



Jonathan Pritchard has been an arbiter in one of the most contentious debates in biology: How much has natural selection influenced human traits?

WRESTLING WITH DARWIN

The discovery of natural selection was both a triumph and a burden for Charles Darwin.

Through careful observations of the living world, he concluded that most organisms have many more offspring than can survive. Those offspring with advantageous characteristics tend to live while others succumb to disease, are eaten by predators, or otherwise fail to reproduce.

This “struggle for life” tends to perpetuate favorable traits, enabling populations of organisms to adapt to their environments. Yet the struggle reveals an amoral ruthlessness at the heart of nature. When Darwin reflected, late in life, on his loss of faith, one consideration he cited was “the sufferings of the millions of lower animals throughout almost endless time.”

Humans are not exempt from this competition for reproductive success. The miscarriage of a fetus, the death of a child from disease, a young couple’s inability to have children—all are more than human tragedies; they also prevent particular versions of genes from passing into future generations. As Darwin said of his theory, “the vigorous, the healthy, and the happy survive and multiply.”

Jonathan Pritchard, an HHMI investigator at the University of Chicago, has been fascinated by evolution and natural selection ever since he began collecting insects and watching birds near his childhood home outside London. “Understanding the role of selection in any species is one of the fundamental questions in biology,” he says.

It’s also a problem with many practical applications. Selection modifies genes that influence our phenotypes—our biological forms and functions—including susceptibility to disease and responses to environmental toxins. If geneticists like Pritchard can identify places in our genomes shaped by selection, they might shine a spotlight on genetic regions implicated in some of the major scourges of humanity. “Selection could influence common diseases—like diabetes, hypertension, and stroke—that fill up hospital beds,” says his University of Chicago colleague Anna Di Rienzo.

More controversial issues are at stake. Some biologists claim that the biological differences between human populations are largely the product of selection. They say that skin color, body shape, and even certain dispositions such as aggressiveness and intelligence are the product of people with particular heritable traits having more successful offspring.

Other biologists scoff at these claims. They insist that complex characteristics like intelligence depend much more on a person’s experiences than on the genetic differences between individuals or groups of people. And they claim that, for most traits, factors like the movement and growth of human populations are more likely than selection to determine genetic inheritance.

Pritchard, a lanky ex-athlete who exudes the calm of a serious runner, has been at the

forefront of these controversies throughout his research career. But he has served more in the role of mediator than combatant. Pritchard is an expert at the mathematical techniques needed to determine how natural selection has influenced our genomes. While others argue in the abstract about how genes might affect human traits, Pritchard focuses on facts: what historical processes could have produced the sequences of genetic letters in our DNA?

AN EXTRA YEAR

Pritchard’s proficiency in both mathematics and biology can be traced in part to a bum knee. He and his father, William G. Pritchard, an applied mathematician who moved the family from England to the United States to take a faculty position at Pennsylvania State University, shared a love of running. Pritchard’s first scientific paper, which he wrote as an undergraduate with his father as coauthor, analyzed the effects of wind on sprinters and concluded that the women’s world record in the 100 meters, set by Florence Griffith-Joyner at the Olympic Trials in 1988, should have been disallowed because of a strong tailwind. However, the anemometer, which recorded a wind speed of zero, appears to have malfunctioned. (“Running officials have occasionally asked us about our results,” says Pritchard, “but they don’t want to change the record.”)

Pritchard planned to run the 1500- and 5000-meter track events for Penn State when he entered as a freshman. But a knee injury forced him to redshirt for a year, which meant he was in college for five years. That gave him plenty of time to double-major in biology and mathematics while still competing on the track and cross-country teams. A freshman class taught by Andrew Clark on population genetics—the study of changes in DNA sequences in populations of organisms



Jonathan Pritchard, fascinated by evolution since childhood and gifted in math, combines computation and population genetics to learn how natural selection has influenced our genomes.

over time—intrigued him. “He was tremendously gifted mathematically,” Clark says. “When a student like that comes along, you pay attention.”

After graduating from Penn State, Pritchard moved to Stanford University to work with Marc Feldman, a prominent geneticist who had also been Clark’s graduate adviser. In Palo Alto, Pritchard quickly fell in with the vibrant community of students and faculty members surrounding Feldman and Luca Cavalli-Sforza, who pioneered the use of population genetics to study the movements of human populations over broad historical periods. “I was fascinated by the idea that you

could use the mathematics of population genetics to learn about human history,” Pritchard says.

In 1998, he returned to England for a postdoctoral fellowship at Oxford University, and there he wrote a computer program that dramatically changed how geneticists think about the genetic relationships among people. Known as *structure*, the program analyzes the differences in DNA sequences in a sample of individuals. It then sorts the individuals into groups based on their genetic similarities.

Pritchard and Noah Rosenberg, a friend from Stanford who’s now a geneticist at the University of Michigan, led a

team of researchers who used *structure* to analyze genetic data from more than a thousand people drawn from 52 worldwide populations. At the time, geneticists thought the extensive genetic overlaps among all humans would make it difficult to divide people into categories. But *structure* clearly sorted the people into groups centered on continents or parts of continents, including sub-Saharan Africa, western Eurasia, eastern Asia, and the Americas. The resulting paper, published in *Science* in 2002, was named “Paper of the Year” by *The Lancet*.

Newspaper stories heralded the results as providing a biological basis for traditional racial classifications, but Pritchard interprets the results somewhat differently. For him, the patterns in our genomes reflect the earth’s geography and the history of populations as much as they do the classifications societies use to divide individuals into groups. Anatomically modern humans evolved in Africa sometime before 150,000 years ago. They spread into the rest of the world and gradually replaced the more archaic forms of humans living in other parts of Africa and in Eurasia, including the Neanderthals in Europe, *Homo erectus* in Asia, and the most recently discovered *Homo floresiensis* in Indonesia.

As modern humans colonized the world, groups developed genetic differences that make it possible to distinguish Africans, Asians, and Europeans today—both visually and by using computer programs like *structure*. People, however, have continued to move within and among continents throughout history, blurring the genetic differences among populations. In some cases, the movements were extensive, as between Europe and Asia. In others, they were small but continuous, as between Asia and the Americas across the Bering Strait. Today,

all human groups appear to be the product of complex mixings and movements of previous groups, not isolated populations that have remained separate and immobile for long periods.

SIGNS OF SELECTION?

Pritchard moved from Oxford to the University of Chicago in 2001, the same year the full sequence of the human genome was published. Completion of the Human Genome Project marked a milestone in the history of science, but it was just one genome and population geneticists wanted more. They wanted to know how DNA sequences differ from person to person, both to gauge the effects of those differences on health and to learn more about human history.

They did not have to wait long. In the 1990s, Cavalli-Sforza at Stanford had initiated an effort known as the Human Genome Diversity Project to gather hundreds of human DNA samples from around the world; the data Pritchard analyzed with *structure* were some of the first results from the project. In 2002, the National Institutes of Health launched a more intensive effort that identified millions of common DNA differences in several hundred people with African, European, and Asian ancestry.

As data on human genetic differences flooded into databases, population geneticists scoured the data for signs of selection. For example, a group led by Pardis Sabeti at Harvard University developed a mathematical technique to look for large sections of DNA that were unusually similar in many people. Nearly identical blocks of DNA suggested that the sections contained a genetic variant that had conferred an advantage on individuals with that variant, causing the representation of the variant to increase in the population. For example, Sabeti's research

team found two genetic variants involved in resistance to malaria that appeared to have increased dramatically in frequency over the past few thousand years—about the same time frame when the development of agriculture caused populations of malaria-carrying mosquitoes to explode.

Soon other signs of selection popped up in DNA data. For example, the strongest signal of selection in the entire human genome emerged from the gene that encodes the enzyme lactase, which breaks down the sugar in milk, lactose, into more easily digested sugars. Most people in the world make lactase when they are children so they can digest their mother's milk, but the gene shuts off when they become adults. Many people with European, Middle Eastern, or African ancestry have a variant of the lactase gene that remains active in adulthood, so that they're able to digest milk their whole lives. These versions of the gene are most common in populations that domesticated animals for milk, which would have created a selective pressure for a lifelong ability to digest lactose. The genetic variants in these populations began to increase in frequency at about the same time that dairy animals were domesticated.

Another strong selective signal turned up in genes that affect skin color. As modern humans expanded out of Africa into more northern latitudes, their dark skin became a distinct disadvantage, probably because in high latitudes it blocks too much of the sunlight that humans need to synthesize vitamin D. Genetic variants that produced lighter skin therefore gained a significant advantage. In early Europeans, variants in several genes that lighten skin color began to increase in frequency. Meanwhile, the same process was occurring on the other side of Eurasia as dark-skinned people from

southeastern Asia moved north, but there, different sets of variants became responsible for lighter skin.

Pritchard and other geneticists also began to find signs of selection in parts of the genome with unknown functions. In a 2006 paper, for example, he and a group of colleagues found selective signals scattered throughout the genome. Some signals were associated with genes of known function, but others appeared in genes of unknown function or even in areas that had no genes.

Meanwhile, other studies suggested that the rate of selection markedly increased in recent human history. A research team led by anthropologist John Hawks at the University of Wisconsin concluded that selection was more than 100-fold faster in recent human history than before the movement of modern humans out of Africa. Two members of that team, anthropologist Henry Harpending and physicist Gregory Cochran, have used the data to speculate that many features of modern populations—such as the higher average scores of Ashkenazi Jews on IQ tests—reflect the influence of selection.

At this point, arguments about selection often acquire political overtones. But Pritchard has avoided those arguments. He wants to know whether selection actually produced the signals he and others have detected. Recently, he's come up with some surprising answers.

AMBIGUITY

Last year, a group of researchers at Stanford used a new technology to measure differences in DNA sequences from the Human Genome Diversity Panel at many more genetic locations than in the past. With postdoctoral fellow Graham Coop, graduate student Joseph Pickrell, and several collaborators at Stanford, Pritchard

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—JONATHAN PRITCHARD

began searching the data for signals of selection.

Previously known signals jumped out right away, including the lactase and skin pigmentation genes. Pritchard and his colleagues also found several interesting signs of selection where they hadn't been seen before, such as in a set of genes involved in the development of heart, neural, and mammary tissue. Geneticists have few clues about how these genes operate and why they might have been selected, but “we're keen to learn what these genes are and how they work,” says Coop, now an assistant professor at the University of California, Davis.

In a paper published in *PLoS Genetics* on June 5, 2009, Pritchard, Coop, Pickrell, and a group of colleagues, including Feldman and Cavalli-Sforza, describe an unexpected result of their analysis. Beyond the clearest signs of selection—like lactase persistence, skin color, and resistance to several infectious diseases—there appear to be few unambiguous cases of strong selection in the human genome. “Natural selection may shape the human genome much more slowly than previously thought,” says Pritchard. In fact, some of the DNA sequences identified earlier as possible signs of selection look like something else to Pritchard. They look like the patterns generated by the

migration of modern humans out of Africa and by the continued movements of people since then.

Pritchard's team has concluded that selection in the human genome is often overwhelmed by the movement and expansion of populations. “Selection is a weaker force than people thought,” says Pickrell. Populations that are closely related genetically, because they split recently or exchange many migrants, have very few genetic variants that are markedly different. With more distantly related populations, demographic processes have usually had a greater influence than selective pressures. Selection may be driving groups of genes that all influence a trait in particular directions, but “simple models of strong selection pushing single variants to high frequencies appear not to be the case,” Pickrell says.

As a result, it may be difficult to determine which human genes have genuinely been affected by recent natural selection. “It's hard to be confident about individual signals beyond the top 10 or so,” says Pritchard.

Some dispute these conclusions. “It depends on the model of population history that you use,” says Hawks. “We believe that populations were larger in the past, which means that there was more selection.”

Sabeti, however, finds Pritchard's conclusions convincing. “There has to be a false-positive threshold,” she says. “We don't really understand the demography of these populations, and there are lots of question marks.”

New data will help answer some questions. The 1000 Genomes Project will soon begin delivering full DNA sequences—not just the most common DNA differences—of more than a thousand people from around the world. Geneticists also will learn more about the genes that have been selected, which will help them separate true examples of selection from misleading signals. “As functional studies go forward, people will start figuring out the phenotypes that are associated with selective signals,” Coop says. “That will be very important, because then we can figure out what the selection pressures were on these phenotypes.”

Pritchard remains cautious about whether new results will answer every question. “For lots of these historical questions, some things are fundamentally unknowable,” he says. But he acknowledges that geneticists may be on the verge of answering a historic question: To what extent has selection shaped both our bodies and our minds? If Darwin were alive today, he would be eagerly awaiting the answer. ■