

EDITORIAL

Proposal for a Human Genome Evolution Project

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Introductory note. The following proposal was submitted to HUGO, the international Human Genome Organization, in March 1999. It was briefly considered by HUGO's Executive Council and was referred to an ad hoc committee for further study. We are publishing the proposal so that the scientific community may be aware of its existence. This publication in no way commits HUGO to act on the recommendations in the proposal, nor does it constitute formal acceptance by HUGO of the views expressed therein.

THE PROPOSAL

What is the genetic basis for the unique features of human anatomy, physiology, and behavior? The technology to answer that fundamental question exists, but there is currently no formal program for organizing and coordinating research on that topic.

The worldwide Human Genome Project will soon provide a complete reference sequence for the human genome and will ultimately produce encyclopedic information on the expression of human genes in health and disease. The Human Genome Diversity Project will accumulate extensive data on genetic variation in diverse human populations. Comparison of the data from those two projects will help to identify regions of the human genome that are common to all humans, likely to be greater than 99%. However, neither of the current genome projects specifically addresses the fundamental question of which genes are responsible for the unique features of our anatomy (e.g., bipedal locomotion and large brain), physiology (e.g., susceptibility to

AIDS), and behavior (e.g., speech, higher order cognitive functions).

Most human genes will have orthologous counterparts in other animals. Comparison of the human genome with that of a distantly related mammal such as the mouse is essential, especially for functional studies, but it will not allow us to pinpoint the small subset of human genes and/or controlling elements responsible for human-specific physiology, anatomy, and behavior. Only comparative sequence data from primates, especially our closest relatives, the common chimpanzee (*Pan troglodytes*) and the bonobo (*Pan paniscus*, alias pygmy chimpanzee), will permit us to identify genes coding for phenotypic aspects and behaviors specific to humans. Without that information, the overall goals of the Human Genome Project cannot be fully met.

Therefore, the authors of this proposal urge HUGO to study the possibility of formally establishing a Human Genome Evolution Project (HGEV). We believe that it would be consistent with HUGO's mission of developing and sustaining cooperation among researchers involved in the Human Genome Project. Moreover, HUGO's role in organizing the Human Genome Diversity Project provides a highly relevant precedent. In response to a published call for a worldwide survey of human genome variation (Cavalli-Sforza *et al.*, 1991), HUGO established an ad hoc committee to explore the subject. After a series of workshops and planning sessions, HUGO established the HGDP and there is now a permanent Executive Committee within HUGO to oversee the HGDP. A similar call for the HGEV was published by McConkey and Goodman (1997), and it was repeated at the Cold Spring Harbor Laboratory

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conference on Human Evolution in April 1999 (McConkey *et al.*, 1999).

The following sections of this proposal are intended to summarize the major technical and ethical issues that may arise in connection with the HGEP. We offer them in the hope that they will be helpful to the HUGO Council in deciding whether to explore the HGEP proposal further.

TECHNICAL ISSUES

Total Genomic Sequencing

Should the HGEP have as one of its goals the total genomic sequence of one or more primates? We believe the answer is *yes*, because full understanding of human-specific genetic structure and function cannot otherwise be obtained. The most directly useful comparative information will come from one of our closest relatives, the common chimpanzee or the bonobo (or both), but that will not be sufficient. To identify which differences are specific to humans and which are specific to the chimpanzees, the sequence of the gorilla will also have to be obtained. In addition to their obvious utility for identifying genes, full genomic sequences from chimpanzees and gorilla will also allow us to understand the genetic processes that have been occurring during recent evolution of the hominid line. It is of fundamental interest to know the relative proportions of point mutations, insertions and deletions, duplications of genes, transpositions, and chromosomal rearrangements.

A full composite sequence of the human genome is likely to be known within 3 to 5 years. The technology and resources that are being used for the human sequence, as well as the experience derived from that project, could then be applied to a chimpanzee and gorilla genome project. The emerging technology of DNA chips should make it possible to do a substantial amount of comparative sequencing on chimpanzee and gorilla genomes at relatively low cost, because of the very high overall sequence identity (98–99%). Another important technical question is how much information on polymorphisms within ape populations will be needed to make reliable interpretations of sequence differences as human-specific, chimpanzee-specific, etc.

Ultimately there will be a need for extensive genomic sequence data on a range of primates. The reason is that some of our most striking human features, such as greatly enlarged brains and prolonged childhood in nurturing societies, have deep roots in our evolutionary history. Thirty or forty million years ago the neocortical portions of the brain increased in the two emerging branches of anthropoid primates, the platyrrhines (New World monkeys) and the catarrhines (now the Old World monkeys, apes, and humans). Within the catarrhine branch further significant enlargements occurred 18 to 6 million years ago in the lineage leading to the

ancestors of modern hominids, and the largest neocortical increases occurred in the last 3 million years in the human lineage. A parallel evolutionary trend prolonged fetal life and the periods of postnatal life needed to reach full maturity. Accordingly, full understanding of the programs of gene expression that underlie the development of the neocortex (for example) in humans will require extensive comparative genomic data from other primates. Whether full genomic sequences of primates other than the chimpanzees and gorilla will be needed and whether it is feasible to obtain them will be topics for discussion in the future.

Functional Genomics

Identifying gene function is a basic goal of genome projects. How might the HGEP be helpful in the search for gene expression patterns that underlie the distinctive aspects of human anatomy, physiology, and behavior?

First, the existence of the HGEP will alert human genome investigators to the need to identify candidate genes. Inevitably, progress of the Human Genome Project will reveal genes that may be involved in producing the anatomical features of bipedal locomotion, cranial enlargement, and larynx structure. Other projects within the HGP will find genes involved in cognition, and additional biochemical differences of unknown evolutionary relevance will be by-products of research on human genetics. Two recent examples of genes that differ between humans and other primates are the gene for CMP-sialic acid hydroxylase (Chou *et al.*, 1998) and evidence for duplication of the FCGR1 gene on chromosome 1 (Maresco *et al.*, 1998). These and others will all become candidate genes for comparative studies, both in terms of DNA sequence and in terms of gene expression, because comparative studies are necessary if predictions about human-specific functions are to advance beyond the hypothetical stage. Comparative genomic analysis of candidate genes could begin on a small scale in individual laboratories at any time, whereas total genomic sequencing projects will require more extensive planning for funding and organization.

The HGEP could also encourage the creation of cDNA libraries from apes and other primates. Evidently, comparative studies of gene expression in the neocortex will be a focus of interest, but cDNA libraries from other organs will also be required. It is likely that various developmental stages, both pre- and postnatal, will need to be studied. How those materials may be obtained and what ethical problems may arise should be subjects of careful and detailed discussion.

When there is good reason to believe that a gene that may account for some aspect of human uniqueness has been found, there will be an intellectual necessity to test that hypothesis. In some cases, the expression of a gene can be studied *in vitro* via its messenger RNA or the protein it encodes, and recombinant DNA tech-

niques also can be used to investigate interactions between genes in cultured cells. However, morphogenetic consequences of gene expression are not usually testable in culture. Presumably, there will be studies with transgenic mice, and we can expect to learn much from them. Many questions pertaining to differential gene expression of human versus nonhuman primate genes and to their effects on development or behavior will be answerable with transgenic mice. If HUGO chooses to establish the HGEP, the potential uses of transgenic animals to achieve the fundamental goals of the project will need to be assessed.

Funding

As far as we are aware, Germany is currently the only nation that has set aside a portion of its Genome Project budget for evolutionary studies, other than the studies that are under way worldwide on the mouse, fruit fly, and worm. A new Max Planck Institute for Evolutionary Anthropology in Leipzig has already mounted a considerable effort to explore human-chimpanzee genomic differences. In the United States, the funding agencies for the Human Genome Project (NIH and DOE) have thus far not supported work on primate genomes. One of HUGO's stated functions is to serve as a brokering agency for building relationships between various governmental agencies and the genome community. Because of its experience in that area, HUGO could perform a valuable service by bringing the administrators of funding agencies from various countries into discussions about the establishment of the HGEP. As stated in the introduction to this proposal, we believe that support of comparative primate genomics by the Human Genome Project is logical and appropriate, because the identity and functions of human-specific genes and gene-control elements cannot be fully understood without comparative studies.

MEDICAL AND COMMERCIAL RELEVANCE

Comparative genomics can produce detailed information on evolutionary adaptations that have conferred resistance to disease or provided unique metabolic solutions to environmental challenges. By physically and biochemically characterizing differences in homologous proteins encoded by human and nonhuman primate genes, one can obtain specific parameters for developing therapeutics for conditions for which humans and nonhuman primates differ in a medically relevant phenotype.

There are several apparent differences between humans and chimpanzees in disease prevalence (e.g., cancer, acne, falciparum malaria, impacted wisdom teeth), in disease severity (e.g., HIV progression to AIDS, hepatitis B, cholera), and in normal biology (e.g., muscle strength, skin structure, breast development, menopause onset). Because the genetic differences be-

tween chimpanzees and humans are quite limited, comparison of the two genomes (as well as other primate genomes) should yield data relevant to understanding the pathogenesis of several human diseases.

As candidate genes that control cognitive abilities are identified, comparative genomics not only will help in determining which genetic changes are relevant to human cognition, but also will be quite useful in designing therapeutic strategies to treat cognitive deficiencies. Detailed knowledge of the encoded proteins will enable investigators to design small molecule screens to develop therapeutic agents. Clearly, these possibilities will be of interest to the biotechnology industry as well as to academic biomedical researchers.

ETHICAL AND LEGAL ISSUES

Substantial progress toward identifying the genes whose expression underlies human-specific anatomy and behavior can be made by analyzing DNA from cultured primate cells already available in cell banks. All of the sequencing can certainly be done on DNA from fibroblasts and/or lymphocytes, and recombinant constructs for incorporation into transgenic mice can also be made from those sources. Much information about gene expression can be deduced from transgenic mice.

However, there will be functional questions that cannot be answered by comparative analysis of DNA sequences or by construction of transgenic mice. There will surely be genes found in humans and apes that have little or no effect in mice, either because they are not expressed in mice or because they do not alter normal mouse development or adult functions. When we have candidate genes for bipedal locomotion, for larynx anatomy, for cranium development, or for many aspects of higher neurological functions, we cannot expect to produce mice that dance the tango, sing opera, play chess, or solve differential equations.

This inescapable experimental obstacle will lead to proposals to create transgenic nonhuman primates. Whether creation of transgenic monkeys would be generally acceptable is not clear, but the possibility of doing genetic experiments on chimpanzees or other apes would surely ignite a storm of controversy. Chimpanzees are so close to humans at the genetic level that a strong argument can be made for including them in the genus *Homo* (Goodman *et al.*, 1998). Behaviorally, the separation between *Pan* and *Homo* is much smaller than once thought. Chimpanzees are emotionally complex and intelligent. They use tools, have material cultures, are ecological generalists, and are highly social. Their anatomical inability to produce most of the sounds of human speech long obscured the fact that they are also capable of understanding and using rudimentary forms of language, as shown by recent studies on communication via sign language and lexi-

grams (Fouts and Mills, 1997; Savage-Rumbaugh *et al.*, 1998).

With that in mind, we suggest that the HGEP should at least include a policy recommending that no transgenic experiments be done on chimpanzees or other apes for the foreseeable future. Moreover, establishment of the HGEP could provide a forum for general consideration of rules regulating the treatment of captive chimpanzees and other apes. Both genetic and medical research will surely lead to increased studies on ape anatomy, biochemistry, and physiology. This need has already been recognized with a call for a Great Ape Phenome Project (Varki *et al.*, 1998). In the United States, a 1997 report by the National Research Council, "Chimpanzees in Research," made frequent reference to the need to recognize their sentience and behavioral complexity, but the report was only advisory and it has not yet led to formal government policies. A Boston-based advocacy group, the Center for Expansion of Fundamental Rights, is seeking to extend such legal rights as bodily integrity and bodily liberty to the great apes. The basis for its legal arguments are the traditional Western legal principles of liberty and equality (Wise, 1998).

The New Zealand Parliament is currently considering legislation based on a proposal submitted by a large group of scientists and others interested in animal rights in that country (Penny *et al.*, unpublished). The proposal recommends that all hominids be given three basic legal rights: the right not to be deprived of life, the right not to be subjected to torture or cruel treatment, and the right not to be subjected to medical or scientific experimentation that is not in the best interests of that hominid. ("Hominid" in this sense refers to humans and the great apes, in conformity with recent classification schemes.)

In any case, recognition of the extremely close relationship between chimpanzees, bonobos, and humans whenever they or other apes are considered for experimental purposes is one of the topics that requires careful and thorough discussion, with the participation of ethicists and animal rights advocates in addition to

representatives from academic and corporate research organizations. HUGO could contribute to this process via workshops organized around the HGEP.

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