

Seeking the signs of selection.

by Steve Olson

New genetic techniques are spurring the search for evidence of natural selection at work in human prehistory, and they may offer insight into ancient and modern pathogens.

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A woman miscarries; a child dies of malaria; a young man is ravaged by AIDS. Each is a human tragedy that leaves its mark on lives and families. But over the sweep of human history, such tragedies also can leave their mark on the human genome. Genetic mutations that help protect against viral infections, for example, should give those who inherit them an advantage in the reproduction and survival sweepstakes. The theory of natural selection predicts that over many generations, these mutations will spread through populations and so appear in genomes today.

Scientists have long sought the genetic imprint of natural selection to understand

the forces that have shaped human traits. But it's been a bit like trying to solve a crossword puzzle in which the clues have been scrambled. Other demographic events such as migrations, population contractions and expansions, and mating traditions have also left their mark on our genomes, making the effects of selection and history hard to untangle.

So until recently, researchers had uncovered few solid cases of human genes under selective pressure. But they now have two powerful tools to guide the search: efficient sequencing techniques and the almost complete human genome sequence. These have already helped add several new genes to the list of those affected by selection (see table). And because some of the most potent selective forces have been pathogens, researchers are hoping the search will help them zero in on parts of the genome involved in disease. "We should be able to find disease genes without actually having patients, because we are descended from people who were resistant to diseases, and that resistance is engraved in our genes," explains geneticist David Reich of the Whitehead Institute in Cambridge, Massachusetts.

Earlier this month, in the fourth of a series of sesquiannual meetings at Cold Spring Harbor Laboratory, * about 150 anthropologists, geneticists, and pharmaceutical company researchers spent 5 days examining progress in the hunt so far and the implications for biomedicine. "What this meeting represents is a fusion of anthropology, population genetics, and clinical medicine to create a new field, evolutionary medicine," said meeting co-organizer Douglas Wallace, director of the new Center for Molecular and Mitochondrial Medicine at the University of California, Irvine.

Direction and balance

The effort to understand human traits and diseases in terms of natural selection began with Darwin, who sought in his last book, *The Descent of Man*, "to see how far the general conclusions arrived at in my former works were applicable to man." But as the quest moved to the genetic level in the 20th century, the task proved more difficult than expected. To detect selection, researchers first must determine how a genetic sequence would change under neutral conditions in which selection was not a factor. That's easy to do for an infinitely large, randomly mating population--but human populations have never met those conditions.

Nevertheless, geneticists have succeeded in finding a few clear examples of directional selection, in which a particular version or allele of a gene has been so beneficial that it has spread quickly and widely, thus reducing levels of genetic variation. The allele that allows adults to digest lactose is a good example: The pastoralists who carried it could drink milk as adults, boosting their survival and reproduction, so the allele became common and in relatively short order displaced other versions of the gene in those populations. Geneticists also have found some cases of what's called balancing selection, in which a gene shows more variation than expected because people with two different versions of it--heterozygotes--have an advantage over those who carry two copies of the same allele. The classic example is a hemoglobin allele that causes sickle cell anemia if inherited from both parents but protects against malaria if paired with a normal version of the gene.

But beyond these well-known examples, the pickings have been slim. "For directional selection, people have been able to find a handful of genes," says geneticist Michael Bamshad of the University of Utah in Salt Lake City. "For balancing

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selection, they have found even fewer."

But now that geneticists can sequence thousands of base pairs from global samples of hundreds of people, the search has gained new life. For example, Bamshad and his colleagues have sequenced the regions surrounding a cell surface receptor gene called CCR5 in more than 200 people worldwide. This is a crucial receptor because many viruses, including HIV, seem to use it to gain entry to cells.

In work published 6 August in the Proceedings of the National Academy of Sciences, Bamshad found up to twice as much genetic variation as usual in a noncoding, regulatory region of CCR5, and characteristics of the variation suggest that it has been maintained for a long time. Bamshad believes that those patterns are the result of balancing selection: As in the case of sickle cell anemia, people with two different copies of the gene apparently suffered from fewer or milder illnesses, thus leaving a legacy of variability that continues to have advantages today. Indeed, among people infected with HIV, heterozygosity in the CCR5 gene seems to slow the progression to AIDS. HIV itself is too new to have been the selective force on CCR5, but older candidates include poxviruses, which ravaged human populations in the past, says Bamshad.

Ken Kidd of Yale University has taken a similar survey of a different set of genes: the ADH genes that produce alcohol-metabolizing enzymes. Many members of eastern Asian populations have a variety of unpleasant reactions to alcohol, including flushed faces, racing hearts, and upset stomachs. Partly as a result, these populations tend to have low levels of alcoholism. These reactions are due to a variety of mutations, some of which hasten the metabolism of ethanol to toxic acetaldehyde and trigger the adverse effects. But any selection seems not to have been acting on human drinking habits; instead, many researchers believe that the reactions offered protection against an unknown parasite that was even more sensitive to acetaldehyde than humans are.

When Kidd examined the frequency of these mutations throughout eastern Asia, he found that certain mutations often occurred together, creating a unique combination of genetic variants that together promote acetaldehyde production. This combination occurred so frequently that it was unlikely to have spread by chance, says Kidd. Thus although no one knows what parasite might have been involved, the prevalence of the mutations suggests that selection was indeed at work, he says.

In a more controversial study, Robert Moyzis of the University of California, Irvine, reported on efforts in his lab by Yuan-Chun Ding and others to detect selection in the human dopamine receptor DRD4. A particular version of the receptor--an allele with seven repeats of a 48-base pair insert--has been linked with the personality traits of novelty-seeking and attention-deficit/ hyperactivity disorder (ADHD).

Moyzis's team found that the seven-repeat allele is surrounded by a large block of sequence in which genetic variations tend to be inherited together, a pattern called linkage disequilibrium. This means that the ancestral chromosomal region on which the mutation first appeared has not yet been broken up by the recombination events that occur each generation, during the formation of sperm and egg cells. That suggests that the allele is much younger than the other common DRD4 alleles, perhaps appearing just 30,000 to 50,000 years ago.

Normally an allele this young would be relatively rare, but instead it is quite common in some populations. Such common young variants can be a sign of selection, because new mutations favored by selection replace other alleles faster than if they were neutral.

But the example is controversial because it's hard to know why an allele that flow predisposes people to ADHD might have had a selective advantage, admits Moyzis. He notes that the allele appeared during an "interesting" time in human history, when modern humans expanded into new environments worldwide. He speculates that the allele increased the probability that some individuals would leave their homelands and seek out new challenges.

Seeking youth and abundance

As these researchers examine particular genes, others are looking more broadly for signs of selection. For example, Pardis Sabeti, David Reich, Eric Lander, and their colleagues at the Whitehead Institute have developed a technique that spotlights the common young variants that can signal directional selection: They seek common alleles surrounded by extensive linkage disequilibrium (see diagram). The team applied this method to variants of two genes, G6PD and CD40L,

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known to confer partial protection against malaria. In work described last month in *Nature*, they uncovered a clear selective signal: Each gene appears to be just a few thousand years old but is much more widespread than expected under a neutral model. Now the team is extending its method to scan the entire genome for other selective episodes that have occurred over the past 10,000 years. (Before that, recombination probably would have scrambled the signal.) "It seems to be a very powerful way of looking for selection and pinpointing important functional variation," said Benjamin Salisbury of Genaissance Pharmaceuticals in New Haven, Connecticut, which is conducting its own search for selection in 7000 genes.

[ILLUSTRATION OMITTED]

The search for selection is generating considerable interest in the pharmaceutical industry. If a pathogen has exerted selective pressure on a gene, that gene could be a promising target for a new drug or vaccine. "We can use the experiment that nature has already conducted to give us a clue about how to combat a disease," said Genaissance's J. Claiborne Stephens.

But many geneticists have cautioned that the new efforts to detect selection will face many of the obstacles that have previously stymied researchers. One problem is that demographic processes and random chance can mimic selection. For example, the seven-repeat allele of the dopamine receptor is common in Native Americans but virtually absent in eastern Asians. But that could be an accident of history, not a sign of selection, if the first people to colonize the Americas just happened to have the allele.

Also, genes and human traits generally have a complex linkage, not a one-to-one correspondence. "No one has found a variant that explains more than a couple of percent of any common disease, and all of these diseases are going to be highly multigenic," said geneticist Jody Hey of Rutgers University in Piscataway, New Jersey. "That's bad news for the gene mappers and pharmaceutical companies."

For example, Kidd calls the link between certain genetic variants and low levels of alcoholism in eastern Asian populations "one of the strongest associations found in the study of complex diseases." Yet he acknowledges that alcoholism has social and psychological dimensions too. And although certain alleles might protect against alcoholism, their absence does not boost susceptibility, because the mechanisms of addiction are distinct from those of alcohol metabolism.

No one expects the search for signs of selection to suddenly become easy. But after years of frustration, researchers are welcoming the new data and methods that might finally yield progress. "We're starting to see a clear connection between the study of history and practical biomedical applications," says geneticist Stephen Wooding of the University of Utah. "We can generate clinically testable hypotheses that we were never able to generate before."

SELECTION AT WORK IN HUMANS: A SAMPLER

Gene	Signs of Selection	Possible Selective Force
Sickle cell gene (hemoglobin [beta])	Unusual genetic variability (balancing selection)	Malaria, sickle cell disease
CCR5	Unusual genetic variability (balancing selection)	Smallpox, other diseases
Lactase	Young, common variant; low sequence variability (directional selection)	Ability to drink milk in adulthood
ADH	Common variant; low sequence variability (directional selection)	Unknown parasite sensitive to acetaldehyde?
DRD4 (seven-repeat allele)	Young, common variant (directional selection?)	?

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G6PD and CD40L Young, common variants Malaria
(directional selection)

* "Human Origins and Disease," 30 October to 3 November, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York.

Steve Olson is a science writer in the Washington, D.C., area and is the author of Mapping Human History: Discovering the Past Through Our Genes.