Flap Arises Over Genetic Map

A newly published genetic linkage map of the human genome has caused a minor furor over what constitutes a map and who, if anyone, can claim scientific precedence

In early October Collaborative Research, Inc., the Bedford, Massachusetts, biotech company, announced with much fanfare that it had completed "the world's first genetic linkage map of the entire human genome." With this map, says Helen Donis-Keller, who led the research effort, there is a 95% chance of being able to determine the rough chromosomal location of any disease gene. As presented, the achievement appeared to be the first major milestone in the current drive to map and sequence the entire human genome (*Science*, 31 July, p. 486).

But almost as soon as Collaborative unveiled its map at the meeting of the American Society of Human Genetics in San Diego, a flap ensued over how complete the map is, whether publication is premature, and how much credit the company can rightfully claim.

Raymond L. White, leader of a rival team pursuing the same goal at the Howard Hughes Medical Institute at the University of Utah, immediately denounced Collaborative's map as premature and challenged their claim to scientific precedence. "What they have accomplished is important. It has been one of Collaborative's main goals, as well as ours, and we have substantial respect for that. The real distinction comes from what you call that collection of markers, at that level of analysis. It is not what we believe should be properly called a map."

Several other leading genetics researchers say Collaborative's map, though rough and incomplete, is a significant achievement. But they question the hoopla with which it was released, which they say overstates its importance and underestimates how much work remains to be done.

This tiff is the most public in a long-simmering and acrimonious feud—some call it a war—between the two research groups. "There is the feeling of having been burned yet again by this group," White says. The normal, if intense, scientific rivalry seems to be heightened by a sort of clash of cultures between an academic researcher and a biotech company with its understandable need for publicity and eye toward profits.

The idea behind a genetic map is to blanket each of the 23 chromosomes with genetic markers, or signposts, ideally evenly spaced, and the closer, the better. The "resolution" of the map increases as additional markers are added. Although opinions vary, many researchers consider 500 to several thousand such markers to be desirable. With the genome thus completely covered, it should be possible to locate any gene between two markers. This still does not hand you the gene, but narrows the search to, say, 5 or 10 million bases rather than the 3 billion that make up the genome.

"We obviously have a different perception about what constitutes scientific usefulness."

Markers are tiny, variable pieces of DNA, usually restriction fragment length polymorphisms (RFLPs). These markers, whose location on the chromosome is known, can be used in linkage studies to search out the rough location of a gene. If the marker is inherited along with disease trait, odds are that the disease gene is positioned close to the marker on the chromosome.

The notion of mapping the entire human genome this way, with DNA polymorphisms, originated about 10 years ago with David Botstein of the Massachusetts Institute of Technology, Mark Skolnick of the University of Utah, and Ron Davis of Stanford. With White, who was then at the University of Massachusetts, they published a paper in 1980 outlining this strategy. They estimated that the entire genome could be mapped with a minimum of 150 informative markers—but at that time they had no idea how many of these polymorphisms actually existed.

Almost since that time White and, later, Donis-Keller have been scouring the genome for these polymorphic pieces of DNA, at first cooperating and then fiercely competing after a disagreement over a planned collaboration on mapping the cystic fibrosis gene. At a certain point, when enough markers have been accumulated and the linkages among them have been determined, maps "fall together cooperatively," says Donis-Keller. For Collaborative, that happened in September.

Collaborative's map, which is described in a scientific paper in the 23 October *Cell*, consists of 404 markers spaced, on average, 10 centimorgans apart. (A centimorgan is a measure of genetic distance but it roughly corresponds to a physical distance of a million bases.) Some markers are as close as 3 centimorgans, Donis-Keller says, and others may be 30 centimorgans or more apart.

Of these 404 markers, Collaborative identified 306; the rest were obtained from other researchers or were drawn from the published literature. Some 40 of these markers were developed by White's group and were available through the Centre d'Etude du Polymorphisme Humain, better known as CEPH, an international data base and cell line repository in Paris. CEPH supplies cell lines or DNA to researchers, who in return submit their data, which are then made available to other CEPH collaborators.

The actual mapping involves determining the linkages among the markers, their arrangement along the chromosomes, and the distances between them. This entails a massive number-crunching exercise, for which Collaborative used two new computer algorithms for multilocus linkage analysis, one developed by Eric Lander of MIT's Whitehead Institute, the other by Collaborative scientist Philip Green.

Collaborative's map still has gaps—distances between linkage groups that are too large to estimate—which Donis-Keller says the company intends to fill in. And while some chromosomes are densely covered, on others, markers are rather sparse. On chromosome 7, for instance, the site of the cystic fibrosis gene, there are some 60 markers arrayed at intervals of roughly 3 centimorgans—a result of Collaborative's intensive search for the cystic fibrosis gene. On the other hand, chromosome 14 contains only two small, unlinked groups of probes. Chromosome 19 is also scantily covered.

Nonetheless, Collaborative calculates that the map is 95% complete, which means,

they say, that there is a 95% chance of being able to link any disease gene with one of their markers and thus determine its approximate chromosomal location. "I think that is a pretty useful map," Donis-Keller says.

Once the approximate location is known, other tools can be used to zero in on the gene and eventually pull it out and clone it. But even before the gene itself is found, nearby markers can be used to develop diagnostic linkage tests, such as Collaborative offers for five single-gene disorders, including cystic fibrosis.

Collaborative expects the biggest payoff to come from mapping diseases with complex modes of inheritance, such as cancer and heart disease. Even at this preliminary stage, Donis-Keller says, the map provides sufficient resolution to enable investigators to begin searching for clusters of genes involved in these complex disorders. The company, for instance, is already gearing up to begin searching for the gene(s) involved in manic-depressive illness.

White is noticeably less enthusiastic. "It is a very useful collection of markers, but it is not what we believe should be properly called a map." The problem, he says, is the gaps. "Our feeling is that what the community needs and what constitutes a complete reference linkage map of the human genome is a continuous linkage group from one end of the chromosome to the other. If there is a region or several regions where the linkage groups are not connected, we feel it is an incomplete map."

White maintains, and others agree, that the Utah group has more markers than does Collaborative (some 470 markers in comparison to Collaborative's 300-odd) and has tested them in more families (60 as compared with 21). "We would never have dreamed of making such a publication with our data set, which is substantially larger than theirs, because we still have significant gaps," says White. "We obviously have a different perception of what constitutes scientific usefulness and appropriateness for scientific publication."

Rather than publishing a map of the entire genome, the Utah group's approach has been to publish maps of chromosomes as they complete them. To date they have published maps of the X chromosome and chromosomes 12, 13, and the short arms of chromosomes 6 and 11. White says they are about to publish maps of 7, 17, and 9.

To which Donis-Keller retorts: "A map is a map. Our map has holes, we make no bones about it. This is *a* genetic map of the genome. It is not Ray White's ideal, but so what? This is the beginning for us. How can one person set the standard for the rest of the world on what constitutes 'the map'?"

Donis-Keller thinks there is a bit of sour grapes in White's reaction. "I think you have a map when there is 95% linkage of DNA. It is significant and should be published and made available to the scientific community. If we hadn't published, I'm sure there would be people accusing us of holding back."

It is not sour grapes, White says, nor is it a matter of Collaborative getting there first. What galls White is that Collaborative is claiming scientific precedence when both groups are at the same stage, and a substantial amount of work remains to be done before *either* map is complete.

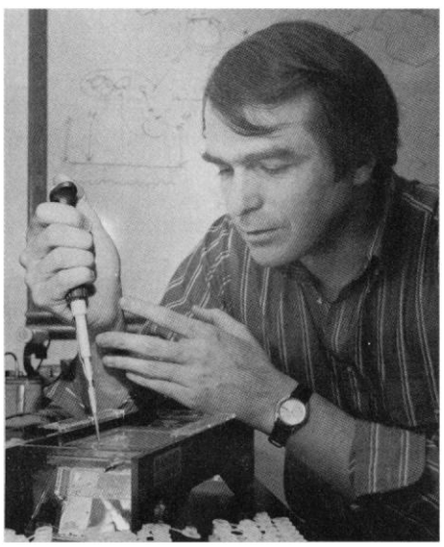
A major part of White's work has involved collecting the families needed for linkage studies of particular diseases, ideally three-generation families with a minimum of 8 children. White has established cell lines from about 50 such Mormon families and has made them available to other researchers, including Collaborative, through CEPH. And that is another sore point. "We supplied Collaborative with the basic tools, the families, they need to do this work." CEPH was created to facilitate just that type of sharing, and White, who sits on its board, is a staunch supporter. But, he says, it does not seem entirely "sporting" for Collaborative to claim scientific precedence when much of its progress is due to the contribution of the broader research community.

"I think there is much credit to be had in building these tools, but I don't think it needs to be taken monolithically," says White. "It is my feeling that Collaborative has been greedy, and rather than taking recognition for those chromosomes they have completed, they have laid claim to the whole genome, knowing full well that the other group has substantially more data, more analysis, and a more precise map.

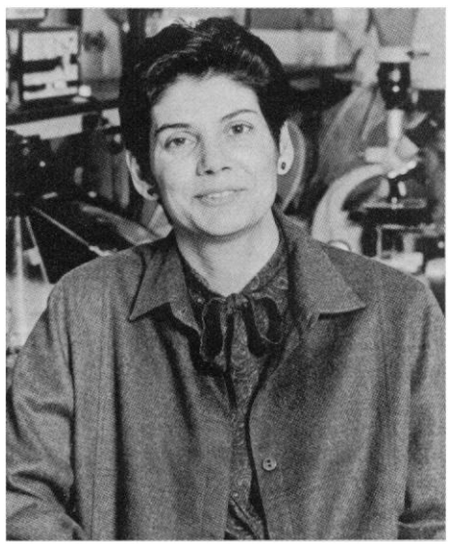
"But a lot depends on how the scientific community judges it," White says. That judgment is somewhat mixed. "It's an advance," says Victor McKusick of Johns Hopkins University of Collaborative's map. "But it is not something that Collaborative can uniquely claim. One can easily see why Ray White is a little unhappy. It doesn't seem exactly cricket, especially since a lot of the family DNA is from his efforts."

"It's a very useful map. It is pretty good," comments Charles Cantor of Columbia University, who is working on a different type of map, a physical map. "Our policy is not to publish incomplete maps," Cantor says, "but some people do. You can argue both ways. An incomplete map can still be useful. But it belies the fact that you can spend as much time getting the last 5% as you did on the first 95%. Ray White apparently won't publish until it is complete. I admire him for that. But he loses out on publicity. It's inevitable."

Both McKusick and Cantor describe Collaborative's achievement as a valuable first step toward the far more difficult goal of developing a fully detailed, fine-resolution map. Just filling in holes in the existing map will take a tremendous effort, Cantor says. What would be "really nice," he adds, is a map in which the distances between markers were at most 10 centimorgans, instead of an average 10 centimorgans. "It would guarantee that any new thing could be located to about 5 centimorgans. But it is much more difficult to obtain." Both Collaborative and the Utah group intend to develop these more detailed maps—Collaborative is aiming for a map with markers spaced 5 centimorgans apart; White's group is aiming to



Ray White: *"It is a very useful collection of markers, but it is not what we believe should be properly called a map."*



Helen Donis-Keller: *"How can one person set the standard for the rest of the world on what constitutes 'the map'?"*

develop a 1-centimorgan map.

Lander, one of the coauthors of the *Cell* paper, thinks there are legitimate reasons for publishing at this stage, although the map itself "is not a big deal," he says. "It is incremental progress. But what is exciting is that both groups are at the stage where the markers are dense enough that maps are condensing out. Now it makes sense to change strategy. Once you pass the 95% threshold, it makes sense to fill in the gaps in a much more directed fashion. So it is a bit of a milestone. But there is lots more to do."

But it sounded like more than "a bit of milestone" when the company heralded the "first genetic map of the entire human genome" at its press conference. And that is what McKusick and several others object to. "Collaborative is doing a disservice to the field by giving the impression that they have finished the map," McKusick says. "There is a tension," admits Lander, "because a company needs publicity."

"Collaborative has done a great service to the scientific community in creating a lot of markers," says Robert Cook-Deegan of the Office of Technology Assessment. "We are 2 years ahead of where we would have been if they had not been in the field. But the fact that they are a company means they have to parade their wares. It is not unjustified that they want a return on their investment."

In the grand scheme of things, who got there first—or who claims to have done so—matters very little, except to those involved. What is of concern to the research community, however, is what effect this dispute will have on progress toward a fully detailed map. The answer, it seems, is not much. Lander is convinced that the competition has quickened the pace of research, "but it probably hasn't made either of them any happier." Both groups have developed far more markers than anyone would have anticipated even a year ago and have made major strides toward what was once considered an impractical goal. And if these markers were combined, the eagerly awaited 5-centimorgan map would be in hand.

"It's a real shame that the only two groups in the world who are doing this haven't communicated and shared probes," rues Leroy Hood of the California Institute of Technology. "Together, it could be a tremendous map."

But the beauty of the CEPH collaboration is that this integration will occur anyway, regardless of the tension between the two groups. Both Donis-Keller and White will submit their latest markers and genotypic data to CEPH in December, the data will be integrated, and a 5-centimorgan map will emerge—whether or not they resolve their current spat. ■ **LESLIE ROBERTS**

Ecological Invasions Offer Opportunities

Ecological communities are constantly under threat of invasion by exotic species: how successful a particular invasion will be is often difficult to predict

WHEN the Polynesian discoverers of Hawaii settled on the islands 1500 years ago, they brought with them dogs, pigs, rats, chickens, and as many as 30 species of plants. This initial invasion of a once pristine environment was extended massively following European contact a couple of centuries ago. As a result, many endemic species of animals and plants have succumbed to extinction on the islands, many others cling on precariously, while at the same time hundreds of exotic species thrive.

"We are biased in our views of invasions. We tend to notice the very obvious successes, while the failures often go undocumented."

"These invading species have altered the face of the community to such an extent that formerly common species can no longer be found on the islands," comment Harold Mooney and James Drake of Stanford University and the University of Tennessee, respectively. "Once the phenomenology and mechanics of invasions are understood, any generalities that emerge may be useful in predicting, managing, and possibly preventing the changes that accompany an invasion." The challenge is to understand the fundamentals of species' invasions, in Hawaii and elsewhere, a task that is turning out to be a tough proposition indeed.

The British ecologist Charles Elton first drew serious attention to the impact of invading species, saying almost three decades ago: "we are seeing one of the great historical convolutions of the world's fauna and flora." In recent times, a major effort has been launched, under the flag of the Scientific Committee on Problems of the Environment (SCOPE), to assemble global information on invasions, from which practical and theoretical benefits should flow.

"There are two fundamental questions you want to address concerning invasions by exotic species," explains Drake. "First, what makes a good invader? And second, what makes a particular community susceptible to invasion?" Underlying these questions is the issue of community assembly: what are the "rules" by which species come together and interact? Clearly, if ecologists had a complete understanding of the rules of assembly, then answering Drake's two questions might be quite tractable. But this is a two-way street, because ecologists are also analyzing specific instances of invasions as one approach to trying to understand the rules of assembly, which so far remain rather elusive.

There have been a number of efforts to characterize good invaders in this overall context, but so far the results have been surprisingly disappointing. "You can come up with a list of characteristics, such as fast growth rate, broad dispersal abilities, and so on," notes Simon Levin of Cornell University. "But that is tautological. We are finding that such generalizations are often so trivial as to be useless, or they are simply wrong."

One reason why it is difficult to come up with an all-purpose profile of "a good invader" is that potential target communities offer such very different environmental conditions. "What you require is a good match between the invading organism and the environment," says Levin. He points out that the process can be broken down into several stages, such as initial establishment, growth, and geographical spread. "Of these, probably the most unpredictable stage is the initial establishment of the species within the community. Here, you are dealing with populations at very low densities, a characteristic that puts the invaders at high risk from stochastic factors leading to local extinction."

Given the caveats about the inadequacy of generalities, University of Tennessee ecologists Stuart Pimm and M. P. Moulton have come up with a set of statements relating to potential success of invading species. Based on data from Hawaiian birds, they are: First, although large ranges make successful inva-