

## EVOLUTIONARY BIOLOGY

# Relative Differences: The Myth of 1%

**Genomewide, humans and chimpanzees are quite similar, but studies are showing that they are not as similar as many tend to believe**

In a groundbreaking 1975 paper published in *Science*, evolutionary biologist Allan Wilson of the University of California (UC), Berkeley, and his erstwhile graduate student Mary-Claire King made a convincing argument for a 1% genetic difference between humans and chimpanzees. “At the time, that was heretical,” says King, now a medical geneticist at the University of Washington, Seattle. Subsequent studies bore their conclusion out, and today we take as a given that the two species are genetically 99% the same.

But truth be told, Wilson and King also noted that the 1% difference wasn’t the whole story. They predicted that there must be profound differences outside genes—they focused on gene regulation—to account for the anatomical and behavioral disparities between our knuckle-dragging cousins and us. Several recent studies have proven them perspicacious again, raising the question of whether the 1% truism should be retired.

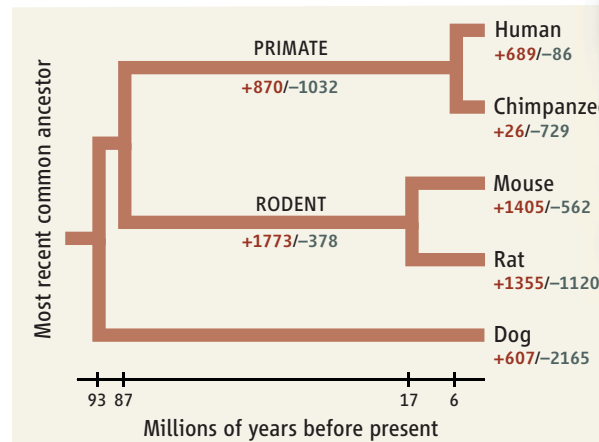
“For many years, the 1% difference served us well because it was underappreciated how similar we were,” says Pascal Gagneux, a zoologist at UC San Diego. “Now it’s totally clear that it’s more a hindrance for understanding than a help.”

Using novel yardsticks and the flood of sequence data now available for several species, researchers have uncovered a wide range of genomic features that may help explain why we walk upright and have bigger brains—and why chimps remain resistant to AIDS and rarely miscarry. Researchers are finding that on top of the 1% distinction, chunks of missing DNA, extra genes, altered connections in gene networks, and the very structure of chromosomes confound any quantification of “humanness” versus “chimpanziness.” “There isn’t one single way to express the genetic distance between two complicated living organisms,” Gagneux adds.

When King and the rest of the researchers in the Chimpanzee Sequencing and Analysis Consortium first detailed the genome of our closest relative in 2005, they simultaneously

provided the best validation yet of the 1% figure and the most dramatic evidence of its limitations. The consortium researchers aligned 2.4 billion bases from each species and came up with a 1.23% difference. However, as the chimpanzee consortium noted, the figure reflects only base substitutions, not the many stretches of DNA that have been inserted or deleted in the genomes. The chimp consortium calculated that these “indels,” which can disrupt genes and cause serious diseases such as cystic fibrosis, alone accounted for about a 3% additional difference (*Science*, 2 September 2005, p. 1468).

Entire genes are also routinely and randomly duplicated or lost, further distinguishing humans from chimps. A team led by



**The 6.4% difference.** Throughout evolution, the gain (+) in the number of copies of some genes and the loss (–) of others have contributed to human-chimp differences.

Matthew Hahn, who does computational genomics at Indiana University, Bloomington, has assessed gene gain and loss in the mouse, rat, dog, chimpanzee, and human genomes. In the December 2006 issue of *PLoS ONE*, Hahn and co-workers reported that human and chimpanzee gene copy numbers differ by a whopping 6.4%, concluding that “gene duplication and loss may have played a greater role than nucleotide substitution in the evolution of uniquely human phenotypes and certainly a greater role than has been widely appreciated.”

Yet it remains a daunting task to link genotype to phenotype. Many, if not most, of

the 35 million base-pair changes, 5 million indels in each species, and 689 extra genes in humans may have no functional meaning. “To sort out the differences that matter from the ones that don’t is really difficult,” says David Haussler, a biomolecular engineer at UC Santa Cruz, who has identified novel elements in the human genome that appear to regulate genes (*Science*, 29 September 2006, p. 1908).

Daniel Geschwind, a neuroscientist at UC Los Angeles (UCLA), has taken a stab at figuring out what matters by applying systems biology to quantifying and analyzing genetic differences between human and chimpanzee brains. Working with his graduate student Michael Oldham and UCLA biostatistician Steve Horvath, Geschwind compared which of 4000 genes were turned on at the same time, or “coexpressed,” in specific regions of the dissected brains.

With these data, they built gene networks for each species. “A gene’s position in a network has huge implications,” Geschwind says. Genes that are coexpressed most frequently with other genes have the most functional relevance, he argues.

Geschwind and his colleagues clustered the networks into seven

modules that correspond to various brain regions, such as the cortex. Comparisons of the map of each cluster’s network in

each species plainly showed that certain connections exist in humans but not chimps. In the cortex, for example, 17.4% of the connections were specific to humans, Geschwind and co-workers reported in the 21 November 2006 *Proceedings of the National Academy of Sciences*. Although the differences don’t immediately

reveal why, say, humans get Alzheimer’s and chimps don’t, the maps clearly organize and prioritize differences. “It really brings the critical hypotheses into strong relief,” says Geschwind.

Could researchers combine all of what’s known and come up with a precise percentage difference between humans and chimpanzees? “I don’t think there’s any way to calculate a number,” says geneticist Svante Pääbo, a chimp consortium member based at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany. “In the end, it’s a political and social and cultural thing about how we see our differences.”

—JON COHEN

