

Massive Molecular Study of the Roundworm Reveals Nature's Complexity

Yale UniversityYale University

New Haven, Conn. — An international collaboration of more than 100 scientists, spearheaded by a team of researchers at Yale University, has revealed in unprecedented detail and scope the multi-faceted functions of the genome of the roundworm, one of science's key model organisms. The research is one of the first big payoffs in a massive campaign to describe how life functions through genomes of several organisms, including humans.

The results are published in the Dec. 22 edition of Science Express, along with a matching paper on the genome of fruit flies. The two main papers are accompanied by more than 16 companion publications in the journals Genome Research and Nature that begin to describe the many ways organisms use their genetic blueprints to carry out functions necessary for survival.

"We have taken the raw parts list from the genome sequence, found the functional elements within it and described how they are connected and how they work together," said [Mark Gerstein](#) [1], the A. L. Williams Professor of biomedical informatics, molecular biophysics and biochemistry, professor of computer science, and lead author of the Science paper on the worm genome.

The studies are an outgrowth of the ENCODE project, or Encyclopedia of DNA Elements, which was launched in 2003 by the National Human Genome Research Institute to identify all functional elements of the human genome. Scientists had recognized that the genome was much richer than the sum of the genes that code for proteins. For instance, only 1 percent of the human genome contains code to make proteins, yet scientists have come to appreciate that the 99 percent of non-coding areas of the genome are full of elements that fundamentally influence our biology.

Such large-scale approaches using multiple technologies have already paid dividends with the discovery of DNA elements that control cell death and are critical in cancer, as well as many forms of RNAs that control how genes are turned off and on — an insight with great therapeutic potential.

However, the regulatory elements that control gene expression in humans are so complex and numerous that the project was expanded to include simpler model organisms, which provide a framework to compare with the human genome. The two Science papers on worms and flies are the first major results of the ENCODE project, and mark the first time the complete non-coding regions of animal genomes have been thoroughly annotated.

The Yale University team and dozens of researchers from other institutions collaborated on the worm genome project. Using several new technologies, the Yale

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team helped delineate the crisscrossing webs of networks that regulate biological behavior in *C. elegans*. Not surprisingly, they found that even in relatively simple animals the operation of life is dauntingly complex.

The project not only catalogues these newly discovered elements but also analyzes how they interact in regulatory networks to turn genes on and off in a coordinated fashion.

The roles that regulatory RNAs and proteins play are determined not only by when they are activated but where on the genome they bind. A companion paper published in *Genome Research* by Valerie Reinke, associate professor of genetics at Yale, illustrates this deeper level of complexity.

Reinke studies a family of regulatory proteins called transcription factors that govern many developmental processes, including migration of cells to the front or back of an organism. Prior to the new study, scientists had identified only about 100 places on the genome where these regulatory proteins bound, the first step in regulating other genes needed in development of the organism. Reinke's team identified the binding sites genome-wide for 22 of these regulatory proteins and found 16,700 binding sites, each with the capacity to initiate a different function.

Reinke points out that 20 percent of the roundworm genome encodes from proteins, leaving scientists with 80 percent of the organism's DNA for more exotic elements that influence function. But in humans, researchers must analyze much larger stretches of DNA to determine these functions.

"It is only going to get a lot more complicated," Reinke said.

Senior author on the paper was Robert Waterson of the University of Washington, one of 26 institutions involved in the study. The 27 Yale researchers who are among the 130 authors of the paper who contributed to the study work in the lab of Frank Slack of the Department of Molecular, Cellular and Development Biology, as well as the Gerstein and Reinke labs.

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