Human Genetics

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Preface

Few sciences hold our interest as intensely as human genetics. All of us have questions about our biological heritage and how that heritage affects our lives today. This book will answer many questions, but it will also raise questions for which we have no answers. It is an excursion into the genetics of the human species, an area of study that is growing more rapidly with each passing day. As a matter of fact, few areas of science are expanding more rapidly.

For decades human genetics languished in relative obscurity. It was overshadowed by the spectacular advances being made in the molecular genetics of bacteria and viruses and in the more easily manipulated genetic system of the fruitfly, *Drosophila*. But human genetics also had the burden of World War II to bear. In Nazi Germany, genetic principles were perverted in their application to human beings, prompting many to turn away from the field. Within the last ten years, though, the situation has changed rather dramatically. New techniques for studying chromosomes, for growing human cells in culture, and for studying the function of human DNA have resulted in some spectacular progress. We will examine some of the progress in this book, but bear in mind that even as you read this book, new and exciting advances will probably have added to our knowledge. These ongoing discoveries help make human genetics so much fun and so exciting.

This book is intended for a one-term introductory course. I do not assume that the readers of this book have any background in college-level biology or chemistry. Nor do I assume that this book will be followed by more advanced studies in biology, though it may.

However, some students may indeed have some prior biology and chemistry courses and may actually be planning to be biology majors. Those in this latter category may choose to skip sections or skim them for quick review.

Organization

The organization of *Human Genetics* reflects the approach I use in classrooms. It is logical and works well, but this is not to say that it is the only organization possible. The first six chapters deal with various aspects of what we might call "classical genet-

ics." That is, they discuss the basic principles of inheritance as formulated by Mendel and applied to humans, the chromosome theory of inheritance, and some of the extensions of those basic principles. The next five chapters focus on the nature and function of the genetic material. Chapters 12 and 13 explore some of the more complicated patterns of inheritance, including human behavior, and the techniques we employ to understand them. The final chapter discusses the genetics of human populations and the biological history of the human species.

Special Features

A variety of features contribute to the usefulness of this book.

- *Coverage of recent advances in genetics* is thorough, and includes accessible treatment of gene structure and function on the molecular level, somatic cell genetics, the relationships of viruses and chromosome abnormalities to cancer, and modern genetic techniques and procedures. I devote an entire chapter to metabolic disorders and hemoglobin variation, and another to the genetics of the immune system.
- *Special topic boxes* are found in almost every chapter. These highlight a variety of subjects, ranging from the technical to the controversial, and provide an element of choice in selecting material for study.
- Many *illustrations* appear throughout. They include over 300 drawings and 100 photographs, many published for the first time.
- *Learning aids in each chapter* include *key terms* in boldface within the text, *chapter summaries* in outline form, *lists of key terms and concepts* at the ends of chapters, *review questions and problems* (with answers provided), and *references* to further reading. At the back of the book is a comprehensive glossary.

Acknowledgments

This book is a very special effort involving many very special people. The outstanding people at Benjamin/Cummings helped to make the writing of this book a unique pleasure. I especially want to thank Jim Behnke, Jane Gillen, Margaret Moore, Patricia Burner, Sue Harrington, Jo Andrews, and Amy Satran for their monumental efforts on behalf of this project. A very special debt of gratitude is owed to Robin Fox for developmental editing of the manuscript, and to Duane E. Jeffery and Joyce Maxwell, who read the manuscript from cover to cover and offered numerous valuable suggestions for improvement. The quality and accuracy of my writing was greatly improved by their thoughtful comments. Duane Jeffery wrote a number of the boxes. In addition, C. K. James Shen, of the University of California, Davis, carefully proofread the entire page proof for the book, on a tight schedule. Dorothy Sivitz, one of my students at Swarthmore, was an invaluable aid in the final phases of the writing. And my colleagues at the Children's Hospital of Philadelphia, especially Beverly Emanuel, were helpful, stimulating, and encouraging throughout this project. To all of these people and numerous others, I want to say thank you.

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Detailed Contents

1 Introduction

A Boy Named Michael

Michael entered this world a healthy, cheerful baby born of young parents who could not have been happier or more optimistic about the future. But Michael's future was to be bleak, for he was born with cystic fibrosis (CF). The symptoms were not immediately apparent, and when they did begin to appear, they were so general that no one suspected their cause. At six months of age, Michael was operated on for an intestinal obstruction, but he continued to be malnourished despite a healthy appetite. The obstruction and the persistent malnutrition led physicians to suspect CF, and further testing confirmed their fears.

As Michael grew, he was by all standards a terrific kid. Intelligent, sensitive, and humorous, he was every parent's dream. But his medical problems multiplied. He was still malnourished despite a voracious appetite. He suffered from deficiencies of vitamins A, D, K, and E. His bowel movements were exceptionally large and smelly. At age three, Michael began to experience recurring symptoms of bronchitis. Thick mucous secretions collected in his lungs, creating a painful emphysemalike condition. Over the next few years, his lung problems became more severe and placed a tremendous strain on his heart.

At age seven, Michael died of congestive heart failure. Death did not come quickly or easily to this little boy, who with his parents fought a brave battle against this unrelenting, genetically rooted disease. But come it did, and in a way that is typical for almost all who suffer from CF.

CF: A Case of Simple Inheritance

What caused Michael's tragedy? We are just now beginning to understand the underlying biochemical defect that leads to cystic fibrosis. Almost all the CF symptoms can be traced to malfunctions in the body's mucus-secreting glands. Pancreatic ducts, which carry enzymes to the intestine, become clogged with mucus, restricting the flow of digestive substances. Thus, food is not properly broken down and utilized, and malnutrition occurs. Excessive mucus in the lungs plugs up the smaller air passages, impairing the exchange of oxygen and carbon dioxide and creating severe breathing difficulties. Most people with CF die before their nineteenth birthday either of lung disease or of heart failure caused by the enormous strain of pumping blood to improperly functioning lungs.

The increased production of mucus that causes the CF symptoms may be associated with an abnormal form of an enzyme called NADH dehydrogenase, though this is not yet proven. **Enzymes** are proteins that catalyze, or assist, biochemical reactions; NADH dehydrogenase is but one of the tens of thousands of enzymes in the human body. No organism can live without enzymes, for without their assis-

tance, the chemical processes on which life is based would occur exceedingly slowly or not at all. As Michael's case demonstrates, the lack of a single enzyme or its occurrence in an abnormal form can severely disrupt the body's normal functioning. For reasons we do not fully understand, the abnormal form of NADH dehydrogenase may cause a calcium buildup in some of the gland cells, and this in turn may lead to abnormal mucus production.

Abnormal NADH dehydrogenase is the product of a specific abnormal gene. **Genes** are the units of hereditary material that carry the encoded instructions for an organism's development and biologic functioning. Each of our genes is a copy of a gene in one of our parents. Why, then, did neither of Michael's parents display any symptoms of CF? Like nearly all gene products, NADH dehydrogenase is coded for by *two* alternative forms of the gene, called **alleles**, in every individual, one derived

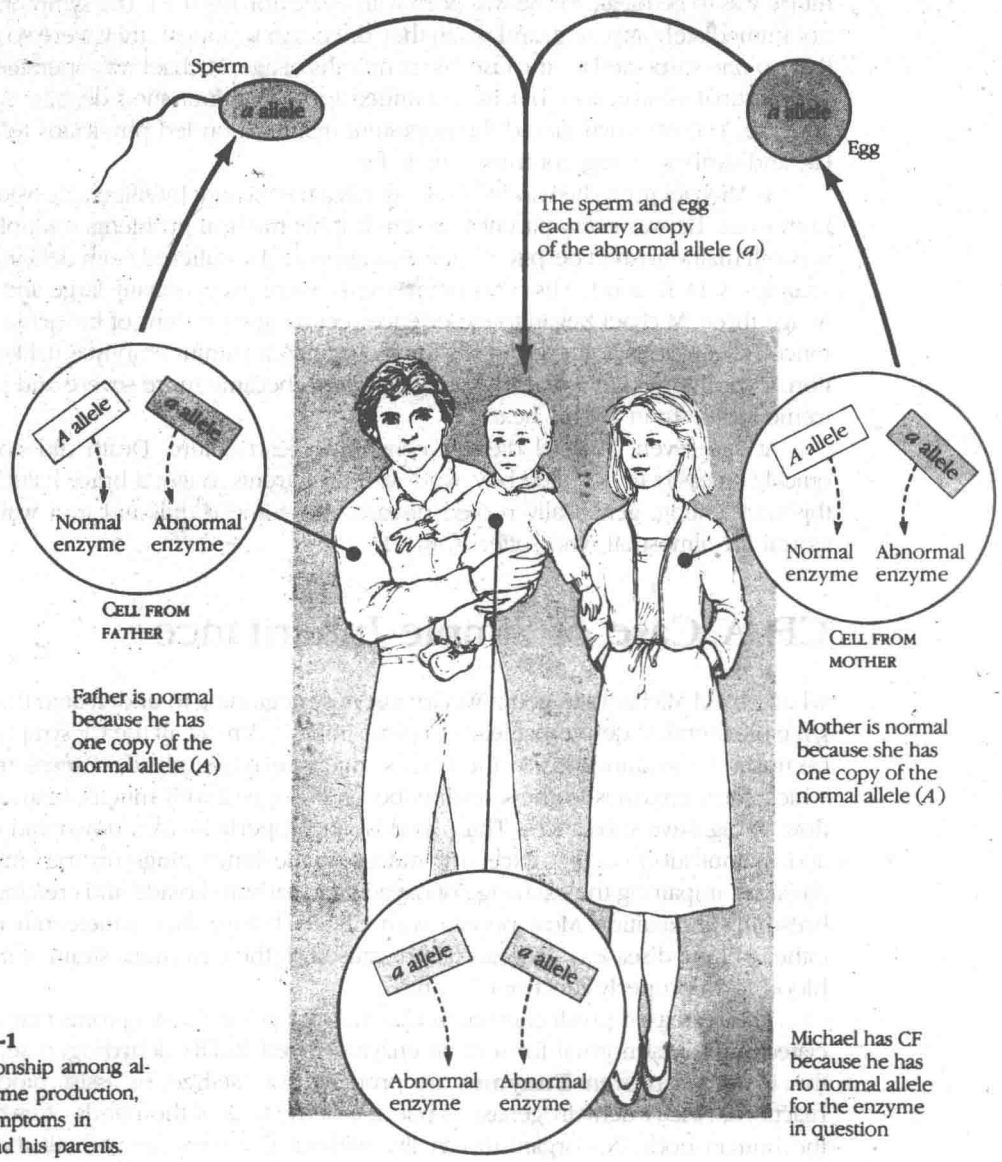

Figure 1–1
The relationship among alleles, enzyme production, and CF symptoms in Michael and his parents.

from the mother and one derived from the father. A person who has even one normal allele will produce enough of the normal enzyme to ensure proper functioning of the mucous glands and will not experience any CF symptoms. In other words, the effects of the abnormal allele will be overcome, or masked, by the effects of the normal one. When two alleles code for different forms of the same trait, such as normal and abnormal enzyme production, and the effects of one allele are masked by the effects of the other, we call the masking allele **dominant** and the masked allele **recessive**. (A dominant allele is usually indicated by an uppercase italic letter and the recessive allele by a lowercase italic letter.) Each of Michael's parents carried one dominant (*A*) and one recessive allele (*a*) for the enzyme, but they were quite unaware of this until each of them passed a copy of the recessive allele on to their child. Without a copy of the dominant normal allele, Michael's body could not produce the normal form of the enzyme—and the symptoms of CF appeared. Figure 1–1 shows the relationship among alleles, enzyme production, and CF symptoms in Michael and in his parents.

The inheritance of CF follows a simple pattern called **Mendelian**, after Gregor Mendel, who first described dominant and recessive traits in peas. Such patterns were well understood long before geneticists had any idea why a trait might be dominant or recessive, or indeed, what a gene might be. Thanks to these patterns, we can make certain statistical predictions. A genetic counselor, knowing that Michael's parents must each carry one recessive allele for CF, can tell them that any future children of theirs will have one chance in four of inheriting two such alleles and thus of having the disease. Each child will have two chances in four of inheriting one dominant and one recessive allele and one chance in four of inheriting two dominant alleles (Figure 1–2). Put the other way around, every child will have three

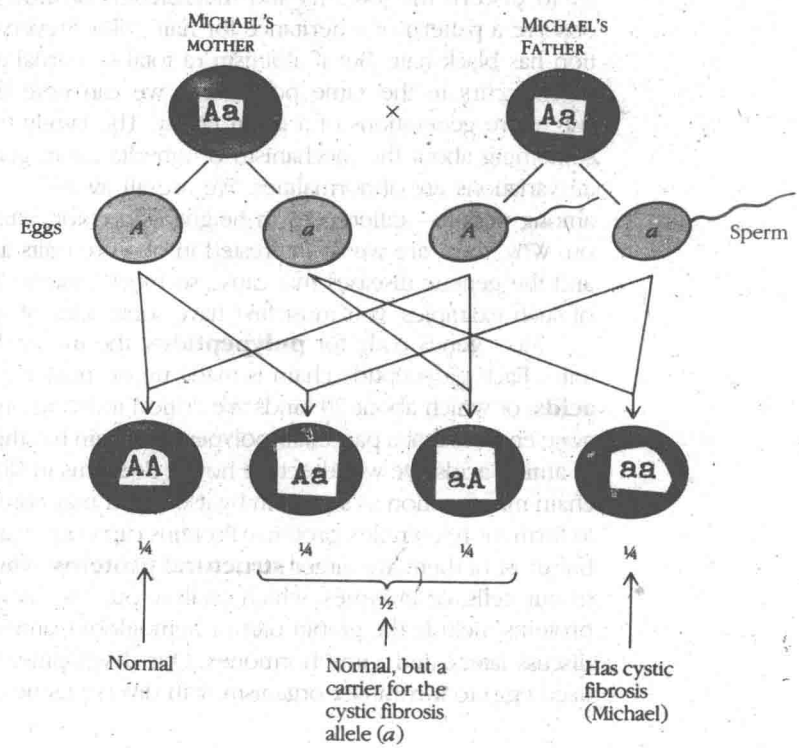

Figure 1–2
Michael's mother and father are carriers of an abnormal allele, *a*. We can make statistical predictions about the genetic makeup of their offspring.