gary Ruvkun of the Massachusetts General Hospital in Boston. "The worm genome, being the first animal genome, becomes the brightest lighthouse for the navigation of all animal genomics."

Compared with viruses, bacteria, or yeast—the other organisms whose genomes have been sequenced—the microscopic *C. elegans* much more closely resembles complex animals, including people. It has a nervous system that includes a simple brain. It digests food, usually a steady diet of bacteria. It even reproduces sexually by fertilizing its eggs with sperm.

Easy to cultivate in the lab, the worm has a transparent body that simplifies the study of how a fertilized egg develops into an adult. Biologists have traced back to the egg the history of each of the nearly 1,000 cells in the adult animal. They've even mapped the connections between every nerve cell in the worm.

The sequencing of *C. elegans* DNA, led by scientists at the Sanger Centre in Cambridge, England, and the Washington University School of Medicine in St. Louis, began about 8 years ago amid skepticism that such a large genome could be deciphered. "There were certainly lots of people who thought we were foolish," says Robert Waterston, who directed the St. Louis effort.

The task turned out to be even more complex than expected. Early estimates suggested that *C. elegans*' six chromosomes had 6,000 or so genes, about half of them essential for life. The completed genome revealed nearly 20,000 genes, however. In comparison, the genome of the yeast *Saccharomyces cerevisiae* contains fewer than 7,000 genes (SN: 5/4/96, p. 278).



The nematode Caenorhabditis elegans, *stained to glow blue in ultraviolet light.*

The overlap between the yeast and worm genomes suggests that there's a core of about 3,000 genes that are crucial to the workings of eukaryotic cells. Such cells, which include human cells, package most of their DNA inside a nucleus. The core genes encode proteins that play roles in basic activities such as DNA synthesis, the making of the cell's skeleton, the transport of proteins, and chemical signaling within the cell.

Curiously, in the worm, most of the essential genes cluster within the central regions of each chromosome. Noting that chromosome ends may evolve more rapidly, Waterston suggests that "evolution found a mechanism to tuck these genes away in a safe place." In contrast, he says, the chromosome arms may be "gene nurseries, or graveyards, or both."

The 17,000 or so additional genes within the worm, compared to yeast, should help biologists explain how multicellular animals differ from single-cell eukaryotes. Many of these genes, for example, encode proteins for cell-cell adhesion and signaling between cells.

To identify all the nematode's genes, the researchers had to spell out a DNA sequence of 97 million bases, the chemical building blocks of DNA. A few small gaps remain, although the scientists are confident they have sequenced more than 99 percent of the worm's genes.

Waterston notes that the many short, repeating DNA sequences in *C. elegans*' genome, and their distribution, made sequencing it even more challenging in some ways than the human genome. The methods developed to analyze the worm genome are already speeding the human genome effort, he says.

The nematode's genome itself should offer insight into human biology. "Because *C. elegans* has so many genes shared with humans . . . we can figure out what they're doing in *C. elegans* and apply that to a whole myriad of human genetic issues," says Waterston.

Scientists also hope that knowledge of the *C. elegans* genome will help people deal with worms that cause human illnesses and agricultural problems. "It is important that the *C. elegans* genome project yields an improved understanding of other nematodes, so as to enable the development of control strategies to alleviate their effects on human populations," Mark Blaxter of the University of Edinburgh says in one of the six articles on the nematode in the Dec. 11 SCIENCE.

The worm genome marks a new era in evolutionary biology, one in which relationships between animals will be based on genomes rather than on fossils or a single gene. Already, scientists are reconsidering whether nematodes developed before or after the time when arthropods and vertebrates parted ways.

What's missing from the *C. elegans* genome may provide as much evolutionary insight as what's there. "What it looks like is that certain things have been deleted in the lineage leading to *C. elegans*," says Ruvkun. "Having genome sequences for a wide zoo of creatures will be very important." The fruit fly's complete genome is expected next, he notes.

Biologists caution that sequencing an animal's genome is but a first step toward a better understanding of the animal. More than half the newfound *C. elegans* genes have no identified function. "We have to fill in a considerable amount of what the gene products do inside the cells they work in," says Brenner, who now is at the Molecular Sciences Institute in Berkeley, Calif.

Researchers plan to inactivate every one of the worm's genes in an attempt to understand each one's role in development and adult life. Also on the drawing board are microchips covered with the worm's DNA, which will allow the simultaneous monitoring of the activity, or expression, of all of *C. elegans*' genes (SN: 3/8/97, p. 144).

Biologists also propose to make movies of every gene's activity in the worm's development and life. To do this, they intend to fuse each of its genes to a jellyfish gene encoding a light-emitting molecule. "We would know exactly when and where each gene was expressed," says Waterston.

With all this attention on *C. elegans*, it's easy to forget *C. briggsae*. That worm did land a supporting role. Scientists are now sequencing parts of its genome for comparison. Why wasn't it chosen for stardom? It's just not as photogenic or easy to work with, notes Brenner. —*J. Travis*