PUBLIC HEALTH GENOMICS

The Essentials

CLAUDIA N. MIKAIL

Foreword by

DOROTHY S. LANE, MD, MPH

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FOREWORD

Claudia Mikail, with her training and experience in preventive medicine, public health, genetics, and psychology, has a keen sense of the biopsychosocial issues that bridge genomics and public health. Ever since the beginning of her career, she has been dedicated to medical and public health education, and she consistently draws rave reviews from her students for her ability to explain complex concepts clearly and effectively, both to people who have a scientific background and to those who have no such experience. Now she has brought her rare gift to the task of creating a single book that seamlessly integrates the essentials of two complex fields: genomics and public health.

This volume draws together the basic biological and clinical principles of genomics with their ethical, legal, and social implications and highlights how genomics may be incorporated into health promotion and disease prevention efforts for individuals and populations. Facilitating the acquisition of core competencies in public health genomics, the book provides the reader with a solid knowledge base in the field and serves as a springboard for further study and exploration. Public health students, medical students, preventive medicine residents, and public health professionals looking for an overview of key concepts in public health genomics will find this text a handy and useful addition to their libraries.

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PREFACE

When I look back on the experiences that led me to write this book, I realize that my innate interest in genomics and public health has been apparent for quite some time. In high school, as a National Science Foundation Young Scholar, I gravitated toward genetics: my first science fair project studied whether musical ability was inherited or acquired, and one of my college application essays explored the ethical and social issues surrounding genetic engineering. As an undergraduate at Princeton, I read *The Selfish Gene,* by Richard Dawkins, for a molecular biology course, and it quickly became a favorite book. As a medical student at Mount Sinai, I was fascinated by the genetics cases I encountered on the pediatrics wards but was equally intrigued by my course work in preventive medicine, public health, and medical ethics.

Given that medical genetics and community medicine were two of the most renowned departments at my medical school, perhaps I was merely a product of my environment. But regardless of the underlying reasons for my interest in these topics, it seems now that all roads were pointing me toward public health genomics. During my clinical training, I remained captivated by the rapid advances being achieved in applied genetics. As a resident in preventive medicine and public health at Stony Brook and Columbia, I enjoyed teaching and learning about the interface between science and society. It was then that I also fully realized my ability and passion for educating others.

My two loves—genetics and public health—finally came together as I completed an NIH fellowship in medical genetics at UCLA/Cedars-Sinai Medical Center and subsequently accepted faculty appointments at the University of Massachusetts, Amherst, and the University of Southern California, Keck School of Medicine, where I created pioneering courses in genomics for graduate students of public health and preventive medicine. Above all else, it was my students' curiosity, fascination, and urge to explore this unique discipline that served as the greatest inspiration for me to write this book.

But none of this would have been possible without the many teachers, professors, physicians, and mentors I have learned from over the years. Out of appreciation for all they have taught me, I am listing a selection of them here: Scott Barnett, MD; Robert Desnick, MD, PhD; John DiMartino; Jonathan Fielding, MD, MPH, MBA; Iris Granek, MD, MPH; Wayne Grody, MD, PhD; Marcia Johnson, PhD; Dorothy Lane, MD, MPH; Edward McCabe, MD, PhD; Barbara Nemesure, PhD; Rosamond Rhodes, PhD; David Rimoin, MD, PhD; Fred Rosner, MD; Lawrence Shapiro, MD; Thomas Valente, PhD; Judith Willner, MD; and Paul Woolf, MD.

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CLAUDIA N. MIKAIL received her BA, summa cum laude and Phi Beta Kappa, from Princeton University, where she was the recipient of the Howard Crosby Warren Jr. Prize in Psychology. She earned her MD degree from Mount Sinai School of Medicine, completed residency training in general preventive medicine and public health at University Hospital, SUNY at Stony Brook, School of Medicine, and was awarded her MPH degree concurrently from Columbia University. She completed an NIH fellowship in medical genetics at UCLA/Cedars Sinai Medical Center, where she trained in clinical genetics (prenatal, pediatric, and adult) and researched the genetic epidemiology of type II diabetes mellitus. A diplomate of the American Board of Preventive Medicine and a member of the American College of Medical Genetics, Dr. Mikail is a clinical assistant professor in the School of Public Health and Health Sciences at the University of Massachusetts at Amherst; a clinical instructor in the Department of Preventive Medicine at the University of Southern California, Keck School of Medicine; and a clinician in private practice. Dedicated also to community service and the arts, Dr. Mikail serves on the boards of directors of several charitable organizations and has won national and international awards for music composition.

RICHARD G. BOLES completed medical school at UCLA, a pediatric residency at Harbor–UCLA, and a genetics fellowship at Yale. He is board certified in pediatrics, clinical genetics, and clinical biochemical genetics. His current positions include associate professor of pediatrics at the University of Southern California, Keck School of Medicine; and director of the Metabolic and Mitochondrial Disorders Clinic at Children's Hospital, Los Angeles. Dr. Boles practices the "bedside to bench to bedside" model of a physician-scientist, combining a very active clinical practice in metabolic and mitochondrial disorders with basic research as director of a mitochondrial genetics laboratory at the Saban Research Institute. Dr. Boles's clinical and research focus is on polymorphisms (common genetic changes) in the maternally inherited mitochondrial DNA and their effects on the development of common functional disorders. Examples include migraine, depression, and cyclic vomiting syndrome. When he is not at work, his interests revolve around his four children, ranging in age from seventeen years to five months.

INTRODUCTION

At first glance, one might think that genomics and public health were two vastly different disciplines, the first inspiring images of scientists extracting DNA in a lab, and the second eliciting visions of activists striving to improve the health of the masses. But, looking more closely at the two, one sees that genomics and public health have many similarities. Both examine trends in populations, and both research social and ethnic contributions to health, but where genomics seeks to determine the most fundamental causes of disease, public health aspires to enhance outcomes.

An important future role of public health leaders will be to develop interventions for combating diseases with genetic components and to evaluate these interventions in terms of their ability to reduce morbidity and mortality in populations. The Centers for Disease Control and Prevention (CDC), in recognition of this fact, has created a list of genomics competencies for the public health workforce; the Association of Schools of Public Health (ASPH) and the Institute of Medicine (IOM) have also recognized genomics as a priority area in the health professions.

This book—which melds the science of genomics with its relevance to such key public health issues as environmental health, ethnic health disparities, health policy and law, research ethics, maternal and child health, clinical preventive medicine, health behavior, health economics, and communicable disease control—is intended to serve as a convenient resource for public health students and professionals who aim to achieve the genomics competencies identified by the CDC.

Chapter One, which begins Part I, opens with a presentation of some background information on the history and philosophy of public health genomics and the role of genomics in clinical preventive medicine. Chapter Two gives an overview of the Human Genome Project and summarizes federal and state programs in public health genomics in the United States. Chapter Three discusses basic molecular genetics and introduces the relationship between genetic variants and disease. Chapter Four focuses on mutations and population genetics and on how genomics has affected our perspectives on race and ethnicity. Chapter Five looks at patterns of inheritance of genetic diseases and at how an individual's family history helps determine his or her risk of disease. Chapter Six discusses multifactorial traits, reviews basic study designs in genetic epidemiology, and discusses the role of molecular epidemiology in exploring gene-environment interactions. Chapter Seven examines the use and misuse of genetic information, privacy laws, legislation against genetic discrimination, and ethical concerns arising from the formation of large-scale genomic databases and the use of genetic testing in clinical settings.

The five chapters in Part II explore the practical impact of genomics on health promotion and disease prevention throughout the life cycle. Chapter Eight reveals links between toxicology and teratology and discusses approaches to prenatal diagnosis for genetic anomalies. Chapter Nine explores the need for cultural competence in devising and implementing genetic screening programs in particular ethnic groups. Chapter Ten reviews the essentials of metabolic genetics and explains recent advances in newborn screening protocols. Chapter Eleven describes the management of pediatric patients with genetic disorders. Chapter Twelve reviews the genetic basis of common adult diseases and explores how knowledge of genetic predispositions can influence health behaviors.

Part III covers areas of general interest to public health practitioners. Chapter Thirteen looks at genomics from the perspective of health economics and discusses the literature on health disparities in the use of genetic services. Chapter Fourteen explains how our understanding of bacterial and viral genomics has influenced our approaches to communicable disease control. Chapter Fifteen covers such popular topics in genomics as personalized medicine, gene therapy, and stem cell research. Chapter Sixteen offers a compendium of online genomics resources that can be accessed for further independent study.

To aid in highlighting important concepts for the reader, each chapter contains a list of key terms. To stimulate further thought and group dialogue on the materials presented, questions for discussion are also included at the end of each chapter.

But first, here are some basic definitions to understand before embarking on the educational adventure that awaits:

gene: a protein-encoding DNA sequence on a chromosome

proteins: compounds that determine the structure and function of living organisms

genome: the complete set of an organism's hereditary material

genetics: study of the structure and function of genes

proteomics: study of the structure and function of proteins

genomics: study of the genome, including genomic structure, the interplay of gene-gene and gene-environment interactions, and dynamic influences on gene expression

public health: a multidisciplinary field that depends on principles of biostatistics, epidemiology, environmental sciences, ethics, health education, health policy and management, health services and outcomes research, law, medicine, occupational health, psychology, and sociology to promote health and prevent disease in populations

public health genetics/genomics: a field that applies advances in genetics and genomics toward health promotion and disease prevention in populations

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PART

1

SCIENTIFIC AND SOCIAL PERSPECTIVES ON GENOMICS

Ask the innocent and obvious questions and make things clear and simple. Through that clarity, you will perceive the depths.

—Rabbi Menachem Schneerson
(cited in Freeman, Bringing Heaven Down to Earth)

Part I of this book seeks to make the intricate and complicated field of genomics accessible to all readers, those with scientific backgrounds and those without that kind of preparation. To place the science in context, the first two chapters describe the history and philosophy of public health genomics and the role that the United States government has played in developing the field. The remaining five chapters of Part I explicate the essentials of molecular genetics, Mendelian genetics, population genetics, pedigree analysis, and genetic epidemiology and raise awareness about the ethical, legal, and social issues they involve.

CHAPTER 1

PAST, PRESENT, AND FUTURE OF PUBLIC HEALTH GENOMICS

LEARNING OBJECTIVES

- Learn about the history of human genetics
- Understand the history of public health genetics
- Realize the role of genetics in disease prevention
- Become familiar with the current status of clinical genetic testing
- Comprehend the future role of public health genomics

INTRODUCTION

To help readers achieve an understanding of how human genetics has evolved until now, this chapter begins by reviewing some of the major genetic discoveries of the past few centuries and how they have given rise to current concepts in genomics. Then the role genetics has come to play in clinical preventive medicine is introduced. The chapter concludes with a description of the future goals of genomics research and of how they are aimed at improving health promotion and disease prevention.

HISTORY OF HUMAN GENETICS

One of the earliest records of human genetic disorders appears in five-thousand-year-old Babylonian clay tablets that describe sixty birth defects (Majumdar, 2003). The Jewish Talmud, written about two thousand years ago, was the first document to accurately record the familial transmission pattern of hemophilia (a genetic blood-clotting disorder).

Khoury, Burke, and Thomson (2000) trace the more recent study of human genetics back to observations made by early philosophers, scientists, and laypeople, who noted similarities and dissimilarities among individuals, family members, tribes, and communities. These early observations have served as stepping stones to our modern-day multifaceted approach to genomics.

Laboratory genetics took its first step in the seventeenth century, when Anton van Leeuwenhoek, inventor of the microscope, discovered the existence of sperm. Although the existence of DNA was not known at the time, knowledge of sperm was a crucial prerequisite for that discovery. The concepts of family history and pedigree analysis (the study of disease transmission patterns in families) established their roots in the nineteenth century, when a physician named Joseph Adams wrote *A Treatise on the Supposed Hereditary Properties of Diseases.* He particularly noted that certain diseases appeared more frequently in the offspring of parents who were blood relatives (the practice of marriage between blood relatives is now known as *inbreeding*).

The beginnings of genetic epidemiology appeared soon after, with the work of Francis Galton. He published *Hereditary Talent and Character* in which he measured and statistically compared intelligence, height, and other quantitative traits in related individuals. At about the same time, Gregor Mendel performed the first, rudimentary experiment in genetic engineering—hybridizing pea plants and discovering the basic laws of human heredity. The foundation of metabolic genetics arose around the turn of the twentieth century, when Sir Archibald Garrod deduced that some hereditary diseases were caused by defects in enzymes and metabolism.

Modern molecular genetics was born when Alfred Day Hershey and Martha Chase proved that deoxyribonucleic acid (DNA) is the substance that transmits hereditary information in the cell. In 1953, a landmark year in genetics history, James Watson and Francis Crick, building on the work of Rosalind Franklin, discovered that the