



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 ele-

ments," 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.

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-



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

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Fateful fetal information



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Vioxx on trial



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A dark secret



tution. But there's been no evidence for it until now," says Eichler. Given the chimp data, "people will rethink the regulatory hypothesis," predicts Huntington Willard of Duke University in Durham, North Carolina.

Another *Nature* paper addresses a controversy about whether the human Y chromosome will vanish within some 10 million years. Geneticist David Page of the Whitehead Institute in Cambridge, Massachusetts, and colleagues report the detailed sequence of the "X-degenerate" region of the chimp Y, which contains functional genes once paired

with those on the X but now being slowly eroded by deleterious mutations. Page's team then compared human and chimp Ys to see whether either lineage has lost functional genes since they split.

The researchers found that the chimp had indeed suffered the slings and arrows of evolutionary fortune. Of the 16 functional genes in this part of the human Y, chimps had lost the function of five due to mutations. In contrast, humans had all 11 functional genes also seen on the chimp Y. "The human Y chromosome hasn't lost a gene in

6 million years," says Page. "It seems like the demise of the hypothesis of the demise of the Y," says geneticist Andrew Clark of Cornell University in Ithaca, New York.

Although the chimp genome should be a boon for biomedical studies, an accompanying *Nature* commentary by Varki and colleagues calls for moderation, using principles generally similar to those that guide human experimentation. The similarity of the two genomes underscores the importance of an ethical approach to our closest living cousins, says Waterston. —ELIZABETH CULOTTA

BIOETHICS

Final NIH Rules Ease Stock Limits

The National Institutes of Health (NIH) in Bethesda, Maryland, has relaxed ethics rules issued 6 months ago that many feared would drive talent away from the agency. NIH Director Elias Zerhouni last week announced that the agency's final rules would no longer require all employees to limit their stock in biotech or drug companies. But NIH will retain a blanket ban on consulting for industry.

The revised rules seem to please both NIH scientists and outside critics. "Dr. Zerhouni has done an admirable job addressing a difficult yet critical issue," said House Energy and Commerce Committee chair Joe Barton (R-TX), whose committee held several hearings on the subject.

The rules appear to end a controversy that has roiled NIH since late 2003, when the *Los Angeles Times* raised questions about several senior NIH researchers who had been paid large sums to consult for drug or biotech companies. NIH eventually found at least 44 cases in which researchers didn't receive proper ethics approval and nine possible criminal violations. To address the problem, Zerhouni issued interim ethics rules in February 2005 that banned all biomedical consulting—even for nonprofits—and limited all employees' ownership of drug company stock (*Science*, 11 February, p. 824).

The interim rules outraged many NIH employees. Some senior intramural scientists cited the rules as a factor in their departure, one institute director threatened to leave, and a newly hired one delayed his arrival.

After receiving 1300 mostly critical comments, NIH "decided to adjust in terms of degree," Zerhouni told reporters. Stock limits will now apply only to about 200 senior staff,

including directors and other top managers of NIH's 27 institutes and centers. By next February, these employees and their families must limit their stock to \$15,000 in any one company "significantly involved" in biomedicine. Previously, this limit would have applied to 12,000 lower-level employees, and about 6000 senior staff would have had to divest all their drug company stock. Those senior staff and clinicians will now have to report their holdings for review.

NIH will no longer ban work done for associations, such as serving as an officer of a

National Heart, Lung, and Blood Institute. "Morale should improve markedly," she adds. Howard Garrison of the Federation of American Societies for Experimental Biology expressed relief that NIH scientists can maintain ties to professional associations.

Dunbar says concerns remain that the industry consulting ban will harm recruitment and retention. Zerhouni says he decided to retain the ban after concluding NIH doesn't have "adequate systems" to prevent abuses. He added, however, that NIH intends to review the rule within a year. Although NIH scientists

can still work with companies through cooperative agreements, some outside biomedical leaders suggest that's not enough: "It is also important to continue to seek ways to foster appropriate interactions with" industry researchers, says Phil Pizzo, dean of the Stanford University School of Medicine, who served on a 2004 NIH advisory panel that favored allowing some industry consulting.

Not everyone thinks the final rules solve NIH's ethics problems. "There's a whole variety of things involving laundered money going to people whose views are favorable," such as drug company-sponsored education courses, says Sidney Wolfe, of the Washington, D.C.-based watchdog group Public Citizen. But Zerhouni defended the new plan as "the most restrictive of any rules we know about in the world of biomedical research." The final regulation was to take effect this week when it was published in the *Federal Register*.

—JOCELYN KAISER



Tight reins. NIH Director Elias Zerhouni says final rules are "most restrictive" in the field.

scientific society. The final rules also allow compensation for reviewing scientific grants and for giving a single lecture—the interim rules exempted only entire courses—and make clear that approval is not needed for hobbies, such as coaching youth soccer.

The NIH Assembly of Scientists' executive committee "is very pleased" by the changes, says member Cynthia Dunbar of the