

HUMAN EVOLUTION

The Mystery of Humanity's Missing Mutations

People like to think of themselves as unique individuals, but in one aspect our species is remarkably alike: our genes. When Harvard University anthropologist Maryellen Ruvolo looks at human DNA, she sees far more genetic similarity in our species than in our close relatives, the common chimpanzees. The story is the same for other apes. Ruvolo can look at genetic sequences from two humans from widely separated continents, and they appear more alike than do sequences from two lowland gorillas from the same forest in West Africa. Other scientists looking at different parts of ape genomes report similar results. "It's a mystery that none of us can explain," says Ruvolo.

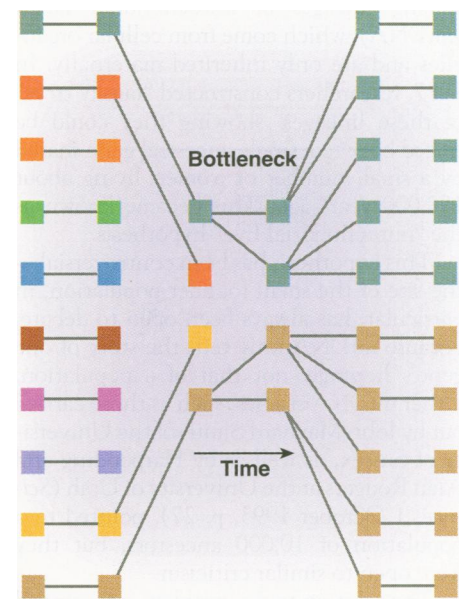
But even if there's no overall explanation for this mystery, a number of scientific sleuths say they have uncovered a clue that may help them solve it. If our ancestors went through a population "bottleneck," a sharp decrease in population over a short period, the squeezed-down group would emerge from the bottle having lost a lot of its genetic variability.

Using the mathematics of population genetics to calculate backward from our current level of genetic diversity, several teams of anthropologists, geneticists, and population biologists have recently concluded that

modern humans were indeed squeezed from a group of about 100,000 to a population of about 10,000 breeding men and women sometime during the last 400,000 years. That group of reproducing individuals is what biologists term an "effective" population (although the total population, including older people and children, would likely have been larger).

The genetic record "gives a remarkably consistent description for the effective population size," says Naoyuki Takahata, a population geneticist at The Graduate University for Advanced Studies in Japan, who has published a series of papers on the topic in the past 4 years. "Our ancestors survived an episode where they were as endangered as pygmy chimpanzees or mountain gorillas are today," agrees Pennsylvania State University anthropologist Henry Harpending. But while a consensus is emerging on the number, there is disagreement as to its meaning. Others, such as evolutionary biologist Jan Klein of the Max Planck Institute for Biology in Tübingen, Germany (who collaborates with Takahata), insist that 10,000 is too large a population to be considered a bottleneck.

Out of the bottle. Population biologists have been trying to figure out whether human ancestors underwent a bottleneck ever



Gene squeeze. This simplified population "bottleneck" shows how a reduction to a few individuals can eliminate genetic variability (different colors indicate different genetic alleles).

since 1942, when Harvard University biologist Ernst Mayr wrote a book in which he explained how new species arise when a few members of a population bud off from their ancestral lineage. "This was the paradigm—everyone assumed humans started with a bottleneck," says Klein.

To prove or disprove that idea, molecular evolutionists look at genetic patterns in modern humans to try to reconstruct their past. Many of these attempts have involved

Tracing Pedigrees of Genes

How does a scientist use contemporary genes to travel back through time to figure out that 5 billion people have all descended from 10,000 breeding men and women? First a population geneticist like Naoyuki Takahata of The Graduate University for Advanced Studies in Japan must find out how many different versions there are of a specific gene in modern humans. Takahata must also know how rapidly the nucleotides at that specific site in the DNA have been mutating over time. He gets this value by comparing how the genes have changed in several different species of apes since they split from a common ancestor—a date ascertained partly from the fossil record. Then he can take these numbers and plug them into an equation that's part of what's called "coalescence theory." It gives him the number of ancestors needed to produce the current genetic diversity.

In a simple example, Takahata will take the sequences of two alleles for the same segment of DNA, known as a neutral gene (see main text). Then, he will count the number of differences in nucleotides between the two alleles and divide that number by the total number of nucleotides that make up that gene. That ratio gives him the genetic distance between the two alleles. And because he knows how long it took for those mutations to accumulate, he can deduce how long ago those two alleles coalesced in a common ancestor.

Those values are inserted into an equation that says that the species' effective population size for that gene is equal to the genetic distance divided by 4 times the mutation rate. (The time it takes to trace the two allelic lineages back to a coalescent gene is equal to twice the effective population size, according to coalescence theory. So, when the two are multiplied, the result is 4.) The premise of the equation is that the more diversity between two alleles, the more time has passed since they split from a common ancestor—and the larger the population needed to maintain the diversity over that time.

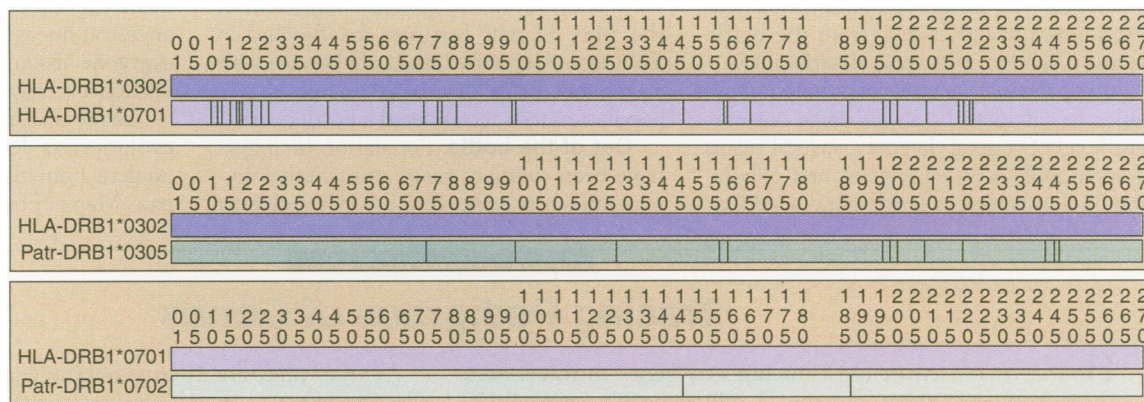
Looking at one pair of alleles is not enough, however. So Takahata and his colleagues did the same analysis for each of 50 pairs of alleles, to reach statistical significance. Each pair of alleles yields a slightly different result, because each of the genetic distances are different. But the mean genetic distance for all 50 pairs of neutral genes is 0.0008 substitutions per nucleotide site. And the estimated mutation rate for so many alleles is one substitution every 50 million generations (or 2×10^{-8} substitutions per site per generation). When those two values are plugged into the equation, the effective population size for all 50 neutral genes is 10,000 (divide the genetic distance of 0.0008 by 4 times the mutation rate of 2×10^{-8} to get 10,000).

—A.G.

But that still left open the bottleneck question, because it was unclear what came before this population. Was this group of

But Takahata and Klein also wanted to know if the MHC genes showed a subsequent bottleneck. So they used computer simulations that took all the MHC-DRB1 alleles in the current population and calculated the minimum population size needed to get

If 10,000 doesn't equal a diversity-squeezing bottleneck, then what did wipe out human diversity? Klein thinks that the explosive population growth that occurred in the past 10,000 years may be the cause. According to computer simulations of population growth, the widespread reproduction that accompanies rapid growth mixes genes up throughout a population to a greater degree than in a small population that isn't repro-



Family resemblance. Comparisons of gene alleles in humans (HLA) and chimps (Patr.) reveals more sequence divergence—indicated by vertical lines—between the human alleles than between human and chimp counterparts. Such diverse human alleles probably originated before the species did.

Making sense of the numbers. But what that number means for modern diversity is

Klein is skeptical that there ever will be complete agreement on what the population number means. Ruvolo thinks, however, that studies of more nuclear genes in humans and other species of primates will help refine estimates of current diversity and uniformity. But for now, while our genes appear similar, opinions on how we got that way remain as disparate as ever.

–Ann Gibbons

N. Takahata, Y. Satta, J. Klein, "Divergence time and population size in the lineage leading to modern humans," *Theoretical and Population Biology*, in press, 1995.