

Almost human...

Sequencing the chimpanzee has emerged as a top genomic priority. David Cyranoski asks the chimp's champions what they hope to gain from studying the genome of our closest living relative.

It was a shocking disappointment to some, and a pleasant surprise to others. On 22 May, when the US National Human Genome Research Institute (NHGRI) announced its list of top-priority organisms for genome sequencing, the chimpanzee had made the cut¹. The rhesus macaque, the most widely used primate in biomedical research, had not.

Arguments about the merits of the decision are still rumbling on. But now the chimp has received the nod, what scientific advances can we hope for? The common chimpanzee (*Pan troglodytes*) is our closest relative. Its genome sequence is about 98.8% identical to our own², and we shared a common ancestor some six million years ago. So one major hope is that the differences between the sequences will reveal the genetic basis for our mental and linguistic capacities, and explain why we are susceptible to some diseases that do not afflict the great apes.

"It will tell us what makes us human," claims Yoshiyuki Sakaki of the University of Tokyo's Institute of Medical Science, who is president of the Human Genome Organization and part of a Japanese consortium that is already sequencing the chimp's chromosome 22 (see 'Will Japan lead the way?', overleaf).

Despite these grand goals, some advocates of chimp sequencing admit that they were surprised by the NHGRI's decision. Given that the rhesus macaque (*Macaca mulatta*) is an important experimental model in fields from cognitive neuroscience to HIV vaccine research, they had expected it to edge the chimp out of the list of top sequencing priorities — but they are delighted with the result. "It was a choice for philosophy and evolution, against current trends towards biomedical

application," says Svante Pääbo, a geneticist at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, who wrote a 'white paper' urging the NHGRI to support chimp sequencing.

But other chimp advocates argue that the animal's genome sequence will have important biomedical applications. "Our case was overwhelming," concludes Maynard Olson of the University of Washington in Seattle, co-author of another pro-chimp white paper submitted to the NHGRI.

Spot the difference

With complete genome sequences from a variety of model organisms now finished or nearing completion, comparative genomics is in full swing. But the chimp will bring a new twist. Until now, researchers have mostly looked for regions of similarity between the genomes of relatively distantly related organisms — reasoning that these must have been conserved by evolution because they have an important function. "Comparative genetics has, until today, looked for conserved regions, but with the chimp we will be looking for differences," says Pääbo.

In the first instance, about 90% of the differences that are uncovered will represent sequencing errors, says Evan Eichler of Case Western Reserve University in Cleveland, Ohio. But although pinpointing such errors will help with the 'proofreading' of the human genome, genuine differences are what really fascinate researchers such as Eichler.

Documenting the differences between the human and chimp genomes will let researchers tackle some thorny problems concerning evolutionary change. A recent study comparing humans, rats and mice³, for

example, suggested that the rate of sequence divergence in mammals has been different for different chromosomes. Preliminary comparisons between the human genome and a sample of chimp DNA sequences have reinforced this view⁴.

To conduct such studies, researchers line up genome sequences next to each other and pick out the differences. This is easiest to do for protein-coding genes — these can be rendered useless by even small changes, so they are relatively well conserved even among distant species. But non-coding regions are harder to align, especially when the structure of the chromosomes on which they sit has drastically diverged — as is the case for rodent–human comparisons. "The problem is knowing whether apparent variation in rates of evolution is real, or due to alignment artefacts," says Laurence Hurst, an evolutionary geneticist at the University of Bath, UK. A complete chimp genome, which is structurally similar to our own, would help to resolve this problem.



Primate objective: Maynard Olson wants to see what genes chimps have that we don't.

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In addition, human–chimp comparisons should shed light on ‘hypervariable’ regions of the human genome. In such regions, the rate of mutation or large-scale chromosomal rearrangements is so high that it is impossible to make any sense of comparisons with the mouse, with which we last shared a common ancestor some 60 million years ago. “The chimpanzee sequence will allow us to reconstruct the history of events and therefore infer the mechanisms involved,” says Eichler.

Meet the ancestors

Genome-wide studies of single-nucleotide polymorphisms (SNPs) could also gain from comparisons with the chimp. SNPs are points in a genome sequence where different individuals can have a different base, or letter of the genetic code. They account for most of the genetic variation across human populations, and can be used to map the locations of genes that influence susceptibility to disease. The chimp genome will help researchers pick out the ancestral form of the variation — assumed to be the one shared with the chimp — and separate it from those derived after the two species diverged.

Leonid Kruglyak of the Fred Hutchinson Cancer Research Center in Seattle, who develops computational models to help map the location of disease genes using SNPs, says that knowing which form is ancestral can help infer the history of human populations, including ancient migrations. This information may help researchers to find genes associated with common conditions such as cancer and cardiovascular disease, he argues.

For many biologists, human–chimp comparisons will prove of greatest value in revealing the molecular secrets of human language and cognitive abilities. This is already moving forward following the discovery of a gene called *FOXP2*, mutations in which cause a severe speech and language disorder⁵. Pääbo and Tony Monaco of the University of Oxford, UK, have now shown that the human version of the gene produces a protein that differs from that of the chimp at two amino acids⁶.

Advocates of chimp sequencing also hope to test what Olson calls the “less is more” theory of human evolution⁷. This argues that many of the genetic changes that separate humans from chimps, and explain our success in a wide variety of environments, involve the loss of genes that adapted primates to their forest habitats. Our decreased muscular strength, loss of body hair and delayed maturation all fit with this idea, as does the observation that there appears to be less genetic diversity in the entire human species than in the small remnant chimp populations of central Africa⁸.

At present, there are few data to test the theory at the level of individual genes. But researchers led by Ajit Varki of the University of California, San Diego, found in 1998 that humans have lost an enzyme that adds a



Comparison of disease susceptibility between chimps and humans

Condition	Human	Chimp
<i>Definite differences</i>		
HIV progression to AIDS	Common	Very rare
Influenza A symptoms	Moderate/severe	Mild
Hepatitis B/C late complications	Moderate/severe	Mild
<i>Plasmodium falciparum</i> malaria	Susceptible	Resistant
Menopause	Universal	Rare
<i>Probable differences</i>		
<i>Escherichia coli</i> K99 gastroenteritis	Resistant	Sensitive?
Alzheimer's disease pathology	Complete	Incomplete
Coronary atherosclerosis	Common	Uncommon
Epithelial cancers	Common	Rare

Source: Olson, M. V. et al. A white paper advocating complete sequencing of the genome of the common chimpanzee, *Pan troglodytes*. (2002).

molecule called Neu5Gc, a type of acidic sugar known as a sialic acid, to proteins carried on cell surfaces⁹. More recently, Varki's team has shown that we also lack a cell-surface receptor that recognizes sialic acids¹⁰. Both are present in chimps.

Missing links

Might such genetic differences explain differences in disease susceptibility between humans and chimps? Olson, for one, believes that genetic loss in the human lineage could explain why we are plagued by certain viruses, cancers and degenerative diseases that pose chimps few problems (see table, above). The sialic-acid findings are intriguing because differences in cell-surface molecules might, for instance, influence the ability of certain viruses to infect human, as opposed to chimp cells.

In particular, the two species' different susceptibility to HIV holds the compelling prospect of revealing the genetic changes that have made the virus such a scourge of human health. “Chimps are infected with the

very same virus that infects humans, and very rarely progress to AIDS,” observes Varki. One company, Evolutionary Genomics of Aurora, Colorado, is already looking for differences between human and chimp genes that might explain this difference. “We want to know how one species has already solved the AIDS question,” says Walter Messier, its chief scientist.

Intriguingly, researchers led by Ronald Bontrop of the Biomedical Primate Research Centre in Rijswijk, the Netherlands, argued earlier this month that the key may lie in major histocompatibility complex (MHC) genes, which are central to immune responses. Chimps appear to have a less diverse MHC than humans, suggesting that a viral epidemic in their evolutionary history selected against individuals carrying MHC variants that conferred susceptibility to HIV-like viruses¹¹.

But it is possible that studies of protein-coding gene sequences may leave the difference between humans and chimps shrouded in mystery. Only a handful of genes that differ between human and chimp have so far been

found¹². And many experts suspect that there won't be a huge number more. "I would be very surprised if there are more than a few," says Tetsuo Yamamori of the National Institute for Basic Biology near Nagoya, Japan.

Instead, the differences between chimp and human might largely be the result of gene-regulatory mechanisms giving different levels of gene expression. Pääbo's team has already used DNA microarrays and gel electrophoresis to investigate differences in gene expression and protein production between humans and chimps¹³. The researchers found that these differences were much more pronounced in the brain than in the liver or blood — which opens new avenues for evolutionary studies of human brain development.

But understanding why expression levels differ between humans and chimps may be difficult. One obvious place to look is at the promoter and other regulatory sequences that sit alongside genes and drive their expression. But the control could also be exercised on more subtle levels, for instance through the operation of non-coding RNAs transcribed elsewhere in the genome — some scientists speculate that these may work in networks of gene regulation by interacting with DNA, RNA and proteins¹⁴.

Rhesus positive

While supporters of chimp sequencing speculate about the findings that lie ahead, the rhesus macaque's supporters are still fuming, and remain convinced that their animal should have been chosen. "Everyone I know — everyone — in my circle of friends in the primate-research community feels unquestionably that the rhesus monkey is the best choice," says virologist Ronald Desrosiers of Harvard University, director of the New England National Primate Research Center in Southborough, Massachusetts.

The main reason for wanting to sequence the rhesus macaque's genome is that it would aid interpretation of the results from the wide variety of experiments in which the

Will Japan lead the way?

Although several groups have sequenced scattered fragments of the chimp's genome, the largest systematic effort has been in Japan. By the end of this year, a Japanese-led consortium hopes to finish sequencing chimp chromosome 22. This effort has drawn heavily on the experience of Yoshiyuki Sakaki of the University of Tokyo's Institute of Medical Science, who led Japan's contribution to sequencing the homologous human chromosome 21.

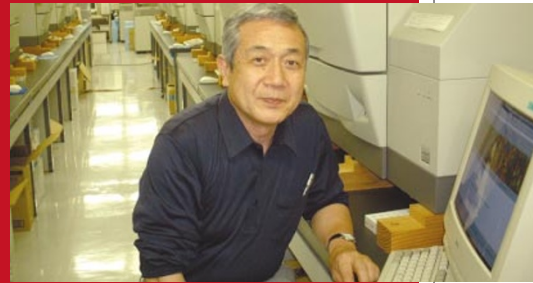
Sakaki and Naruya Saitou of the National Institute of Genetics in Mishima, south of Tokyo, have repeatedly applied for grants to expand the project, but have so far been unsuccessful — despite strong lobbying from Akiyoshi Wada, director of the Genomic Sciences Center in Yokohama, where Sakaki has a joint appointment.

"Japan is two years ahead in sequencing the chimp, and so it should take the lead with the project,"

says Wada, who complains that Japan always seems to await a cue from the United States before committing to large projects. "Only then will Japan move, but then it's already too late," sighs Wada, who feels a sense of *déjà vu* — he urged Japan to begin high-throughput sequencing of the human genome in the late 1980s, before the project built momentum elsewhere.

The chimp project also faces opposition from the leaders of rival genomic projects. One floor up from Sakaki at the Institute of Medical Science is the lab of Yusuke Nakamura, director of the Human Genome Center, who is genotyping vast numbers of human single-nucleotide polymorphisms for use in searching for disease susceptibility genes. He has been an outspoken critic of the chimp project, arguing that taxpayers' money should go to projects with more obvious medical benefits.

Japanese supporters of chimp sequencing feel vindicated by the US National Human Genome Research Institute's decision to make the chimp a top sequencing priority. "Of course there is also a competitive aspect to it," admits Sakaki, who hopes that US interest will spur the Japanese government to provide further support.



Off and running: Yoshiyuki Sakaki is helping to sequence chimp chromosome 22.



Akiyoshi Wada wants to keep Japan's lead.

species is involved. AIDS researchers, who study a virus called SIV in macaques that causes a disease very similar to human AIDS, are particularly disappointed — and see a bitter irony in the arguments being made for the chimp's value to HIV research. "Most research on AIDS now is on preventing progression of the disease," says John Vandenberg, director of the Southwest National Primate Research Center in San Antonio, Texas. For this, he argues, the rhesus macaque is by far superior. Desrosiers agrees: "Experimental infection of rhesus macaques is the only model on the radar screen for AIDS."

Some researchers even question the chimp advocates' strongest suit — that of evolution. They claim that the macaque's genome sequence, which differs from ours by some 5–7%, will be more informative for many comparative studies.

Then there is the fact that, for ethical reasons, chimps cannot be widely used in invasive biomedical experiments — or even be kept under the uniform lab conditions that may be necessary to produce meaningful results. "Patterns of gene expression in different areas of the brain will vary so much just due to environmental factors that it is often impossible to tell human patterns apart from chimp patterns," says Yamamori. "The macaque, whose activity, diet and lifespan can be regulated and kept constant by researchers, thus offers a better research tool."

NHGRI officials have answered these criticisms by noting that there is no firm commitment to sequencing any organism — all that has been produced is a list of priorities to be considered as spare capacity opens up at the sequencing centres now finishing the human genome. They say that the list is not fixed, so the macaque may get included at a later date.

Ideally, say researchers on both sides of the debate, both chimp and macaque would be sequenced, along with a range of other primates to allow extensive comparative studies. "With advances in sequencing capacity, I hope this unfortunate competition will become a moot point in a few years' time," says Varki. ■

David Cyranoski is Nature's Asian-Pacific correspondent.

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Talking point: Svante Pääbo believes the chimp genome will shed light on our linguistic abilities.