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Geography and History Shape Genetic Differences in Humans

In recent years, geneticists have identified a handful of genes that have helped human populations adapt to new environments within just a few thousand years—a strikingly short timescale in evolutionary terms. But new research indicates that in most cases, natural selection may shape the human genome much more slowly than previously thought. Other factors -- the movements of humans within and among continents, the expansions and contractions of populations, and the vagaries of genetic chance -- have heavily influenced the distribution of genetic variations in populations around the world.

The research was carried out by Jonathan Pritchard, a Howard Hughes Medical Institute investigator at the University of Chicago, and a team of colleagues including Graham Coop at the University of California, Davis; Joseph Pickrell at the University of Chicago; and Marcus Feldman, Richard Myers, and Luca Cavalli-Sforza at Stanford University. The team found that for most genes, it can take at least 50,000-100,000 years for natural selection to spread favorable traits through a human population. According to their analysis, gene variants tend to be distributed throughout the world in patterns that reflect ancient population movements and other aspects of population history -- suggesting that the geographic distributions of these variants are determined only in part by local selection pressures such as climate or diet.

Natural selection occurs when a particular genetic difference -- which researchers call a variant -- gives an individual a greater opportunity to have children and pass on his or her genes to future generations. These genetic differences, which arise by mutation and then are inherited from parent to child, might confer a survival advantage in a given environment, such as being able to survive malaria or digest milk from animals. As individuals thrive and pass on their genes to their offspring, the variant can become more common in a population. This natural selection of advantageous genes—the raw material of evolution—leaves signals in our DNA that can be detected when researchers compare human genomes.

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"But we don't think that selection has been strong enough to completely fine-tune the adaptation of individual human populations to their local environments," says Pritchard. "In addition to selection, demographic history -- how populations have moved around -- has exerted a strong effect on the distribution of variants."

Pritchard and his colleagues published the results of their analysis on June 5, 2009, in *Public Library of Science (PLOS) Genetics*.

Pritchard says the genetic variants responsible for light skin are good examples of the effects of natural selection. Modern humans evolved in Africa more than 150,000 years ago and then spread throughout Africa and the rest of the world. As these humans moved into northern latitudes, natural selection favored traits that helped them survive in their new environment. Dark skin became a disadvantage, possibly because it blocked too much of the sunlight that humans need to synthesize vitamin D for healthy bones. People with genetic variants that produced lighter skin therefore tended to be healthier and had more children, and today those variants are common in people of European and northern Asian ancestry.

Selection may also play a role in determining susceptibility to several common diseases. This is another reason why geneticists would like to identify genes that have undergone selection. For example, the "thrifty gene" hypothesis holds that natural selection favored being able to put weight on quickly when food was abundant to tide humans through periods of scarcity. Now that humans in many areas of the world have access to virtually unlimited amounts of food, genetic variants associated with this trait may be contributing to an epidemic of obesity and diabetes.

However, Pritchard points out that selection is not the only factor that influences the fate of genetic variants in populations. Unlike selection, the other mechanisms that are at work do not necessarily help populations adapt to their environments. For example, if a small population of people undergoes a rapid expansion -- because they enter a new territory, perhaps, or develop a technology that supports larger numbers -- some of the genetic variants carried by that population can increase rapidly in number, even if the variants do not provide a reproductive advantage. The pool of genes within a population also tends to fluctuate due to chance events and random

differences in the number of children people have and the particular genes they pass on to their children.

Pritchard and his colleagues set out to answer a fundamental question facing human geneticists: Is it possible to determine which genetic variants have increased because of selection and which have increased because of population changes or genetic chance? New data that became available last year from the Human Genome Diversity Project at Stanford University provided a much denser sampling of worldwide genetic differences than was previously available. Pritchard and his colleagues used this resource to carry out a new and more rigorous test for selection.

To determine whether the frequency of a particular variant resulted from natural selection, Pritchard and his colleagues compared the distribution of variants in parts of the genome that affect the structure and regulation of proteins to the distribution of variants in parts of the genome that do not affect proteins. Since these neutral parts of the genome are less likely to be affected by natural selection, they reasoned that studying variants in these regions should reflect the demographic history of populations. Genetic variants that have been influenced by selection, in contrast, should show different patterns of distribution.

Their analysis immediately identified known examples of selection, including those involved in determining skin pigmentation, resistance to pathogens, and the ability to digest milk as an adult, the last is a trait that arose in Europe, the Middle East, and Africa following the domestication of dairy animals. The study also revealed several genes of unknown function that appear to have been under strong selective pressures. “We’re keen to learn what these genes are and how they work,” says Coop, who was the lead author on the *PLoS Genetics* paper.

Yet the researchers also found that many previously identified genetic signals of selection may have been created by historical and demographic factors rather than by selection. Those earlier studies –including a 2006 paper from Pritchard’s group – analyzed data sets that were not as complete as those provided by the more recent Human Genome Diversity Project. In the new analysis, when the team compared closely related populations – those that recently came from the same ancestral population or those that have exchanged many migrants throughout history – they found few large genetic differences. If the individual populations’ environments were exerting strong selective pressure, such differences should have been apparent.

“A handful of selective signals are clear,” says Pritchard, “but it’s hard to be confident about individual cases beyond the top ten or so that we understand well right now.” Even with genetic variants where evidence of selection is strong -- such as those for skin color -- the movements of populations have been a powerful influence on current patterns of variation.

Selection may still be occurring in many regions of the genome, says Pritchard. But if so, it is exerting a moderate effect on many genes that together influence a biological characteristic. “We don’t know enough yet about the genetics of most human traits to be able to pick out all of the relevant variation,” says Pritchard.

In the next few years, a wealth of new data will become available to investigate these questions. For example, the 1000 Genomes Project, supported by the Wellcome Trust Sanger Institute and the National Human Genome Research Institute, is seeking to produce the complete DNA sequences of more than a thousand people from around the world. Geneticists also will make progress in linking the functions of particular genes to biological characteristics or phenotypes. “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 selection pressures underlie these episodes of natural selection.”

But even with better data, much will remain unknown about the processes that have resulted in human traits. In particular, Pritchard and Coop urge great caution in trying to link selection with complex characteristics like intelligence. “We’re in the infancy of trying to understand what signals of selection are telling us,” says Coop, “so it’s a very long jump to attribute cultural features and group characteristics to selection.”