

SEPTEMBER 22, 1999

Roundworms Provide Clues to Human Kidney Disease



Image Title: An illustration of the roundworm *Caenorhabditis elegans*. - John Kachik

There would seem to be little connection between roundworm reproduction and human kidney disease, yet HHMI investigators have found such a link.

Paul Sternberg, an HHMI investigator at the California Institute of Technology, and colleague Maureen Barr had been studying the mating behavior of the tiny roundworm, *Caenorhabditis elegans*, when they found that a gene crucial to roundworm mating strongly resembles a gene involved in polycystic kidney disease.

"We set out to study how genes control neurons that control behavior," Sternberg said. To understand how genes influence reproductive behaviors, Sternberg and Barr introduced mutations into the roundworm's genome and then looked for males that had difficulty mating.

Reproduction in *C. elegans* involves two sexes, males and hermaphrodites. Hermaphrodites are females that produce sperm, which the hermaphrodite worm can use to self-fertilize the first 300 or so eggs. After self-fertilizing the first batch of eggs, the hermaphrodite preferentially accepts sperm from males in hopes of producing a larger number of offspring. This unusual mating system makes males nonessential which is convenient for molecular biologists because it allows them to mutate males without altering the viability of the test strain.

When a male roundworm encounters a hermaphrodite, he places his tail, which contains sensory structures, flush with the hermaphrodite's body and glides it along the length of her body until he locates the vulva. After observing mutant worms under a microscope for many hours, Barr noticed that some males glided right past the vulva. Closer observation revealed that many of these mutants did not respond to the hermaphrodites at all.

Genetic analysis of these mating-deficient worms revealed that they had a mutation in a gene Sternberg and Barr called *lov-1*, for location of vulva. They sought further confirmation of *lov-1*'s importance in mating by injecting a healthy copy of the gene into mutant males. Mutant males who received the *lov-1* gene mated normally. The researchers also found that only male sensory neurons vital to vulva location contained the protein encoded by *lov-1*, further verifying the protein's role in mating behavior.

Sternberg and Barr then compared the DNA sequence of *lov-1* to gene sequences recorded in gene databases. As reported in the September 23, 1999, issue of the journal *Nature*, the closest match was *PKD1*, a gene involved in human polycystic kidney disease.

"The work is a surprise intersection of two different areas," Sternberg said. The agreement in the amino acid sequences of the two proteins suggests that the LOV-1 and PKD1 proteins encoded by these two genes might perform similar roles in worm and kidney cells. PKD1's function is still a mystery, although scientists do know that defective PKD1 can cause the formation of cysts in the kidneys, a potentially fatal condition affecting 12.5 million people worldwide.

If the LOV-1 protein is indeed similar in function to PKD1, then male roundworms could be useful for deducing the role that PKD1 plays in kidney disease. "At first glance it seems very odd that you have a gene that's acting in a neuron which is a very different cell type than those cells in the kidney," Barr said. But, she continued, if you look at what the gene is doing in the cell, regardless of cell type, you can learn about its function.

The tiny roundworms are easier and faster to work with than mammalian cells, and the entire sequence of the *C. elegans* genetic code is already

known. "The advantage is that we can do a lot of experiments faster," Sternberg said. "It would be exciting to find more genes that work with *lov-1* in the worm because those genes may also work together in the kidney."