THE CODE OF CODES

SCIENTIFIC AND SOCIAL ISSUES IN THE HUMAN GENOME PROJECT

EDITED BY

DANIEL J. KEVLES AND LEROY HOOD

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Preface

The human genome comprises, in its totality, all the different genes found in the cells of human beings. The Nobel laureate Walter Gilbert has called it the "grail of human genetics," the key to what makes us human, what defines our possibilities and limits as members of the species *Homo sapiens*. What makes us human beings instead of chimpanzees, for example, is a mere 1 percent difference between the ape genome and our own. That distinction amounts to no more than a gross reckoning, however. The substance and versatility of the human genome lie in its details, in specific information about all the genes we possess—the number has been variously estimated at between 50,000 and 100,000—about how they contribute to the vast array of human characteristics, about the role they play (or do not play) in disease, development, and behavior.

The search for the biological grail has been going on since the turn of the century, but it has now entered its culminating phase with the recent creation of the human genome project, the ultimate goal of which is the acquisition of all the details of our genome. That knowledge will undoubtedly revolutionize understanding of human development, including the development of both normal characteristics, such as organ function, and abnormal ones, such as disease. It will transform our capacities to predict what we may become and, ultimately, it may enable us to enhance or prevent our genetic fates, medically or otherwise.

Unquestionably, the connotations of power and fear associated

with the holy grail accompany the genome project, its biological counterpart. The project itself has raised professional apprehensions as well as high intellectual expectations. Undoubtedly, it will affect the way that much of biology is pursued in the twenty-first century. Whatever the shape of that effect, the quest for the biological grail will, sooner or later, achieve its end, and we believe that it is not too early to begin thinking about how to control the power so as to diminish—better yet, abolish—the legitimate social and scientific fears.

The project incorporates—indeed, is a product of—the development of genetics since the turn of the century, and perceptions of its social implications are strongly colored by the social uses of genetics in the past. In recognition of these facts, Part I of the book provides a historical introduction to acquaint the reader with the project's technical, social, and political background. Parts II and III explore the substance and implications of the project in relation both to genetics, technology, and medicine and to ethics, law, and society.

It is our conviction that the social and ethical issues of human genetics—which the project is not so much raising as intensifying—are analyzed most usefully when they are tied to the present and prospective realities of the science and its technological capacities. Science-fiction fantasies about the genetic future distract attention from the genuine problems posed by advances in the study of heredity. Many of the chapters examine or refer to a common set of technical ideas and methods that are fundamental to the mapping and sequencing of the human genome. To assist the reader, we have included a glossary of technical terms. We have also sought to minimize repetition of technical material from one chapter to the next, while permitting it to occur where it seems to facilitate comprehension.

Seven of the chapters in this book derive from lectures delivered at the California Institute of Technology during the 1989–90 academic year in a series on the human genome project that was jointly sponsored by the Program in Science, Ethics, and Public Policy, in the Humanities and Social Sciences Division, and the National Science Foundation Center for Molecular Biotechnology, in the Biology Division. We would like to express our thanks for the grants that made the series possible to President Thomas

Everhart, of Caltech, and to the National Science Foundation and the Program on Ethical, Legal, and Social Implications of the National Center for Human Genome Research. Also gratefully acknowledged is the support of the Andrew W. Mellon Foundation, which enabled one of us to contribute substantial time to the organization of the series, the editing of all the chapters, and the final preparation of the manuscript.

Our understanding of many of the issues covered in this book was enlarged by comments provided at the lectures at Caltech by Shirley M. Hufstedler, Leslie Steven Rothenberg, and Lucy Eisenberg; and by extensive post-lecture discussions that were made possible by Valerie Hood's opening her home and offering her dining table to the discussants. We would also like to thank the Audio Visual Department of Caltech for taping the lectures and discussions; Glenn Bugos for handling the equipment when necessary; Jane Dietrich for wrestling the raw lecture transcriptions into readable drafts; Rebecca Ullrich and Karen Thompson for assistance with editorial and administrative details; Bettyann Kevles for sharing her knowledge about special aspects of genetics and society; Gordon Lake for supplying documents on the European Community's genome project; Mark Cantley and his staff for facilitating use of the valuable BioDoc collection that he has created in the science section of DG-XII of the European Commission in Brussels; and Robert Cook-Deegan and Tracy Friedman for providing important information on the early development of the genome project in the United States.

Sheryl Cobb transcribed the original lecture tapes. We are deeply indebted to her and to Sue Lewis for dealing cheerfully and reliably with the endless administrative and secretarial details involved in mounting the lecture series and in preparing a book of this type. We are also grateful to Karen McCarthy for assistance with the final typing and preparation of the figures, and to Helga Galvan and Eloisa Imel for backup secretarial aid at a critical time. And we wish to thank Howard Boyer, our editor at Harvard University Press, who was quick to express interest in this book and has expedited its production, and Kate Schmit for her superb copyediting of the manuscript.

Neither of us necessarily agrees with everything in the chapters that follow. Our purpose in forging this book has not been to

advance a uniform view of the human genome project and its implications but to stimulate thought about the diversity of issues that it provokes—and about the diversity of opinions and ideas that different people may hold about them.

Daniel J. Kevles
Leroy Hood

Contents

PART III ETHICS, LAW, AND SOCIETY

HISTORY, POLITICS, AND GENETICS

I

DANIEL J. KEVLES

Out of Eugenics: The Historical Politics of the Human Genome

1

The scientific search for the "Holy Grail" of biology dates back to the rediscovery, in 1900, of Gregor Mendel's laws of inheritance. Mendel had arrived at his law by studying the transmission of characters only in peas, but scientists quickly showed that his dominant and recessive factors of heredity—"genes," to use the term soon coined for them—governed inheritance in many other organisms. They also demonstrated that genes are located on chromosomes, the tiny, thread-like entities in the cell nucleus that color upon staining.* After 1910, they learned many of the details of Mendelian heredity from studies of fruit flies, which are advantageous subjects for genetic research because they breed rapidly and their breeding can be experimentally controlled. Human beings, who reproduce slowly, independently, and privately, are not good subjects for research. Nevertheless, since no creature fascinates us as much as ourselves, efforts began almost immediately after the rediscovery of Mendel's laws to test their applicability to human inheritance. By 1907 it had been shown convincingly that Mendelism could account for the transmission of eye color as well as of the inborn error of metabolism called alkaptonuria. (See Figure 1.)

*See Chapter 2 for a historical introduction to the key technical terms and concepts of genetics from Mendel to molecular biology.

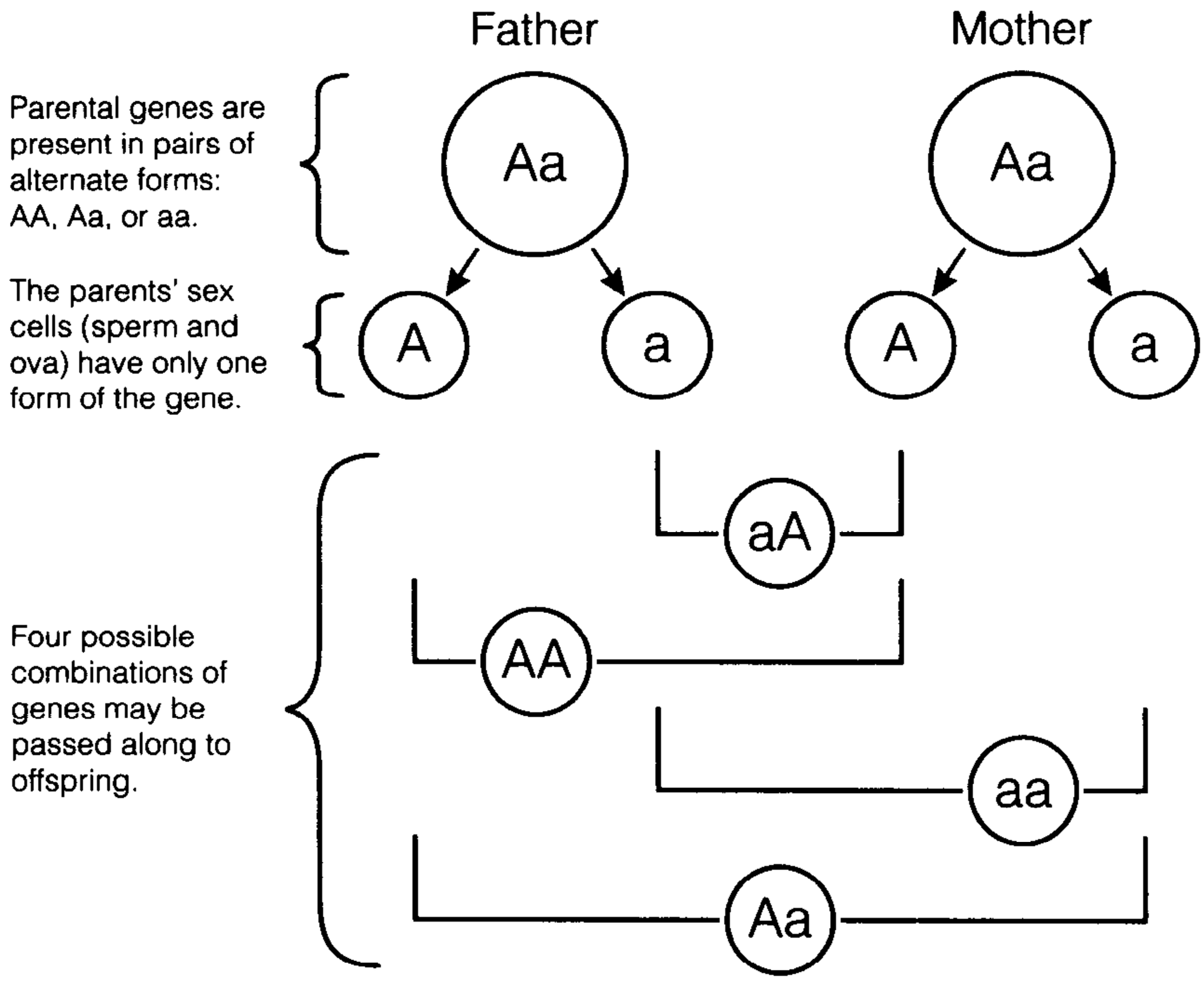

Figure 1 The simplest type of Mendelian inheritance. If *A* and *a* represent the dominant and recessive forms, respectively, of a gene encoding a particular trait, then the chances for each offspring are 3 out of 4 that the dominant trait will be expressed and 1 out of 4 that the recessive trait will be expressed. In human beings, blue eye color and alkaptonuria are examples of recessive traits. With a very large number of offspring, the distribution of outcomes is $AA + 2Aa + aa$, but the ordinary human family is too small to exhibit this distribution.

In succeeding decades, a small number of scientists and physicians took it upon themselves to further the quest for the biological grail. Some were drawn to understand human heredity for its own sake, others were motivated by its relationship to medicine. However, perhaps most seekers were socially attracted and professionally nourished by its connection with eugenics—the cluster of ideas and activities that aimed at improving the quality of the human race through the manipulation of its biological heredity.

The goal of breeding better people goes back at least to Plato, but its modern version, eugenics, originated with Francis Galton, a younger first cousin of Charles Darwin's and a brilliant scientist in his own right. In the late nineteenth century Galton proposed

that the human race might be improved in the manner of plant and animal breeding. It was Galton who named this program of human improvement "eugenics" (he took the word from a Greek root meaning "good in birth" or "noble in heredity"). Through eugenics Galton intended to improve human stock by getting rid of so-called undesirables and multiplying so-called desirables.[1]

Galton's eugenic ideas took popular hold after the turn of this century, developing a large following in the United States, Britain, Germany, and many other countries. The backbone of the movement was formed by people drawn from the white middle and upper-middle classes, especially professional groups. Its supporters included prominent laymen and scientists, particularly geneticists, for whom the science of human biological improvement offered an avenue to public standing and usefulness. Eugenicists declared that they were concerned with preventing social degeneration, which they found glaring signs of in the social and behavioral discordances of urban industrial society—for example, crime, slums, and rampant disease—and the causes of which they attributed primarily to biology—to "blood," to use the term of inheritable essence common at the turn of the century.[2]

To eugenically minded biologists, the biological roots of social degeneration had to be analyzed if they were to be extirpated—which made the study of human heredity essential to the eugenic program. Such biologists understood eugenics to be the application of human genetic knowledge to social problems and the development of that knowledge to be the basic branch of eugenic "science." As a result, the human genetics program included the study of medical disorders—for example, diabetes and epilepsy—not only for their intrinsic interest but because of their social costs. A still more substantial part of the program consisted of the analysis of traits alleged to make for social burdens—traits involving qualities of temperament and behavior that might lie at the bottom of, for example, alcoholism, prostitution, criminality, and poverty. A major object of scrutiny was mental deficiency—then commonly termed "feeblemindedness"—which was often identified by intelligence tests and was widely interpreted to be at the root of many varieties of socially deleterious behavior.

A large fraction—perhaps most—of research in human heredity was pursued in laboratories established to develop eugenically useful knowledge. In the English-speaking world, the most prom-

inent of these institutions, both of which were created early in the century, were the Galton Laboratory for National Eugenics, at University College London, under the directorship of the statistician and population biologist Karl Pearson; and the Eugenics Record Office, which was affiliated with, and eventually became part of, the biological research facilities that the Carnegie Institution of Washington sponsored at Cold Spring Harbor, on Long Island, New York, under the directorship of the biologist Charles B. Davenport. Eugenic science was institutionalized in Germany beginning in 1918, with the establishment of what became the Kaiser Wilhelm Institute for Research in Psychiatry. The institutionalization continued with the creation, in 1923, of a chair for race hygiene at Munich, to which the biologist Fritz Lenz was appointed; and with the founding, in 1927, of the Kaiser Wilhelm Institute for Anthropology, Human Heredity, and Eugenics in Berlin, which was directed by the anthropologist Eugen Fischer, a conservative nationalist who then headed the Society for Racial Hygiene.[3]

Researchers at or affiliated with these laboratories gathered information bearing on human heredity by examining medical records or conducting extended family studies, often relying upon field-workers to construct trait pedigrees in selected populations—say, the residents of a rural community—on the basis of interviews and the examination of genealogical records. An important feature of German eugenic science was twin studies (the idea being that what is or is not genetic about human traits might be revealed by analysis of genetically similar or identical children raised in different family environments). By 1926, as a result of its surveys and studies, the Eugenics Record Office had accumulated about 65,000 sheets of manuscript field reports, 30,000 sheets of special traits records, 8,500 family trait schedules, and 1,900 printed genealogies, town histories, and biographies.

Karl Pearson, an adamant anti-Mendelian, sought to determine heritabilities by calculating correlations among relatives or between generations for the frequencies of occurrence of different diseases, disorders, and traits. Studies emanating from his laboratories typically explored the relationship of physique to intelligence; the resemblance of first cousins; the effect of parental occupation upon children's welfare or the birthrate; and the role of heredity in alcoholism, tuberculosis, and defective sight. How-

ever, the approach that dominated eugenic science in most laboratories was not correlational but Mendelian evaluation—the analysis of phenotypical and family data to account for the inheritance of a variety of medical afflictions and social behaviors in genetic terms.

Typical of Mendelian work in eugenic science were the studies of Charles B. Davenport and his associates, which appeared in his comprehensive 1911 book, *Heredity in Relation to Eugenics,* and in later publications. Wherever family pedigrees seemed to show a high incidence of a given character, Davenport concluded that the trait must be biologically inheritable and he attempted to fit the pattern of inheritance into a Mendelian frame. Although he noted that single genes did not seem to determine important mental and behavioral characteristics, he did argue that patterns of inheritance were evident in insanity, epilepsy, alcoholism, "pauperism," and criminality. The mental and behavioral characteristics of different races were a major concern for Davenport, who, like eugenic scientists elsewhere, held different national groups and "Hebrews" to represent biologically different races and to express different racial traits. However, although he declared himself frequently on the subject, he actually did little research in it, particularly of a Mendelian type, except for an inquiry into "race crossing" between blacks and whites in Jamaica, the effects of which, he concluded, were biologically and socially deleterious.[4]

Davenport helped introduce Mendelism into the studies of "feeblemindedness" conducted by Henry H. Goddard, the psychologist who introduced intelligence testing into the United States. Goddard speculated that the feebleminded were a form of undeveloped humanity: "a vigorous animal organism of low intellect but strong physique—the wild man of today." He argued that the feebleminded lacked "one or the other of the factors essential to a moral life—an understanding of right and wrong, and the power of control," and that these weaknesses made them strongly susceptible to becoming criminals, paupers, and prostitutes. Goddard was unsure whether mental deficiency resulted from the presence in the brain of something that inhibited normal development or from the absence of something that stimulated it. But whatever the cause, of one thing he had become virtually certain: it behaved like a Mendelian character. Feeblemindedness was "a condition of mind or brain which is transmitted as regularly and surely as

color of hair or eyes.''[5] According to later studies by Goddard and others, it also occurred with disproportionately high frequency among lower-income and minority groups—notably recent immigrants in the United States from eastern and southern Europe.

Eugenic research in Germany before the Nazi period was similar to that in the United States and Britain, and much of it remained similar after Hitler came to power. The Institute for Anthropology, Human Heredity, and Eugenics, for example, continued to press investigations into subjects such as the genetics of diabetes, tuberculosis, and brain disease; the heritability of criminality; the effects of race crossing (with no particular emphasis on Jews or Aryans). During the Hitler years, however, Nazi bureaucrats provided eugenic research institutions with handsome support and their research programs were expanded to complement the goals of the Third Reich. They exploited ongoing investigations into the inheritance of disease, intelligence, behavior, and race to advise the government on its biological policies.[6]

Davenport, Lenz, and eugenic scientists in other countries managed, in the end, to expose genuinely Mendelian patterns in the inheritance of traits that could be well specified—color blindness, for example—and were entirely physical. Their works showed that single genes might account for such abnormalities as brachydactyly, polydactyly, and albinism, and for such diseases as hemophilia, otosclerosis, and Huntington's chorea. Lenz, in particular, also developed important mathematical methods for overcoming ascertainment bias—the tendency in human genetic field surveys to find a higher frequency for a given trait among siblings than its true probability of occurrence. Some fraction of their work thus contributed usefully to the early study of human genetics.

But the fraction was rather small. Combining Mendelian theory with incautious speculation, eugenicists often neglected polygenic complexities—the dependence of a trait on many genes—in favor of single-gene explanations. They also paid far too little attention to cultural, economic, and other environmental influences in their accounts of mental abilities and social behaviors. Some of Davenport's trait categories were ludicrous, particularly in studies on the inheritance of what he called ''nomadism,'' ''shiftlessness,'' and ''thalassophilia''—the love of the sea that he discerned in naval officers and concluded must be a sex-linked recessive trait