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EVOLUTION

How We Are Evolving

New analyses suggest that recent human evolution has followed a different course than biologists would have expected

By Jonathan K. Pritchard

IN BRIEF

As early *Homo sapiens* spread out from Africa starting around 60,000 years ago, they encountered environmental challenges that they could not overcome with prehistoric technology.

Many scientists thus expected that surveys of our genomes would reveal considerable evidence of novel genetic mutations that have recently spread quickly throughout different populations by natural selection—that is, because those who carry the mutations have greater numbers of healthy babies than those who do not.

But it turns out that although the genome contains some examples of very strong, rapid natural selection, most of the detectable natural selection appears to have occurred at a far slower pace than researchers had envisioned.

Illustrations by Owen Gildersleeve

THOUSANDS OF YEARS AGO HUMANS MOVED FOR THE first time into the Tibetan plateau, a vast expanse of steppelands that towers some 14,000 feet above sea level. Although these trailblazers would have had the benefit of entering a new ecosystem free of competition with other people, the low oxygen levels at that altitude would have placed severe stresses on the body, resulting in chronic altitude sickness and high infant mortality. Earlier this year a flurry of genetic studies identified a gene variant that is common in Tibetans but rare in other populations. This variant, which adjusts red blood cell production in Tibetans, helps to explain how Tibetans adapted to those harsh conditions. The discovery, which made headlines around the world, provided a dramatic example of how humans have undergone rapid biological adaptation to new environmental circumstances in the recent past. One study estimated that the beneficial variant spread to high frequency within the past 3,000 years—a mere instant in evolutionary terms.

The Tibet findings seemed to bolster the notion that our species has undergone considerable biological adaptation of this sort since it first left Africa perhaps 60,000 years ago (estimates range from 50,000 to 100,000 years ago). The transition to high altitude is just one of many environmental challenges *Homo sapiens* encountered as it migrated from the hot grasslands and shrublands of East Africa to frigid tundras, steamy rain forests and sunbaked deserts—practically every terrestrial ecosystem and climate zone on the planet. To be sure, much of human adaptation was technological—to combat the cold, for instance, we made clothing. But prehistoric technology alone could not have been enough to overcome thin mountain air, the ravages of infectious disease and other environmental obstacles. In these circumstances, adaptation would have to occur by genetic evolution rather than through technological solutions. It was reasonable to expect, then, that surveys of our genomes would reveal considerable evidence of novel genetic mutations that have spread recently throughout different populations by natural selection—that is, because those who carry the mutations have more healthy babies who survive to reproduce than those who do not.

The genome actually contains few examples of very strong, rapid natural selection. Instead most of the visible natural selection appears to have occurred over tens of thousands of years.

Six years ago my colleagues and I set out to look for the imprints of these profound environmental challenges on the human genome. We wanted to figure out how humans have evolved since our predecessors set out on their relatively recent global journey. To what extent do populations in disparate parts of the world differ genetically because natural selection recently adapted them to different environmental pressures, as in the case of the Tibetans? What proportion of these genetic differences stems instead from other influences? Thanks to advances in technologies for studying genetic variation, we were able to begin to address these questions.

The work is still under way, but the preliminary findings have surprised us. It turns out that the genome actually contains few examples of very strong, rapid natural selection. Instead most of the natural selection visible in the genome appears to have occurred over tens of thousands of years. What seems to have happened in many cases is that a beneficial mutation spread through a population long ago in response to a local environmental pressure and then was carried into faraway locales as the population expanded into new territories. For example, some gene variants involved in determining light skin color, an adaptation to reduced sunlight, are distributed according to ancient migration routes, rather than just latitude. That these ancient selection signals have persisted over millennia without new environmental pressures overwriting them indicates that natural selection often operates at a far more leisurely pace than scientists had envisioned. The rapid evolution of a major gene in the Tibetans, it appears, is not typical.

As an evolutionary biologist, I am often asked whether humans are still evolving today. We certainly are. But the answer to the question of how we are changing is far more complicated. Our data suggest that the classic natural selection scenario, in which a single beneficial mutation spreads like wildfire through a population, has actually occurred relatively rarely in humans in the past 60,000 years. Rather this mechanism of evolutionary change usually seems to require consistent environmental pressures over tens of thousands of years—an uncommon situation once our ancestors started globe-trotting and the pace of technological innovation began accelerating.

Already these findings are helping to refine our understanding not only of recent human evolution but also of what our collective future might hold. For a number of the challenges currently facing our species—global climate change and many infectious diseases, for example—natural selection probably occurs too slowly to help us much. Instead we are going to have to rely on culture and technology.

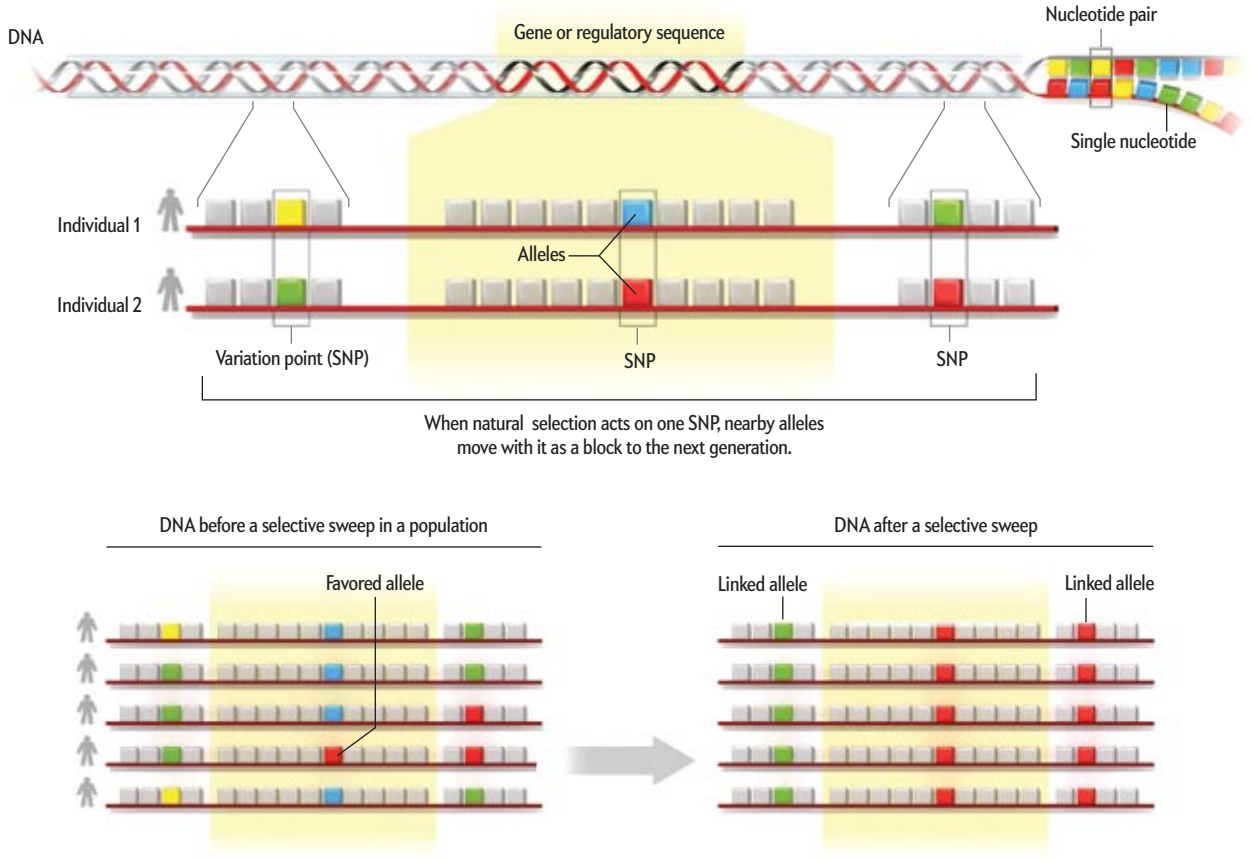
FINDING THE FOOTPRINTS

JUST 10 YEARS AGO it was extremely difficult for scientists to trace our species' genetic responses to our environment; the needed tools just did not exist. All that changed with the completion of the human genome sequence and the subsequent cataloguing of genetic variation. To understand exactly what we did, it helps to know a bit about how DNA is structured and how small changes can affect its function. The human genome sequence consists of about three billion pairs of DNA nucleotides, or "letters," that serve as an instruction manual for how to assemble a human [*see box on next page*]. The manual is now known to contain a parts list of about 20,000 genes—strings of DNA letters that spell out the information required to build proteins. (Proteins, which include enzymes, do much of the work in cells.) About 2 percent of the human genome encodes proteins, and a roughly similar amount seems to be involved in gene regulation. Most of the rest of the genome has no known role.

Overall the genomes of any two people are extremely similar, differing in only about one out of every 1,000 nucleotide pairs. Sites where one nucleotide pair substitutes for another are referred to as single-nucleotide polymorphisms, or SNPs (pronounced "snips"), and the alternative versions of the DNA at

Selection Signal

Scientists can infer that natural selection has acted on a region of DNA if they observe a lack of variability in that region. The genomes of any two people differ at only approximately one out of every 1,000 pairs of DNA nucleotides, or "letters." These points of difference are known as single-nucleotide polymorphisms (SNPs), and the alternative versions of nucleotides at each SNP are called alleles. When a particular allele ends up improving reproductive success, it ultimately spreads through a population, or is "selected." At the same time, nearby alleles travel along with the favored one and thus become more common in the population as well. The resulting reduction of SNP variation in this part of the genome in a population is termed a selective sweep.



each SNP are called alleles. Because most of the genome does not encode proteins or regulate genes, most SNPs probably have no measurable effect on the individual. But if a SNP occurs in a region of the genome that does have a coding or regulating function, it may affect the structure or function of a protein or where and how much of the protein is made. In this way, SNPs can conceivably modify almost any trait, be it height, eye color, ability to digest milk, or susceptibility to diseases such as diabetes, schizophrenia, malaria and HIV.

When natural selection strongly favors a particular allele, it becomes more common in the population with each generation, while the disfavored allele becomes less common. Eventually, if the environment remains stable, the beneficial allele will spread until everyone in the population carries it, at which point it has become fixed in that group. This process typically takes many generations. If a person with two copies of the beneficial allele produces 10 percent more children and someone with one copy produces 5 percent more, on average, than someone without the beneficial allele, then it will take that allele about 200 generations, or roughly 5,000 years, to increase in frequency from 1 percent of the population to 99 percent of it. In theory, a helpful allele could become fixed in as little as a few hundred years if it conferred an extraordinarily large advantage. Conversely, a less advantageous allele could take many thousands of years to spread.

It would be great if in our efforts to understand recent human evolution, we could obtain DNA samples from ancient remains and actually track the changes of favored alleles over time. But DNA usually degrades quickly in ancient samples, thereby hindering this approach. Thus, my research group and a number of others around the world have developed methods of examining genetic variation in modern-day humans for signs of natural selection that has happened in the past.

One such tactic is to comb DNA data from many different people for stretches that show few differences in SNP alleles within a population. When a new beneficial mutation propagates rapidly

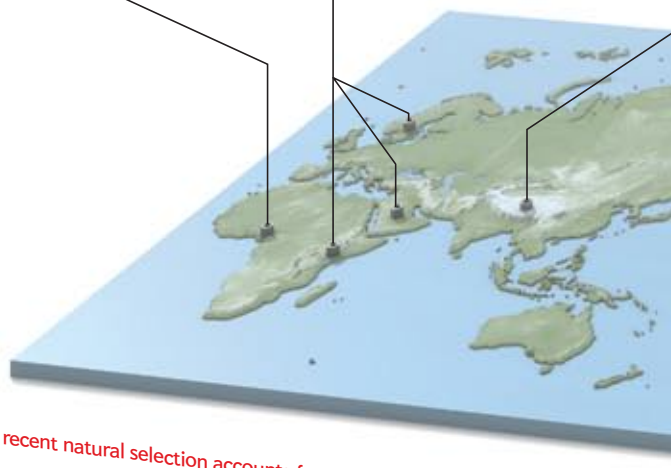
Illustration by Emily Cooper

Surprising Findings from Population Studies

Researchers have identified a handful of favorable alleles that spread to high frequency as a result of strong natural selection acting quickly to adapt people to local environmental pressures (*right*). A new analysis of hundreds of other apparent signals of natural selection (such as sweeps) suggests, however, that most do not represent recent adaptations. Most of the selected alleles detected in this study exhibit one of just three geographical patterns (*bottom map*): either they occur at high frequency in all populations outside of Africa but not within Africa (*orange arrow*); or they are common throughout West Eurasia—an area composed of Europe and West and South Asia—but rare elsewhere (*red arrow*); or they dominate in North Asia, East Asia, Oceania and the Americas (*yellow arrow*) but occur only at low frequency in West Eurasia. These patterns suggests that ancient migrations have influenced where these alleles occur.

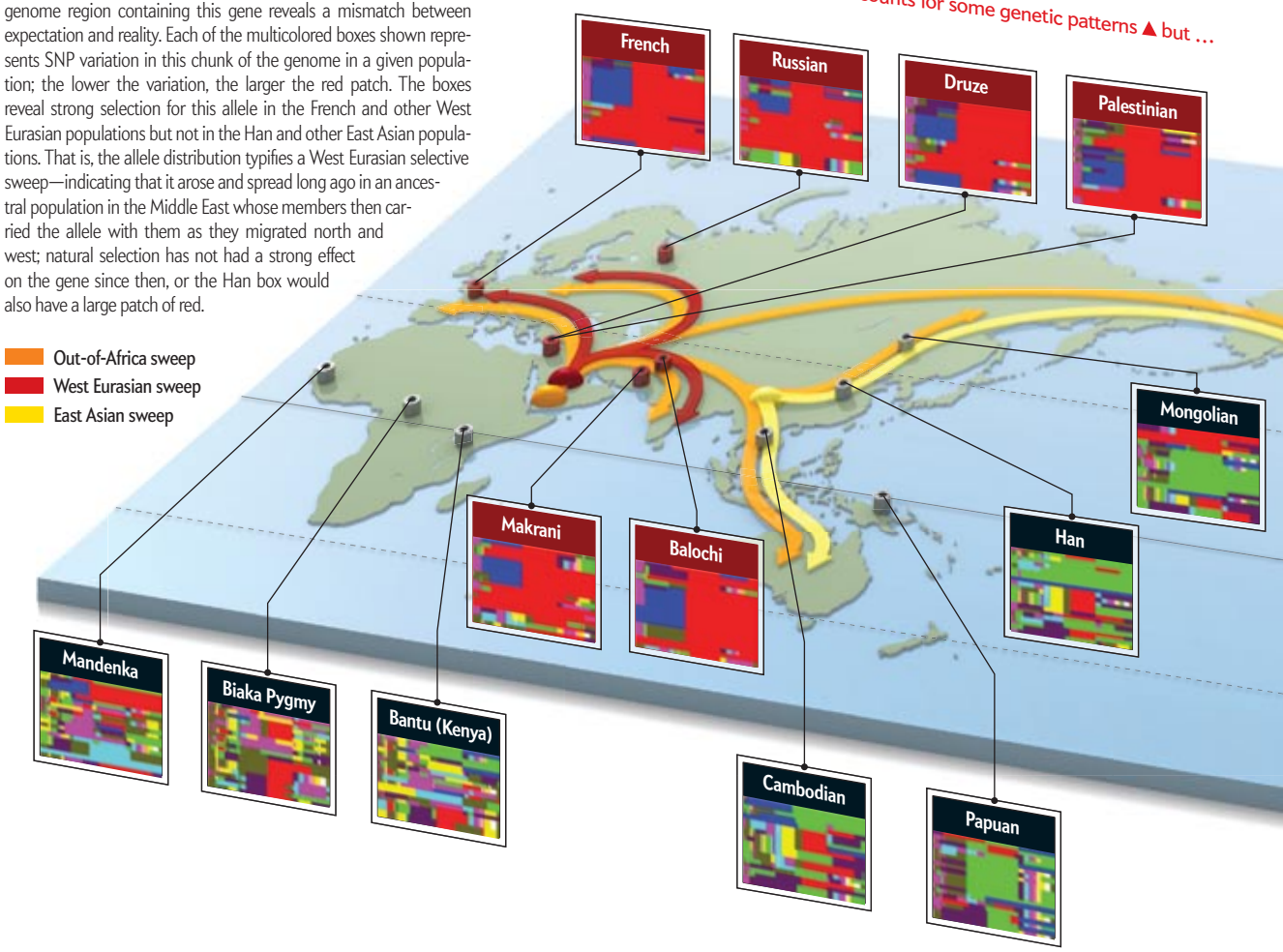
A gene known as *LARGE* that participates in the body's response to infection with the Lassa fever virus has undergone strong, recent natural selection in a population in Nigeria, where the pathogen is endemic.

The gene for the lactase enzyme that digests the sugar in milk has undergone rapid evolution among dairy-farming populations in Europe, the Middle East and East Africa over the past 5,000 to 10,000 years.

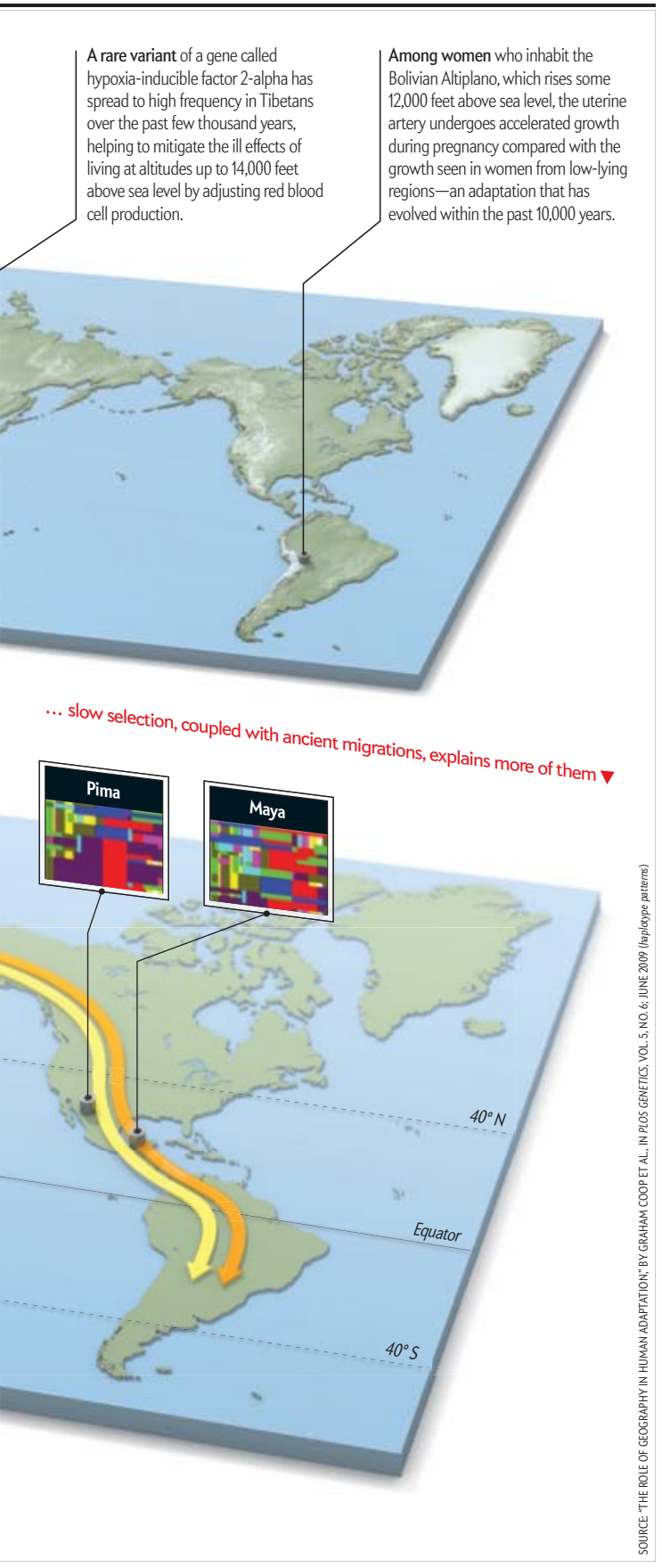


Fast, recent natural selection accounts for some genetic patterns ▲ but ...

An example: a variant of the so-called *SLC24A5* gene that lightens skin color. It is an adaptation to reduced sunlight, so one would expect similar, high frequencies of the allele in populations that live at northerly latitudes—the French and the Han Chinese, for instance. But examining populations around the world for SNP variation in the genome region containing this gene reveals a mismatch between expectation and reality. Each of the multicolored boxes shown represents SNP variation in this chunk of the genome in a given population; the lower the variation, the larger the red patch. The boxes reveal strong selection for this allele in the French and other West Eurasian populations but not in the Han and other East Asian populations. That is, the allele distribution typifies a West Eurasian selective sweep—indicating that it arose and spread long ago in an ancestral population in the Middle East whose members then carried the allele with them as they migrated north and west; natural selection has not had a strong effect on the gene since then, or the Han box would also have a large patch of red.



Maps by Emily Cooper



SOURCE: "THE ROLE OF GEOGRAPHY IN HUMAN ADAPTATION," BY GRAHAM COOP ET AL., IN *PLOS GENETICS*, VOL. 5, NO. 6; JUNE 2009 (*haplotype patterns*)

through a group because of natural selection, it takes a surrounding chunk of the chromosome with it in a process called genetic hitchhiking. As the frequency of the beneficial allele increases in the group over time, so, too, do the frequencies of nearby "neutral" and nearly neutral alleles that do not affect protein structure or amount appreciably but ride along with the selected allele. The resulting reduction or elimination of SNP variation in the region of the genome containing a beneficial allele is termed a selective sweep. The spread of selected alleles by natural selection can also leave other distinctive patterns in the SNP data: if an existing allele suddenly proves particularly helpful when a population finds itself in new circumstances, that allele can reach high frequency (while remaining rare in other populations) without necessarily generating a hitchhiking signal.

Over the past few years multiple studies, including one my colleagues and I published in 2006, have identified several hundred genome signals of apparent natural selection that occurred within the past 60,000 years or so—that is, since *H. sapiens* left Africa. In a few of these cases, scientists have a pretty good grasp on the selective pressures and the adaptive benefit of the favored allele. For example, among dairy-farming populations in Europe, the Middle East and East Africa, the region of the genome that houses the gene for the lactase enzyme that digests lactose (the sugar in milk) shows clear signs of having been the target of strong selection. In most populations, babies are born with the ability to digest lactose, but the lactase gene turns off after weaning, leaving people unable to digest lactose as adults. Writing in the *American Journal of Human Genetics* in 2004, a team at the Massachusetts Institute of Technology estimated that variants of the lactase gene that remain active into adulthood achieved high frequency in European dairy-farming groups in just 5,000 to 10,000 years. In 2006 a group led by Sarah Tishkoff, who is now at the University of Pennsylvania, reported in *Nature Genetics* that they had found rapid evolution of the lactase gene in East African dairy-farming populations. These changes were surely an adaptive response to a new subsistence practice.

Researchers have also found pronounced signals of selection in at least half a dozen genes involved in determining skin, hair and eye color in non-Africans. Here, too, the selective pressure and adaptive benefit are clear. As humans moved out of their tropical homeland, they received reduced ultraviolet radiation from the sun. The body requires UV radiation to synthesize vitamin D, an essential nutrient. In the tropics, UV radiation is strong enough to penetrate dark skin in amounts needed for vitamin D synthesis. Not so in the higher latitudes. The need to absorb adequate amounts of vitamin D almost certainly drove the evolution of lighter skin color in these locales, and changes in these genes that bear signals of strong selection enabled that adaptive shift.

Selection signals also show up in a variety of genes that confer resistance to infectious diseases. For instance, Pardis Sabeti of Harvard University and her colleagues have found a mutation in the so-called *LARGE* gene that has recently spread to high frequency in the Yoruba of Nigeria and is probably a response to the relatively recent emergence of Lassa fever in this region.

MIXED SIGNALS

THOSE EXAMPLES and a small number of other cases provide strong evidence of natural selection acting quickly to promote helpful alleles. For most of the rest of the hundreds of candidate signals, however, we do not yet know which circumstances

favored the spread of the selected allele, nor do we know what effect the allele exerts on the people who harbor it. Until recently we and others interpreted these candidate signals to mean that there have been at least a few hundred very rapid selective sweeps within the past 15,000 years in several human populations that have been studied. But in newer work my colleagues and I have found evidence suggesting that instead most of these signals are not actually the result of very recent, rapid adaptation to local conditions at all.

Working with collaborators at Stanford University, we studied a massive SNP data set generated from DNA samples obtained from about 1,000 individuals from around the world. When we looked at the geographical distributions of selected alleles, we found that the most pronounced signals tend to fall into one of just three geographical patterns. First there are the so-called out-of-Africa sweeps, in which the favored allele and its hitchhikers exist at high frequency in all non-African populations [*see box on preceding two pages*]. This pattern suggests that the adaptive allele appeared and began to spread very shortly after humans left Africa but while they were still restricted to the Middle East—thus perhaps around 60,000 years ago—and was subsequently carried around the globe as humans migrated north and east. Then there are two other, more restricted, geographical patterns: the West Eurasian sweeps, in which a favored allele occurs at high frequency in all of the populations of Europe, the Middle East, and Central and South Asia, but not elsewhere; and the East Asian sweeps, in which the favored allele is most common in East Asians, as well as usually Native Americans, Melanesians and Papuans. These two patterns probably represent sweeps that got under way shortly after the West Eurasians and East Asians split off and went their separate ways. (It's not known precisely when this occurred, but probably around 20,000 to 30,000 years ago.)

These sweep patterns reveal something very interesting: ancient population movements have heavily influenced the distributions of favored alleles across the globe, and natural selection has done little to fine-tune those distributions to match modern environmental pressures. For example, one of the most important players in the adaptation to lighter skin color is a variant of the so-called *SLC24A5* gene. Because it is an adaptation to reduced sunlight, one might expect its frequency in the population to increase with latitude and its distribution to be similar in people from North Asia and Northern Europe. Instead we see a West Eurasian sweep: the gene variant and the hitchhiking DNA that travels with it are common from Pakistan to France but essentially absent in East Asia—even in the northern latitudes. This distribution indicates that the beneficial variant arose in the ancestral population of the West Eurasians—after they diverged from the ancestors of the East Asians—who carried it throughout that region. Thus, natural selection drove the beneficial *SLC24A5* allele to high frequency early on, but ancient population history helped to determine which populations today have it and which do not. (Other genes account for light skin in East Asians.)

A closer look at the selection signals in these and other data reveals another curious pattern. Most of the alleles with the most extreme frequency differences between populations—those that occur in nearly all Asians but no Africans, for example—do not exhibit the strong hitchhiking signals one would expect to see if natural selection swiftly drove these new alleles to high frequency. Instead these alleles seem to have propagated gradually during the roughly 60,000 years since our species set out from Africa.

In light of these observations, my collaborators and I now believe that textbook selective sweeps—in which natural selection drives an advantageous new mutation rapidly to fixation—have actually occurred fairly rarely in the time since the *H. sapiens* diaspora began. We suspect that natural selection usually acts relatively weakly on individual alleles, thus promoting them very slowly. As a result, most alleles experiencing selection pressure may attain high frequency only when the pressure persists for tens of thousands of years.

ONE TRAIT, MANY GENES

OUR CONCLUSIONS MAY SEEM PARADOXICAL: if it usually has taken 50,000, not 5,000, years for a helpful allele to spread through a population, how would humans ever manage to adapt quickly to new conditions? Although the best understood adaptations arise from changes in a single gene, it may be that most adaptations do not arise that way but rather stem from genetic variants having mild effects on hundreds or thousands of relevant genes from across the genome—which is to say they are polygenic. A series of papers published in 2008, for example, identified more than 50 different genes that influence human height, and certainly many more remain to be found. For each of these, one allele increases average height by just three to five millimeters compared with the other allele.

It is possible that human genomes have undergone more adaptive change recently than scientists can yet identify by examining the genome in the usual way.

When natural selection targets human height—as has occurred in the pygmy populations that live in rain forest habitats in Africa, Southeast Asia and South America, where small body size may be an adaptation to the limited nutrition available in these environments—it may operate in large part by tweaking the allele frequencies of hundreds of different genes. If the "short" version of every height gene became just 10 percent more common, then most people in the population would quickly come to have more "short" alleles, and the population would be shorter overall. Even if the overall trait were under strong selection, the strength of selection on each individual height gene would still be weak. Because the selection acting on any one gene is weak, polygenic adaptations would not show up in genome studies as a classic signal of selection. Thus, it is possible that human genomes have undergone more adaptive change recently than scientists can yet identify by examining the genome in the usual way.

STILL EVOLVING?

AS TO WHETHER HUMANS ARE STILL EVOLVING, it is difficult to catch natural selection in the act of shaping present-day populations. It is, however, easy to imagine traits that might be affected. Infectious diseases such as malaria and HIV continue to exert potent selection forces in the developing world. The handful of

known gene variants that provide some measure of protection against these scourges are probably under strong selective pressure, because people who carry them are more likely to survive and live to have many more children than those who do not. A variant that shields carriers from the vivax form of malaria has become ubiquitous in many populations in sub-Saharan Africa. The variants that protect against HIV, meanwhile, could spread throughout sub-Saharan Africa in hundreds of years if the virus were to persist and continue to be thwarted by that resistance gene. But given that HIV is evolving faster than humans are, we are more likely to overcome that problem with technology (in the form of a vaccine) than with natural selection.

In the developed world relatively few people die between birth and adulthood, so some of the strongest selection forces are probably those acting on genes that affect the number of children each person produces. In principle, any aspect of fertility or reproductive behavior that genetic variation affects could be the target of natural selection. Writing in the *Proceedings of the National Academy of Sciences USA* in 2009, Stephen C. Stearns of Yale University and his colleagues reported on the results of a study that identified six different traits in women that are associated with higher lifetime numbers of children and that all show intermediate to high heritability. Women with larger numbers of children, the team found, tend to be slightly shorter and stouter than average and to have later age at menopause. Hence, if the environment stays constant, these traits will presumably become more common over time because of natural selection: the authors estimate that the average age at menopause will increase by about one year over the next 10 generations, or 200 years. (More speculatively, it is plausible that genetic variation influencing sexual behavior—or use of contraceptives—would be subject to strong selection, although just how strongly genes affect complex behaviors such as these remains unclear.)

Still, the rate of change of most traits is glacially slow compared with the rate at which we change our culture and technology and, of course, our global environment. And major adaptive shifts require stable conditions across millennia. Thus, 5,000 years from now the human milieu will no doubt be very different. But in the absence of large-scale genomic engineering, people themselves will probably be largely the same. SA

MORE TO EXPLORE

Positive Natural Selection in the Human Lineage. P. C. Sabeti et al. in *Science*, Vol. 312, pages 1614–1620; June 16, 2006.

The Role of Geography in Human Adaptation. Graham Coop et al. in *PLoS Genetics*, Vol. 5, No. 6, e1000500; June 5, 2009.

Sequencing of 50 Human Exomes Reveals Adaptation to High Altitude. Xin Yi et al. in *Science*, Vol. 329, pages 75–78; July 2, 2010.

Measuring Selection in Contemporary Human Populations. Stephen C. Stearns et al. in *Nature Reviews Genetics*, Vol. 11, pages 611–622; August 10, 2010.

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