

tivity, especially the latter, have revealed that individuals both compete and cooperate by making inferences about what others know and intend (10, 11). These studies have revolutionized our understanding of what chimpanzees think and feel, raising profound philosophical questions about the nature of thought without language, as well as ethical questions concerning the rights and welfare of these animals (12).

Constraining our continued understanding of this wonderful animal is one annoying hurdle: our own species. In the very near future, we may ironically face the possibility of having a detailed map of the chimpanzee genome, but no individuals to study. Illegal hunting, the bushmeat trade, and deforestation

are destroying chimpanzee populations (see, for example, www.chimpcollaboratory.org). If the same amount of effort that is going into genetic analyses went into chimpanzee conservation and behavioral biology, not only would we save this species from extinction, but we would write the most detailed story of our past—as rich as the Bible, but grounded in science.

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## GENOMICS

# Thoughts on the Future of Great Ape Research

Edwin H. McConkey and Ajit Varki

When the Human Genome Project was established in 1991, the planners wisely included sequencing the genomes of model organisms in the project's goals. At that time, the only nonhuman mammalian genome scheduled for sequencing was that of the laboratory mouse. Although the relevance of the mouse genome for interpreting the human sequence was beyond dispute, some biologists were disappointed that no nonhuman primate genome had been included. The remarkable similarity of the chimpanzee genome to that of humans was already predicted from overall DNA comparisons, and it seemed clear that questions about the genetic basis for human uniqueness would eventually require detailed comparisons with the genomes of great apes (1), our closest evolutionary relatives. A formal presentation of the need for sequencing the chimpanzee genome was published in 1997 (2). Soon thereafter it was pointed out (3) that there should also be a project to increase our knowledge of the great ape "phenome" (the complete body of information about an organism's phenotype under various environmental conditions), about which very little is known. Scientists from a variety of disciplines rallied in support of

sequencing the chimpanzee genome, also citing biomedical reasons and the potential importance for proper care and conservation of great apes (4, 5).

We now have a draft sequence of the common chimpanzee genome (*Pan troglodytes*) and a detailed comparison with the human genome (6). The results include extensive information on comparative genomics, such as the number of single base pair and insertion/deletion differences and transposable elements unique to either human or chimpanzee. The report clarifies much previously conflicting or confusing information in existing human nucleotide sequence databanks and addresses several important questions about genomic and population evolution mechanisms. It also adopts a rational orthologous chromosomal numbering system to facilitate comparisons of human and ape genomic organization (7).

Can we now provide a DNA-based answer to the fascinating and fundamental question, "What makes us human?" Not at all! Comparison of the human and chimpanzee genomes has not yet offered any major insights into the genetic elements that underlie bipedal locomotion, a big brain, linguistic abilities, elaborated abstract thought, or any other unique aspect of the human phenome. This state of affairs may seem disappointing, but it is merely the latest example of a generalization that genomics research has already established—interpretation of DNA sequences requires functional information from the organism that cannot be

deduced from sequence alone. Functional genomics investigations must determine where a gene is expressed within an organism, when it is expressed during development and life history, and what the level of expression is at various times. Furthermore, these data must be integrated with information about the related phenotypes, as well as critical environmental influences under which the genotype generates the phenotype (see the figure).

There are three general reasons for substantially increasing research on chimpanzees (and the other great apes—bonobos, gorillas, and orangutans): First, to understand the contribution of genomic DNA to human and great ape evolution; second, to improve our understanding of human and ape phenomes (at all levels, from molecular to behavioral to states of diseases); and third, to help preserve populations of these important human relatives. These goals must be pursued in the face of challenging ethical issues that still need to be resolved by open debate.

Understanding the genetic basis of uniquely human traits will require increasing the accuracy and completeness of the currently available chimpanzee genome sequence, as well as sequencing other primate genomes as out-groups. The genomes of the orangutan and the rhesus macaque are currently being sequenced, but other genomes are needed to obtain a complete picture. Among other benefits, such multispecies comparisons are essential for identifying human-specific coding and regulatory regions.

A parallel requirement is the comparison of human gene expression with those of chimpanzees and other primates. There are formidable obstacles to achieving this goal, the most obvious of which is obtaining experimental material from great apes. It is not ethically acceptable to sacrifice a great ape simply to obtain tissue samples.

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