# Branching out

The chimp was a great start. But the genomes of our other primate relatives will help to reveal a whole lot more, says **Carina Dennis**.

T. MCHUGH/SFL

"It's a dream come true," says Caro-Beth Stewart of the chimp genome. The evolutionary biologist from the University at Albany in New York State never imagined that primate genomes would be sequenced in her lifetime. She can barely contain her excitement, not only over the draft chimp genome sequence[1] but also about those of the other primates, including the orang-utan and rhesus macaque, which will soon be available.

Stewart is one of many who hope that looking at several primate genomes will help answer fundamental questions about our own evolution and that of other primates (see graphic, overleaf). What underlies the differences between humans, apes and the other primates? How did the physical structure and content of our ancestors' genomes enable primates to evolve the way they have? Will this give us more insight into how evolution itself operates?

Chimps, our closest living relatives, are a great starting point. But our genomes are too much alike to get meaningful answers to many of these questions. "It's frustrating that humans and chimps are so similar," says Andrew Clark of Cornell University in Ithaca, New York. It's difficult to tell whether a DNA sequence in humans that is missing in chimps was really added during human evolution or has simply been lost in the chimp lineage.

Another problem is that it is hard to be sure straight away that any differences found are significant. "You find a difference that you think could be very exciting, but it could just turn out to be a natural variant within one species," says Ajit Varki at the University of California, San Diego. Chimps, like humans, differ genetically from each other, although the extent is debatable. More chimps from different subspecies must be sequenced to capture the full extent of sequence diversity. And the chimp genome sequence is still only a draft. To ensure that the differences found are real, the chimp sequence needs to be improved to match the polished 'finished' standard of the human genome. This is now under way.

Even so, researchers need other primate genomes if they are to address the question of which genetic changes are unique to humans or chimps (see page 50). The rhesus macaque, an Old World monkey, will be the first available — a preliminary assembly of its genome sequence was released into the public databases earlier this year and an improved version is expected by the end of the year. The push to sequence its genome stems from its popularity in biomedical research[2]. It will help researchers figure out whether the differences arose in the lineages leading to modern chimps or humans after they split from their last common ancestor approximately 6 million years ago.

But although the macaque is a useful reference, it is not ideal for identifying genetic changes that happened after the human–chimp split, as it diverged from a common ancestor some 25 million years ago. "There have been so many changes, it will be harder to tell what's gone on," says Varki.

To better understand how the human genome has evolved, researchers want to look at a primate that is sufficiently different from humans and chimps, but which shares a more recent common ancestor. "The obvious one is the orang-utan," says Varki. The orang-utan, a great ape like the chimpanzee, diverged from a common ancestor with chimps and humans approximately 12 million years ago. Its genome is currently being sequenced and a draft is expected early next year. "Identifying sequences common to human, chimp and orang-utan, but different in the rhesus monkey, would provide valuable clues to the genomic features distinguishing great apes from other primates," says Eddy Rubin, director of the Joint Genome Institute in Walnut Creek, California.

But for others, the most exciting primate genome to follow chimp will be that of the gorilla. This is our next closest primate relative, and some parts of the gorilla genome are closer to humans than is the chimp genome[3]. "The sequence will help us understand how the species formed that went on to become gorilla, chimp and humans," says Svante Pääbo of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany.

Generally speaking, the closer a primate

sequence is to human, the more useful it is for figuring out more recent, human-specific traits. And the more species that can be compared the better. If orang-utan, gorilla and chimp were all identical at one DNA position and humans were different, for example, then geneticists could be quite confident that that change happened in the most recent history of the human lineage. "We expect to start sequencing the gorilla in October this year," says Jane Rogers of the Wellcome Trust Sanger Institute near Cambridge, UK. A draft assembly should be available in a couple of years, she adds.

## Back to our roots

While some researchers are working on the the youngest shoots of the primate family tree, others are delving at the roots, to understand what the earliest primate genomes were like. To this end molecular palaeontologists are keen to sequence representatives from each of the major primate lineages. The sequencing of the marmoset, a New World monkey, has just begun. "I would also like the lemur sequence," says Asao Fujiyama of the National Institute of Informatics in Tokyo, Japan, who was part of the team that sequenced the first chimpanzee chromosome last year[4]. The suborder of primates to which lemurs belong arose earlier than the branch leading to monkeys and apes. "My interest is to trace how modern human chromosomes have evolved from our ancestor," he says.

David Haussler of the University of California, Santa Cruz, and his collaborators want to peer even further back in time[5]. They are analysing sequence data from across the animal kingdom to reconstruct the genome of the ancestor of placental mammals, which lived around the time of the dinosaurs more than 75 million years ago. "Our goal is to reconstruct the complete history of the DNA changes from the placental ancestor to the modern human," says Haussler. Reconstructing this genome and comparing it with the human sequence will make the key genetic changes in our evolution from that ancestor much easier to see, he explains. "Additional primate genomes will help fill in the missing details." His team is now assembling the first draft of the ancestor's reconstructed DNA sequence and, although preliminary, the results show that it is at least computationally feasible, says Haussler.

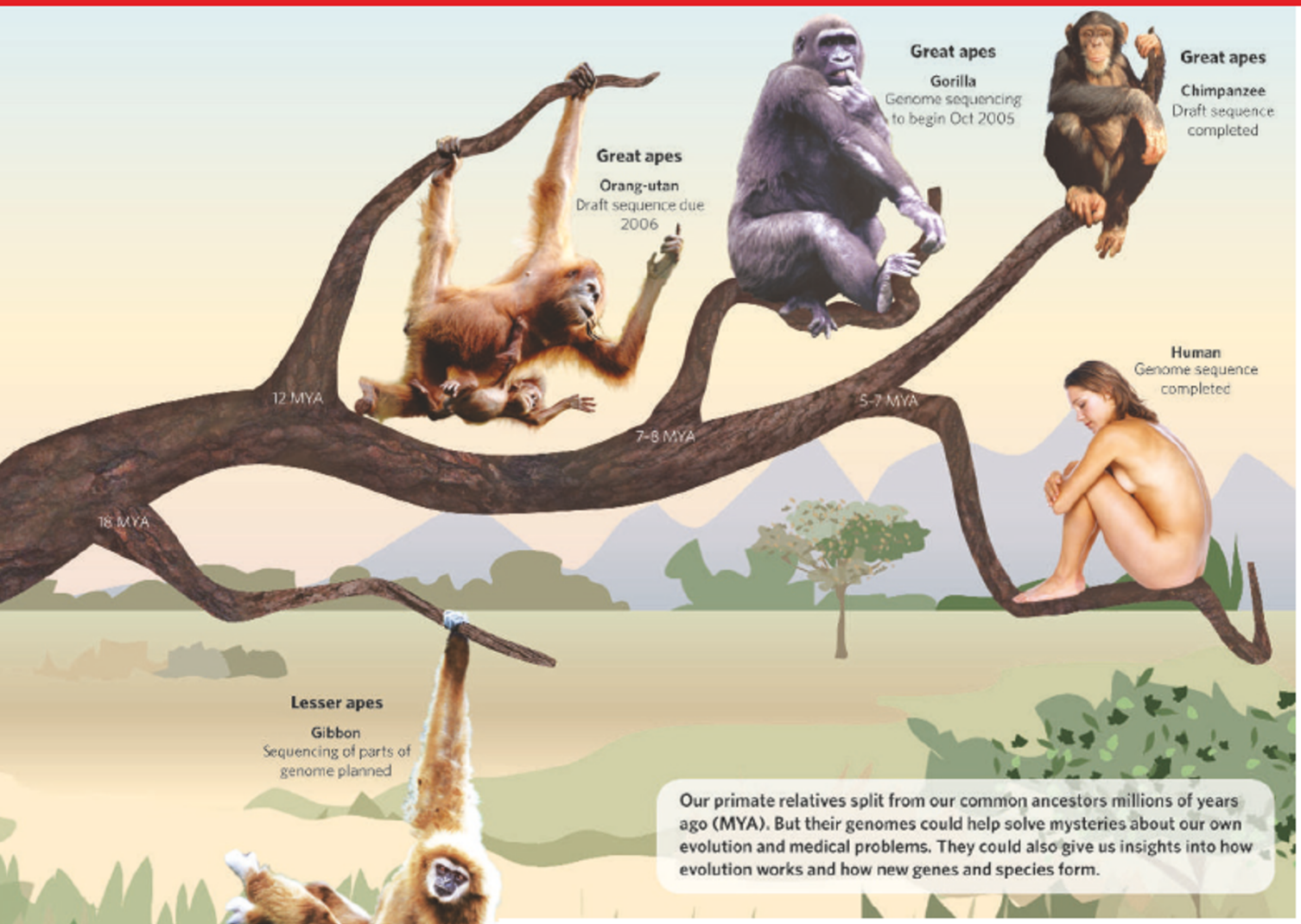
Clambering back up the tree will add to the picture of how genomes evolve and how the genes within them work. The gibbon, which shares a common ancestor with the great apes, has a most peculiar genome, according to Todd Disotell, a molecular anthropologist at New York University. Its chomosomes seem to have changed and evolved faster than those of other apes. "Its genome looks like it has been put in a blender," says Disotell. It seems to have virtually the same DNA content as humans and chimps, but all churned up. It will be interesting to find out whether the functions of genes change in their new chromosomal locations, says Disotell.


William Murphy of Texas A&M University is also excited by the genomic clues thrown out by gibbons. His team has reconstructed the chromosomal architecture of a mammalian ancestral genome by comparing stretches of genomic sequence from eight very different mammals. The results suggest that stretches of duplicated sequence promote chromosomal rearrangements. In turn, these contribute to genetic changes that can lead to new species. If the same holds true in the gibbon, we might get a better handle on the mechanism of genome rearrangement, says Murphy.

When a chromosome breaks and rejoins, clues to the mechanism and molecular machinery involved can be left behind in the sequence. Because the gibbon genome contains so many rearrangements, it might be easier to identify the tell-tale footprints of the machinery involved. Earlier this year, the US National Human Genome Research Institute in Bethesda, Maryland, announced it would fund the sequencing of small portions of the gibbon genome to capture some of these rearrangement sites.

Structural changes like these may have been important in driving human evolution. The draft chimp genome revealed that 2.7% of its genome differs from humans because of duplications, compared with 1.2% differing at single base-pairs[6]. Structural changes such as duplications are often hotspots for the birth of new genes. But right now it's impossible to tell whether single base changes or structural variations have had the biggest influences on how we evolved. "I couldn't hazard a guess," says Evan Eichler of the University of Washington in Seattle.

The emerging picture is of primate genomes that have been shaped in a variety of ways. Some changes were single-base alterations; others were 'structural variations', such as insertions, deletions or duplications of sequence. And, periodically, a transposable element — a parasitic DNA sequence— would infect and spread through the genome, tending to pool in the non-coding regions. In




Our primate relatives split from our common ancestors millions of years ago (MYA). But their genomes could help solve mysteries about our own evolution and medical problems. They could also give us insights into how evolution works and how new genes and species form.

PICTUREARTS/NEWSCOM; CREDITS A. RO USE/NHPA

S. BLOOM IMAGES/ALAMY; A. SHAH/NATUREPL.COM

addition, a whole genome doesn't change at an even pace; comparisons of many primate sequences will reveal how different genomic regions have evolved at different rates.

## Beyond evolution

Primate genomes can give us much more than a fascinating history lesson. They are, for example, providing valuable insights into human disease. Rubin has devised a method for comparing similar genomes and picking out functional genes and control sequences from 'junk' DNA. Dubbed 'phylogenetic shadowing', the technique has let him compare numerous different primate DNA sequences (including human), and to spot stretches of DNA that have remained broadly the same throughout relatively recent evolution. This suggests that the correct sequence of these regions is so important for the survival of the animal that evolution cannot tinker with it. Rubin's team first used this approach to discover primate-specific stretches of sequence that control the production of the protein apolipoprotein A, whose faulty regulation is implicated in susceptibility to atherosclerosis[7]. They are now looking for important regulators of the gene for the low-density lipoprotein receptor, which is involved in controlling blood cholesterol.

The good news, says Rubin, is that only a handful of carefully chosen primate genomes are needed to identify the most interesting genetic elements. The phylogenetic spread that would capture most of the genetic diversity in primates, he adds, would be — in addition to human — the Old World monkeys rhesus macaque and colobus and the New World monkeys marmoset, titi and spider monkey.

Molecular biologists aren't the only ones who hope to benefit from the chimp genome. The ancestors of most primates — unlike those of humans — seem to have left behind few fossils (see page 105), probably because they died in environments unfavourable to fossilization. "We are very fortunate that humans had the decency to evolve in good places for preserving fossils," says David Penny of Massey University in Palmerston North, New Zealand. This means that there are lingering questions over when certain primate lineages diverged, the size of populations at the time of the splits, and phylogenetic relationships among the more than 60 genera of living primates[8]. More primate genome sequences will help to calibrate the times of divergence and resolve phylogenetic discrepancies.

And genome sequences have limitations. "You can only learn so much from the genome sequence," says Penny. To make sense of the sequence differences between primates, researchers need information on the expression of genes in different tissues and the genetic variation in family pedigrees and different populations. Obtaining samples from these endangered animals in an ethical way is hard, say researchers (see page 27). "There are bits of dead gorillas in freezers but they're not great to use," says Rogers. With wild apes threatened with extinction, it is imperative to collect blood and tissue from captive populations and from animals that die in the wild. "The opportunity is fast disappearing," says Eichler. "We have only a short window to act in." ■

**Carina Dennis is *Nature*'s Australasian correspondent.**


1. The Chimpanzee Sequencing and Analysis Consortium *Nature* **437**, 69–87 (2005).
2. Cyranoski, D. *Nature* **418**, 910–912 (2002).
3. Chen, F.-C. & Li, W.-H. *Am. J. Hum. Genet.* **68**, 444–456 (2001).
4. The International Chimpanzee Chromosome 22 Consortium *Nature* **429**, 382–388 (2004).
5. Blanchette, M., Green, E. D., Miller, W. & Haussler, D. *Genome Res.* **14**, 2412–2423 (2004).
6. Cheng, Z. *et al. Nature* **437**, 88–93 (2005).
7. Boffelli, D. *et al. Science* **299**, 1391–1394 (2003).
8. Goodman, M., Grossman, L. I. & Wildman, D. E. *Trends Genet.* **21**, 511–517 (2005).