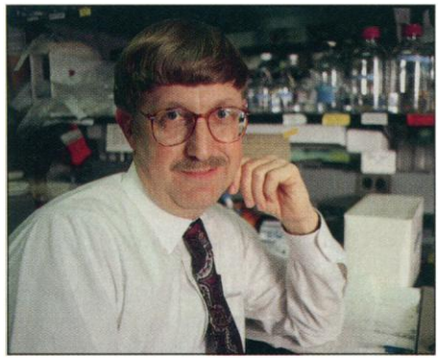
'Playing Chicken' Over Gene Markers

In a race with industry, Human Genome Project leaders are scrambling to collect a diverse set of single-base human DNA variations before they are patented

The U.S. government is getting set to launch a big addition to its human genome project this winter, and it is doing so with "some urgency," says geneticist Francis Collins, the chief architect of the new initiative. Details of the venture—which involves sequencing snippets of DNA from hundreds of individuals of different racial backgrounds and putting them in a public repository—were discussed at a meeting at the National Institutes of Health (NIH) last week, and a strategic plan will be put together over Christmas. NIH hopes to issue a funding announcement in December or January, winners will be selected by summer, and investigators are supposed to begin putting out data in less than a year. "Some urgency" seems to be an understatement.



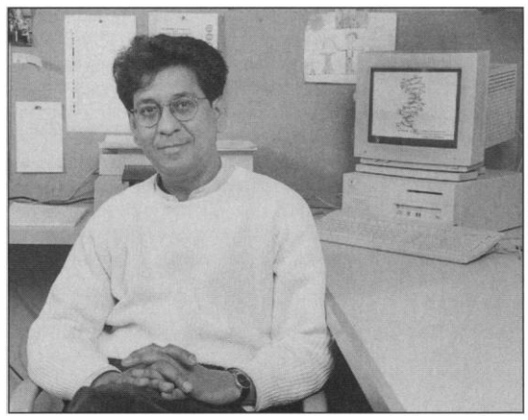
PAULINE LUBENS

Setting the pace. Francis Collins sees "urgent" need to collect DNA variations.

Unofficially, it's known as the SNPs project (for single nucleotide polymorphisms, pronounced "snips"). The basic strategy, decided upon at last week's meeting, is to collect at least 100,000 single-base variations in human DNA donated by 100 to 500 people in four major population categories: African, Asian, European, and Native American. These variable sites will serve as landmarks for creating a new, very fine-grained map of the genome, says Collins, director of the National Human Genome Research Institute (NHGRI), which will help investigators track down elusive genes that cannot be found using family studies. The collection would also provide some data on variable forms of known genes, and it may breathe life into the beleaguered human diversity project, which was supposed to survey DNA variation in populations around the world, but has become bogged down in politics (*Science*, 24 October, p. 568). Most important, according to Collins and other advocates, the project should encourage researchers to adopt a common format and quality-assurance methods when collecting and reporting DNA variations, which should make the data more useful to other scientists.

After organizers identify a reliable way of finding new SNPs, they hope to move quickly into production mode, collecting thousands of SNPs before they are locked up in a hodgepodge of other DNA collection schemes—many of them commercial (see sidebar). The effort is likely to cost $20 million to $30 million over the next 3 years—and probably tens of millions more after that. Collins has already received the green light from NHGRI's advisory council, and he says that 18 NIH institute directors have promised to share the costs. NIH is now providing seed money with funds from its current budget.

Funding may not be the biggest problem, however. Concerns over how to protect confidentiality and ensure that DNA donors have given informed consent for the use of their genetic data could present a far more difficult set of obstacles. Indeed, there were some tense moments at last week's meeting—a gathering of an ad hoc working group of scientists, bioethicists, and government officials who are advising Collins on the project—over a proposal to use some existing DNA collections to kick-start the venture. Some felt that it would be improper to use these collections without going back to the original donors for their consent, yet without a ready-made source of DNA, the new project will be slow to get started.



CASE WESTERN RESERVE UNIVERSITY

Academic support. Aravinda Chakravarti heads an independent working group planning the SNP project.

Why hurry?

Collins first began promoting this project about 3 months ago (*Science*, 19 September, p. 1752), and it is already on the verge of getting under way. The main reason it is moving at warp speed, say scientist-advisers on the project, is that big academic labs and companies have jumped into genomic data collection in the past year, and U.S. genome project leaders want to make sure that they don't patent most SNPs before the smaller labs have a chance to use them as low-cost genomic mapping tools. Or, as one geneticist said: "It's a game of chicken between Francis and the companies."

Aravinda Chakravarti, a geneticist at Case Western Reserve University in Cleveland and the most prominent academic champion of the SNP project, co-authored with Collins a Policy Forum in *Science* last month where they warned that if this effort doesn't get public support, much of the SNP data will be socked away in "private collections" (28 November, p. 1580). The information might then be subject to "a tangled web of restrictive intellectual property attachments ... inhibiting many researchers from using these powerful tools."

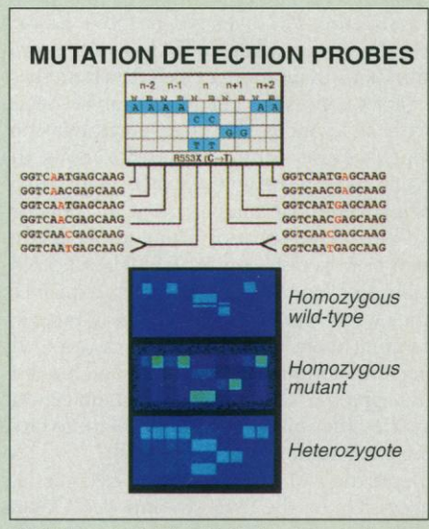
Besides, says Chakravarti, the "cottage-industry style" of gathering such data is coming to an end. Today, much information about genetic variation is acquired haphazardly, as researchers collect information about polymorphisms in families or explore clinical data about a particular gene. For example, the intense focus on two genes linked to breast cancer (*BRCA1* and *BRCA2*) has turned up hundreds of alleles, scores of which have been patented. But new technology may make it possible to sift thousands of small variations out of a collection of DNA in minutes, simply by using a mutation-sensing "chip" to scan a person's genome for anomalies. Such devices could enable companies to scoop up massive amounts of data on DNA variation. "When you consider the magnitude of what's coming down the pike," says Chakravarti, "we will lose information if we don't combine it all in one place."

The Hunting of the SNP

The government's plan to create a genomewide catalog of human DNA variation (see main text) represents a twist on the way big research projects like this usually get started. Often, government-sponsored research galvanizes industry, but this time the impetus is going the other way. The academics are worried that private companies wielding new technologies for scanning the genome will snap up the SNPs (single nucleotide polymorphisms) and patent them.

Two projects in particular have caught people's attention. One is a 5-year, $40 million collaboration between biochipmaker Affymetrix Inc. of Santa Clara, California, two pharmaceutical companies, and geneticist Eric Lander's lab at the Massachusetts Institute of Technology's Whitehead Institute Center for Genome Research. They are creating a sensor that identifies 2000 or more SNPs. It's an electronic device coated with a preset DNA sequence that probes a test material, yielding a readout of variants in shaded dots (see photo). The output is easy to scan robotically. While it includes more genomic SNPs than have been screened in parallel before, the chip holds just a fraction of the 100,000-plus SNPs the National Human Genome Research Institute (NHGRI) is seeking.

Last month, Whitehead staffer David Wang told a symposium at NHGRI that a prototype chip has proved its ability to find new SNPs. In one recent test, Wang said, it achieved a 90% accuracy rate. Affymetrix staffer Robert Lipshutz says the gadget will be ready for distribution next year.



Rapid readout. Biochip technology that can detect mutations in the cystic fibrosis gene (top) may be used to find SNPs.

The second initiative is a $20 million to $43 million joint venture between the drug manufacturer Abbott Laboratories of Chicago and Genset of Paris, a company that acquired the gene-mapping resources of the former nonprofit Centre d'Étude du Polymorphisme Humain. Genset has published few technical details, but genetics chief Daniel Cohen and other officials have sketched out the plan. They aim to identify 60,000 SNPs distributed over the entire human genome, patent them, and create a SNP map of the genome. Genset intends to sell this map to researchers who want to scan a person's genome for basic genetic studies or for drug research. Abbott wants specialized SNP maps to screen out patients who are less likely to respond to drugs in clinical trials because of the variant genes they carry. Many other companies are jumping into the SNP race as well.

At the same time, academic labs are developing their own collections of SNPs and SNP-hunting systems. At Stanford, for example, David Cox is involved with one group, and Ronald Davis, Peter Oefner, and Luca Cavalli-Sforza are in another group, both of which are tinkering with fast methods to identify genetic variation. Pui-Yan Kwok of Washington University in St. Louis has been funded by NHGRI to look for 3500 SNPs in genomic data generated by standard methods. And Debbie Nickerson at the University of Washington, Seattle, is also refining standard methods. All are potential competitors for funding under the new NHGRI project, whose first goal is to develop an efficient way of locating new SNPs. **–E.M.**

Companies that are generating their own SNP collections don't buy the argument for a big public investment in a database, however. "There's a lot of me-too-ism in this field right now," says Gualberto Ruaño, a Yale University geneticist and founder of Genaissance Therapeutics Inc. in New Haven, Connecticut. His company is attempting to develop what Ruaño calls "personalized medicine" by identifying variant forms of important human genes—such as those that code for the estrogen receptor—patenting them, and designing drugs that conform to the particular molecular structures associated with the most common types of genes.

Ruaño says it might be wiser for the public agency to "keep its focus" on completing the full sequence of the human genome. Later, he said, it can add variation data. Fred Ledley, president of another small company that's exploiting human DNA variation for drug development—Variagenics Inc. of Cambridge, Massachusetts—says, "We welcome efforts by the NIH to systematize sequence variation in a public database." But, like Ruaño and other industry people, he says that to secure private investment he must continue to patent human genetic variations.

That argument bothers Kenneth Weiss, an anthropologist at Pennsylvania State University in University Park, an adviser to Collins on the SNP project and a strong supporter of it. "For the good of science, [this information] should be made available as widely as possible so as many scientists as possible can think about it," he says. Weiss personally opposes patenting any human genetic sequences.

Although many academic scientists agree with that sentiment, some question the need to move ahead so rapidly with the SNP project. "This is incredibly hasty," says one researcher who asked not to be identified. "Why can't they slow down and improve the science?" he asks, arguing that polymorphism data would be far more valuable if it were linked to detailed biomedical information about the donors. Such information (and permission to use it) would take more time to obtain.

But Collins and his NHGRI staff say that they want quick access to the best DNA samples currently available, because this may prove to be the biggest hurdle to getting started. The grant money for analyzing the DNA won't begin flowing until October 1998. By then, NHGRI needs to have access to a large source of DNA from individuals of diverse backgrounds, ensure that donors have given proper consent, and place the DNA into immortalized cell lines. These issues occupied most of the working group's meeting last week.

DNA on tap

The strategy session, chaired by Chakravarti, came up with a scheme for sampling four major population groups, leaving it to a technical subcommittee to devise numerical targets. For example, evolutionary geneticists have shown that there is far greater genetic variation within African populations than in non-African populations, and also that certain alleles considered rare in European DNA samples are common in African samples. This reflects the greater age and diversity of the African gene pool. Yet publicly available DNA collections contain little African material; Native American and Asian contributions are similarly scant. As a result, say NHGRI staffers, it will be essential to collect DNA from a racially struc-

tured set of donors. Once the DNA has been sampled, however, all personal and racial data will have to be removed to protect privacy—diminishing the scientific value of the project, but bolstering its ethical foundation.

Where those samples would come from—and how to ensure that donors have given appropriate consent and that their privacy is safeguarded—prompted the most intense debates. NHGRI staffers had set their hopes on getting a set of ready-made cell lines containing DNA from a broad sample of the U.S. population, created by the National Center for Health Statistics (NCHS). From 1989 to 1994, that agency's National Health and Nutrition Examination Survey (NHANES) collected blood from more than 17,000 representative individuals around the country to obtain a snapshot of the health of the U.S. population. Karen Steinberg of the Centers for Disease Control and Prevention later converted more than 8000 of these samples into immortalized cell lines. But Chakravarti warned that "it is not a done deal" that genome researchers would be allowed use this material. The reason: Because DNA studies had not been foreseen, NHANES staff did not ask the donors for permission to put their DNA in a database.

Managers of the NHANES data asked their human subject research panel for guidance on this issue more than a year ago. In September, the panel said it would be acceptable to run some health studies on the cell lines, but only if the samples were made completely anonymous by stripping them of all identifiers (*Science*, 21 November, p. 1389). Edward Sondik, director of the NCHS, has interpreted this ruling to mean that DNA data from these samples cannot be put in a database—even with anonymous identifiers—without consent, because a third party who knows the name and genes of an individual might still be able to ferret out unique genetic information.

But the prospect of asking for fresh consent from donors concerned NHANES officials. As Diane Wagener of NCHS explained, they worry that if people receive a letter informing them that their DNA has already been immortalized in cell lines and requesting approval for hard-to-understand genetic studies, they might say, "I don't want to have anything to do with [NHANES]."

As the cell lines seemed to become less accessible by the hour, an annoyed Collins declared that, after months of discussion, "I am very troubled to learn that there still doesn't seem to be a clear answer" about whether they can be used. After a coffee break, Sondik announced that 600 DNA samples that are not part of the primary NHANES set will be made available for the SNP project, and possibly a small fraction of the primary set, as well. Consent will have to be obtained from the donors, only 75% of whom are expected to be reachable through old addresses. But even with a strong response, the NHANES contribution will not be enough. For example, it is short on Asian and Native American DNA. NHGRI will therefore have to find other donors, perhaps among patients in ongoing NIH projects.

The NHANES samples will, at least, allow the SNP project to get started. Now NHGRI staffers must lay out the technical parameters, the sequencing goals, deadlines, and cost limitations. They hope to complete all of this by January. Then, if the whole scheme doesn't run into a wall, the genome community will witness a brand-new competition in gene discovery.

–Eliot Marshall

CLIMATE CHANGE

Thirty Kyotos Needed to Control Warming

When exhausted delegates emerged from round-the-clock negotiations in Kyoto, Japan, last week with a global agreement to curb emissions of heat-trapping gases, some observers hailed the deal as a diplomatic miracle. Climate scientists say, however, that it will be miraculous indeed if the Kyoto pact—which calls for 38 industrialized nations to cut their emissions by an average of 5.2% from 1990 levels by 2012—even temporarily slows the accumulation of warming gases in the atmosphere. The cuts are too small and are likely to be overwhelmed by developing nations, they say. "It is a laudable and reasonable first step," says Jorge Sarmiento of Princeton University, "but much deeper emissions cuts will be needed in the not too distant future if we are going to meaningfully reduce the rate of warming."

If approved by major industrialized nations such as the United States and Japan—and that is far from certain—the new Kyoto Protocol to the 1992 Climate Change Treaty could reduce emissions of six greenhouse gases, including carbon dioxide, methane, and nitrous oxide. The United States—the world's leader in greenhouse emissions, with 25% of the total—agreed to a 7% cut from 1990 levels by 2012, while the 15 nations of the European Union committed themselves to an 8% reduction and Japan to 6%. If the cuts are achieved, industrialized nations will reduce their collective greenhouse emissions to two-thirds of what they would be in 2012 without action, according to the United Nations.

Even this significant reduction, however, won't prevent total global greenhouse emissions from rising, analysts predict. The cuts will be swamped early in the next century by increases in emissions from developing nations, such as China and India, which successfully resisted being bound by the protocol. For example, China, currently in second place, is expected to overtake the United States as the world's leading emitter of carbon dioxide within decades, as it burns more of its massive coal reserves. From 1990 to 2015, the U.S. Energy Information Administration predicts, carbon dioxide emissions from developing countries—including Russia and Eastern European nations—will nearly double, and will account for 58% of the global total even if industrial countries do not cut back.

PHIL BORDEN/PNI

Haze over Beijing. Emissions from developing nations like China could overwhelm Kyoto cuts.

At that rate, the 1992 treaty will not achieve its major objective—stabilizing atmospheric concentrations of carbon dioxide—says Tom Wigley, a climate researcher at the National Center for Atmospheric Research in Boulder, Colorado. Currently, carbon dioxide levels stand at about 360 parts per million (ppm), up from preindustrial levels of 280 ppm. Computerized climate models created by Wigley and others suggest that concentrations will at least double by 2100 unless developing nations hold their emissions steady and industrial nations progressively reduce emissions by roughly half.

"A short-term target and timetable, like that adopted at Kyoto, avoids the issue of stabilizing concentrations entirely," Wigley says. As a result, it will at best delay the predicted warming trend by just a few decades. Jerry Mahlman, director of the Geophysical Fluid Dynamics Laboratory at Princeton, adds that "it might take another 30 Kyotos over the next century" to cut global warming down to size.

Still, says Sarmiento, "you have to start somewhere, and the protocol at least provides a framework for revisiting the issue as our understanding improves."

–David Malakoff

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