Traces of a DISTANT PAST

DNA furnishes an ever clearer picture of the multimillennial trek from Africa all the way to the tip of South America

BY GARY STIX

KEY CONCEPTS

- Scientists trace the path of human migrations by using bones, artifacts and DNA. Ancient objects, however, are hard to find.
- DNA from contemporary humans can be compared to determine how long an indigenous population has lived in a region.
- The latest studies survey swathes of entire genomes and produce maps of human movements across much of the world. They also describe how people's genes have adapted to changes in diet, climate and disease.

—The Editors

A development company controlled by Osama bin Laden's half brother revealed last year that it wants to build a bridge that will span the Bab el Mandeb, the outlet of the Red Sea to the Indian Ocean. If this ambitious project is ever realized, the throngs of African pilgrims who traverse one of the longest bridges in the world on a journey to Mecca would pass hundreds of feet above the probable route of the most memorable journey in human history. Fifty or sixty thousand years ago a small band of Africans—a few hundred or even several thousand—crossed the strait in tiny boats, never to return.

The reason they left their homeland in eastern Africa is not completely understood. Perhaps the climate changed, or once abundant shellfish stocks vanished. But some things are fairly certain. Those first trekkers out of Africa brought with them the physical and behavioral traits—the large brains and the capacity for language—that characterize fully modern humans. From their bivouac on the Asian continent in what is now Yemen, they set out on a decamillennial journey that spanned continents and land bridges and reached all the way to Tierra del Fuego, at the bottom of South America.

Scientists, of course, have gained insight into these wanderings because of the fossilized bones or spearheads laboriously uncovered and stored in collections. But ancestral hand-me-downs are often too scant to provide a complete picture of this remote history. In the past 20 years population geneticists have begun to fill in gaps in the paleoanthropological record by fashioning a genetic bread-crumb trail of the earliest migrations by modern humans.

Almost all our DNA—99.9 percent of the three billion "letters," or nucleotides, that make up the human genome—is the same from person to person. But interwoven in that last 0.1 percent are telltale differences. A comparison among, say, East Africans and Native Americans can yield vital clues to human ancestry and to the inexorable progression of colonizations from continent to continent. Until recent years, DNA passed down only from fathers to sons or from mothers to their children has served as the equivalent of fossilized footprints for geneticists. The newest research lets scientists adjust their focus, widening the field of view beyond a few isolated stretches of DNA to inspect hundreds of thousands of nucleotides scattered throughout the whole genome.

Scanning broadly has produced global migratory maps of unprecedented resolution, some of which have been published only during recent months. The research provides an endorsement of modern human origins in Africa and shows how that continent served as a reservoir of genetic diversity that trickled out to the rest of the world. A genetic family tree that begins with the San people of Africa at its root ends with South American Indians and Pacific Islanders on its youngest-growing branches.

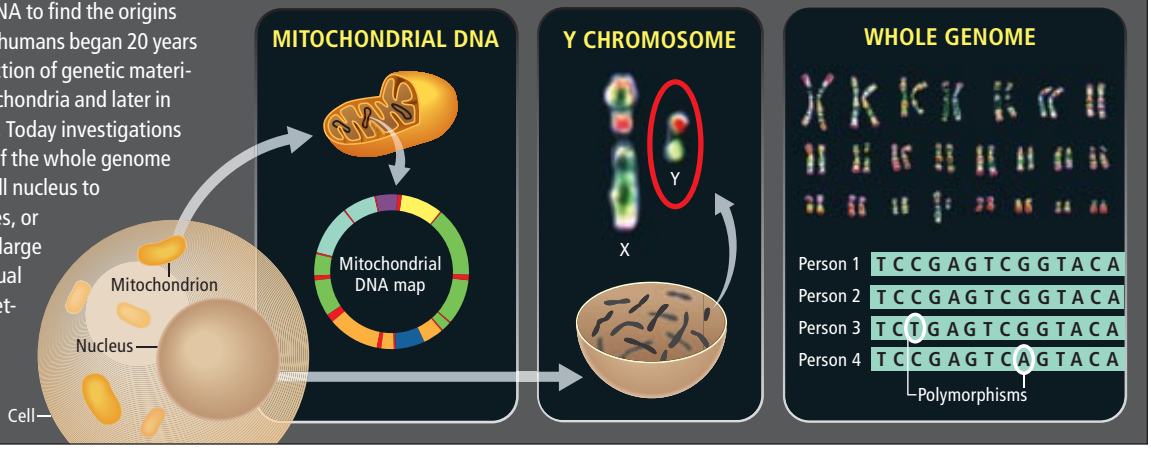
The study of human genetic variation—a kind of historical Global Positioning System—goes back to World War I, when two physicians work-

ILLUSTRATION BY SEAN McCABE; SOURCES: DANIEL SAMBRAUS (*human skull*), PASCAL GOETGHELUCK (*Neandertal skull*), BIOPHOTO ASSOCIATES (*chromosomes*) *Photo Researchers, Inc.*

[METHODS]

GENETIC PROSPECTING

Digging through DNA to find the origins of the first modern humans began 20 years ago through inspection of genetic material in the cell's mitochondria and later in the Y chromosome. Today investigations can scan sections of the whole genome contained in the cell nucleus to compare differences, or polymorphisms, in large numbers of individual nucleotides, the "letters" of the DNA alphabet.



ing in the Greek city of Thessaloníki found that soldiers garrisoned there had a differing incidence of a given blood group depending on their nationality. Beginning in the 1950s, Luigi Luca Cavalli-Sforza started formalizing the study of genetic differences among populations by examining distinct blood group proteins. Variations in proteins reflect differences in the genes that encode them.

Then, in 1987, Rebecca L. Cann and Allan C. Wilson of the University of California, Berkeley, published a groundbreaking paper based on analyzing the DNA of mitochondria, the cell's energy-producing organelles, which are passed down through the maternal line. They reported that humans from different populations all descended from a single female in Africa who lived about 200,000 years ago—a finding that immediately made headlines trumpeting the discovery of the "Mitochondrial Eve." (Despite the Biblical allusion, this Eve was not the first woman: her lineage, though, is all that has survived.)

All about Eve

The fast, relatively predictable rate of "neutral" mitochondrial mutations—ones that are neither beneficial nor harmful—lets the organelles operate as molecular clocks. Counting the differences in the number of mutations (ticks of the clock) between two groups, or lineages, allows a researcher to construct a genetic tree that tracks back to a common ancestor—Mitochondrial Eve or another woman who founded a new lineage. Comparison of the ages of the lineages from different regions permits the building of a timeline of human migrations.

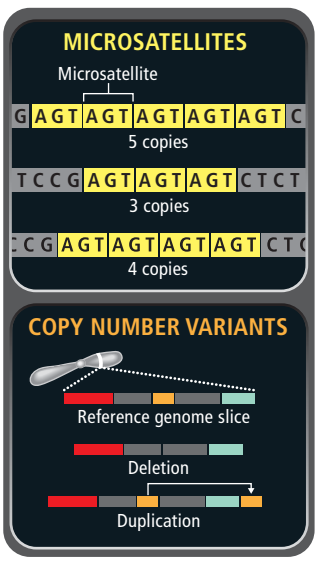
Since 1987 the data bank on human diversity has broadened to encompass the Y chromosome—the sex chromosome passed down only by males to their sons. The male-transmitted DNA carries many more nucleotides than mitochondrial DNA does (tens of millions, as opposed to just 16,000), enhancing investigators' ability to distinguish one population from another. Analyzing mitochondrial and Y chromosome DNA from human populations has turned up hundreds of genetic markers (DNA sites having identifiable mutations specific to particular lineages).

The route humans took from Africa to the Americas over the course of tens of thousands of years can now be tracked on the map as if the travelers were moving, albeit extremely slowly, on a series of interconnected superhighways. Alphanumeric route signs, such as I-95, can be recast as alphanumeric genetic markers. In the case of the Y chromosome, for instance, cross the Bab el Mandeb on highway (genetic marker) M168, which becomes M89 when heading north through the Arabian Peninsula. Make a right at M9 and set out toward Mesopotamia and beyond. Once reaching an area north of the Hindu Kush, turn left onto M45. In Siberia, go right and follow M242 until it eventually traverses the land bridge to Alaska. Pick up M3 and proceed to South America [*see map on opposite page*].

Mitochondrial DNA and the Y chromosome remain powerful analytical instruments. The National Geographic Society, IBM and the Waitt Family Foundation have joined in a privately funded $40-million collaboration through 2010, research that is primarily devoted to using these tools. With the help of 10 regional academic institutions, the so-called Genographic Project is gathering DNA from up to 100,000 indigenous people worldwide. "What we're focusing on is the details of how people made the jour-

MANY WAYS TO SLICE A GENOME

Scientists continually seek genetic markers—characteristic patterns of nucleotides—that differ from one population group to another and that can be used when comparing whole genomes. Microsatellites, short repetitive nucleotide segments found on all the chromosomes (*top*), have served as markers for a number of years. A new type of whole-genome analysis looks for what are called copy number variants—deletions or duplications of up to one million nucleotides (*bottom*).



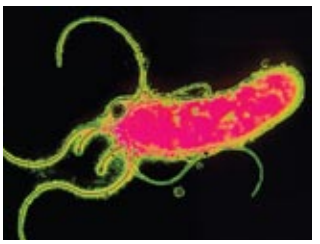
JEN CHRISTIANSEN; CNRI/PHOTO RESEARCHERS, INC. (*chromosome images*)

neys," says Spencer Wells, who heads the project. In a recent report its researchers found that the Khoisan people of southern Africa remained genetically separate from other Africans for 100,000 years. In another study, they demonstrated that some of the gene pool of Lebanese men can be traced to Christian Crusaders and Muslims from the Arabian Peninsula.

Power Tools

Genetic researchers have sampled the DNA of many people living along the migratory routes they have discovered. Yet the seeming certainty of the data sometimes deceives. Scientists who study human origins still would prefer a fossil they can hold in their hands over a genealogical tree. DNA differs from the radioactive isotopes used to date fossils. The rate of mutation can fluctuate from one stretch of DNA to another.

But paleoanthropologists are in a fix. Fossil remains are rare and too often incomplete. The earliest migration from Africa to Australia shows up in mitochondrial and Y genetic material (thanks to Andaman Islanders, among others), but the physical artifacts are largely missing along the route.



HITCHHIKING

Microorganisms that ride in or on people can help researchers confirm discoveries about human migrations. The genes of *Helicobacter pylori* (*above*), the ulcer-causing bacterium endemic to humans, indicate that the microbe left Africa about 55,000 years ago, just when humans did. One lineage of the microbe appears both in East Asian and in native South American populations, supporting the notion that South Americans originally came from Asia.

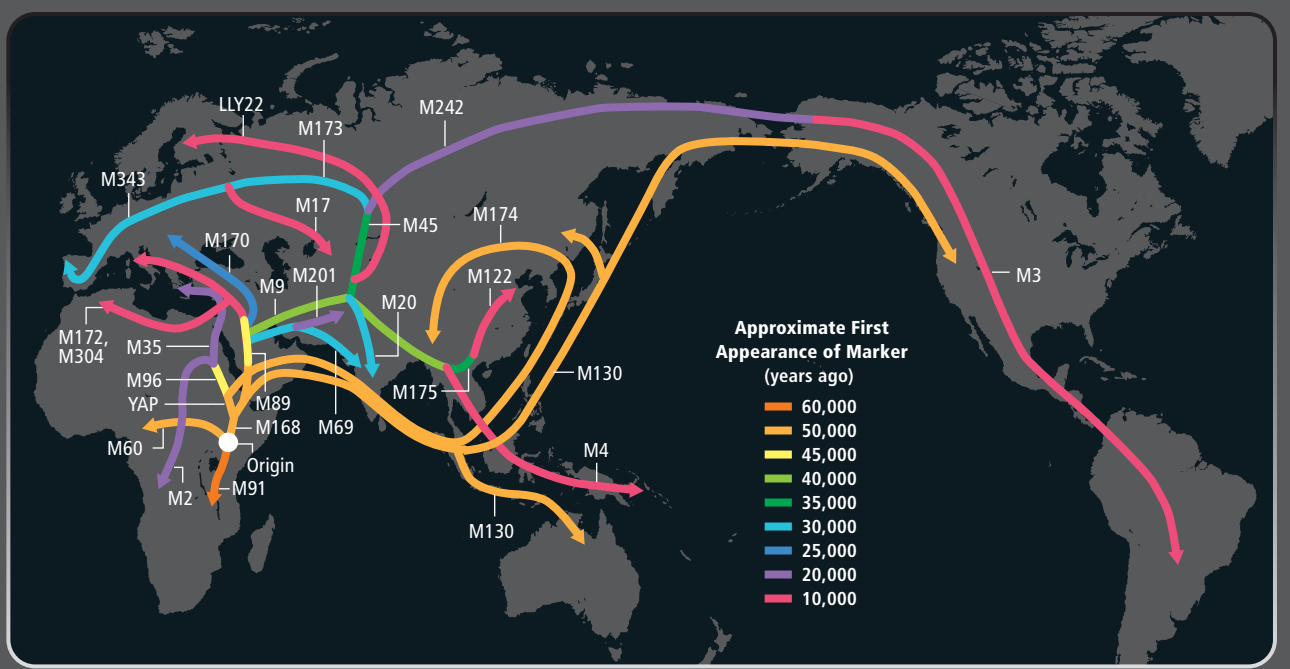
The answer to the absence of stones and bones: more DNA, from wherever. To bolster the case for genetics, researchers have looked to microbes that have hitched a ride on humans, inspecting their genes to look for similar patterns of migration. Freeloaders include bacteria, viruses and even lice. Besides microorganisms, the Human Genome Project and related efforts to look across the expanse of whole genomes have yielded a set of power tools that are helping to compensate for deficiencies in genetic methods. "You can look at so many different places in the genome from many individuals and in many populations to achieve more statistical power in testing different hypotheses," says Tim Weaver, a professor of anthropology at the University of California, Davis.

During this decade, researchers have made dramatic discoveries by simultaneously comparing a multitude of variable, or polymorphic, sites interspersed throughout the genome's three billion nucleotides. The first whole-genome studies earlier in this decade looked at differences among populations in short repetitive stretches of DNA known as microsatellites. More recently, the scope afforded by whole-genome scans

[ROUTE MAPS]

TRACKING Y CHROMOSOMES THROUGH TIME

Geneticists can track the path of ancient migrations by examining genetic markers in Y chromosomes from men who hail from different parts of the world. Each marker, such as M168 or M89, identifies a lineage of men and where the lineage originated. By building an evolutionary tree based on observing many living people with the markers, investigators can determine the approximate ages of the lineages.



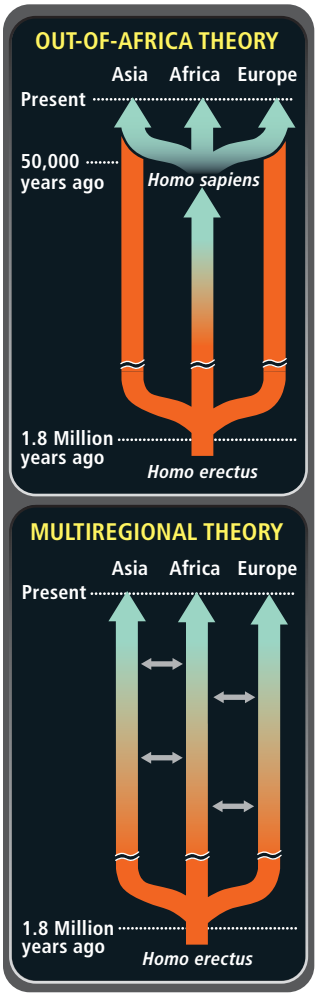
JEN CHRISTIANSEN; INFORMATION SOURCE: NATIONAL GEOGRAPHIC MAPS; P. HAWTIN *Photo Researchers, Inc.* (*bacterium*)

has widened further. In February two papers, one in *Science*, the other in *Nature*, reported the largest surveys to date of human diversity. Both examined more than 500,000 single nucleotide polymorphisms (SNPs)—swaps of one nucleotide for another at a particular spot in the DNA—from the Human Genome Diversity Panel. These cell lines were drawn from about 1,000 individuals from 51 populations worldwide and are maintained by the Center for the Study of Human Polymorphisms in Paris.

The two research teams analyzed the wealth of data in various ways. They compared SNPs directly among distinct populations. They also looked at haplotypes, blocks of DNA containing numerous SNPs that are inherited intact through many generations. The group that wrote the *Nature* paper also explored a new technique for surveying human variation by comparing repetitions or deletions of DNA stretches of up to 1,000,000 nucleotides long (copy number variations) throughout a person's genome, consistent with the larger trend to mine the genome for ever more markers of variation. "Any one piece of the genome will have a history that doesn't necessarily reflect the ancestry of the genome as a whole," says Noah A. Rosenberg of the University of Michigan at Ann Arbor and lead author of the *Nature* paper. But looking at many areas at once, he explains, can overcome that problem: "With thousands of markers, it's possible to determine the overall story of human migrations."

Looking at hundreds of thousands of SNPs allowed the researchers to resolve the identities of individual populations—and to see how genetically close relations spread far and wide. Native South American ancestry was tracked back to Siberians and some other Asians. The Han people, China's principle ethnic group, has distinct northern and southern populations. Bedouins are related to groups from Europe and Pakistan as well as the Middle East.

The findings, which jibed with previous research from anthropology, archaeology, linguistics and biology (including previous mitochondrial and Y DNA studies), also provided a broader statistical foundation for the out-of-Africa hypothesis, supporting the idea that a small population of humans moved out of the continent, then grew in size in a new home until another subgroup of "founders" broke off and moved away—a process that repeated itself until the entire world was settled. These wayfarers edged out archaic human populations—*Homo neanderthalensis* and *Homo erectus*—with little or no interbreeding when they met. The new DNA work indicates that each time a smaller group split off, it carried only a subset of the genetic diversity originally present in the African population. So as distance (and time) removed from Africa lengthens, diversity diminishes, providing a means to follow population movements. Native Americans, sojourners on the last major continental migrations, have much less variety in their genomes than Africans do.



DUELING THEORIES

The out-of-Africa theory postulates that humans with modern traits left Africa from 50,000 to 60,000 years ago to settle the world. Along the way, they replaced archaic hominids, such as *Homo erectus,* that left Africa as early as 1.8 million years ago. The competing multiregional theory holds that modern characteristics evolved not just in Africa but in archaic hominid populations in Asia and Europe. Interbreeding among all these groups (*horizontal arrows*) ensured that they remained a single species.

Many scientists believe that the weight of evidence, now backed by large statistical analyses such as the ones in *Science* and *Nature*, gives the out-of-Africa proponents a clear edge in a long-running debate over human origins. The multiregional hypothesis—a competitor to the out-of-Africa one—argues that populations that descended from archaics, such as *H. erectus*, evolved over the past 1.8 million years in Africa, Europe and Asia, and gradually emerged as *Homo sapiens*. Occasional interbreeding ensured that the groups did not split off into separate species.

Few scientists still hold a banner for a strict interpretation of multiregionalism. But modified versions still circulate, mostly as attempts to pinpoint whether *H. sapiens* bear genetic signatures of our encounters with hominid cousins. Vinayak Eswaran of the Indian Institute of Technology, aided by Henry C. Harpending and Alan R. Rogers of the University of Utah, came up with a set of simulations in recent years that suggest that after humans migrated out of Africa they interbred extensively with archaic species such as *H. erectus*. Eswaran's model suggests that as much as 80 percent of the modern human genome may have been subject to the effects of this kind of interbreeding.

The genetic imprint is not as visible as might be expected if interbreeding occurred, but Harpending offers an explanation. A set of beneficial genes carried by African emigrants, perhaps ones that assisted in childbearing, brought a selective advantage that eventually blotted out the signature of some archaic genes. "The result is that the population seems more closely related to the [African] source population of the favored genes than it really is," he says.

Are We Part Neandertal?

Eswaran and Harpending are not the only ones suggesting the possibility of interspecies trysts. Some fossilized skeletal remains of *H. sapiens* have features reminiscent of earlier hominids,

JEN CHRISTIANSEN

and the genetic record of contemporary humans has also provided fuel for discussion.

According to the tree diagrams that document genetic lineages, some gene variants show "deep ancestry"—they are much older than they should be if humans evolved from a single homogeneous group no more than 200,000 years ago; a hint of possible interbreeding. In one study that drew attention in 2006, Bruce T. Lahn of the University of Chicago and his colleagues reported that a version of the *Microcephalin* gene, which is involved in regulating brain size, contains a haplotype that may have been passed on during an encounter with Neandertals 40,000 years ago.

A more definitive answer may arrive within the next 12 months. The Neandertal Genome Project—a collaboration of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, and 454 Life Sciences, a Connecticut-based sequencing company—is scheduled by the end of this year to have finished a rough draft of some 70 percent of the sequences of DNA from 40,000-year-old Neandertal bones from a Croatian cave. Its results are expected to be published about six months later.

So far the project has unearthed no sign of any genetic pattern that would suggest DNA transfer between the two hominid lineages. "We see no evidence of that, but we can't exclude it," says Svante Pääbo, the Max Planck professor who heads the project. An earlier publication by his group that surveyed one million nucleotides, a minuscule fraction of the whole genome, suggested that some gene exchange might have occurred, but the result was later found to have been a false signal because of sample contamination. The researchers have not yet encountered the *Microcephalin* variant cited by Lahn.

Handling or even breathing on a sample remains an impediment to working with ancient DNA: some anthropologists wrap themselves in the clean-room "bunny suits" used in microchip factories when they head to the field on a dig. Since that initial paper, Pääbo's laboratory has altered the procedures used in the clean room at Max Planck. Researchers place tags made up of four nucleotides of synthetic DNA at the beginning of each strand of Neandertal genetic material. Each strand that exits the sequencing machine goes through a molecular identity check.

An understanding of the genetic makeup of the closest cousin in the human line—estimates from previous studies show that the two genomes are about 99.5 percent alike—could provide the most incisive exercise to date in comparative genomics, allowing identification of sites in the human genome where interbreeding took its course and where natural selection favored certain traits. "I think if you're interested in human evolution, Neandertals are the unique thing," Pääbo says. "They are our closest relatives. You can access their genomes, even though it's technically difficult. But for most other ancestral human groups, that will not be possible."

New, still unpublished work reveals that the Neandertal Y chromosome differs from the human one. "No human man has a Y chromosome like that of the Neandertal," Pääbo observes, mirroring earlier results showing that human and Neandertal mitochondrial DNA also are readily distinguishable. Last November Pääbo and his team did report one similarity between the two hominids. Neandertal remains from Spain had a version of a gene known as

JUST LOOK IN THE PHONE BOOK

The genetic record of human history may be bolstered by simply paging through a phone book for certain names. A team led by Mark A. Jobling of the University of Leicester reported last year that men in northwestern England with surnames that had been used there before 1600 had high levels of Scandinavian ancestry on their Y chromosomes, a legacy of a Viking heritage. Jobling has suggested in another paper that criminal investigators might be able to use this method to link DNA evidence to a set of surnames to narrow down a pool of suspects.

CONTAMINATION from human DNA complicates genetic analyses of Neandertals. Workers in the El Sidron cave in Spain have taken to wearing clean-room suits to protect newly excavated samples.

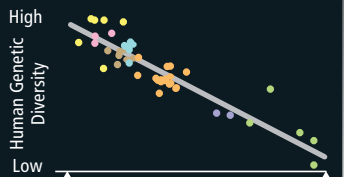
JAY H. MATTERNES (*Neandertal*); EL SIDRON RESEARCH TEAM (*excavation*)

[WHOLE-GENOME RESULTS]

LOOKING FAR AND WIDE

High-powered genetic sequencing and computational techniques developed for the Human Genome Project and in its aftermath have furnished a wealth of data that lets researchers compare genomes drawn from distinct populations around the globe.

The diversity of DNA—measured as the variation of nucleotides within blocks of DNA called haplotypes—decreases with distance from Addis Ababa, Ethiopia, a pattern that corresponds to the chronology of human migrations.



A genomic map of the world, crafted by researchers at the University of Michigan at Ann Arbor, shows that genetic diversity decreases outside of Africa. Each colored tile represents a common haplotype. Africa has more tiles than found on other continents and ones that correspond to haplotypes found nowhere else.

FOXP2 that is identical to one in humans that is involved with the development of speech and language. Again, speculation emerged in a paper by a separate group in April about whether the gene could have resulted from interbreeding, although the possibility of contamination could not be discounted.

How Have We Adapted?

As researchers continue sequencing DNA from shards of old bone to explore whether humans mated with other species of the genus *Homo*, other investigators are applying genome-wide analyses of DNA to see which genetically controlled traits changed through genetic drift (random mutations) and natural selection as migrants adapted to their new homes.

A study published in February in *Nature* showed the consequences of the declining genetic diversity as humans left Africa. The project compared 40,000 SNPs from a group of 20 European-Americans and 15 African-Americans. It found that the European-Americans had a higher proportion of harmful genetic changes, ones potentially related to disease, than the African-Americans did, although the authors refrained from speculation about any specific health effects. The research shows what lead scientist Carlos D. Bustamante called a "population genetic echo" of Europe's founding. The low genetic diversity of Europe's small initial population permitted a set of harmful mutations to disperse widely and new harmful ones to emerge when the numbers of people began to grow. Natural selection has not yet had time to remove deleterious changes.

Genome-wide research is also starting to furnish a panoramic picture of how natural selection helped migrants adapt to new environs. A spate of studies in the past two years have looked for genetic alterations that have occurred since humans left Africa or took up agriculture and that appear to have been useful for surviving in novel circumstances. Genetic prospectors mined the International HapMap, a catalogue of haplotypes and the 3.9 million SNPs contained therein from North Americans with ancestry in northwestern Europe and from individuals sampled in Nigeria, China and Japan.

One study, co-authored by Harpending, showed that the rate of change of DNA, and thus the pace of evolution, has accelerated over the past 40,000 years. Another by Pardis C. Sabeti of the Broad Institute in Cambridge, Mass., and her colleagues indicated that hundreds of regions

MARTIN SOAVE University of Michigan at Ann Arbor (map); JEN CHRISTIANSEN (graph and genetic tree); SOURCE: *WORLDWIDE HUMAN RELATIONSHIPS INFERRED FROM GENOME-WIDE PATTERNS OF VARIATION*, BY JUN Z. LI ET AL., IN *SCIENCE*, VOL. 319, 2008

[FUTURE CHALLENGES]

Can You Spare Some DNA?

In their quest for a more in-depth picture of human origins, geneticists need more samples from indigenous populations the world over. "There's a need for greater resolution in the data," says Marcus W. Feldman of Stanford University and a co-author of a recent whole-genome comparative analysis. "If you were to give me $1 million tomorrow, I'd find 100 more populations out of the 5,000 we need."

An equal hurdle may be overcoming objections to this kind of research. In 1991 Luigi Luca Cavalli-Sforza and his colleagues outlined a vision for the Human Genome Diversity Project, which would have created a store of cells from 25 unrelated individuals from each of some 400 populations worldwide. The project foundered, however, because of resistance from indigenous groups to providing samples: one group called it a "Vampire Project." Despite extensive informed consent procedures, some groups worried about whether the samples would be used in research for patenting and developing new drugs, which they considered to be a form of biopiracy.

The project never received more than planning support from the federal government, but a more modest version began in this decade, based on cell lines that various population geneticists had brought together on their own from more than 1,000 individuals. This collection, known as the Human Genome Diversity Panel, is stored at the Center for the Study of Human Polymorphisms in Paris. So far it has provided a database containing information on 51 populations that has been used for various studies, including two large, transgenomic investigations reported in *Nature* and *Science* this past February.

Like the Human Genome Diversity Project, the more recent Genographic Project, which intends to gather DNA from 100,000 indigenous people, is also facing opposition. The project has careful protocols for ensuring informed consent in sample gathering, and it does not intend to make collections for medical research. Yet it has still run into resistance, in particular, from Native American groups.

No matter what assurances are given, some groups will be reluctant to yield a cheek swab or blood sample. Investigators in this field may never achieve their goal of obtaining a set of samples that fully reflects every subtle gradation of human genetic diversity. —***G.S.***

COLLECTION OF DNA for the Genographic Project moves forward in Chad. Spencer Wells, who heads the project, takes a cheek swab.

of the genome are still undergoing selection, including areas that govern resistance to disease and the development of skin color, and hair follicles, which regulate sweat. Such findings imply that human populations are continuing to adapt to regional differences in sun exposure, foods and pathogens they encountered when they left their ancestral African home. And Africans have also evolved as their environs changed.

One of the most recent studies, led by Lluis Quintana-Murci of the Pasteur Institute in Paris, showed that 580 genes, including ones that play a role in diabetes, obesity and hypertension, are undergoing selection differently among the HapMap populations, perhaps explaining geographical differences in disease patterns and providing clues to new targets for developing drugs.

Consideration of the processes underlying human diversity sometimes moves beyond the dimensions of hair follicles and the ability to digest milk. Debate over what constitutes race and ethnicity can quickly enter the picture. What does it mean if a gene variant related to cognition is found more in Europeans than in Africans? Better public understanding of genetics—that a single gene does not act like a light switch that toggles between intelligence and doltishness—may quell misguided speculations.

Genetic literacy will let a term like "Asian" or "Chinese" be replaced by more subtle classifications based on the differences in ancestral genetic makeup found in recent genome-wide scans, such as the distinction between China's southern and northern Han groups. "There is no race," Quintana-Murci says. "What we see [from the standpoint of genetics] is geographical gradients. There are no sharp differences between Europeans and Asians. From Ireland to Japan, there is no sharp boundary where something has changed completely."

The journey through evolutionary history set in place by comparative genomics is still starting. In the meantime, the hunger for more data and more powerful computers and algorithms knows no limits. Amassing larger databases—an international consortium announced in January its intention to sequence 1,000 genomes from various regional populations—will let researchers run ever more realistic simulations of alternative models of human evolution and weigh the probabilities of each one, yielding the best picture yet of who we are and where we came from. ■

MORE TO EXPLORE

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DAVID EVANS *National Geographic*