Whatever Happened to the Genetic Map?

The first goal of the genome project—a fine-grained genetic map—may just be too tough to reach, at least on schedule

HAS A MAJOR GOAL of the human genome project already gone off track? That was the impression that emerged from a recent meeting when several prominent geneticists questioned whether the project has lost sight of what everyone thought was its first priority—the completion of a high-quality genetic map to track down the genes that cause 4000 or so hereditary diseases.

In 1987, when a partial map had already helped to narrow the search for the genes that cause cystic fibrosis, Duchenne muscular dystrophy, and Huntington's disease, the National Research Council called for an immediate effort to develop a genetic linkage map as the first goal of the genome project.

That goal has since been reiterated in every major report on the genome project, including the 5-year plan that the National Institutes of Health and the Department of Energy are now drafting for Congress. During this time no one said that developing a fine-resolution genetic map would be easy. Still, they predicted that it could be completed in 3 to 5 years, for a cost of $10 to $15 million a year.

So people were a bit taken aback when, at a December meeting of the NIH advisory committee on the genome project, where the draft 5-year plan was being reviewed, geneticist Maynard Olson of Washington University questioned the feasibility of reaching that oft-stated goal.

"There is zero probability that we will develop a 1-centimorgan [genetic] map unless there is a major change in policy. Is this a goal or not?" asked Olson, who is, as one colleague describes it, a widely respected skeptic of easy solutions and overblown expectations. Said Olson: "We all agree we want one, but saying so won't get us one."

As Olson and others pointed out, 3 years have passed since the National Research Council called for an immediate effort, but the map is not that much further along. If the goal is to be achieved, they said, then a mid-course correction is in order.

"There are very few things we know how to do in the short term that would really make a difference, and one of those is a high-resolution genetic map," said David Botstein of Genentech, Inc., in South San Francisco. "It is remarkable that few resources have been committed to it, since it is a goal, and it is realizable and useful to people."

What happened? Despite all the lip service, the genetic map has gotten lost in the shuffle, said Olson, Botstein, and Leroy Hood of the California Institute of Technology at the December meeting. The Center for Human Genome Research at NIH has not been aggressively pursuing the map. And the mappers themselves have been distracted by the hunt for the very disease genes the map helps them find. The upshot, asserted Botstein, is that "there is no one out there with the responsibility to get it done."

Helen Donis-Keller: *"I am not sure anyone wants a genetic map."*

"That's a little exaggerated," replies Elke Jordan, deputy director of the genome center at NIH, who claims that people are working on the genetic map, though clearly not on the scale envisioned by the NRC and other committees. When those reports were being written several years ago, the map was already well under way. Two groups, one led by Helen Donis-Keller, then at Collaborative Research in Bedford, Massachusetts, and the other by Ray White at the University of Utah, had just completed rough maps of all the chromosomes. And they were gearing up to work on a more detailed map.

The idea behind a genetic map is to blanket the chromosomes with genetic markers—tiny, variable pieces of DNA—ideally evenly spaced, and the closer the better. With the chromosomes thus covered, it should be possible to locate any gene between two markers. This still isn't enough to pluck out the gene, but it narrows the search considerably—from 3 billion bases in the entire genome to, say, 5 or 10 million bases between two markers. The usefulness of the map, then, depends on its resolution, or the distance between the markers, which is measured in centimorgans. A centimorgan translates roughly into a physical distance of 1 million bases.

The maps Donis-Keller and White completed in 1987 had markers spaced, on average, every 10 centimorgans. What would be ideal, concluded the NRC panel, and the later committees as well, would be a map with markers 1 centimorgan apart. That would mean that any gene could be localized to a stretch of DNA just 1 million bases in length. Other techniques could then be used to zero in on the gene.

But today, at about the time the NRC committee said the map could be nearing completion, that goal is nowhere in reach. The NIH genome center is spending about $5.5 million on genetic mapping, but most of that is going for mapping the regions around known disease genes and not to the more global strategy of blanketing all the chromosomes with markers, says Jordan. "The current approach, in and of itself, may not lead to a map with a resolution as fine as 1 centimorgan," she admits. And though the map's resolution has improved, from 10 centimorgans to about 6, it is still not a very good map, says Donis-Keller. In some places, near sought-after disease genes, the markers are tightly clustered. In others, they are few and far between.

All of which led Olson to suggest at the December meeting that perhaps the genome center should admit that this goal will be too tough to achieve and settle instead for a more realistic target—perhaps a 5-centimorgan or a 2-centimorgan map.

It's hard to pin down exactly why the genetic map is proving so difficult to complete. At least part of the problem is that the hunt for disease genes is far more tantalizing than generating thousands of markers and mapping them to chromosomes, which is undeniably hard slogging. It can be a thankless task, says Jordan, "to generate markers that are not of immediate use to you. After all this rather routine work, people hit on something interesting and pursue it." Adds Olson: "It is very difficult to interest groups in anything but local, high-resolution mapping"—the kind of mapping that can hand them disease genes.

White disagrees. He says his Utah lab is still churning out "the markers that everyone uses. I spend a lot of my time on it. It is a big deal." And White, who has a sizable grant

from the genome office, says he is committed to pursuing a 1-centimorgan map. "Remember, a 1-centimorgan map is what got us the cystic fibrosis gene," he says, referring to the detailed map of part of chromosome 7 that he and others prepared. But for now, he is concentrating on just three chromosomes, 17, 16, and 5, which house disease genes he is also looking for.

"Such a major goal should not be dependent on one person," argues Botstein, and White agrees. "One person can get the job done, given enough time. But you can't do it in 5 years."

Meanwhile, Donis-Keller puts the onus for the missing genetic map squarely on NIH, as do others. "I am not sure anyone wants a genetic map, despite what they say. My first love is the genetic linkage map, to create a high-quality biological tool," says Donis-Keller, who recently moved from Collaborative to Washington University. "But in this atmosphere of tight money, I have had trouble obtaining funds, and others have too."

This is just not the kind of work that excites most peer reviewers, notes Donis-Keller, who says that the study section complained that her application was not innovative. "I never said it was innovative. But it is important and doable."

"There were grants that didn't get funded, but that is true of any area," replies Jordan. "We haven't made a policy of not funding genetic mapping."

Nonetheless, the center is now rethinking its strategy. The advisory committee has set up a new working group to look at, among other things, how to obtain a fine-resolution genetic map. Should the genome center actively solicit proposals, or is it time to switch to contracts? People are also coming up with ideas on how to staff such an endeavor, says Jordan. "One idea would be to recruit people for a limited time to work on the map, then let them exploit the data. Until it is all done by machine, it will be a problem, because postdocs need publications."

Meanwhile, the advisory committee has already heeded Olson's advice and scaled back the goal for the map. Although the ultimate goal is still a 1-centimorgan map, for the next 5 years they are aiming for a map in which the average distance between markers is 2 centimorgans, with no gap greater than 5 centimorgans—still a very ambitious goal, says Olson, and one that will require a major push.

As Botstein pointed out, genetic mapping is trivial compared to sequencing the entire 3 billion bases in the human genome. "If we are stuck on the logistics of this little task, then I'm worried about the rest."

■ LESLIE ROBERTS

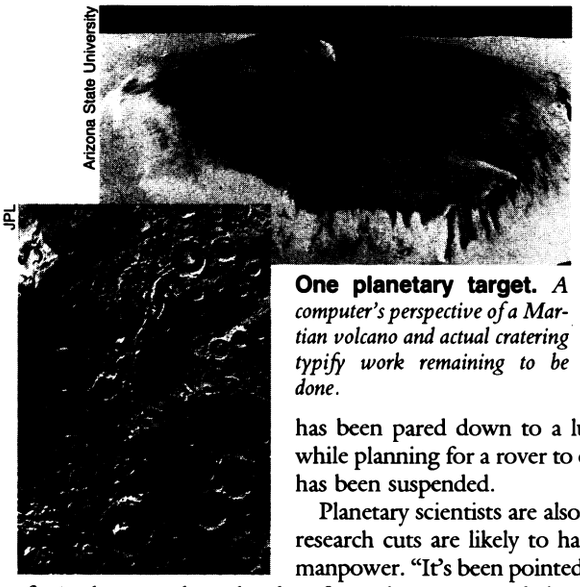
Planetary Science Funds Cut

Just when launches of scientific missions to the planets are gearing back up after a 12-year hiatus, planetary scientists are reeling under another budget cut—this time in the funding that they need to help figure out what all their new observations mean. "We've had a rather severe hit," says William Quaide, chief of the planetary science branch of NASA's solar system exploration division. "It's harder still because we had a big cut of $10 million last year."

NASA officials have had to chop $12 million from the current fiscal year budget for planetary science that Congress approved just last October. This is a modest sum compared to what it takes to run a planetary mission. For example, the Galileo spacecraft, which recently began its long-delayed, 6-year trip to Jupiter, will consume $1.3 billion before its mission is completed. But spacecraft funding can be pared back only so far without jeopardizing the whole project. Budgets for planetary spacecraft flights in the 1990s are "barely able to ensure successful operation," Quaide says.

So this year's $12-million worth of cuts are concentrated in the $79-million budget for research and analysis, thus reducing to just $67 million the money available for analyzing the data collected by previous planetary missions. Even funding for analysis of data yet to be acquired by the Magellan spacecraft, which is due to arrive at Venus this August, is being cut back.

Other projects will have to be postponed or scrapped entirely. "I can only spread the pain so much [across the board]," says Quaide, "before terminating whole programs."



One planetary target. *A computer's perspective of a Martian volcano and actual cratering typify work remaining to be done.*

New programs for studying the origins of the solar system and upgrading laboratory instrumentation have been put off to next year. Funding for U.S. investigators working on the data returned by the ill-fated Soviet Phobos mission to Mars has been ended early. In addition, advanced planning for future planetary missions has been pared down to a lunar orbiter mission only, while planning for a rover to explore the surface of Mars has been suspended.

Planetary scientists are also dismayed by the effect the research cuts are likely to have on the training of new manpower. "It's been pointed out that there's a shortage of people to analyze the data from the programs being planned by NASA," says planetary meteorologist Andrew Ingersoll of the California Institute of Technology, who is the current chairman of the Division of Planetary Science of the American Astronomical Society. "Where do these people come from if not from among those analyzing the data already in hand?"

This year's decline results from an odd assortment of budgetary pressures. About a third can be attributed to the budget reductions mandated by the Gramm-Rudman Act and by the levy on all federal programs to pay for the war on drugs. Another third can be blamed on better relations with the Soviets. As part of a 1994 Soviet mission to Mars, a low-flying balloon will return closeup views of the surface through a $4.4-million radio relay system added to the Mars Observer, the first U.S. mission to the red planet in 17 years. Because the Mars Observer's budget could not handle the cost of the relay, NASA officials took it out of scientific research. They took a couple million dollars more to pay for cost overruns on other flight programs.

U.S. planetary scientists have a lot on their plate for the 1990s. In addition to Magellan, Galileo, and the Mars Observer, work is getting started on a dual mission to a comet and Saturn. But how, the researchers ask, will they be able to digest all the data these missions bring back?

■ RICHARD A. KERR