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GENOMICS

Chimp Genome Catalogs Differences With Humans

Anyone who has ever looked into the eyes of a chimpanzee has wondered what separates them from us. Now, in a raft of papers in this week's *Nature* and other journals, including *Science* (see pp. 1457, 1498, and 1499), international teams of researchers present a genetic answer to that question.

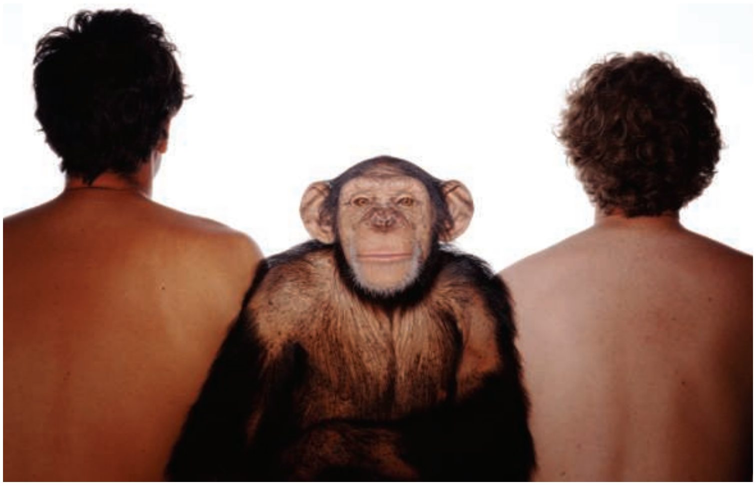
Scientists produced a rough draft of the chimpanzee DNA sequence, and aligned it with the human one, and made an intimate comparison of the chimp and human genomes. "It's wonderful to have the chimp genome," says geneticist Mark Adams of Case Western Reserve University in Cleveland, Ohio, who was not on the papers. "It's the raw material … to figure out what makes us unique."

The papers confirm the astonishing molecular similarity between ourselves and chimpanzees. The average protein differs by only two amino acids, and 29% of proteins are identical. The work also reveals that a surprisingly large amount of genetic material—2.7% of the genomes—has been inserted or deleted since humans and chimps went their separate evolutionary ways 6 million years ago.

But those hoping for an immediate answer to the question of human uniqueness will be disappointed. "We cannot see in this why we are phenotypically so different from the chimps," says Svante Pääbo of the Max Planck Institute of Evolutionary Anthropology in Leipzig, Germany, a co-author on one *Nature* paper and leader of a study in *Science* comparing gene expression in chimps and humans (see www.sciencemag.org/cgi/content/abstract/1108296). "Part of the secret is hidden in there, but we don't understand it yet."

Instead, the papers delve deeply into the genomic differences between us and our closest living relatives, revealing a flurry of relatively recent insertions and deletions in both human and chimp DNA, and mutational hotspots near the ends of chromosomes. "[A] genome is like the periodic table of the elements," says Ajit Varki of the University of California, San Diego. "By itself it doesn't tell you how things work—it's the first step along a long road."

The researchers in the Chimpanzee Sequencing and Analysis Consortium deciphered DNA taken from an adult male named Clint; the draft sequence was announced but not formally published in 2003. Now the team, led by Robert Waterston of the University of Washington (UW), Seattle, confirms in *Nature* the oft-cited statistic that on average only 1.23% of nucleotide bases differ between chimps and humans.



All in the family. Genome data reveal a few surprising differences between chimps and humans but overall confirm our close kinship.

But as suggested by earlier work on portions of the chimp genome, other kinds of genomic variation turn out to be at least as important as single nucleotide base changes. Insertions and deletions have dramatically changed the landscape of the human and chimp lineages since they diverged. Duplications of sequence "contribute more genetic difference between the two species—70 megabases of material—than do single base pair substitutions," notes Evan Eichler, also of UW, Seattle, who led a team analyzing the duplications. "It was a shocker, even to us."

The total genetic difference between humans and chimps, in terms of number of bases, sums to about 4% of the genome. That includes 35 million single base substitutions plus 5 million insertions or deletions (indels), says Waterston.

Somewhere in that catalog of 40 million evolutionary events lie the changes that made us human. But where? In another *Nature* paper, a team led by Barbara Trask of UW, Seattle, and the Fred Hutchinson Cancer Research Center reports that almost half of the indels in the regions near the ends of chromosomes are unique to humans. Many of the insertions contain gene duplications, which in other organisms have fostered evolutionary novelty by allowing one copy of a gene to adapt to a new function without disrupting the original. "It'll be very exciting to see how many indels actually made a difference in our own evolution," says David Haussler of the University of California, Santa Cruz.

To narrow the number of genes that might have been favored in the primate lineage, Waterston's team searched for genes evolving more rapidly than the background rate of mutation. Among both human and chimp lineages, genes involved in ion transport, synaptic transmission, sound perception, and spermatogenesis stood out. The researchers also used the chimp data to identify 585 genes evolving more quickly in people, including genes involved in defense against malaria and tuberculosis. And they uncovered a handful of regions of the human genome that may have been favored in "selective sweeps" relatively recently in human history; one region contains the *FOXP2* gene, proposed to be important in the evolution of speech.

Overall, however, "the vast majority of changes between humans and chimps appear to be neutral, and there's no smoking gun on which are the important changes for making us human," says Adams.

One notable finding was that the fastest evolvers among human proteins are transcription factors, which regulate gene expression. Thirty years ago, Mary-Claire King and Allan Wilson proposed that altered gene regulation could solve the paradox of how a few genetic changes drove the wide anatomic and behavioral gulf between humans and chimps. "That's how you could get lots of morphological change without much nucleotide substi-

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