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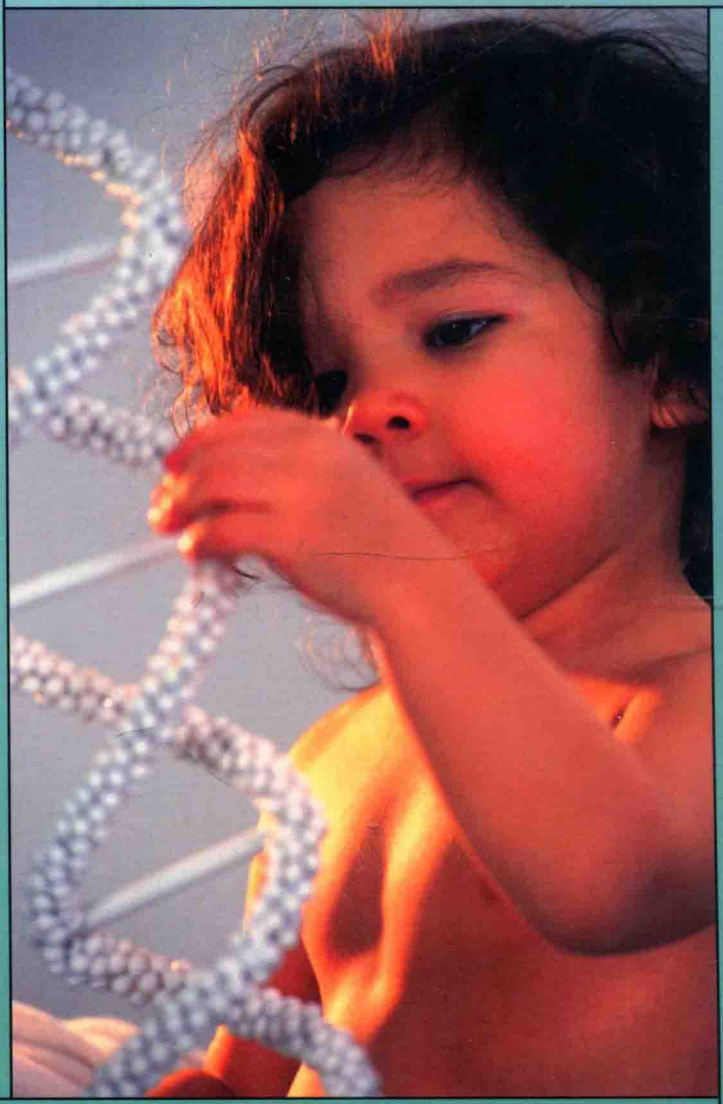
Julia E. Richards
R. Scott Hawley

The Human Genome

SECOND EDITION



A User's Guide

Elsevier Science in Society Series

THE HUMAN GENOME
A USER'S GUIDE

SECOND EDITION

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Acquisition Editor: Jeremy Hayhurst
Project Manager: Paul Gottehrer
Editorial Assistant: Desiree Marr
Marketing Manager: Linda Beattie
Cover Design: Cate Barr
Composition: SNP Best-Set Typesetter Ltd., Hong Kong
Printer: China Translation & Printing Services Ltd.

Elsevier Academic Press
200 Wheeler Road, Burlington, MA 01803, USA
525 B Street, Suite 1900, San Diego, California 92101-4495, USA
84 Theobald's Road, London WC1X 8RR, UK

This book is printed on acid-free paper.

Library of Congress Cataloging-in-Publication Data
Application submitted

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN: 0-12-333462-4

For all information on all Academic Press publications
visit our Web site at www.academicpressbooks.com

Printed in China
04 05 06 07 08 09 9 8 7 6 5 4 3 2 1

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To Jesse
and the many unsung heroes
who have helped create modern medicine
through their participation in research

Acknowledgments

Many people have contributed to the existence of this book, and each of them has our profound gratitude. We thank our families for their love, patience, and support throughout the process of writing this book. They are the foundations in our lives that make such endeavors possible.

We especially thank Jeremy Hayhurst, Desiree Marr and Elsevier for giving us the opportunity to share this book with you. We also thank Catherine Mori, for her efforts both in the creation of the concept of *The Human Genome: A User's Guide* and for her work on the first edition. That work was a substantial stepping-stone as we embarked on creating the current version of this book.

Thanks for reading chapters and for many excellent suggestions go to Beverly Yashar, Paula Sussi, Paul Gelsinger, James Knowles, Jill Robe-Gaus, Randy Wallach, Rick Guidotti at Positive Exposure, Jerrilyn Ankenman of NOAH, Julie Porter of the Hereditary Disease Foundation, Linda Selwa, Marcy MacDonald, Sayoko Moroi, Christina Boulton, Leeann Weidemann and Alice Domurat Dreger. Thanks go to Carl Marrs and the students in Epidemiology 511, including Miatta Buxton and Gail Agacinski, for reading the whole book and providing feedback. We also thank the artists who contributed to this book including Kathy Bayer, Ed Trager, Sophia Tapio and Sean Will and the artists at Dartmouth Publishing, Inc.

We thank the members of our research groups who have helped in numerous ways over the years, and we want to express special appreciation for the efforts of our administrative assistants, Linda Hosman, Nina Kolich, and Diana Hiebert. Scott Hawley also thanks both the Stowers Institute and its president, Dr. Bill Neaves, for support and encouragement during the writing process, and Julia Richards wishes to thank Dr. Paul Lichter for creating an environment in which genetics can bridge the gap between basic research and clinical practice.

We often use the first person in this book, but when speaking of scientific findings ("We now know that ..."), we do not mean to lay claim to this vast body of work we discuss. Many researchers have expended great amounts of time and energy for more than a century to arrive at the frankly amazing body of knowledge presented here. Although we are both active researchers in the field of genetics, in this book we speak as users of the human genome, teachers of genetics, and continual students of this fascinating topic.

We owe thanks to the individuals and families who contributed the stories in the book, each of which was included not only because it makes some scientific or educational point but also because these are stories that have touched our hearts. We want to offer special thanks to Jim Knowles, for letting us share Brenda's tale with you, and to Paula Sussi and Paul Gelsinger, who each continue working in education and policy areas to try to ensure that what happened to their children Marlaina and Jesse will not happen again. Others who shared their stories anonymously are just as much deserving of

our thanks, even if we must leave them unnamed here. For some of those stories, we have simplified the tale to keep it focused on the lesson to be learned from the tale, and in some cases we have changed minor details where necessary to preserve confidentiality, such as through avoiding use of real names. In general, where we use no names or only first names, these are still true stories unless we have indicated otherwise. In rare cases in which we present a hypothetical situation derived from many similar stories, we try to indicate that we are doing this by stating that the tale is hypothetical or saying, "What if we looked at a family with these characteristics?" With many of the families we encountered the hope that helping other people understand what has happened will help them cope with the genetic situations in their lives. We also encountered the hope that the sharing of their tales would keep someone else from going through the same thing that had happened to their families. If this book accomplishes that goal for even one family, the writing will have been well worth all of the effort.

Preface

Huge changes in health care and in our understanding of ourselves will emerge during the first half of the twenty-first century, and those who take the time to understand the issues will be in the best position to take advantage of what is to come. If you have picked up this book expecting to find the biological cousin of the books used in organic chemistry and calculus classes, you may be surprised by the material that follows. We interweave personal anecdotes, discussions of ethical issues, historical remarks, and our own opinions right alongside an eclectic mix of scientific facts, molecular models, and cartoon figures. If you are not a student of the sciences but would really like to know more about genetics, this book was written with you especially in mind. It offers all of the fundamental concepts without requiring that you know anything about hydrogen bonding, hybridization kinetics, or differential equations. Keep in mind as you read that we are all astonishingly complex organisms and that there are exceptions to almost everything we will tell you since it is difficult, if not impossible, to arrive at generalizations that can truly encompass that complexity.

It is not our intention to turn any of you into geneticists, although that wouldn't be such a bad thing. Our real hope is to impart enough knowledge that you will be able to bring this subject into your own lives. It is hoped that by the end of this book you will know when and why to seek the council of a medical geneticist or genetic counselor, should you ever need one. It is also hoped that you will have become sophisticated enough to sort out some of the myths and misconceptions about human heredity that pass for simple truths in folklore and in the press. To the extent that we achieve even a small measure of success with either of these goals, we will consider this book a success.

Science is often presented as a dry recitation of objective facts so devoid of opinions and feelings that it is hard to derive a mental image of the author of the work. In many cases, this objectivity is a good thing. After all, there are powerful reasons for identifying solid facts and distinguishing them from opinions. To us, genetics is highly personal and not some abstraction removed from ourselves, so we have made a point of interjecting ourselves into this book about the genome that we share with each other and with all of you. We, authors and readers alike, are the end users of the information in our own genomes. So join us on a journey through this user's guide to the human genome.

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Section 1

THE BASICS OF HEREDITY

This section provides a description of how traits are inherited and introduces the concept of the gene. We talk about how some of the basic genetic concepts apply to human inheritance and about how patterns of inheritance can look very different depending on the trait you are studying.

SLAYING MOLECULAR DRAGONS: BRENDA'S TALE

1

"To dream . . . The impossible dream . . ."
—Don Quixote in Man of La Mancha

Healthy young people aren't supposed to die. Even amidst the many dangers that arise from the exuberance and hazards of youth, the death of someone young is always a shock. And when the blow is delivered from some direction we never expected, were not waiting for, had never considered, when someone young is felled by an illness such as leukemia, we are left feeling stunned. It seems impossible to understand such an outcome, and we find ourselves asking, "How could this have happened?" And the next question that comes to mind is, "What can be done so that this does not happen again?"

Brenda Knowles was a graduate student in Scott's lab back in the late 1980s (Figure 1.1). She was bright and funny and totally unimpressed by Scott's supposed seniority. She was trained as a chemist and had begun graduate school doing biochemistry. However, Brenda had a strong connection to biology and the organisms that embody so much more complexity than simple biochemistry. Soon she found her way into a lab where there were organisms to work on, maybe just fruit flies, but organisms nonetheless.

She shared her time in Scott's lab with the usual array of characters that populate a "working lab". Science is a business that cherishes eccentricity, even

FIGURE 1.1 Brenda Brodeur Knowles (1962–1996). (Photo courtesy of James Knowles.)

encourages it. A healthy, growing lab will have its share of unusual characters. The basic foundation on which any new lab is started is unusual and novel ideas. Such ideas often come from and attract unusual and novel people.

In some ways, Brenda resembled the classic image of a young scholar. Her radio played classical music or National Public Radio, drowning out the competing styles of rock music from other desks or that much-ridiculed country music emanating from Scott's office. Her desk was neat and her ideas were equally well organized. She was rigorous in her critical thinking and tenacious in her pursuit of answers to scientific questions. She wrote (on her own) two papers from Scott's lab and went on to continue her scientific training by taking on a postdoctoral fellowship at Yale.

On her way to that fellowship, she married a handsome young doctor and they bought a beautiful little house in rural Connecticut. If you sense a fairy tale being told here, there's a reason: Brenda's life always seemed a bit of a fairy tale to Scott. This fairy tale was unusual only in the sense that Brenda was enough of a feminist to slay most of her own dragons.

That is, until Brenda got sick. Sometime in the early 1990s, Brenda acquired acute myelogenous leukemia (AML). We'll talk more about leukemia later in this book. The disease results from a rather nasty genetic alteration that occurs in one of the stem cells that produce the circulating cells in our blood. The result is an instruction for the altered stem cell to divide repeatedly. Leukemia was the ultimate dragon in Brenda's life, and she committed all of her resources to slaying it. She tried everything that was available, or even close to available. She suffered more than our words can convey. In the end, she lost the battle.

The battle she lost was just one battle in what the press often refers to as the "war on cancer". In 1969 a full-page ad in the *New York Times* urged President Nixon to begin a war on cancer, saying ". . . We are so close to a cure for cancer. We lack only the will and the kind of money and comprehensive planning that went into putting a man on the moon." The war on cancer was proposed in 1969. Brenda lost her battle with cancer in 1996.

There have been too many such battles. For most of history the idea of a cure for cancer has seemed like an impossible dream. We daresay that there will not be a single reader of this book who does not know someone touched by cancer. After all, one in four of us will get cancer in our lifetimes. But not all the battles are lost. There are some cures, many remissions, and many cases in which the cancer is simply held in check for years at a time. Still, Brenda died.

With impatient excitement, we watch advances in cancer treatment begin building on the results coming out of genetic studies of cancer. Breakthroughs in understanding of the molecular mechanisms of various forms of leukemia have led to breakthroughs in the development of new treatment approaches. Scientists have begun creating molecular "lances" aimed at slaying the monsters that are the various kinds of leukemia. Their molecular lances are drugs designed based on an understanding of what has gone wrong at the molecular level in the leukemia cells. How wonderful that these weapons against leukemia are emerging; how terrible that they will come too late for Brenda. Increasingly, we are seeing "magic bullets" emerge based on breakthroughs in our understanding of the underlying mechanisms of diseases caused by defects in genes. Some of these new cures use gene therapy, but we are going

to see a lot of other pharmaceutical treatments emerge that will not use gene therapy even though they will be based on the information gained from the study of genes.

In a very real sense the scientists who are developing these new genetically based anti-cancer drugs are having to decipher a "lock" smaller than a thousandth of a pinpoint. That lock had been created by a change in the genes of a human cell. That lock committed that cell to a future of unrelenting cell division. The cure comes from building a "key" that releases that lock. If you understand that metaphor, that's wonderful. It would be even better if you understood the "magic bullet" and the "dragon-slaying" metaphors that we used before.

But we hope, we really hope, that you find such trite metaphors to be entirely unsatisfying. We hope you want to know what we mean by cells, and genes, in order to understand what all of these metaphors really mean. Because the scientist who builds this "magic bullet" isn't a wizard or a magician, he or she is a biologist. And as much magic as we biologists do see in the living world, we need to describe living systems, and manipulate them, in terms of molecules that interact with and within structures called cells.

That need to describe the chemistry of molecules and the structures of cells has been interpreted by others as a need to use terminology that requires a bachelor's degree in biology (and, better yet, chemistry!) to comprehend. However, we think that we can keep the chemistry in hand, by focusing on the processes that go on in a cell and on the functions that certain types of molecules play in the cell. We don't need to understand polymer chemistry to play with Legos made of plastic polymers. Similarly, to understand molecular genetic processes, we need only to know what overall structure the cell is trying to build, what pieces we have in our toy box, and how to snap them together. This does not mean that the chemical terms and structures are unimportant. Such details are in fact critical to anyone who is going to carry out studies of these systems. However, a lot of the concepts unveiled by such studies can then be understood without needing the expertise that was required to make the discovery in the first place.

Using that kind of framework, we will build you the verbal equivalent of Lego models of cells and, more importantly, of genes. We'll try to show you how genes work and how they control the activity of the cell. In time, we'll build a model of an "engine" that controls when cells divide and describe the "lock" that forces that engine to be locked "on." And we'll tell you how scientists are finding keys that disarm some of the locks that commit cells to relentless division and growth.

Treatments for leukemia are just one such example of the kinds of "genetic" medicines that will emerge with increasing frequency in the future. There will be ever so many more. The sad news is that the "cure" will have come too late for Brenda; the good news is that it will come at all! There will be more Brendas, but now we can dream the impossible dream, that there will be cures and the outcome will be better. Much better.

2 THE ANSWER IN A NUT SHELL: GENES, PROTEINS, AND THE BASIS OF LIFE

There are always those who ask, what is it all about? For those who need to ask, for those who need points sharply made, who need to know "where it's at," this: —*Harlan Ellison*[1]

Our genes provide a blueprint for our bodies. In doing so they set some upper and lower limits on our potential. Our interaction with the world and others defines the rest. —*R. Scott Hawley*

Marlaina Susi was a beautiful little eight-year-old girl who was active and friendly. She was an energetic child who was filled with a love of life and embraced everyone she encountered. She earned above average grades, participated in a variety of sports and other activities, and had not missed a single day of school due to illness during the previous school year. She has also been described as a picky eater, but no one realized at the time that her aversion to dietary protein might have been protecting her by helping her avoid high levels of protein that could be harmful to people with some types of metabolic defects. In 1999 her happy and seemingly healthy life was interrupted one day by a brief illness and fever from which she should have recovered, as young children normally recover from the usual array of "bugs" that get passed around an elementary school. Instead of recovering and rejoining her friends at school, she developed elevated levels of ammonia in her blood, was hospitalized, and died thirty three days later. After her death, her grief-stricken family continued their search for an answer to what had caused her death. They were told that she had a defect in the ornithine transcarbamylase (OTC) gene, one of several genes responsible for helping our bodies cope with the ammonia (NH_3) that forms as a normal part of metabolizing protein that we consume. If her OTC defect had been diagnosed during her hospital stay, there were medical remedies that would have been available to help her. But getting a correct diagnosis on time was complicated by several things: OTC defects are rare, they usually manifest in infants, they are usually seen in boys rather than girls, and Marlaina's defect was partial rather than complete. So what is an OTC defect, how can it have such a devastating effect, and why did the problem not show up until Marlaina was eight years old? To understand what happened to Marlaina, and to eventually find ways to protect other children with similar gene defects, we need to understand how a defect in a gene can lead to such devastating consequences.[2]

Marlaina Susi (1991–1999)
(Photo courtesy of the Susi family)

[1] From "Repent Harlequin!" Said the Ticktockman by Harlen Ellison.

[2] On the web site for the National Urea Cycle Disorders Foundation (NUCDF), there is a page that talks about Marlaina and the two memorial marches that have been held in her name to raise money for the Foundation. Information on OTC and other urea cycle disorders can be obtained from NUCDF, the Canadian Society for Metabolic Disease, or the National Organization for Rare Disorders.