BASIC HUMAN GENETICS

SECOND EDITION

ohansen Mange • Arthur P. Mange

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The Cover

Red hair has always stirred interest, but how it is inherited has never been clear. One recently discovered gene encodes a hormone-binding receptor on pigment-forming cells. See Chapter 7.

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Dedicated to the memory of
Laurence (Larry) M. Sandler, 1929–1987,
teacher, scholar, friend

Preface

In this edition, as in our first edition (which won awards from the American Medical Writers Association and the Text and Academic Authors Assocation), we have tried to be interesting, accurate, up-to-date, and clear. The book is intended as a one-semester course in human genetics for students with diverse interests. We introduce the findings of genetics, show how they operate in humans, and discuss their implications for individuals and for society. Readers with a good background in high school biology and chemistry should have little difficulty with the material.

User-friendly features include new full-color illustrations with distinctive "balloon" captions, case histories of genetic disorders, sidelights of human interest, and an extensive glossary. In a few special cases, we provide the context of discovery, because science is more than just methods, facts, and concepts. Learning aids include chapter summaries, lists of key terms, questions (with full answers), and a detailed index. For readers who may need review, we have retained the appendix on basic chemical concepts. A new appendix cross-references human genetic disorders to the print and on-line versions of the encyclopedic *Mendelian Inheritance in Man* (McKusick 1997). Citations to Internet sources are given where appropriate.

The text is divided into six parts, with a total of 20 chapters:

Part	Topic	Number of chapters
One	Essential Ideas	5
Two	DNA	3
Three	Extensions	4
Four	Cytogenetics and Development	3
Five	Genetic Disease	3
Six	Practices and Prospects	2

Compared to the first edition, the chapters on the structure, function, and manipulation of DNA are closer to the beginning of the book. Molecular explanations of facets of human genetics appearing throughout the book have thus been made more useful. We describe, of course, dozens of new research results that have come to light in the last few years, including:

- The discovery, science, and politics of genes that influence the occurrence of breast cancer
- The role of pattern formation genes in early embryonic development, and the striking similarity of these genes among widely different animals

- The cloning of mammals from single embryonic and adult cells
- Progress of the Human Genome Project
- New discoveries about many genetic conditions, including Williams syndrome, hemochromatosis, albinism, facial and limb defects, and heart problems among well-conditioned athletes
- The position of Neandertal man in human evolution
- The proper forensic use of DNA fingerprinting and the reaction of the jury in the Simpson trial
- Maintaining genetic privacy in an age of increasing genetic testing

Despite all the new material, the text is the same length as before. The chapters on population genetics and evolution have been merged and condensed, the chapter on immunogenetics has been shortened, and nonessential details throughout have been omitted.

We hope that our readers will sharpen their ability to evaluate reports about scientific discoveries. However, the problem with virtually all science textbooks, including this one, is that they do not tell the whole truth. Instead, they give shortened and therefore unrealistic accounts of how science operates. But telling the whole truth would take more space than we have been allotted, and reading the whole truth would take more time than the average student can devote to a one-semester course.

Real science often wanders, sometimes without a map, and may wind up far astray on dead-end trails. But just as travelers occasionally stumble into fascinating out-of-the-way places that provide new experiences and insights, scientists may find some amazing things during their meanderings. For many of them, this uncertainty is what makes the trip worthwhile. We hope that our short account of basic human genetics has captured some of both the uncertainty and the wonder of science.

We have carefully chosen references to past and current scientific literature. The citations in the text, giving the author's name and year of publication, refer the reader to a listing of bibliographic data at the back of the book. Non-science students should be able to enrich their comprehension by looking up many of these references, which include articles in *The New York Times*, *Scientific American*, and the news sections of *Science* and *Nature*.

We are grateful for the help of many people in the library system at the University of Massachusetts at Amherst. We thank especially the staffs of the Biological Sciences Library and the Interlibrary Loan Office at the W. E. B. Du Bois Library. We are also grateful to the following persons for reviewing parts of the manuscript:

- Robert E. Braun (University of Washington, Seattle)
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Their comments and suggestions for improvement were extremely helpful. We also owe a continuing debt of gratitude to the many colleagues and students who reviewed our previous books. The responsibility for any errors that remain, however, is ours.

We thank J/B Woolsey Associates for preparing the multitude of excellent illustrations. Finally, we are pleased to acknowledge the help of the entire staff of Sinauer Associates, especially Andrew Sinauer (president), Carol Wigg (editor), Christopher Small (production manager), Janet Greenblatt (copy editor), Wendy Beck (page layouts), Jeff Johnson (book and cover design), and Dean Scudder, Marie Scavotto, and Susan McGlew (marketing). Their expertise, attention to detail, creativeness, and endless patience have contributed greatly to the finished product.

Elaine Johansen Mange

Arthur P. Mange

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PART 1

Essential Ideas

CHAPTER 1

A Frame for Genetics

Genetics and Social Issues
Science and Scientists
Genetics in Agriculture, Medicine, and Society
Using the Literature

The year was 1934 and the place was Norway. Mrs. E., an intelligent and persistent young mother, had consulted many doctors, hoping that somebody could explain why her two children were profoundly retarded and why they gave off such an odd, mousy odor. Both her 7-year-old daughter and 4-year-old son had seemed completely normal at birth, but within a few months had begun to show serious developmental problems. The girl did not walk until she was 22 months old. She could only speak in single words and was only partly toilet trained. She was hyperactive, always moving about aimlessly. She showed some muscle rigidity and a skin rash, but otherwise her physical health was relatively good. The boy could not walk, sit without support, speak, feed himself, be toilet trained, or focus his eyes. All he could do was cry, smile, and gurgle unintelligibly. Aside from some urinary problems, irregular muscle spasms, and rough skin, his physical health was also fairly good.

Finally, the mother brought her children to Professor Asbjørn Følling, a biochemist and physician. He noted the severe

retardation and peculiar odor and also a somewhat stooped posture and quite fair skin in both children. While analyzing their urine, he discovered that it turned green after he added a chemical called ferric chloride—a very unusual reaction. In two months he isolated and purified the unexpected compound that was responsible for the green color.

Følling then undertook a nationwide search for more cases of what he suspected was a newly discovered disease associated with severe retardation. After testing the urine from hundreds of patients in institutions for the retarded, mentally ill, or aged, he found a total of 34 cases from 22 families. With the help of a Norwegian geneticist, Følling also showed that the condition was inherited in a simple way. Although the mothers and fathers of affected individuals were themselves normal, they both carried the same undetected (*recessive*) disease-causing hereditary factor (*gene*) and passed it on to their children. The children, having two doses of the defective gene and lacking a normal counterpart of that gene, would thus be affected.

In 1938, Følling and a colleague reported that all of the patients had too much of a substance called *phenylalanine* in their urine and blood and hypothesized that these patients suffered from a defect in the way their bodies handled phenylalanine (Følling and Closs 1938). But the exact cause was not known until 1947, when the American scientist George Jervis reported that the culprit was a specific enzyme that in normal people converts phenylalanine to a substance called *tyrosine*:

$$\text{Phenylalanine} \xrightarrow{\text{Normal enzyme}} \text{Tyrosine}$$

An **enzyme** is a protein molecule that is specialized to greatly increase the rate of a certain chemical reaction without itself being changed by that reaction. Enzymes are made by cells under the control of genes. The reaction described here (the conversion of phenylalanine to tyrosine) did not occur in people whose enzyme was either missing or defective. So they had too little tyrosine in their bodies and far too much accumulated phenylalanine—some of which was converted to another substance and excreted in their urine. There it was detected by the ferric chloride reaction. The excess of phenylalanine (and perhaps some derivatives) or the lack of tyrosine (and its derivatives), or some combination of these, must cause the brain damage in all these patients.

Følling and many others continued to study this disease, which later was named **phenylketonuria**, or **PKU**. (The name refers to the phenyl ketones—conversion products of excess phenylalanine—found in the urine.) It turns out that most of the phenylalanine present in our bodies comes from the breakdown of the proteins we eat. Thus, the scientists reasoned, maybe the disease could be treated by removing much of the protein and phenylalanine from patients' diets. This strategy was tried in the 1950s—and, amazingly, it worked. If PKU was detected within a few weeks of birth, babies who were fed a specially concocted low-phenylalanine diet escaped brain damage (Figure 1.1). If kept on the restrictive diet until their teen years, they usually developed intelligence and behavior patterns within the range shown by normal people.

But the special diet was ineffective if started later than one or two months after birth, so early identification of affected babies was the key to preventing brain damage. By 1963, a simple test had been devised that would detect excess phenylalanine in a few drops of blood. Soon after, entire populations of babies were being tested for PKU within a few days of birth. Clearly, there was much to rejoice about. For the first time, an inherited disease was being conquered: Its tragic effects could be prevented by a change in the environment, namely, dietary therapy. Those who were born with a double dose of the PKU gene variant (and no normal version of this gene) could be detected. Indeed, thousands of young people who previously would have been doomed to profound retardation by PKU have been rescued and allowed to live normal lives.

Unfortunately, the story does not end here. When the young women who were spared the ravages of this condition reached child-bearing age, it was found that their babies were often irreversibly retarded. The reason is this: The mothers had been allowed to stop their restrictive diets some years before, and with a regular protein-rich diet the levels of phenylalanine in their blood increased dramatically. This situation did not seem to seriously affect the young mothers, but it was devastating for the babies they bore. Now it is clear that unless these women return to the restrictive low-phenylalanine diet before they become pregnant, the medical triumph over PKU will be largely undone. So the struggle to conquer PKU continues.

Genetics and Social Issues

The case of phenylketonuria illustrates how far the science of human genetics has progressed in the past 60 years. It also shows how the solution to one medical/scientific/social problem can sometimes quite unexpectedly give rise to other medical/scientific/social problems that are equally complex and difficult to solve. Finally, it exemplifies the extremely important but often ignored principle that genetic conditions can be treatable:

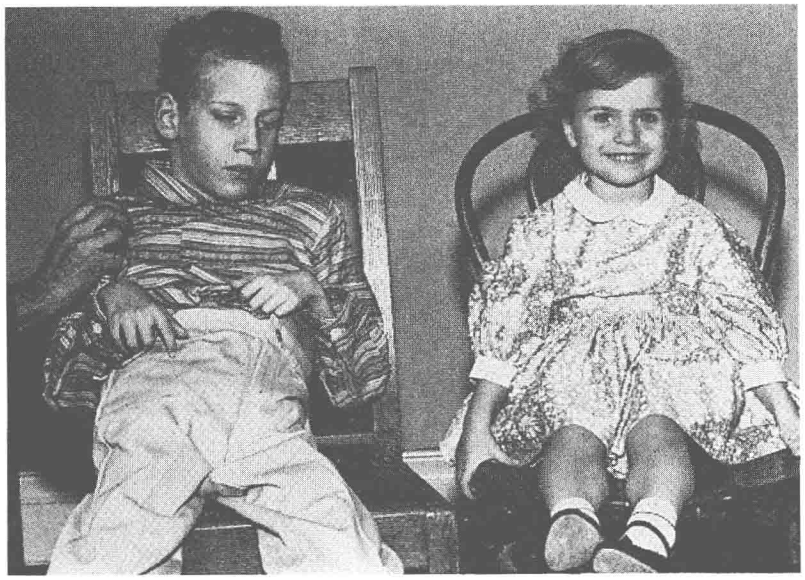

Figure 1.1 A photograph of siblings born with phenylketonuria (PKU). The untreated 11-year-old boy (left) is severely retarded. His 2½-year-old sister (right), who was treated from early infancy with a low-phenylalanine diet, has normal intelligence. (Photograph by Willard Centerwall, from Lyman 1963.)

> It would be well at an early stage in this book to dispel a common misconception. This is the concept that what is inherited is fixed and immutable, and nothing can be done about it. At the very least, this may become a convenient excuse for all one's shortcomings. Carried to an extreme, it leads to a philosophy of "biological determinism" which may stifle initiative and justify all manner of personal failures. That this concept is spurious is quite apparent from a brief consideration of everyday medical practices. We have already quoted several illustrations of the environmental modification of the expression of the [genetic makeup of a person]. Many more instances could be quoted from the field of medicine, involving the successful treatment of inherited disability. (Neel and Schull 1954)

The science of human genetics is now a thriving discipline with sophisticated techniques for the diagnosis and treatment of many inherited conditions. Indeed, these days we can hardly pick up a paper or magazine or watch the news on TV without hearing about some new genetic breakthrough. Along with these possibilities for reducing human suffering, however, have come many personal, social, political, and legal problems:

- What happens if a woman who was born with PKU (and rescued by dietary therapy) refuses to return to the low-phenylalanine diet before or just after she becomes pregnant? Does society have any right to interfere in this individual's decision-making process?
- It is now possible for the relatives of individuals suffering from certain devastating but incurable disorders (such as Huntington disease) to be tested for the presence or absence of the causative gene. How might the knowledge of their future fate affect their everyday lives? If results of such tests are not kept private, how might they affect employment and insurance opportunities?
- Should certain populations be screened to detect medically normal individuals who carry certain recessive detrimental genes, such as the sickle-cell gene in blacks or the cystic fibrosis gene in whites? Will such carriers feel tainted or defective?
- Should families be told when a child is born with a poorly understood genetic abnormality? Will the benefits of studying and perhaps later helping such children be offset by the possibility of stigmatizing them?
- Should society be asked to pay for expensive treatments for individuals with genetic disease? If so, should society have a say in whether such affected individuals ought to be born, perhaps even preventing their birth through prenatal diagnosis and selective abortion?
- Should parents be allowed to choose the sex of their children? Could such choices lead to significant changes in the sex ratio of some populations? (In China, where sons are favored and couples are limited to one child, male children now outnumber females by over 10%.)
- If it becomes possible to change our genetic destiny through techniques such as gene therapy, how should these methods be controlled? Might they lead to changed ideas of what constitutes a "normal" body and "normal" behavior? Might they cause parents (and society) to expect and demand ever more "perfect" children?

Tidy answers to such questions do not appear at the back of this book, or anywhere else for that matter. The facts and their interpretations often turn out to be quite slippery, changing as scientists ask new questions and develop new techniques for answering them. However unsatisfying (and perhaps risky) it may be, and however much we crave certainty, we usually have to make do with incomplete information. And because public policy decisions on complex social issues must be based on much more than the facts alone, they should involve the thoughtful participation of all citizens, and not just the scientists.