

Every generation of anthropologists sets out to explore what it is that makes us human. Famed paleo-anthropologist Louis Leakey thought tools made the man, and so when he uncovered hominid bones near stone tools in Tanzania in the 1960s, he labeled the putative toolmaker *Homo habilis*, the earliest member of the human genus. But then primatologist Jane Goodall demonstrated that chimps also use tools of a sort, and today researchers debate whether *H. habilis* truly belongs in *Homo*. Later studies have honed in on traits such as bipedality, culture, language, humor, and, of course, a big brain as the unique birthright of our species. Yet many of these traits can also be found, at least to some degree, in other creatures: Chimps have rudi-

these will help reveal the ancestral genotype at key places on the primate tree.

The genetic differences revealed between humans and chimps are likely to be profound, despite the oft-repeated statistic that only about 1.2% of our DNA differs from that of chimps. A change in every 100th base could affect thousands of genes, and the percentage difference becomes much larger if you count insertions and deletions. Even if we document all of the perhaps 40 million sequence differences between humans and chimps, what do they mean? Many are probably simply the consequence of 6 million years of genetic drift, with little effect on body or behavior, whereas other small changes—perhaps in regulatory, noncoding sequences—may have dramatic consequences.

What Genetic Changes Made Us Uniquely Human



mentary culture, parrots speak, and some rats seem to giggle when tickled.

What is beyond doubt is that humans, like every other species, have a unique genome shaped by our evolutionary history. Now, for the first time, scientists can address anthropology's fundamental question at a new level: What are the genetic changes that make us human?

With the human genome in hand and primate genome data beginning to pour in, we are entering an era in which it may become possible to pinpoint the genetic changes that help separate us from our closest relatives. A rough draft of the chimp sequence has already been released, and a more detailed version is expected soon. The genome of the macaque is nearly complete, the orangutan is under way, and the marmoset was recently approved. All

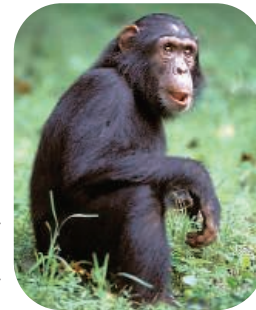
Half of the differences might define a chimp rather than a human. How can we sort them all out?

One way is to zero in on the genes that have been favored by natural selection in humans. Studies seeking subtle signs of selection in the DNA of humans and other primates have identified dozens of genes, in particular those involved in host-pathogen interactions, reproduction, sensory systems such as olfaction and taste, and more.

But not all of these genes helped set us apart from our ape cousins originally. Our genomes reveal that we have evolved in response to malaria, but malaria defense didn't make us human. So some researchers have started with clinical mutations that impair key traits, then traced the genes' evolution, an

approach that has identified a handful of tantalizing genes. For example, *MCPHI* and *ASPM* cause microcephaly when mutated, *FOXP2* causes speech defects, and all three show signs of selection pressure during human, but not chimp, evolution. Thus they may have played roles in the evolution of humans' large brains and speech.

But even with genes like these, it is often difficult to be completely sure of what they do. Knockout experiments, the classic way to reveal function, can't be done in humans and apes for ethical reasons. Much of the work will therefore demand comparative analyses of the genomes and phenotypes of large numbers of humans and apes. Already, some researchers are pushing for a "great ape 'phenome' project" to match the incoming tide of genomic data with more phenotypic information on apes. Other researchers argue that clues to function can best be gleaned by mining natural human variability, matching mutations in living people to



subtle differences in biology and behavior. Both strategies face logistical and ethical problems, but some progress seems likely.

A complete understanding of uniquely human traits will, however, include more than DNA. Scientists may eventually circle back to those long-debated traits of sophisticated language, culture, and technology, in which nurture as well as nature plays a leading role. We're in the age of the genome, but we can still recognize that it takes much more than genes to make the human.

—ELIZABETH CULOTTA

Is inflammation a major factor in all chronic diseases?

It's a driver of arthritis, but cancer and heart disease? More and more, the answer seems to be yes, and the question remains why and how.



ART DAVIS/USDA

How do prion diseases work?

Even if one accepts that prions are just misfolded proteins, many mysteries remain. How can they go from the gut to the brain, and how do they kill cells once there, for example.

How much do vertebrates depend on the innate immune system to fight infection?

This system predates the vertebrate adaptive immune response. Its relative importance is unclear, but immunologists are working to find out.



JUPITER IMAGES

continued >>

Does immunologic memory require chronic exposure to antigens?

Yes, say a few prominent thinkers, but experiments with mice now challenge the theory. Putting the debate to rest would require proving that something is not there, so the question likely will not go away.