GENOME PROJECTS

Yeast Genome Sequence Ferments New Research

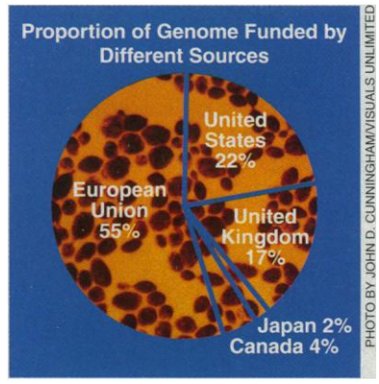
It all began 7 years ago as something of a European cottage industry: a few labs working together to sequence a single chromosome. But these humble beginnings soon turned into a global collaboration that culminated this week. In simultaneous press conferences in Brussels and Washington, researchers unveiled the complete genome of the most complex organism yet sequenced—brewer's yeast. The 12-million-base sequence is the first for a member of the eukaryotes—organisms that, unlike bacteria, have nucleated cells, among them all multicelled animals and plants. "We now have the complete set of genes needed to make a complex organism with a nuclear structure like our own," says genome researcher John Sulston, head of the Sanger Centre near Cambridge, U.K. "It's a really major step forward."

Since the beginning of the project, sequence data have been trickling out, growing to a flood of data over the past 12 months. Researchers have been excited because yeast's 16 chromosomes contain many genes resembling those found in other organisms, including humans. As a result, the yeast sequence may hold clues to everything from the evolution of eukaryotes to human disease. "With all the new information it's hard now to imagine how geneticists managed without it," says Bernard Dujon of the Institut Pasteur in Paris, one of the project's coordinators. "It's going to change completely the way we operate," says another coordinator, Stephen Oliver of the University of Manchester.

The project got started in 1989 as a European Union (EU) effort to sequence chromosome 3 of *Saccharomyces cerevisiae*, involving 37 laboratories. That effort was so successful at getting laboratories to collaborate in sequencing different parts of the chromosome that the EU decided to attack the entire yeast genome in an ambitious program involving more than 100 European laboratories. This project also led to collaborations with other major centers in the United Kingdom, United States, Canada, and Japan. The involvement of three key sequencing laboratories—the Sanger Centre, the Genome Sequencing Center at Washington University in St. Louis, and Stanford University—sped up the task, which cost an estimated $30 million.

The main challenge for yeast sequencers was the size of the genome—more than six times larger than the first complete bacterial sequence, reported last year. Within that expanse, says another project coordinator, Bart Barrell of the Sanger Centre, "we anticipated we'd find on average one gene in every 2000 bases, with an estimated total of around 6000 genes"—estimates that proved to be spot on. Now that the final sequence data have been released from the Martinsried Institute for Protein Sequence in Munich, Germany, which has collated the yeast data, researchers are pushing ahead with functional analysis of the newly discovered genes.

One surprise has been the degree of redundancy in the genome: Often several genes appear to have homologous sequences and probably the same function. "People are trying hard to understand what this means," says André Goffeau at the Catholic University of Louvain in Belgium, the program's overall coordinator. Another was the large number of genes for which the sequence gave no clue to the function. About 30% of the genes appear to have no known function, although that figure is shrinking as genes with known functions from other organisms are matched to yeast genes.



Strange brew. Funding from other countries aided the European Union's yeast genome project.

Last month, for example, Chris Sander and his colleagues at the European Bioinformatics Institute near Cambridge linked a number of computers together to create a supercomputer that performed some 19 billion sequence comparisons between genes from other organisms and the yeast genes then available—about 85% of the total. Based on the comparisons, Sander and his colleagues estimated that only about 12% of the yeast genes showed no similarities to any other genes, although for a further 14% showing some similarity, the function of the corresponding gene in another organism isn't known. The EU is keeping up the momentum with a new project, called Eurofan, in which 144 laboratories will study gene functions by systematically disrupting each gene and analyzing changes in the mutant yeast cells. Researchers hope to get a biochemical function for every gene by 2000, says Goffeau.

Knowledge of the full set of genes should give researchers a sharper picture of the workings of a yeast cell, enabling them, for example, to pin down all of the components of particular biochemical pathways. As Goffeau explains, "It's hard to understand drug metabolism, for example, if you don't know all the genes involved." Now, however, "the systematic sequencing has revealed more than two dozen putative members of one membrane transport pathway in yeast." Determining patterns of gene regulation is another goal. "I'd love to know all the glucose-regulated genes in yeast, and this now seems possible," says project coordinator Mark Johnston at Washington University. Even though the new genes may make research more complex, says Howard Bussey of McGill University in Montreal, another coordinator, "they're like fish in a barrel; you've got them all."

Researchers also hope the sequence data will boost evolutionary studies of yeast and eukaryotes in general because they can now do detailed comparisons between yeast and other organisms. One goal is to compare the sequence with that of a distant relative—the fission yeast, *Schizosaccharomyces pombe*. This yeast is separated from baker's yeast by 500 to 1000 million years of evolution, and although their genomes are a similar size they have evolved quite differently, says Barrell. "Around 40% of the fission-yeast genome has been sequenced, and there appear to be up to 20% fewer genes and much less redundancy," he says. When the rest of the fission yeast's genome is sequenced, a comparison should help pin down the basic set of genes essential to all eukaryotes.

The newly discovered yeast genes are even exciting interest in medical researchers. Among 51 cloned human genes associated with disease, 13 show similarities with yeast genes and a further 12 show some weaker links, says Goffeau. By disrupting these genes in yeast, which is not possible in humans, researchers should get clues to their function in humans. "It will be extremely important to determine the function of yeast genes which have human homologs," says Paul Nurse of the Imperial Cancer Research Fund in London.

With the completed sequence and rush of new work, Sander believes yeast will pave the way to a new quantitative and predictive cell biology. "We've a long way to go, but I look forward to when we'll have theoretical models which will predict how cells behave in different states," he says. "It's clear the sequence is not something just to look at," says Bussey.

–Nigel Williams