Research News

A Genetic Survey of Vanishing Peoples

Racing the clock, two leaders in genetics and evolution are calling for an urgent effort to collect DNA from rapidly disappearing indigenous populations

INDIGENOUS PEOPLES ARE DISAPPEARING across the globe—victims of war, famine, disease, or simply what Cole Porter called the "urge to merge." As they vanish, they are taking with them a wealth of information buried in their genes about human origins, evolution, and diversity.

Now a group of scientists, including population geneticist Luigi Luca Cavalli-Sforza of Stanford University and molecular anthropologist Allan Wilson of the University of California, Berkeley, is calling for an urgent, last-ditch effort—involving geneticists, anthropologists, and medical researchers worldwide—to collect, analyze, and preserve for future study DNA from these populations as part of a massive survey of human genetic diversity. The group, which also includes geneticist Mary-Claire King of the University of California, Berkeley, Charles Cantor of Lawrence Berkeley Laboratory, and Robert Cook-Deegan of the Institute of Medicine, makes its impassioned plea for funds and assistance for this new survey in an article to appear this summer in *Genomics*.

They want to study, among others, the Bushmen of South Africa, the Hill People of New Guinea, the African Pygmies, the Etas of Japan, the Basques of Spain, the unique peoples of the Andaman Islands, and the Yanomami Indians of the Amazon rain forest, who are literally becoming extinct (see box on p. 1616). What these populations have in common is that each has been isolated and has only rarely—if ever—intermixed with its neighbors. Consequently, each offers "a window into the past," explains population geneticist Kenneth Kidd of Yale—a unique glimpse into the gene pool of our ancestors who lived thousands of years ago. In an accompanying article in *Genomics*, Cavalli-Sforza and Anne Bowcock of the University of Texas Southwestern Medical Center put it this way: "It is only from the knowledge of the gene pools of these populations that we can hope to reconstruct the history of the human past."

And time is of the essence, according to Cavalli-Sforza, who views humans as an endangered species in terms of genetic diversity. He says this survey should be done within the next 5 years, or 10 at the outside. For some groups it may already be too late, he says, citing the peoples of Basra, Iraq, who are believed to be the descendants of the Sumerians, as well as the Kurds of eastern Turkey.

In this survey of human diversity, the group plans to exploit the new molecular genetic techniques emerging from the Human Genome Project and, with any luck, some of the project's money as well. Both Cavalli-Sforza and Wilson see this survey as a fitting, indeed long-overdue, expansion of the 15-year, $3-billion effort to map and sequence the human genome, which in their view has been too narrowly defined. For reasons of expediency, the human genome being mapped and sequenced is essentially a Caucasian one, a composite of the genomes already present in DNA banks around the world. Sequencing this "reference" genome will provide a wealth of information, both scientists agree, but they argue that what is sorely lacking is a study of genetic variation, both among individuals and among populations. It is that variation, the minute differences in DNA from one person to another, that researchers want to use to trace the movements of ancient tribes and build what Wilson describes as "a genealogic tree of the peoples of the world."


Francis Black

Vanishing resource. *Geneticists want to collect DNA from such groups as the Arawete. Just 130 members of this tribe remain on the middle Xingu River in Brazil.*

What's more, says Cavalli-Sforza, it can be done for a mere pittance, 1% or less than the total tab for the genome project. "How can we afford to ignore diversity and not study it when we have a chance?" asks Wilson. "It's an insult to a lot of people."

Already the idea has garnered a groundswell of support, from genome project researchers to anthropologists and other scientists who want to use the data. "Intellectually, it is one of the most interesting things to come out of the genome project," says Cantor, who is principal scientist for the Department of Energy's (DOE) genome project.

Kenneth Weiss, a molecular anthropologist at Pennsylvania State University, is equally enthusiastic. "This is the future of the whole area. Even archeologists are trying to get genes out of bones. I am not saying genes are everything but [these techniques] are a major tool for reconstructing history, taxonomy, and phylogeny."

Nor are the benefits strictly intellectual, Weiss adds. Both he and Yale epidemiologist Frank Black have a very practical interest in the project. Weiss is studying diabetes in Native Americans; Black is looking at infectious disease and isolation. Both think that data on genetic variation may shed light on why some groups are more susceptible to certain diseases than others—insights they would be hard-pressed to garner from the Human Genome Project.

Indeed, the only question seems to be who will pay for the project, which falls between the cracks of the federal funding agencies. By Cavalli-Sforza's admittedly rough estimate, the project might cost $10 million over 5 years—far too much for the National Science Foundation's (NSF) anthropology program, which has an annual budget of $8.5 million. And while $10 million or even $20 million is a small chunk of the genome project's total budget, the survey is clearly a bit far afield from what either the National Institutes of Health (NIH) or the DOE typically supports.

However, Elke Jordan of the NIH genome center suggests that the center might be willing to contribute to an international effort, though it would not pick up the entire tab. And that would be just fine with Cavalli-Sforza, Wilson, and their colleagues. They already have plans to persuade a consortium of agencies, including NIH, DOE, NSF, the equivalent agencies in other countries, as well as international organizations, like UNESCO, to each kick in some money.

Already, the Human Genome Organisation, or HUGO, has offered to help, urged on by its president, Sir Walter Bodmer, who calls the new survey "a cultural obligation of the genome project." Bodmer's enthusiasm is perhaps not surprising, as he wrote a classic text on population genetics with Cavalli-Sforza in the 1970s. While HUGO is not a funding agency, it will act as a broker to help raise funds, pledges Bodmer. Meanwhile, HUGO has set up a committee on human diversity, cochaired by Cavalli-Sforza and Marcello Siniscalco of the University of Sassari, Italy. The committee, which includes Wilson, Kidd of Yale, King of Berkeley, and others, will meet this summer to hammer out a firmer budget and gameplan.

If the project does get off the ground, it will bring to fruition a 7-year quest by Cavalli-Sforza and longtime collaborator Kidd, who first came up with this idea in 1984 while trapped on a transatlantic flight.

Scientific Split Over Sampling Strategy

Allan Wilson and Luigi Luca Cavalli-Sforza, who were long at intellectual loggerheads in the debate over human origins, have now joined forces to push for an ambitious new project to survey human genetic diversity (see story). Indeed, a big part of that project's appeal is that it unites these two leaders in the study of genetics and evolution. But while both men agree on the goal—to build a repository of genetic diversity by collecting and preserving DNA samples from vanishing indigenous peoples—they have very different ideas about how to do it.

Both would probably agree on a list of "must sample" populations—say, the African Pygmies or the Yanomami of the Amazon rain forest. But beyond that, arguments begin over how to define an "indigenous" population and where, exactly, to sample. Cavalli-Sforza wants to sample in depth the truly isolated peoples—those who have been living in geographic pockets for hundreds if not thousands of years. Wilson would cast a wider net, setting up a grid across the globe and sampling representatives of indigenous populations wherever he can find them, every 50 or 100 miles or so. Their ancestry would be more mixed up, he concedes, but their genes nonetheless harbor clues to human evolution.

The differences between these two researchers are rooted in the technologies they have used for years. Indeed, their split comes as no surprise to their colleagues. "Each has his own unique perspective on the world," says geneticist Mary-Claire King of the University of California, Berkeley. In his efforts to develop a phylogenetic tree of man, Cavalli-Sforza has mainly studied the variation contained within nuclear genes. In the nuclear DNA, any particular gene variant, or allele, is likely to be geographically widespread. In other words, an allele found in Africa will be found in the rest of the world. What differs is the frequency with which they occur in the various populations. Using the nuclear approach, the unit of measurement is a population, not an individual. On this basis, Cavalli-Sforza uses cultural and linguistic criteria to identify well-defined populations, and preferably those that have been geographically and thus genetically isolated for many years. He then samples DNA from members of a series of families—ideally, both parents and their children.

Wilson, on the other hand, has pioneered the study of mitochondrial DNA—a separate genome inherited only from the mother. Says Wilson: "There is a big potential conflict between the nuclear way of looking at things and the mitochondrial way." Because the mitochondrial DNA accumulates mutations much faster than does nuclear DNA, it is far more variable, yielding a stronger genetic fingerprint. And because it does not recombine, each person Wilson samples will be informative, which eliminates the need to measure gene frequencies in populations.

What's more, in his work in Africa and elsewhere, Wilson has found that, unlike the nuclear DNA, the mitochondrial DNA bears "a strong geographic imprint." By that he means that a distinctive mitochondrial allele found in an indigenous person will occur within a fairly small radius, perhaps 50 or 100 miles. Beyond that, you virtually never see it again. And that leads him to his current conviction: "If you want to understand the geography of the human gene pool you need to sample at least every 50 miles all over the world, and I think every 10 miles, really." He concedes, however, that his way might cost a bit more.

To Wilson, Cavalli-Sforza's approach is too full of presuppositions. Instead, he asserts, we should "abandon previous concepts of what populations are and go by geography. We need to be explorers, finding out what is there, rather than presuming we know what a population is."


Photo Researchers

African Pygmies. *Cells from the two Pygmy populations in the Central African Republic* (above) *and Zaire have already been preserved for future study.*

"We seem to start from very different perspectives," sighs Cavalli-Sforza, who adds that Wilson's type of grid survey would be "very difficult. You can't just sample whomever you come across." It might work in Europe, where people haven't moved around as much as they have, say, in southern Africa, he concedes, but in most places you simply won't find indigenous people every 50 miles. "Certainly we can find a compromise that takes into account both of our needs," Cavalli-Sforza adds diplomatically.

But Wilson says he is "digging in his heels" and will lobby for the grid strategy when he, Cavalli-Sforza, and others members of a new committee set up by the Human Genome Organisation meet later this summer to flesh out plans for the survey. King, for one, does not see the differences between the two as irreconcilable. "The goals are agreed on, and they arrived at them independently," she says. As for the strategy, "we just need to sort out which to use where. I think we need some of Wilson's grid, as well as Cavalli's populations in depth." Ultimately, she acknowledges, the amount of money the group raises will determine just how ambitious the survey will be. ■ L.R.

For years the two population geneticists had been studying the genetics of aboriginal populations in an attempt to reconstruct the movements of early peoples, whom they bred with, and how they were related. But the research was handicapped because the "old style" genetic markers, such as the ABO blood group antigens, were "cumbersome and awkward to work with," says Kidd. These markers are used to compare how people vary at specific spots along their chromosomes, thereby creating genotypes or distinctive genetic "fingerprints."

What's more, there simply weren't very many of these markers around. Says King: "Ten years ago, you could determine the genotype of perhaps 50 loci [along the chromosomes]. That was the end of the story." Indeed, for that reason, Cavalli-Sforza and Kidd essentially stopped their phylogenetic studies in the early 1970s. "We ran out of data," says Kidd.

But by 1984, recalls Kidd, the new molecular tools coming on line promised to transform the field. He and Cavalli-Sforza were particularly excited by the new genetic markers, or DNA polymorphisms, that were being developed at the University of Utah and elsewhere. Not only did they provide a much more direct measure of genetic variation than the older methods, but they would soon be available in unprecedented numbers. "What's changed," says Kidd, "is the availability of thousands of genetic markers, scattered around the genome."

The irony was that just as the new markers and other techniques were becoming available, the populations Cavalli-Sforza and Kidd wanted to study were disappearing. What they needed to do, the two decided, was to collect DNA samples from members of indigenous groups immediately and preserve them. That could be done by collecting blood and then inducing the white cells to grow permanently in culture. Cavalli-Sforza and Anne Bowcock at Stanford and Kidd's team at Yale began that year, establishing cell lines from two groups of African Pygmies, whom Cavalli-Sforza had studied since the early 1960s, and others.

They have continued ever since, working on a shoe string. Says Kidd: "Both Luca and I have been frustrated by the difficulty of getting grants for this kind of work." Indeed, they have not mounted any special expeditions, which would be costly, but rather have persuaded anthropologist friends to collect blood samples for them, often meeting them at Kennedy Airport and rushing the samples off to the lab. So far, the Stanford and Yale teams have established permanent cell lines from individuals in 13 of the 250 populations the researchers identified on their 1984 flight. Clearly, they would need international help to complete the project.

Meanwhile, Wilson at Berkeley was pioneering the use of a new technique—the direct sequencing of mitochondrial, as opposed to nuclear, DNA—to study aboriginal populations in Africa and elsewhere. This led him to, among other things, his controversial theory about mitochondrial Eve. While pursuing these studies, Wilson also came up with essentially the same idea that Cavalli-Sforza and Kidd had. And by the late 1980s, Cavalli-Sforza and Wilson, who had earlier been on opposite sides of a heated debate on human origins, had begun

Yanomami People Threatened

Just 3 years ago, the Yanomami people were the largest group of native Amazonians still living in relative isolation in the jungles of Brazil. Almost 10,000 of them inhabited 125 villages, spread throughout a 94,191-square-kilometer region near the border of Venezuela. There they hunted and thrived in the tropical forest much as their ancestors had for thousands of years before them. But today, the Yanomami are a threatened people. According to anthropologists who have just returned from a fact-finding mission to Brazil, they will become extinct in the next decade if the Brazilian government does not move to protect them.

The warning is part of a hard-hitting report released this week—timed to coincide with Brazilian President Fernando Collor's visit to Washington—by the American Anthropological Association. Earlier this year, the association had taken the unprecedented step of sending a special commission of anthropologists to check out reports of the devastation of the Yanomami. What they found shocked even those prepared for the worst: Malaria and other diseases are killing the Yanomami at a rate of 13% per year and have thinned their ranks to 8000 already. As a result of the rampant malaria, fertility is near zero, and those people who have survived are sick and starving. "It's a desperate situation. A lot of villages have no more children and old people," says University of Chicago anthropologist Terence Turner, chair of the special commission.

What has visited this plague upon the Yanomami? The report lays the blame squarely at the feet of the Brazilian government, saying that it has failed to honor the Brazilian constitution, which guarantees Yanomami land rights, as well as its own promises to protect the indigenous people of the Amazon. Although the government had taken steps in the mid-1980s to turn the Yanomami territory into a special refuge, it later reneged on that promise and opened much of the region to miners of gold and the tin ore cassiterite.

In the gold rush that followed, as many as 40,000 miners invaded the region, using high-powered hoses and mercury to blast gold out of the soil. The mercury and soil runoff polluted the rivers and streams where the Yanomami fish, while the noise scared off the wildlife they hunted. Worse yet, the pools of stagnant water from the mining operations became breeding grounds for malaria-carrying mosquitoes. "Brazilian policies and economic activities have turned the land of the Yanomami into a death camp for its own people," says the report.

But there are some signs of hope. The report notes that President Collor, who assumed office in 1990, announced in April that he would revoke earlier decrees that had expropriated most of the land of the Yanomami. But he stopped short of giving the Yanomami legal title to the land, in favor of allowing the government to study the issue for 6 months. The anthropologists question the need for further study, as does the Environmental Defense Fund, which released a report of its own this week decrying the Brazilian government's policies on the Yanomami and other environmental issues. But Jose Goldemberg, Brazilian secretary for science and technology, said that the extra time was needed to figure out how much land to include in the reserve. The original Yanomami territory comprises 40% of the state of Roraima, which is home to about 500,000 other people, many of whom would have to be displaced for the reserve.

At press time, the anthropologists and environmentalists were hoping to meet with Collor during his Washington visit to discuss their report, which calls for the immediate return of the land to the Yanomami, the expulsion of miners from the region, and the provision of adequate medical supplies. No less is at stake than the future of one of the oldest Native American cultures.

■ ANN GIBBONS

talking and exchanging DNA samples, if not collaborating. Thus, it was only logical that they should team up on this new venture.

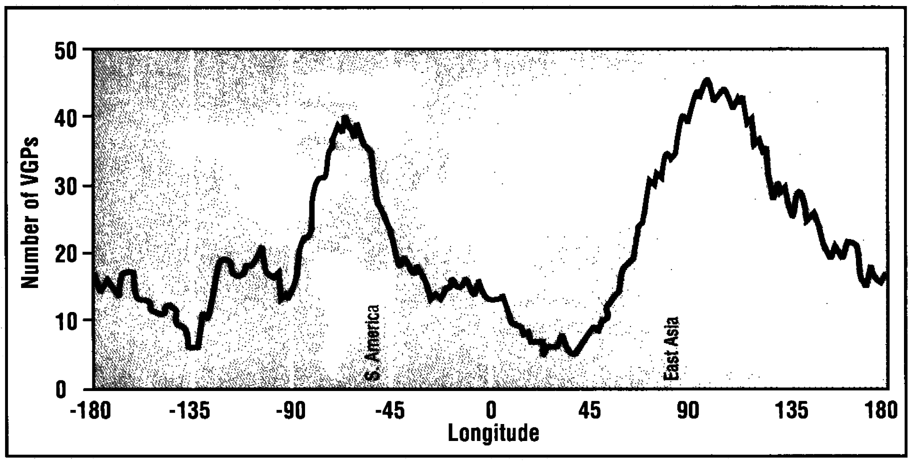
While the exact plan is still a matter of considerable debate (see box), the general idea is to collect blood and other tissue samples from 100 or so indigenous populations—in, for example, the Amazon, sub-Saharan Africa, and across southern Asia. "One hundred is a minimum," says Cavalli-Sforza, adding that the number could climb to 500, if money allowed. "Even at 100, you are leaving out some important populations." Within each group, the researchers would sample perhaps 100 individuals.

What they definitely don't envision is a planeload of Western geneticists descending on the jungle, collecting blood, and then disappearing. Rather, they hope to enlist the help of anthropologists, medical researchers, and local scientists who already have access to the more isolated groups. Already, says King, the group is thinking of what it can offer to the populations in return, such as medical supplies.

The bulk of the cost and the major technical obstacles will come from setting up the cell lines. The procedure itself is not complicated, he says, but the samples must be transported to a lab within a day or two—no small feat if they come from the upper reaches of the Amazon. The hope, he says, is to establish regional collection centers and train local workers in the technique, if need be. Eventually, all the cell lines would be collected in central repository, though the identify of each donor would be kept private.

Once the long-sought DNA is in hand, the group wants to determine genotypes of each individual for the same basic set of genes or DNA markers. This work might take several years and would probably be shared among numerous collaborators, says Cavalli-Sforza. After that, the anonymous DNA would be available to researchers around the world who wanted to use it, whether for investigating the population distribution of disease genes or for doing basic studies of evolution or human diversity.

Already, there are indications of the wealth of information harbored in the DNA of aboriginal peoples. Both Wilson and Cavalli-Sforza's data indicate that the prevailing view of race, which divides the world into blacks, whites, and so forth, is outmoded and mistaken, says Wilson. They and others have found that the genetic variation within a race is far greater than the variation between races. Says Berkeley colleague King: "The concept of race in America has a social meaning that does not correspond to its scientific meaning." She, like Wilson, predicts more surprises will emerge from their study of human variation. ■ LESLIE ROBERTS



Redrawn from Clement 1991

Two roads to reversal. *Geomagnetic pole locations (VGPs) seen from sites around the globe cluster on two paths during a reversal some 730,000 years ago.*

A Core-Mantle Link?

Records of magnetic-field reversals point to a connection between the mantle and the underlying molten core

AT INTERVALS OF HUNDREDS OF THOUSANDS of years, Earth's magnetic field flip-flops, the north and south magnetic poles trading places. Geologists struggling to understand these reversals have concentrated on the churning liquid metal of the outer core, where the field is generated in the first place. They have paid little attention to the solid, rocky mantle encasing the core. Mantle and core, it seemed, were like ice floating on water—in contact but unlikely to influence each other.

Now researchers at a variety of institutions around the globe have stumbled on a hint that the mantle does leave its mark on magnetic reversals. They have found that as the poles wander from south to north or vice versa during successive reversals, they show a startling tendency to trace out the same paths across the surface of the planet. Something about the processes that generate or modulate the field must be persisting for millions of years, through reversal after reversal, the researchers realized. And that could only happen, they feel, with the help of the mantle, a far less mercurial layer of the deep interior than the core. Of course, the precise connection between mantle and core is far from clear, but if proven and understood it might shed light on the larger mystery of why the reversals happen in the first place.

The intriguing discovery of repetitive behavior during magnetic reversals emerged as paleomagneticians collected more and more geologic records that caught the field in the act of flipping. Ocean sediments and lava flows, accumulating layer by layer, capture snapshots of the field's orientation as they form. Most such records show the field in one of two orientations—either the present one, with magnetic field lines looping out of Earth's south geographic pole and into the north pole, or the reverse. But every few hundred thousand years or so, sediments or lavas record the 4000- to 8000-year period during which the field switches orientation. And these rarer specimens told scientists an interesting tale.

"We all started to see this startling pattern," says Bradford Clement of Florida International University (FIU). The presumption had been that there would be no consistency at all. The core churns too rapidly, researchers had thought, for any memory of a reversal to linger until the next one. During each reversal, the north magnetic pole as viewed from a given site should appear to follow a random path from one geographic pole to the other.

To Clement and colleagues it was an "astonishing thing" to find that the poles actually tend to follow one of two well-worn routes. One leads through North and South America; the other, less heavily traveled, path stretches across eastern Asia and Australia. Eric Tric of the Center for Studies in Weak Radioactivity in Gif-sur-Yvette, France, recently pointed out that fully two-thirds of 48 reversal records from the past 3 million years show the poles following one of these two paths. Despite its short memory, the core seems to recall where its magnetic poles should go during reversals hundreds of thousands or even millions of years apart.

The paleomagneticians suspect it is the mantle that reminds the core where the preferred pole paths are. In independent papers appearing this month, Clement of