Objection #2: Why Sequence The Junk?

Genes and their corresponding proteins get most of the attention, but they make up only a tiny fraction—1.5% or less—of the human genome. The other 98% of DNA sequence that does not code directly for proteins was once dismissed as "junk DNA," and numerous researchers argued that it would be a waste of time and money to include the repetitive, hard-to-sequence regions in the genome project. But scientists have discovered many riches hidden in the junk, and as the project nears completion, several researchers predict that some of the most intriguing discoveries may come from areas once written off as genetic wastelands.

Included among the noncoding DNA, for example, are the crucial promoter sequences, which control when a gene is turned on or off. The repetitive sequences at the ends of chromosomes, called telomeres, prevent the ends of the chromosome from fraying during cell division and help determine a cell's life-span. And several teams have begun to make a strong case that repetitive, noncoding sequences play a crucial role in X inactivation, the process by which one of the two X chromosomes in a female is turned off early in development. Other genes are turning up in areas previously dismissed as barren. Scientists had assumed, for example, that the regions next to telomeres were buffer zones with few important sequences. But in this week's issue of *Nature*, H. C. Reithman of the Wistar Institute in Philadelphia and his colleagues report that these regions contain hundreds of genes. "The term 'junk DNA' is a reflection of our ignorance," says Evan Eichler of Case Western Reserve University in Cleveland.

The human genome has much more noncoding DNA than any other animal sequenced so far. No one yet knows why. At least half of the noncoding DNA seems to be recognizable repeated sequences—perhaps genomic parasites that invaded the genomes of human ancestors. Eichler suspects that such repeats might provide some genomic wiggle room. Long stretches of noncoding DNA provide "a built-in plasticity that may be bad at the individual level, but if an organism is going to evolve, it may be a huge selective advantage," he says.

"There is a rich record of our history" in the repeats, agrees Francis Collins of the National Human Genome Research Institute in Bethesda, Maryland. "It's like looking into our genome and finding a fossil record, seeing what came and went."

–GRETCHEN VOGEL

asked Paul Berg of Stanford University.

As the biology community wrestled with the merits of the project, NIH staked out a position firmly on the fence. By contrast, DeLisi and Smith were decidedly gung ho. DeLisi aggressively gained support for the project, first from his superiors at DOE and then from Congress, starting a small Human Genome Initiative within DOE in 1986. The following year, a prestigious advisory panel to DOE called for an all-out effort and urged the agency to take the lead. DOE was the logical choice, DeLisi argued, because this was "big science," DOE's stock-in-trade, whereas NIH had never attempted a project of this scope (*Science*, 8 August 1986, p. 620; 31 July 1987, p. 486).

The fact that DOE—not NIH—was lobbying for the project only heightened some biologists' unease, because they put great store in NIH's peer-review system. "The fear is not big science so much as bad science," said Botstein, who in 1986 denounced DOE's proposal as "a scheme for unemployed bombmakers."

Emerging consensus

Political posturing continued until 1988, when a National Research Council (NRC) panel gave the project its official seal of approval (*Science*, 12 February 1988, p. 725). Chaired by Bruce Alberts, then at UC San Francisco, the panel contained some of the project's staunchest advocates, such as Gilbert and Watson, and also some skeptics, including Botstein, mouse geneticist Shirley Tilghman of Princeton University, and yeast expert Olson, then at Washington University in St. Louis. Within a year, the panel endorsed the project unanimously, calling for a rapid scale-up in "new and distinctive" funds to $200 million a year over the next 15 years.

In the process, the panel redefined the project, laying out a phased approach that mollified critics and has guided the initiative ever since. Rather than plunge into sequencing—which no one knew how to do on a massive scale anyway—the project should begin by constructing maps of the human chromosomes. These would greatly speed the search for disease genes, offering immediate medical payoffs. The panel recommended that full-scale sequencing be postponed until new technologies made it faster and cheaper.

Charles DeLisi. An early advocate, he launched the Human Genome Initiative within the Department of Energy in 1986.

But it was the panel's recommendation to analyze the genomes of simple organisms, such as *Escherichia coli*, yeast, and the roundworm *C. elegans*, and eventually the mouse, that proved most persuasive. Tilghman and Botstein, in particular, argued vociferously that biologists had no hope of understanding the human genome if they couldn't compare it to the genomes of experimental organisms. Luckily for biologists, evolution has been remarkably conservative, retaining the same genes over and over again in different organisms, explains Tilghman—and it is far easier to figure out a gene's function by experimenting with it in a fruit fly than in a human. Looking back, Tilghman sees this as one of the panel's smartest decisions: "Model organisms were an extraordinary investment. We learned how to sequence on these simpler organisms. And more important, we got a preview of the human genome by sequencing these organisms."

Gilbert, however, was impatient with the panel's cautious approach and with the interagency dithering. Arguing that the technology was already good enough to sequence the human genome, he left the NRC panel to launch his own company, Genome Corp. His plan, remarkably similar to J. Craig Venter's vision a decade later, was to set up a sequencing factory to churn out the data, which he intended to copyright and sell. "[It will be] available to everyone ... for a price," he explained (*Science*, 24 July 1987, p. 358). The plan infuriated Watson, who rankled at the idea of selling something as