
PRINCIPLES OF MOLECULAR MEDICINE

SECOND EDITION

SECTION EDITORS

RICHARD C. BOUCHER, MD

*CYSTIC FIBROSIS RESEARCH AND TREATMENT CENTER
DIVISION OF PULMONARY DISEASES
DEPARTMENT OF MEDICINE
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, NC*

DAVID A. BRENNER, MD

*DEPARTMENT OF MEDICINE
COLLEGE OF PHYSICIANS AND SURGEONS
COLUMBIA UNIVERSITY MEDICAL CENTER
NEW YORK, NY*

LUIS A. DIAZ, MD

*DEPARTMENT OF DERMATOLOGY
SCHOOL OF MEDICINE
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, NC*

JAMES P. EVANS, MD, PhD

*DEPARTMENT OF GENETICS
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, NC*

DANIEL J. GARRY, MD, PhD

*DEPARTMENTS OF INTERNAL
MEDICINE AND MOLECULAR BIOLOGY
UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER
DALLAS, TX*

LOWELL A. GOLDSMITH, MD, MPH

*DEPARTMENT OF DERMATOLOGY
SCHOOL OF MEDICINE
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, NC*

STEVEN M. HOLLAND, MD

*LABORATORY OF CLINICAL INFECTIOUS DISEASES
NATIONAL INSTITUTE OF ALLERGY
AND INFECTIOUS DISEASE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD*

SAMUEL KLEIN, MD

*CENTER FOR HUMAN NUTRITION
DIVISION OF GERIATRICS AND NUTRITIONAL SCIENCES
WASHINGTON UNIVERSITY SCHOOL OF MEDICINE
St. LOUIS, MO*

TERRY MAGNUSON, PhD

*DEPARTMENT OF GENETICS
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, NC*

W. STRATFORD MAY, JR., MD, PhD

*UNIVERSITY OF FLORIDA SHANDS CANCER CENTER
UNIVERSITY OF FLORIDA
GAINESVILLE, FL*

MICHAEL J. MCPHAUL, MD

*DEPARTMENT OF INTERNAL MEDICINE
UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
DALLAS, TX*

WILLIAM E. MITCH, MD

*DIVISION OF NEPHROLOGY
BAYLOR COLLEGE OF MEDICINE
HOUSTON, TX*

CHARLES B. NEMEROFF, MD, PhD

*DEPARTMENT OF PSYCHIATRY
AND BEHAVIORAL SCIENCES
EMORY UNIVERSITY SCHOOL OF MEDICINE
ATLANTA, GA*

PEADAR G. NOONE, MD

*CYSTIC FIBROSIS RESEARCH AND TREATMENT CENTER
DIVISION OF PULMONARY DISEASES
DEPARTMENT OF MEDICINE
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, NC*

KERRY J. RESSLER, MD, PhD

*DEPARTMENT OF PSYCHIATRY
AND BEHAVIORAL SCIENCES
EMORY UNIVERSITY SCHOOL OF MEDICINE
ATLANTA, GA*

ANTHONY ROSENZWEIG, MD

*CENTER FOR IMMUNOLOGY
AND INFLAMMATORY DISEASES
MASSACHUSETTS GENERAL HOSPITAL
BOSTON, MA*

STEPHEN M. STRITTMATTER, MD, PhD

*DEPARTMENT OF NEUROLOGY
YALE UNIVERSITY SCHOOL OF MEDICINE
NEW HAVEN, CT*

SWEE LAY THEIN, DSc, FRCP, FRCPath, FMedSci

*DEPARTMENT OF HAEMATOLOGICAL MEDICINE
GUY'S, KING'S AND ST. THOMAS'
SCHOOL OF MEDICINE
LONDON, UK*

PRINCIPLES OF
**MOLECULAR
MEDICINE**

SECOND EDITION

EDITED BY

MARSCHALL S. RUNGE, MD, PhD

*DEPARTMENT OF MEDICINE, DIVISION OF CARDIOLOGY
CAROLINA CARDIOVASCULAR BIOLOGY CENTER
UNIVERSITY OF NORTH CAROLINA SCHOOL OF MEDICINE
CHAPEL HILL, NC*

CAM PATTERSON, MD

*DEPARTMENT OF MEDICINE, DIVISION OF CARDIOLOGY
CAROLINA CARDIOVASCULAR BIOLOGY CENTER
UNIVERSITY OF NORTH CAROLINA SCHOOL OF MEDICINE
CHAPEL HILL, NC*

FOREWORD BY

VICTOR A. MCKUSICK, MD

*JOHNS HOPKINS UNIVERSITY
BALTIMORE, MD*




HUMANA PRESS
TOTOWA, NEW JERSEY

© 2006 Humana Press Inc.
999 Riverview Drive, Suite 208
Totowa, New Jersey 07512

www.humanapress.com

All rights reserved. No part of this book may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, microfilming, recording, or otherwise without written permission from the Publisher.

All papers, comments, opinions, conclusions, or recommendations are those of the author(s), and do not necessarily reflect the views of the publisher.

This publication is printed on acid-free paper. 
ANSI Z39.48-1984 (American Standards Institute)
Permanence of Paper for Printed Library Materials.

Production Editor: Jennifer Hackworth

Cover design by Patricia F. Cleary

For additional copies, pricing for bulk purchases, and/or information about other Humana titles, contact Humana at the above address or at any of the following numbers:
Tel.: 973-256-1699; Fax: 973-256-8341; E-mail: orders@humanapr.com; or visit our Website: www.humanapress.com

Photocopy Authorization Policy:

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Humana Press, provided that the base fee of US \$30.00 per copy is paid directly to the Copyright Clearance Center at 222 Rosewood Drive, Danvers, MA 01923. For those organizations that have been granted a photocopy license from the CCC, a separate system of payment has been arranged and is acceptable to Humana Press Inc. The fee code for users of the Transactional Reporting Service is: [1-58829-202-9/06 \$30.00].

Printed in the United States of America. 10 9 8 7 6 5 4 3 2 1
1-59259-963-X (e-book)

Library of Congress Cataloging in Publication Data

Principles of molecular medicine / edited by Marschall S. Runge ; foreword by Victor A. Mckusick. -- 2nd ed.

p. ; cm.

Includes bibliographical references and index.

ISBN 1-58829-202-9 (alk. paper)

1. Medical genetics. 2. Pathology, Molecular. 3. Molecular biology.

I. Runge, Marschall Stevens, 1954- .

[DNLM: 1. Genetics, Medical. 2. Gene Therapy. 3. Molecular Biology. QZ 50 P9573 2006]

RB155.P695 2006

616'.042--dc22

2005034346

Foreword

The concept of molecular medicine dates back to Linus Pauling, who in the late 1940s and early 1950s generalized from the ideas that came from the study of the sickle cell hemoglobin molecule. With the first cloning of human genes about 1976, molecular genetics took the molecular perspective on disease to the level of DNA. The term molecular medicine achieved wide currency in the 1980s with the assignment of this designation to journals, at least one society, institutes, and academic divisions of departments of internal medicine. Undoubtedly, molecular medicine has been abetted by the Human Genome Project, which has aided greatly in the molecular characterization of disease. Map-based gene discovery, as in positional cloning of previously unknown genes responsible for “mystery diseases,” could be now replaced by sequence-based gene discovery.

What is molecular medicine? In the first edition of *Principles of Molecular Medicine*, Francis Collins seems to define it as “molecular genetics and medicine”—the last four words of his Foreword. He was referring to the pervasive relevance of genetics and genomics to all of medicine. In essence, molecular medicine is genetic medicine.

Since the publication of the first edition *Principles of Molecular Medicine* in 1998, the Human Genome Project has provided a “complete” sequence of the human genome with several surprising revelations relevant to molecular medicine.

As indicated in the Preface of the first edition, the total count of genes was thought to be 50,000 to 80,000. Scrutiny of the complete human sequence leads to a count only half that, perhaps fewer than 30,000. It has come to be realized that each gene can give rise to multiple protein gene products through alternative splicing of pre-messenger RNA, as well as through different posttranscriptional modification of the gene products. Each gene may on the average have as many as 10 different protein products. Mutations in different ones of these can cause quite different clinical disorders. Thus the focus has shifted to the transcriptome and to the proteins that constitute the proteome—a shift from genomics to proteomics.

Compilation of the rapidly expanded topic of molecular medicine since the edition of some 8 years ago is a daunting task. The rate at which new discoveries have been made

means that there are many new opportunities and challenges for clinical medicine. One of the effects of the completion of the Human Genome Project is the increasing application of the fields of molecular biology and genetics to the understanding and management of common diseases. Assimilation of the new developments since the first edition has been ably accomplished by Drs. Runge and Patterson with the help of their many knowledgeable authors.

As was evident in the first edition, molecular genetics is involved in every specialty of medicine. A recurrent theme in that edition, perhaps even more striking in the present one, is that information gleaned and research methods designed in one specialty have been highly influential on researchers and physicians in other fields—often in ways that could not have been foreseen. The editors have succeeded in considering all the disciplines while searching for connections and correlations that might otherwise be missed.

The organization selected by the editors allows for the molecular bases of disease, as well as the constantly evolving areas of ethical issues and counseling that affect all disciplines, to be covered in the opening section. Specifics in the several medical disciplines are then handled splendidly in the sections that follow. Each chapter resounds with the amazing detail of what is known and simultaneously probes the many unanswered questions that provide new avenues for research in the 21st century. The state-of-the-art focus in each specialty will be much appreciated by the reader, whether practitioner, researcher or student.

The authors and section editors that participated in this text are recognized leaders in their fields from around the globe. They and Drs. Runge and Patterson, who have led and coordinated this extraordinary effort, deserve commendation. The product is a text that will be useful for all interested in the molecular pathogenesis of disease.

Victor A. McKusick, MD

Foreword to the First Edition

Until recently, medical genetics and molecular medicine were considered the exclusive province of academic specialists in tertiary-care medical centers. Queried about their familiarity with molecular genetic aspects of clinical medicine, most primary-care providers only a few years ago would have responded that such matters were irrelevant to their daily practice.

Yet few could say that today. Few internists or general practitioners have not prescribed recombinant insulin, tPA, or erythropoietin; few pediatricians have not gone through the molecular evaluation of a child with dysmorphology or learning disability; few obstetricians have not performed amniocentesis or CVS for couples at increased genetic risk; and few general surgeons have not faced penetrating questions about the role of genetic testing or prophylactic surgery from women with a strong family history of breast or ovarian cancer.

This level of emergence of molecular genetics into clinical medicine is still quite modest, however, compared to what is coming. As the human genome project hurtles toward completion of the sequence of a reference human genome, and the identification of all human genes, by 2005, the pace of revelations about human illness will continue to accelerate. Until recently, most disease-gene discoveries have related to single-gene disorders (cystic fibrosis, fragile X syndrome, and so on) or to Mendelian subsets of more common illnesses (BRCA1 and BRCA2, the hereditary nonpolyposis colon cancer syndromes, and so on). But with

the initiation in 1998 of an aggressive new genome project goal, cataloging all common human sequence variations, it is expected that the weaker polygenic contributors to virtually all diseases will begin to be discerned. Many consequences will result. Individualized preventive medicine strategies, rooted in the gene-based determination of future risk of illness, will become part of the regular practice of medicine. New designer drugs, based not on empiricism but on a detailed understanding of the molecular pathogenesis of disease, will appear. Pharmacogenomics, wherein the efficacy and toxicity of a particular drug regimen can be predicted based on patient genotype, will become a standard component of designing optimum therapy for the individual. And gene therapy, fed by a wealth of disease-gene discoveries, will mature into a significant part of the physician's armamentarium against disease.

As we watch this train coming down the track, this is an ideal time to collect information about molecular medicine into one authoritative text. *Principles of Molecular Medicine* aims to do just that, bridging the current gap between basic science and the bedside. It will thus be useful to researchers and clinicians alike. With more than 100 chapters covering a wide variety of topics, its distinguished cohort of section editors, and its abundant tables and illustrations, it provides an accessible and much needed manual to the present and the future of molecular genetics and medicine.

Francis S. Collins

Preface

Since publication of the first edition of *Principles of Molecular Medicine*, dramatic discoveries in molecular medicine along with concomitant rapid technological advances have revolutionized the diagnosis and treatment of a broad range of human diseases. Given the pace of new discovery, genetic- and cell-based therapies may well become a common part of the physicians' armamentarium in the near future. Direct links between genetic mutations and diseases are being mapped almost routinely. Genomic approaches to diseases such as breast cancer have led to identification of previously unrecognized malignancies and the ability to prognosticate outcomes to therapy. The delicate interplay between adipocytes and regulation of insulin sensitivity, the roles of bone morphogenetic proteins in pulmonary hypertension, and the discovery of mutations involved in an array of cardiomyopathies are but a few of the important recent advances that have direct implications for patient care.

It is virtually impossible to keep track of the breadth of discovery that has led to these biomedical advances. The goal of the many authors and editors of this second edition of the *Principles of Molecular Medicine* has been to present the voluminous discoveries of the past decade in a format that captures the essence of scientific discovery but allows rapid assimilation in each particular area.

This second edition again includes chapters describing advances in fields paralleling traditional medical texts, and will be especially useful to specialists who are updating their education, practicing physicians interested in keeping abreast of new developments, and students appropriately curious about what is known and what lies ahead. Although only 8 years have passed since the first edition was published, we have made every effort to comprehensively update chapters with recent advances and have added chapters for disease entities and areas in which discovery has accelerated during the past five years.

As we have participated in the assembly of this volume, we have had the good fortune to review in depth the molecular discoveries that are transforming medical practice. For example, in the interval since the first edition of this text, stem cell populations have been discovered that regenerate muscle, heart, and neural cell populations, and that have the

potential to serve as cell-based therapies in chronic and degenerative diseases. New cell growth and cell death mechanisms that are dysregulated in neoplasia and that may serve as new anticancer targets have been elucidated. Advances have been made in understanding the biology of previously untreatable neurodegenerative diseases such as Huntington's disease. These and many other important advances in our understanding of human diseases are elucidated in this edition.

In addition, we have been able to note the new epistemologies in the genetic basis of human disease that are rapidly emerging. For instance, characterization of candidate genes for human diseases has expanded well beyond monogenic diseases, the study of late-onset diabetes being a notable example. Molecular alterations can have far-reaching effects on many systems. The identification of genes for epithelial sodium channels has led to a deeper understanding of their role in disorders of total body Na⁺ homeostasis, blood volume, and blood pressure. As a result of advances like these, views that had been held for much of the 20th century are being reconsidered. For example, hereditary hemochromatosis, a familial disease characterized by excess tissue deposits of iron leading to end-organ damage, has traditionally been thought to result from mutations in a single gene. Very recently, the identification of similar phenotypes associated with mutations of at least four different iron-metabolism genes has expanded our understanding of the pathophysiology of this relatively common genetic disease.

One common theme repeated in the chapters in this text is that the pathophysiology of disease is often a succession of genetic alterations, not just a single mutation. Although understanding these genetic relationships is never simple, their role in human diseases is all the more fascinating to consider. Human health often appears tenuous, but the discovery that a series of genetic missteps is often required to produce many disease states can be reassuring. The presence of several genetic steps in a disease process also suggests that multiple therapeutic targets may exist to modulate the course of these diseases. Less exhilarating is the knowledge that numerous diseases result not just from a complex succession of genetic missteps, but also from an individual's

interaction with the environment. Abundant examples of this principle are present throughout clinical medicine, and are described in detail in this edition of *Principles of Molecular Medicine*.

Paradoxically, as new discoveries are made, new mysteries appear. The many advances described in this volume often raise as many new questions as they answer. On the one hand, this indicates that biomedical discovery and medical practice will continue to evolve. On the other hand, the changes in medical care described in the chapters of this text are an indication that the unresolved questions of today may be harbingers of new therapeutic approaches in years to come.

It has been our pleasure to bring together in-depth expositions of the most recent advances in molecular medicine. We invite you to enjoy this magnificent point in biomedical history, as genetics and molecular medicine continue to merge with clinical practice. The compendium of information in *Principles of Molecular Medicine: Second Edition*, has been made possible by the tireless efforts of our section editors. Without their expertise and commitment to this project, this textbook would not be possible. In addition, we

thank the individual authors for sharing their expertise with all of us.

In addition to the phenomenal work of the editors and contributors, we would like to extend special thanks to Ms. Katie O'Brien for her commitment to this project; to Ms. Angela Clotfelter-Rego, whose tireless efforts despite numerous obstacles made this project possible; and to Ms. Carolyn Kruse, who synthesized the work of numerous authors to create a blazingly readable text. The editors thank our families, who have tolerated yet another joint effort. Finally, we would like to dedicate this volume to the first chairmen of medicine we had the privilege to serve under, Juha P. Kokko, MD, PhD, and Victor McKusick, MD. As physicians and scientists, these gentlemen nurtured many of the contributors to this edition, and their own work as scientists is frequently cited directly and indirectly in these chapters. It is on the shoulders of men like these that the principles of molecular medicine have been determined.

Marschall S. Runge, MD, PhD
Cam Patterson, MD

Contents

FOREWORD	V	11	Inherited Cardiomyopathies 98
FOREWORD TO THE FIRST EDITION	VII		<i>Carolyn Y. Ho and Christine E. Seidman</i>
PREFACE	IX	12	Heart Failure: <i>Emerging Concepts</i> <i>in Excitation–Contraction Coupling</i> <i>and β-Adrenoceptor Coupling</i> 105
CONTRIBUTORS	XV		<i>Clive J. Lewis, Federica del Monte, Sian E.</i> <i>Harding, and Roger J. Hajjar</i>
LIST OF COLOR PLATES	XXV	13	Aortic Diseases 116
			<i>Saumya Das, James L. Januzzi, Jr.,</i> <i>and Eric M. Isselbacher</i>
I. GENETICS		14	Atherosclerotic Coronary Disease 121
TERRY MAGNUSON AND JAMES P. EVANS			<i>Robert E. Gerszten and Anthony Rosenzweig</i>
1 Mendelian Inheritance 3		15	Lipid Metabolism and Coronary Artery Disease 130
<i>Bruce R. Korf</i>			<i>Mason W. Freeman</i>
2 Nontraditional Inheritance 9		16	Hypertension 138
<i>Shawn E. McCandless and Suzanne B. Cassidy</i>			<i>Khurshed A. Katki and Donald J. DiPette</i>
3 Identifying Causal Genetic Factors 19		17	Cardiac Hypertrophy 146
<i>Christopher I. Amos, John S. Witte,</i> <i>and William G. Newman</i>			<i>Thomas Force and Jeffrey D. Molkentin</i>
4 Cancer Genetics and Molecular Oncology 27		18	Arrhythmias 157
<i>Sharon E. Plon</i>			<i>Barry London</i>
5 Pharmacogenetics 34		19	Genomics 166
<i>Renee E. Edkins and Dennis J. Cheek</i>			<i>Calum A. MacRae and Christopher J. O'Donnell</i>
6 Hemophilia as a Model Disease for Gene Therapy of Genetic Disorders 39		20	Cardiovascular Gene Therapy 175
<i>Jay Lozier</i>			<i>David A. Dichek</i>
7 Genetic Counseling 46			
<i>Robin L. Bennett</i>		III. PULMONARY DISEASES	
8 Animal Models in Biomedical Research: <i>Ethics, Challenges,</i> <i>and Opportunities</i> 53		RICHARD C. BOUCHER AND PEADAR G. NOONE	
<i>Robert W. Williams</i>		21	Idiopathic Interstitial Pneumonias 188
9 Ethical, Legal, and Social Implications 61			<i>Talmadge E. King, Jr.</i>
<i>Marcia Van Riper</i>		22	Asthma 198
			<i>Stephen T. Holgate, Gordon Dent,</i> <i>and Mark G. Buckley</i>
II. CARDIOLOGY		23	Pulmonary Emphysema 214
ANTHONY ROSENZWEIG			<i>Steven D. Shapiro</i>
10 Congenital Heart Disease 69			
<i>Lazaros K. Kochilas and Alvin J. Chin</i>			

24	Pulmonary Hypertension	223	43	Disorders of Pubertal Development	453
	<i>Brian Fouty and David M. Rodman</i>			<i>Tomonobu Hasegawa</i>	
25	Acute Lung Injury	231	44	Defects of Androgen Action	466
	<i>David C. Christiani and Michelle Ng Gong</i>			<i>Michael J. McPhaul</i>	
26	Primary Ciliary Dyskinesia	239	45	Molecular Endocrinology of the Testis	473
	<i>Peadar G. Noone, Maimoona Zariwala, and Michael R. Knowles</i>			<i>Marco Marcelli, Glenn R. Cunningham, José M. Garcia, Kirk C. Lo, and Dolores J. Lamb</i>	
27	Cystic Fibrosis	251	46	Ovarian Diseases	495
	<i>Scott H. Donaldson and Richard C. Boucher</i>			<i>Elizabeth A. McGee and Tammy L. Loucks</i>	
28	Gene Therapy for Lung Diseases	259	V. METABOLIC DISORDERS		
	<i>Jane C. Davies, Duncan M. Geddes, and Eric W.F.W. Alton</i>		SAMUEL KLEIN		
29	Sarcoidosis	269	47	Gastrointestinal Regulation of Food Intake	513
	<i>Kelly D. Chason and Stephen L. Tilley</i>			<i>Patrick Tso and Min Liu</i>	
30	Disorders of Pulmonary Surfactant Homeostasis	277	48	Cellular Regulation of Lipolysis	518
	<i>Jeffrey A. Whitsett, Susan E. Wert, and Bruce C. Trapnell</i>			<i>Allan Green</i>	
IV. ENDOCRINOLOGY			49	Fat-Induced Insulin Resistance and Atherosclerosis	524
MICHAEL J. MCPHAUL				<i>Guenther Boden</i>	
31	Mechanisms of Hormone Action	291	50	Metabolic and Molecular Aspects of Sarcopenia	529
	<i>Stephen R. Hammes, Carol A. Lange, and Michael J. McPhaul</i>			<i>W. Todd Cade and Kevin E. Yarasheski</i>	
32	Diabetes Mellitus	308	51	Adipose Tissue Development and Metabolism	535
	<i>William L. Lowe, Jr.</i>			<i>Sheila Collins, Yushi Bai, and Jacques Robidoux</i>	
33	Pituitary Function and Neoplasia	319	VI. GASTROENTEROLOGY		
	<i>Shlomo Melmed</i>		DAVID A. BRENNER		
34	Growth Hormone Deficiency Disorders	327	52	Hepatitis C	542
	<i>Amy Potter and John A. Phillips, III</i>			<i>Johnson Yiu-Nam Lau, Jane Wing-Sang Fang, Masashi Mizokami, Robert G. Gish, and Teresa L. Wright</i>	
35	Thyroid Disorders	337	53	Molecular Diagnostics in Hepatitis B	554
	<i>Peter Kopp</i>			<i>Scott Bowden and Stephen Locarnini</i>	
36	Disorders of the Parathyroid Gland	357	54	Hereditary Hemochromatosis	567
	<i>Andrew Arnold and Michael A. Levine</i>			<i>Francesca Ferrara, Elena Corradini, and Antonello Pietrangelo</i>	
37	Congenital Adrenal Hyperplasia	365	55	Pancreatic Exocrine Dysfunction	573
	<i>Robert C. Wilson and Maria I. New</i>			<i>David C. Whitcomb and Jonathan A. Cohn</i>	
38	Adrenal Diseases	377	56	Small and Large Bowel Dysfunction	581
	<i>Richard J. Auchus, William E. Rainey, and Keith L. Parker</i>			<i>Deborah C. Rubin</i>	
39	Multiple Endocrine Neoplasia Type 1	386	57	The Molecular Mechanisms of <i>Helicobacter pylori</i> -Associated Gastrointestinal Disease	590
	<i>Rajesh V. Thakker</i>			<i>Peter B. Ernst</i>	
40	Multiple Endocrine Neoplasia Type 2	393			
	<i>Robert F. Gagel, Sarah Shefelbine, Hironori Hayashi, and Gilbert Cote</i>				
41	Disorders of Sex Determination and Differentiation	400			
	<i>Charmian A. Quigley</i>				
42	Sex Chromosome Disorders	446			
	<i>Andrew R. Zinn</i>				

VII. NEPHROLOGY**WILLIAM E. MITCH**

- 58 Nitric Oxide Synthase and Cyclooxygenase
in the Kidneys 606
Christopher S. Wilcox
- 59 Hypertension and Sodium Channel Turnover 613
*Douglas C. Eaton, Bela Malik,
and He-Ping Ma*
- 60 Nephrogenic Diabetes Insipidus:
Water and Urea Transport 622
Jeff M. Sands and Daniel G. Bichet
- 61 Glomerulonephritis and Smad Signaling 629
Hui Y. Lan and Richard J. Johnson
- 62 Interstitial Nephritis 636
Carla Zoja and Giuseppe Remuzzi
- 63 The Pathophysiology of Acute
Renal Failure 643
*Didier Portilla, Gur P. Kaushal, Alexei G.
Basnakian, and Sudhir V. Shah*
- 64 Loss of Lean Body Mass in Uremia 650
S. Russ Price and William E. Mitch
- 65 Mechanisms of Renal Allograft Rejection 656
*Daniel R. Goldstein, Anirban Bose,
and Fadi G. Lakkis*

VIII. MUSCULOSKELETAL**DANIEL J. GARRY**

- 66 Muscle Development and Differentiation 665
Eric N. Olson
- 67 Skeletal Muscle Structure and Function 674
*Elizabeth M. McNally, Karen A. Lapidos,
and Matthew T. Wheeler*
- 68 Stem Cells and Muscle Regeneration 682
*Cindy M. Martin, Thomas J. Hawke,
and Daniel J. Garry*
- 69 Skeletal Muscle Hypertrophy
and Response to Training 688
Zhen Yan and R. Sanders Williams
- 70 Muscular Dystrophies: *Mechanisms* 693
Peter B. Kang and Louis M. Kunkel
- 71 Rhabdomyosarcomas 700
Stephen J. Tapscott

IX. ONCOLOGY**W. STRATFORD MAY, JR.****SOLID TUMORS**

- 72 Apoptosis 709
W. Stratford May, Jr. and Xingming Deng

- 73 Colorectal Cancer 720
Satya Narayan
- 74 Breast Cancer 728
Yi Huang and Nancy E. Davidson
- 75 Lung Cancer 736
Lei Xiao
- 76 Discoveries and Frontiers in Prostate Cancer
Translational Sciences 743
Jonathan W. Simons
- 77 Cutaneous Melanoma 752
Moira R. Jackson and Stephen P. Segrue
- 78 Applications of Gene Expression
Profiling to the Study
of Malignant Gliomas 760
Anthony T. Yachnis and Henry V. Baker

HEMATOLOGICAL MALIGNANCIES

- 79 Acute Myeloid Leukemias 767
Iris T. Chan and D. Gary Gilliland
- 80 Acute Lymphoblastic Leukemia 776
Alexander E. Perl and Donald Small
- 81 Chronic Myelogenous Leukemia 789
Brian J. Druker
- 82 Non-Hodgkin's Lymphoma and Chronic
Lymphocytic Leukemia 794
Ayad M. Al-Katib and Anwar N. Mohamed
- 83 Multiple Myeloma: *A Story of Genes
and the Environment* 804
Kenneth H. Shain and William S. Dalton
- 84 HIV-1, AIDS, and Related Malignancies 818
Maureen M. Goodenow and James J. Kohler

X. HEMATOLOGY**SWEE LAY THEIN**

- 85 Disorders of the Red Cell Membrane 830
Jean Delaunay and Gordon W. Stewart
- 86 Paroxysmal Nocturnal Hemoglobinuria 838
*Bruno Rotoli, Khedoudja Nafa,
and Antonio M. Risitano*
- 87 Iron Metabolism 848
Nancy C. Andrews
- 88 Correction of Genetic Blood Defects
by Gene Transfer 854
*Marina Cavazzana-Calvo, Salima Hacein-
Bey-Abina, Adrian J. Thrasher, Philippe
Leboulch, and Alain Fischer*
- 89 Bone Marrow Failure Syndromes 862
J. Eric Turner and Thomas C. Shea

- 90 Coagulation Disorders **871**
Stephan Moll and Gilbert C. White II
- 91 Advances in Transfusion Safety **883**
Lorna M. Williamson and Jean-Pierre Allain
- XI. IMMUNOLOGY
AND INFECTIOUS DISEASES**
STEVEN M. HOLLAND
- 92 Immunomodulation **893**
Juan C. Gea-Banacloche
- 93 HIV Molecular Biology, Treatment,
and Resistance **905**
Frank Maldarelli
- 94 Cellular and Molecular Aspects
of Pneumonia **912**
Marcus J. Schultz and Tom van der Poll
- 95 Molecular Pathogenesis
of Fungal Infections **920**
Brahm H. Segal
- XII. DERMATOLOGY**
LUIS A. DIAZ AND LOWELL A. GOLDSMITH
IMMUNE MEDIATED
- 96 Psoriasis **939**
James T. Elder
- 97 Atopic Dermatitis **948**
*Kefei Kang, Donald Y. M. Leung,
and Kevin D. Cooper*
- 98 Pemphigus Foliaceus, Pemphigus Vulgaris,
Paraneoplastic Pemphigus, Bullous
Pemphigoid, Herpes Gestationis
and Cicatricial Pemphigoid **959**
*Ning Li, David S. Rubenstein, Zhi Liu,
and Luis A. Diaz*
- 99 Systemic Lupus Erythematosus **970**
*Amr H. Sawalha, Luis A. Diaz,
and John B. Harley*
- 100 Systemic Sclerosis **979**
Chris T. Derk and Sergio A. Jimenez
- NONIMMUNE**
- 101 Diseases With Signaling and Transcriptional
Abnormalities **991**
*David S. Rubenstein, Amy Stein,
and Lowell A. Goldsmith*
- 102 Genetic Skin Diseases With Neoplasia **998**
David S. Rubenstein
- 103 Melanoma and Nevi **1004**
Nancy E. Thomas
- 104 Disorders of Hypopigmentation **1011**
Julie V. Schaffer and Jean L. Bologna
- 105 Epidermolysis Bullosa **1024**
*Jouni Uitto, Gabriele Richard,
and Angela M. Christiano*
- 106 Connective Tissue Disorders: *The
Paradigms of Ehlers-Danlos Syndrome
and Pseudoxanthoma Elasticum* **1035**
Jouni Uitto and Franziska Ringpfeil
- 107 Genetic Epidermal Diseases **1043**
Amy Stein and Lowell A. Goldsmith
- 108 Genetic Hair and Nail Defects **1052**
*Marija Tadin-Strapps
and Angela M. Christiano*
- 109 Metabolic Genetic Disorders
With Prominent Skin Findings **1059**
*Christopher B. Mizelle
and Lowell A. Goldsmith*
- 110 Heritable Conditions Affecting Tissues
of the Oral Cavity **1065**
J. Tim Wright
- XIII. NEUROLOGY**
STEPHEN M. STRITTMATTER
- 111 The Genetic Basis of Human Cerebral
Cortical Malformations **1073**
Bernard S. Chang and Christopher A. Walsh
- 112 Muscular Dystrophies:
Molecular Diagnosis **1080**
Eric P. Hoffman and Erynn S. Gordon
- 113 Channelopathies of the Nervous System **1088**
Stephen C. Cannon
- 114 Charcot-Marie-Tooth Disease and Related
Peripheral Neuropathies **1097**
James R. Lupski
- 115 Amyotrophic Lateral Sclerosis
and Related Motor Neuron Disorders:
*Lessons in Pathogenesis
and Therapy From Genetics* **1105**
Robert H. Brown, Jr.
- 116 Trinucleotide Repeat Disorders **1114**
Huda Y. Zoghbi
- 117 Parkinson's Disease **1123**
Deepak M. Sampathu and Virginia M.-Y. Lee

118	Genetics and Neurobiology of Alzheimer's Disease and Frontotemporal Dementias	1130	124	The Complex Genetics of Psychiatric Disorders	1184
	<i>Peter H. St. George-Hyslop</i>			<i>Ming T. Tsuang, Stephen J. Glatt, and Stephen V. Faraone</i>	
119	Prion Diseases	1142	125	Treating Depression: Antidepressant-Activated Signaling Pathways as a Source for Novel Drug Targets	1191
	<i>Adriano Aguzzi</i>			<i>Marcelo Páez-Pereda and Florian Holsboer</i>	
120	Narcolepsy and Other Neurological Sleep Disorders	1153	126	Anxiety Disorders	1197
	<i>Thomas E. Scammell</i>			<i>Gregory M. Sullivan and Jack M. Gorman</i>	
121	Neurofibromatosis 1 and 2	1160	127	Trauma Spectrum Disorders	1203
	<i>Gregory J. Esper and David H. Gutmann</i>			<i>Christine Heim, J. Douglas Bremner, and Charles B. Nemeroff</i>	
122	Axonal Regeneration and Recovery From Chronic Central Nervous System Injury	1165	128	Schizophrenia	1211
	<i>Stephen M. Strittmatter</i>			<i>Carol A. Tamminga, Deborah C. Medoff, and Guntant Thaker</i>	
XIV. PSYCHIATRY			129	Disorders of Substance Abuse and Dependence	1220
KERRY J. RESSLER AND CHARLES B. NEMEROFF				<i>Eric J. Nestler and Jennifer Chao</i>	
123	Molecular Mechanisms Regulating Behavior: Focus on Genetic and Environmental Influences	1175	130	Autism and Related Disorders	1228
	<i>Kerry J. Ressler and Charles B. Nemeroff</i>			<i>Linmarie Sikich, Thomas H. Wassink, Kevin A. Pelphrey, and Joseph Piven</i>	
			INDEX		1237

Contributors

- ADRIANO AGUZZI, MD, PhD, FRCP, FRCPath**, *Institute of Neuropathology, University Hospital, Zurich, Switzerland*
- ERIC WFW ALTON, MD, FRCP**, *Department of Gene Therapy, Imperial College London, National Heart and Lung Institute, London, UK*
- CHRISTOPHER I. AMOS, PhD**, *Section Head of Computational and Genetic Epidemiology, Departments of Epidemiology, and Biostatistics and Applied Mathematics, University of Texas M.D. Anderson Cancer Center, Houston, TX*
- AYAD M. AL-KATIB, MD**, *Lymphoma Research Laboratory, Wayne State University School of Medicine, Detroit, Michigan and Van Elslander Cancer Center, Grosse Pointe Woods, MI*
- JEAN-PIERRE ALLAIN, MD, PhD**, *Department of Haematology, University of Cambridge, Cambridge, UK*
- NANCY C. ANDREWS, MD, PhD**, *Howard Hughes Medical Institute, Children's Hospital Boston, Harvard Medical School, Boston, MA*
- ANDREW ARNOLD, MD**, *Center for Molecular Medicine and Division of Endocrinology and Metabolism, University of Connecticut School of Medicine, Farmington, CT*
- RICHARD J. AUCHUS, MD, PhD**, *Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX*
- YUSHI BAI, MD, PhD**, *Endocrine Biology Program, Division of Biological Sciences, CIIT Centers for Health Research, Research Triangle Park, NC*
- HENRY V. BAKER, PhD**, *Department of Molecular Genetics and Microbiology, College of Medicine, University of Florida, Gainesville, FL*
- ALEXEI G. BASNAKIAN, MD, PhD**, *Department of Internal Medicine, Division of Nephrology, University of Arkansas for Medical Sciences, Central Arkansas Veterans Healthcare System, Little Rock, AR*
- ROBIN L. BENNETT, MS, CGC**, *Department of Medicine, Division of Medical Genetics, University of Washington Medical Center, Seattle, WA*
- DANIEL G. BICHET, MD**, *Department of Medicine, University of Montreal, Hôpital du Sacré-Coeur de Montreal, Quebec, Canada*
- GUENTHER BODEN, MD**, *Department of Medicine, Section of Metabolism, Diabetes and Endocrinology, Temple University Hospital, Philadelphia, PA*
- JEAN L. BOLOGNIA, MD**, *Department of Dermatology, Yale University, New Haven, CT*
- ANIRBAN BOSE, MD**, *Section of Nephrology, University of Rochester, Rochester, NY*
- RICHARD C. BOUCHER, MD**, *Division of Pulmonary Diseases, Department of Medicine, Cystic Fibrosis Research and Treatment Center, University of North Carolina, Chapel Hill, NC*
- SCOTT BOWDEN, PhD**, *Victorian Infectious Diseases Reference Laboratory (VIDRL), North Melbourne and Department of Microbiology, Monash University, Clayton, Victoria, Australia*
- J. DOUGLAS BREMNER, MD**, *Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA*
- DAVID A. BRENNER, MD**, *Department of Medicine, College of Physicians and Surgeons, Columbia University Medical Center, New York, NY*
- ROBERT H. BROWN, JR., MD, PhD**, *Day Neuromuscular Research Laboratory, Department of Neurology, Harvard Medical School, Massachusetts General Hospital, Boston, MA*
- MARK G. BUCKLEY, PhD**, *Respiratory Cell and Molecular Biology, University of Southampton School of Medicine, Southampton, UK*
- W. TODD CADE, PT, PhD**, *Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO*
- STEPHEN C. CANNON, MD, PhD**, *Department of Neurology, University of Texas Southwestern Medical Center, Dallas, TX*
- SUZANNE B. CASSIDY, MD**, *Department of Pediatrics, Division of Human Genetics, University of California, Irvine, Irvine, CA*
- MARINA CAVAZZANA-CALVO**, *INSERM, Department of Biotherapy AP-HP, Hôpital Necker, Paris, France*
- IRIS T. CHAN, MD, PhD**, *Dana-Farber Cancer Institute, Brigham and Women's Hospital, Howard Hughes Medical Institute, Harvard Medical School, Boston, MA*
- BERNARD S. CHANG, MD**, *Division of Neurogenetics, Howard Hughes Medical Institute, Beth Israel Deaconess Medical Center, Department of Neurology, Harvard Medical School, Boston, MA*
- JENNIFER CHAO, MD, PhD**, *Department of Ophthalmology, University of Southern California, Los Angeles, CA*
- KELLY D. CHASON, BS**, *Division of Pulmonary and Critical Care Medicine, University of North Carolina, Chapel Hill, NC*
- DENNIS J. CHEEK, PhD, RN, FAHA**, *Texas Christian University, Harris College of Nursing and Health Sciences and School of Nurse Anesthesia, Fort Worth, TX*

- ALVIN J. CHIN, MD**, *Department of Pediatrics, Division of Cardiology, University of Pennsylvania School of Medicine and Joseph Stokes Research Institute, The Children's Hospital of Philadelphia, Philadelphia, PA*
- DAVID C. CHRISTIANI, MD, MPH, MS**, *Pulmonary and Critical Care Unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Environmental Health Department, Harvard School of Public Health, Boston, MA*
- ANGELA M. CHRISTIANO, PhD**, *Departments of Dermatology, and Genetics and Development, College of Physicians and Surgeons, Columbia University, New York, NY*
- JONATHAN A. COHN, MD**, *Division of Gastroenterology, Duke University, Durham, NC*
- SHEILA COLLINS, PhD**, *Departments of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, and Endocrine Biology Program, Division of Biological Sciences, CIIT Centers for Health Research, Research Triangle Park, NC*
- KEVIN D. COOPER, MD**, *Department of Dermatology, University Hospitals of Cleveland, Cleveland, OH*
- ELENA CORRADINI, MD**, *Center for Hemochromatosis and Hereditary Liver Diseases, Department of Internal Medicine, University of Modena and Reggio Emilia, Modena, Italy*
- GILBERT COTE, PhD**, *Department of Endocrine Neoplasia and Hormonal Disorders, University of Texas M.D. Anderson Cancer Center, Houston, TX*
- GLENN R. CUNNINGHAM, MD**, *Departments of Medicine and Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX*
- WILLIAM S. DALTON, MD, PhD**, *Experimental Therapeutics, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*
- SAUMYA DAS, MD**, *Thoracic Aortic Center and Cardiology Division, Massachusetts General Hospital, Boston, MA*
- NANCY E. DAVIDSON, MD**, *The Breast Cancer Program, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD*
- JANE C. DAVIES MRCP, MD**, *Department of Gene Therapy, Imperial College London, National Heart and Lung Institute, London, UK*
- JEAN DELAUNAY, MD, PhD**, *Service d'Hématologie, d'Immunologie et de Cytogénétique, INSERM, Hôpital de Bicêtre, Le Kremlin-Bicêtre, France*
- FEDERICA DEL MONTE MD, PhD**, *Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA*
- XINGMING DENG, MD, PhD**, *University of Florida Shands Cancer Center, University of Florida, Gainesville, FL*
- GORDON DENT, PhD**, *Institute of Science and Technology in Medicine, Keele University, Keele, UK*
- CHRIS T. DERK, MD**, *Division of Rheumatology, Department of Medicine, Thomas Jefferson University, Philadelphia, PA*
- LUIS A. DIAZ, MD**, *Department of Dermatology, School of Medicine, University of North Carolina, Chapel Hill, NC*
- DAVID A. DICHEK, MD**, *Department of Medicine, Division of Cardiology, University of Washington, Seattle, WA*
- DONALD J. DIPETTE, MD**, *Department of Medicine, Scott and White, The Texas A&M University System Health Science Center College of Medicine, Temple, TX*
- SCOTT H. DONALDSON, MD**, *Cystic Fibrosis Research and Treatment Center, University of North Carolina, Chapel Hill, NC*
- BRIAN J. DRUKER, MD**, *Oregon Health and Science University Cancer Institute is usually noted as Oregon Health and Science University Cancer Institute, Portland, OR*
- DOUGLAS C. EATON, PhD**, *Department of Physiology, The Center for Cell and Molecular Signaling, Emory University School of Medicine, Atlanta, GA*
- RENEE E. EDKINS, MA, RN, CCRN**, *Critical Care: Nursing Practice, Education and Research, University of North Carolina, Chapel Hill, NC*
- JAMES T. ELDER, MD, PhD**, *Departments of Dermatology and Radiation Oncology, University of Michigan, Ann Arbor, MI*
- PETER B. ERNST, DVM, PhD**, *Internal Medicine and Microbiology, Division of Gastroenterology and Hepatology, Digestive Health Center of Excellence, University of Virginia, Charlottesville, VA*
- GREGORY J. ESPER, MD**, *Department of Neurology, Washington University School of Medicine, St. Louis, MO*
- JAMES P. EVANS, MD, PhD**, *Department of Genetics, University of North Carolina, Chapel Hill, NC*
- JANE WING-SANG FANG, MBBS, MRCP, FAAP**, *Kinex Pharmaceuticals, Buffalo, NY*
- STEPHEN V. FARAONE, PhD**, *Medical Genetics Research Program and Department of Psychiatry and Behavioral Sciences; SUNY Upstate Medical University, Syracuse, NY*
- FRANCESCA FERRARA, MD**, *Center for Hemochromatosis and Hereditary Liver Diseases, Department of Internal Medicine, University of Modena and Reggio Emilia, Modena, Italy*
- ALAIN FISCHER, INSERM**, *Unité d'Immunologie et d'Hématologie Pédiatriques, Hôpital Necker, Paris, France*
- THOMAS FORCE, MD**, *Center of Translational Medicine, Jefferson Medical College, Philadelphia, PA*
- BRIAN FOUTY, MD**, *Division of Pulmonary Medicine, Center for Lung Biology, University of South Alabama School of Medicine, Mobile, AL*
- MASON W. FREEMAN, MD**, *Lipid Metabolism Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA*
- ROBERT F. GAGEL, MD**, *Division of Internal Medicine, University of Texas M.D. Anderson Cancer Center, Houston, TX*
- JOSÉ M. GARCIA, MD**, *Department of Medicine, Baylor College of Medicine, Houston, TX*
- DANIEL J. GARRY, MD, PhD**, *Departments of Internal Medicine and Molecular Biology, University of Texas Southwestern Medical Center, Dallas, TX*
- JUAN C. GEA-BANACLOCHE, MD**, *Infectious Diseases Section, Experimental Transplantation and Immunology Branch, National Cancer Institute, Bethesda, MD*
- DUNCAN M. GEDDES, MD, FRCP**, *Department Thoracic Medicine, Royal Brompton Hospital, London, UK*
- ROBERT E. GERSZTEN, MD**, *Program in Cardiovascular Gene Therapy, Cardiovascular Research Center, Center for Immunology and Inflammatory Diseases, Massachusetts General Hospital, Boston, MA*

- D. GARY GILLILAND, MD, PhD**, *Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, Howard Hughes Medical Institute, Boston, MA*
- ROBERT G. GISH, MD**, *Department of Hepatology and Liver Transplantation, California Pacific Medical Center, San Francisco, CA*
- STEPHEN J. GLATT, PhD**, *Center for Behavioral Genomics, Department of Psychiatry, University of California, San Diego, La Jolla, CA; and Veterans Medical Research Foundation, San Diego, CA*
- LOWELL A. GOLDSMITH, MD, MPH**, *Dermatology, School of Medicine, University of North Carolina, Chapel Hill, NC*
- DANIEL R. GOLDSTEIN, MD**, *Section of Cardiovascular Medicine, Department of Internal Medicine, Yale University, New Haven, CT*
- MICHELLE NG GONG, MD, MS**, *Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Mount Sinai School of Medicine, New York, NY*
- MAUREEN M. GOODENOW, PhD**, *Department of Pathology, Immunology, and Laboratory Medicine, Department of Pediatrics, Division of Immunology and Infectious Diseases, College of Medicine, University of Florida, Gainesville, FL*
- ERYNN S. GORDON, MS, CGC**, *Research Center for Genetic Medicine, Children's National Medical Center, Washington, DC*
- JACK M. GORMAN, MD**, *Partners Psychiatry and Mental Health, Harvard Medical School, McLean Hospital, Belmont, MA*
- ALLAN GREEN, D.Phil.**, *The Mary Imogene Bassett Hospital, Bassett Research Institute, Bassett Healthcare, Cooperstown, NY*
- DAVID H. GUTMANN, MD, PhD**, *Department of Neurology, Washington University School of Medicine, St. Louis, MO*
- SALIMA HACEIN-BEY-ABINA**, *INSERM, Department of Biotherapy AP-HP, Hôpital Necker, Paris, France*
- ROGER J. HAJJAR, MD**, *Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA*
- STEPHEN R. HAMMES, MD, PhD**, *Department of Internal Medicine, University of Texas Medical Center, Dallas, TX*
- SIAN E. HARDING, PhD**, *Imperial College, National Heart and Lung Institute, London, UK*
- JOHN B. HARLEY MD, PhD**, *Department of Medicine, University of Oklahoma Health Sciences Center, US Department of Veterans Affairs Medical Center, Arthritis and Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK*
- TOMONOBU HASEGAWA, MD, PhD**, *Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan*
- THOMAS J. HAWKE, PhD**, *Department of Pure and Applied Science, York University, Toronto, Ontario, Canada*
- HIRONORI HAYASHI, MD**, *University of Texas M.D. Anderson Cancer Center, Houston, TX*
- CHRISTINE HEIM, PhD**, *Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA*
- CAROLYN Y. HO, MD**, *Cardiovascular Division, Brigham and Women's Hospital, Boston, MA*
- ERIC P. HOFFMAN, PhD**, *Children's National Medical Center, Washington, DC*
- STEPHEN T. HOLGATE, MD, FRCP, DSc**, *Respiratory Cell and Molecular Biology, University of Southampton School of Medicine, Southampton, UK*
- STEVEN M. HOLLAND, MD**, *Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, MD*
- FLORIAN HOLSBOER, MD, PhD**, *Max Planck Institute of Psychiatry, Munich, Germany*
- YI HUANG, MD, PhD**, *The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD*
- ERIC M. ISSELBACHER, MD**, *Thoracic Aortic Center and Cardiology Division, Massachusetts General Hospital, Boston, MA*
- MOIRA R. JACKSON, PhD**, *Department of Anatomy and Cell Biology, University of Florida College of Medicine, Gainesville, FL*
- JAMES L. JANUZZI, JR., MD**, *Thoracic Aortic Center and Cardiology Division, Massachusetts General Hospital, Boston, MA*
- SERGIO A. JIMENEZ, MD**, *Division of Rheumatology, Department of Medicine, Thomas Jefferson University, Philadelphia, PA*
- RICHARD J. JOHNSON, MD**, *Department of Medicine, Baylor College of Medicine, Houston, TX*
- KEFEI KANG, MD**, *Department of Dermatology, Case Western Reserve University, Cleveland, OH*
- PETER B. KANG, MD**, *Program in Genomics, Department of Neurology, Children's Hospital, Harvard Medical School, Boston, MA*
- KHURSHED A. KATKI, PhD**, *Department of Medicine, Scott and White, The Texas A&M University System Health Science Center College of Medicine, Temple, TX*
- GUR P. KAUSHAL, PhD**, *Departments of Internal Medicine and Biochemistry and Molecular Biology, Division of Nephrology, University of Arkansas for Medical Sciences, Central Arkansas Veterans Healthcare System, Little Rock, AR*
- TALMADGE E. KING JR., MD**, *Medical Services, San Francisco General Hospital, Department of Medicine, University of California, San Francisco, CA*
- SAMUEL KLEIN, MD**, *Center for Human Nutrition, Division of Geriatrics and Nutritional Sciences, Washington University School of Medicine, St. Louis, MO*
- MICHAEL R. KNOWLES, MD**, *Division of Pulmonary Diseases, Department of Medicine, University of North Carolina, Chapel Hill, NC*
- LAZAROS K. KOCHILAS, MD**, *Department of Pediatrics, Division of Pediatric Cardiology, Hasbro Children's Hospital/RIH, Brown University Medical School, Providence, RI*
- JAMES J. KOHLER, PhD**, *Department of Pathology, College of Medicine, Emory University, Atlanta, GA*
- PETER KOPP, MD**, *Division of Endocrinology, Metabolism and Molecular Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL*
- BRUCE R. KORF, MD, PhD**, *Department of Genetics, University of Alabama, Birmingham, AL*

- LOUIS M. KUNKEL, PhD**, Program in Genomics, Howard Hughes Medical Institute, Children's Hospital, Harvard Medical School, Boston, MA
- FADI G. LAKKIS, MD**, Thomas E. Starzl Transplantation Institute, University of Pittsburgh, Pittsburgh, PA
- DOLORES J. LAMB, PhD**, Scott Department of Urology and Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX
- HUI Y. LAN, MD, PhD**, Department of Medicine, Baylor College of Medicine, Houston, TX
- CAROL A. LANGE, PhD**, University of Minnesota Cancer Center, Minneapolis, MN
- KAREN A. LAPIDOS, PhD**, Department of Molecular Genetics and Cell Biology, The University of Chicago, Chicago, IL
- JOHNSON YIU-NAM LAU, MBBS, MD, FRCP**, Managing Director, Roth Capital Partners, Newport Beach, CA
- PHILIPPE LEBOULCH**, Harvard Medical School and Genetics Division, Brigham and Women's Hospital, Boston, MA
- VIRGINIA M.-Y. LEE, PhD**, Center for Neurodegenerative Disease Research, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA
- DONALD Y.M. LEUNG, MD, PhD**, Department of Pediatrics, University of Colorado Health Sciences Center, Pediatric Allergy/Immunology Division, National Jewish and Medical Research Center, Denver, CO
- MICHAEL A. LEVINE, MD**, The Children's Hospital at The Cleveland Clinic, Department of Pediatrics, The Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, Cleveland, OH
- CLIVE J. LEWIS, MD**, Imperial College, National Heart and Lung Institute, London, UK
- NING LI, PhD**, Department of Dermatology, School of Medicine, University of North Carolina, Chapel Hill, NC
- MIN LIU, MD, PhD**, Department of Pathology, University of Cincinnati Medical Center, Cincinnati, OH
- ZHI LIU, PhD**, Department of Dermatology, Department of Microbiology and Immunology, School of Medicine, University of North Carolina, Chapel Hill, NC
- KIRK C. LO, MD, CM**, Male Reproductive Medicine and Surgery, Scott Department of Urology, Baylor College of Medicine, Houston, TX
- STEPHEN LOCARNINI, MD, PhD**, Victorian Infectious Diseases Reference Laboratory (VIDRL), North Melbourne and Department of Microbiology, Monash University, Clayton, Victoria, Australia
- BARRY LONDON, MD, PhD**, Cardiovascular Institute, University of Pittsburgh, Pittsburgh, PA
- TAMMY L. LOUCKS, MPH**, Magee-Women's Research Institute, Pittsburgh, PA
- WILLIAM L. LOWE, JR., MD**, Division of Endocrinology, Metabolism, and Molecular Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL
- JAY LOZIER, MD, PhD**, Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD
- JAMES R. LUPSKI, MD, PhD**, Department of Molecular and Human Genetics, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, TX
- HE-PING MA, MD**, Department of Medicine, University of Alabama at Birmingham School of Medicine, Birmingham, AL
- CALUM A. MACRAE, MD**, Cardiology Division and Cardiovascular Research Center, Massachusetts General Hospital, Harvard Medical School, National Heart, Lung and Blood Institute's Framingham Heart Study, Boston, MA
- TERRY MAGNUSON, PhD**, Department of Genetics, University of North Carolina, Chapel Hill, NC
- FRANK MALDARELLI, MD, PhD**, HIV Drug Resistance Program, National Cancer Institute, National Institutes of Health, Bethesda, MD
- BELA MALIK, PhD**, Department of Physiology, The Center for Cell and Molecular Signaling, Emory University School of Medicine, Atlanta, GA
- MARCO MARCELLI, MD**, Departments of Medicine and Molecular and Cellular Biology, Baylor College of Medicine, Division of Endocrinology, Michael E. DeBakey VA Medical Center, Houston, TX
- CINDY M. MARTIN, MD**, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX
- W. STRATFORD MAY, JR., MD, PhD**, University of Florida, Shands Cancer Center, University of Florida, Gainesville, FL
- SHAWN E. MCCANDLESS, MD**, Department of Genetics, Case Western Reserve University, Center for Human Genetics, University Hospitals of Cleveland, Cleveland, OH
- ELIZABETH A. MCGEE, MD**, Magee-Women's Research Institute, Pittsburgh, PA
- ELIZABETH M. MCNALLY, MD, PhD**, Department of Medicine, Section of Cardiology, Department of Human Genetics, The University of Chicago, Chicago, IL
- MICHAEL J. MCPHAUL, MD**, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX
- DEBORAH C. MEDOFF, PhD**, Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD
- SHLOMO MELMED, MD**, Academic Affairs, Cedars-Sinai Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, CA
- WILLIAM E. MITCH, MD**, Division of Nephrology, Baylor College of Medicine, Houston, TX
- CHRISTOPHER B. MIZELLE, MD**, School of Medicine, University of North Carolina, Chapel Hill, NC
- MASASHI MIZOKAMI, MD, PhD**, Department of Clinical Molecular Informative Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
- ANWAR N. MOHAMED, MD**, Cancer Cytogenetic Laboratory, Department of Pathology, Wayne State University School of Medicine, Detroit, MI
- JEFFERY D. MOLKENTIN, PhD**, Department of Pediatrics, Division of Molecular Cardiovascular Biology, Children's Hospital Medical Center, Cincinnati, OH
- STEPHAN MOLL, MD**, Department of Medicine, Division of Hematology-Oncology, University of North Carolina, Chapel Hill, NC

- KHEDOUDJA NAFA, PhD**, *Memorial Sloan Kettering Cancer Center, New York, NY*
- SATYA NARAYAN, PhD**, *Department of Anatomy and Cell Biology, UF Shands Cancer Center, College of Medicine, University of Florida, Gainesville, FL*
- CHARLES B. NEMEROFF, MD, PhD**, *Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA*
- ERIC J. NESTLER, MD, PhD**, *Department of Psychiatry and Center for Basic Neuroscience, The University of Texas Southwestern Medical Center, Dallas, TX*
- MARIA I. NEW, MD**, *Adrenal Steroid Disorders Program, Department of Pediatrics, Mount Sinai School of Medicine, The Mount Sinai Hospital, New York, NY*
- WILLIAM G. NEWMAN, MD, PhD**, *University of Manchester, UK, St. Mary's Hospital, Manchester, UK*
- PEADAR G. NOONE, MD**, *Cystic Fibrosis Research and Treatment Center, Department of Medicine, Division of Pulmonary Diseases, University of North Carolina, Chapel Hill, NC*
- CHRISTOPHER J. O'DONNELL, MD, MPH**, *Cardiology Division, Massachusetts General Hospital, Harvard Medical School and the National Heart, Lung and Blood Institute's Framingham Heart Study, Boston, MA*
- ERIC N. OLSON, PhD**, *Department of Molecular Biology, University of Texas Southwestern Medical Center, Dallas, TX*
- MARCELO PÁEZ-PEREDA, PhD**, *Affectis Pharmaceuticals and Max Planck Institute of Psychiatry, Munich, Germany*
- KEITH L. PARKER, MD, PhD**, *Department of Internal Medicine, Division of Endocrinology and Metabolism, University of Texas Southwestern Medical Center, Dallas, TX*
- KEVIN A. PELPHREY, PhD**, *Department of Psychological and Brain Sciences, Duke University, Durham, NC*
- ALEXANDER E. PERL, MD**, *Division of Hematology-Oncology, Department of Medicine, University of Pennsylvania, Philadelphia, PA*
- JOHN A. PHILLIPS III, MD**, *Division of Medical Genetics, Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN*
- ANTONELLO PIETRANGELO, MD, PhD**, *Center for Hemochromatosis and Hereditary Liver Diseases, Department of Internal Medicine, University of Modena and Reggio Emilia, Modena, Italy*
- JOSEPH PIVEN, MD**, *Departments of Psychiatry and Pediatrics, Neurodevelopmental Disorders Research Center, University of North Carolina, Chapel Hill, NC*
- SHARON E. PLON, MD, PhD**, *Departments of Pediatrics, and Molecular and Human Genetics, Baylor College of Medicine, Houston, TX*
- DIDIER PORTILLA, MD**, *Department of Internal Medicine, Division of Nephrology, University of Arkansas for Medical Sciences, Central Arkansas Veterans Healthcare System, Little Rock, AR*
- AMY POTTER, MD**, *Adult and Pediatric Endocrinology, Division of Endocrinology, Department of Pediatrics, Division of Endocrinology and Metabolism, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN*
- S. RUSS PRICE, PhD**, *Renal Division, Department of Medicine, Emory University, Atlanta, GA*
- CHARMIAN A. QUIGLEY, MBBS**, *Department of Pediatrics, Indiana University School of Medicine, Lilly Research Laboratories, Indianapolis, IN*
- WILLIAM E. RAINEY, PhD**, *Department of Physiology, Medical College of Georgia, Augusta, GA*
- GIUSEPPE REMUZZI, MD**, *Mario Negri Institute for Pharmacological Research, and Division of Nephrology and Dialysis, Azienda Ospedaliera, Ospedali Riuniti di Bergamo, Bergamo, Italy*
- KERRY J. RESSLER, MD, PhD**, *Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA*
- GABRIELE RICHARD, MD**, *Department of Dermatology and Cutaneous Biology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA*
- FRANZISKA RINGPFEIL, MD**, *Department of Dermatology and Cutaneous Biology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA*
- ANTONIO M. RISITANO, PhD**, *Dipartimento di Biochimica e Biotecnologie Mediche, Federico II University of Naples, Naples, Italy*
- JACQUES ROBIDOUX, PhD**, *CIIT Centers for Health Research, Endocrine Biology Program, Division of Biological Sciences, Research Triangle Park, NC*
- DAVID M. RODMAN, MD**, *Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado Health Sciences Center, Denver, CO*
- ANTHONY ROSENZWEIG, MD**, *Program in Cardiovascular Gene Therapy, Cardiovascular Research Center, Center for Immunology and Inflammatory Diseases, Massachusetts General Hospital, Boston, MA*
- BRUNO ROTOLI, MD**, *Dipartimento di Biochimica e Biotecnologie Mediche, Federico II University of Naples, Naples, Italy*
- DAVID S. RUBENSTEIN, MD, PhD**, *Department of Dermatology, School of Medicine, University of North Carolina, Chapel Hill, NC*
- DEBORAH C. RUBIN, MD**, *Division of Gastroenterology, Departments of Medicine and Molecular Biology and Pharmacology, Washington University School of Medicine, St. Louis, MO*
- DEEPAK M. SAMPATHU, PhD**, *Center for Neurodegenerative Disease Research, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA*
- JEFF M. SANDS, MD**, *Renal Division, Department of Medicine, Department of Physiology, Emory University School of Medicine, Atlanta, GA*
- AMR H. SAWALHA, MD**, *Department of Medicine, University of Oklahoma Health Sciences Center, US Department of Veterans Affairs Medical Center, Arthritis and Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK*
- THOMAS E. SCAMMELL, MD**, *Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA*
- JULIE V. SCHAFFER, MD**, *Department of Dermatology, New York University School of Medicine, New York, NY*

- MARCUS J. SCHULTZ, MD, PhD**, *Department of Intensive Care Medicine, Laboratory of Experimental Intensive Care and Anesthesiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands*
- BRAHM H. SEGAL, MD**, *Department of Medicine, Division of Infectious Diseases, The University at Buffalo, The State University of New York (SUNY), Roswell Park Cancer Institute, Buffalo, NY*
- CHRISTINE E. SEIDMAN, MD**, *Cardiovascular Division, Brigham and Women's Hospital, Howard Hughes Medical Institute and Department of Genetics, Harvard Medical School, Boston, MA*
- SUDHIR V. SHAH, MD**, *Department of Internal Medicine, Division of Nephrology, University of Arkansas for Medical Sciences, Central Arkansas Veterans Healthcare System, Little Rock, AR*
- KENNETH H. SHAIN, MD, PhD**, *Experimental Therapeutics, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*
- STEVEN D. SHAPIRO, MD**, *Pulmonary and Critical Care, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*
- THOMAS C. SHEA, MD**, *Division of Hematology and Oncology, Bone Marrow and Stem Cell Transplant Program, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC*
- SARAH SHEFELBINE, MD**, *Department of Otolaryngology, University of Florida, Gainesville, FL*
- LINMARIE SIKICH, MD**, *Department of Psychiatry, University of North Carolina, Chapel Hill, NC*
- JONATHAN W. SIMONS, MD**, *Winship Cancer Institute, Emory University, Atlanta, GA*
- DONALD SMALL, MD, PhD**, *Departments of Pediatrics, Oncology, Cellular and Molecular Medicine, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*
- PETER H. ST GEORGE-HYSLOP, MD, FRCPC, FRS**, *Centre for Research in Neurodegenerative Diseases, University of Toronto, Department of Medicine, Division of Neurology, University Health Network, Toronto, Ontario, Canada*
- AMY STEIN, MD**, *Department of Dermatology, School of Medicine, University of North Carolina, Chapel Hill, NC*
- GORDON W. STEWART, MD, FRCP**, *Department of Medicine, The Rayne Institute, London, UK*
- STEPHEN M. STRITTMATTER, MD, PhD**, *Department of Neurology, Yale University School of Medicine, New Haven, CT*
- STEPHEN P. SUGRUE, PhD**, *Department of Anatomy and Cell Biology, University of Florida College of Medicine, Gainesville, FL*
- GREGORY M. SULLIVAN, MD**, *Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY*
- MARIJA TADIN-STRAPPS, PhD**, *Department of Dermatology, College of Physicians and Surgeons, Columbia University, New York, NY*
- CAROL A. TAMMINGA, MD**, *Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX*
- STEPHEN J. TAPSCOTT, MD, PhD**, *Fred Hutchinson Cancer Research Center, Department of Neurology, University of Washington, Seattle, WA*
- GUNVANT THAKER, MD**, *Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD*
- RAJESH V. THAKKER, MD, FRCP, FRCPath, FMedSci**, *Nuffield Department of Clinical Medicine, University of Oxford, Academic Endocrine Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM), Churchill Hospital, Headington, Oxford, UK*
- SWEE LAY THEIN, DSc, FRCP, FRCPath, FMedSci**, *Department of Haematological Medicine, Guy's, King's and St. Thomas' School of Medicine, London, UK*
- NANCY E. THOMAS, MD, PhD**, *Department of Dermatology, University of North Carolina, Chapel Hill, NC*
- ADRIAN J. THRASHER**, *Molecular Immunology Unit, Institute of Child Health, London, UK*
- STEPHEN L. TILLEY, MD**, *Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of North Carolina, Chapel Hill, NC*
- BRUCE C. TRAPNELL, MD, MS**, *Department of Pediatrics, Division of Pulmonary Biology, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH*
- PATRICK TSO, PhD**, *Department of Pathology, University of Cincinnati Medical Center, Cincinnati, OH*
- MING T. TSUANG, MD, PhD**, *Center for Behavioral Genomics, Department of Psychiatry, University of California, San Diego, La Jolla, CA; Veterans Affairs San Diego Healthcare System, San Diego, CA; and Harvard Institute of Psychiatric Epidemiology and Genetics, Harvard Departments of Epidemiology and Psychiatry, Boston, MA*
- J. ERIC TURNER, MD**, *Division of Hematology and Oncology, University of North Carolina, Chapel Hill, NC*
- JOUNI UITTO, MD, PhD**, *Department of Dermatology and Cutaneous Biology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA*
- TOM VAN DER POLL, MD, PhD**, *Laboratory of Experimental Internal Medicine, Department of Infectious Diseases, Tropical Medicine and AIDS, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands*
- MARCIA VAN RIPER, PhD, RN**, *School of Nursing, University of North Carolina, Carolina Center for Genome Sciences, Chapel Hill, NC*
- CHRISTOPHER A. WALSH, MD, PhD**, *Division of Neurogenetics, Howard Hughes Medical Institute, Beth Israel Deaconess Medical Center, Department of Neurology, Harvard Medical School, Boston, MA*
- THOMAS H. WASSINK, MD**, *Department of Psychiatry, Carver College of Medicine, University of Iowa, Iowa City, IA*
- SUSAN E. WERT, PhD**, *Department of Pediatrics, Division of Pulmonary Biology, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH*
- MATTHEW T. WHEELER, MD, PhD**, *Department of Molecular Genetics and Cell Biology, The University of Chicago, Chicago, IL*
- DAVID C. WHITCOMB, MD, PhD**, *Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh, Pittsburgh, PA*

- GILBERT C. WHITE, II, MD**, *Richard H. and Sarah E. Aster Chair for Medical Research, Blood Center of Wisconsin, Blood Research Institute, and Biochemistry, and Pharmacology and Toxicology, Medical College of Wisconsin*
- JEFFREY A. WHITSETT, MD**, *Department of Pediatrics, Division of Pulmonary Biology, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH*
- CHRISTOPHER S. WILCOX, MD, PhD**, *Division of Nephrology and Hypertension, Cardiovascular Kidney Institute, Georgetown University, Washington, DC*
- R. SANDERS WILLIAMS, MD**, *Department of Medicine, Division of Cardiology, Duke University Medical Center, Durham, NC*
- ROBERT W. WILLIAMS, PhD**, *Department of Anatomy and Neurobiology, Department of Pediatrics, Center for Genomics and Bioinformatics, University of Tennessee, Memphis, TN*
- LORNA M. WILLIAMSON, BSc, MD, FRCP, FRCPath**, *Department of Haematology, University of Cambridge/ National Blood Service, Cambridge, UK*
- JOHN S. WITTE, PhD**, *Departments of Epidemiology and Biostatistics, and Urology, University of California, San Francisco, San Francisco, CA*
- ROBERT C. WILSON, PhD**, *Department of Pediatrics, Mount Sinai School of Medicine, New York, NY*
- J. TIM WRIGHT, DDS, MS**, *Department of Pediatric Dentistry, School of Dentistry, University of North Carolina, Chapel Hill, NC*
- TERESA L. WRIGHT, MD**, *Department of Medicine, University of California, San Francisco, Gastroenterology Division, Veterans Affairs Medical Center, San Francisco, CA*
- LEI XIAO, PhD**, *Department of Anatomy and Cell Biology, University of Florida, Gainesville, FL*
- ANTHONY T. YACHNIS, MD, MS**, *Department of Pathology and Laboratory Medicine, College of Medicine, University of Florida, Gainesville, FL*
- ZHEN YAN, PhD**, *Department of Medicine, Division of Cardiology, Duke University Medical Center, Durham, NC*
- KEVIN E. YARASHESKI, PhD**, *Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO*
- MAIMOONA ZARIWALA, PhD**, *Division of Pulmonary Diseases, Department of Medicine, University of North Carolina, Chapel Hill, NC*
- ANDREW R. ZINN, MD, PhD**, *McDermott Center for Human Growth and Development, Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas, TX*
- HUDA Y. ZOGHBI, MD**, *Departments of Pediatrics, Neurology, Molecular and Human Genetics, Neuroscience, Baylor College of Medicine, Howard Hughes Medical Institute, Houston, TX*
- CARLA ZOJA, PhD**, *Mario Negri Institute for Pharmacological Research, Bergamo, Italy*

Color Plates

Plate 1 (Fig. 2, Chapter 4). Fluorescent *in situ* hybridization of a pediatric leukemia sample demonstrating that one chromosome 5 contains a deleted segment that includes the EGR1 gene.

Plate 2 (Fig. 1, Chapter 10). The left side of the figure depicts fetal circulation in the human. The right side of the figure depicts neonatal circulation in the human.

Plate 3 (Fig. 2, Chapter 10). Dosage sensitive role of *Tbx1* in the etiology of cardiovascular defects in mice.

Plate 4 (Fig. 1A–C, Chapter 11). Gross pathological specimens of a heart with (A) hypertrophic cardiomyopathy (HCM) and (C) dilated cardiomyopathy (DCM). Note the marked increased in left ventricular hypertrophy (HCM) and chamber dimensions (DCM) as compared with (B) the normal heart.

Plate 5 (Fig. 2, Chapter 11). Histopathology of distinct human cardiomyopathies revealed by hematoxylin and eosin staining.

Plate 6 (Fig. 3, Chapter 15). The palmar and tubero-eruptive xanthomas are classically seen in patients with increased concentrations of intermediate density lipoproteins whereas the eruptive xanthomas are typically found in patients with massive serum triglyceride elevations resulting from excess chylomicrons and/or very low-density lipoproteins.

Plate 7 (Fig. 5, Chapter 22). Increased immunostaining for the caspase 3 p85 cleavage product of poly ADP-ribose polymerase in asthmatic mucosal biopsies and bronchoalveolar lavage epithelial cells.

Plate 8 (Fig. 4, Chapter 24). Plexiform lesion. The end-stage of pulmonary hypertension is associated with the formation of occlusive intimal lesions.

Plate 9 (Fig. 1, Chapter 29). Development of granulomatous inflammation. Antigen presenting cells interact with CD4+ T lymphocytes by presenting antigenic peptides, bound to major histocompatibility complex molecules, to T-cell receptors.

Plate 10 (Fig. 2A–D, Chapter 30). Histopathology of surfactant abnormalities found in the lungs of human patients with (A) mutations in the *SFTPB* gene, (B) mutations in the *SFTPC* gene, (C) mutations in the *ABCA3* gene, (D) and antibodies to granulocyte macrophage-colony-stimulating factor.

Plate 11 (Fig. 1, Chapter 66). Activation of MHC expression in fibroblasts expressing exogenous MyoD.

Plate 12 (Fig. 6, Chapter 66). Diagrammatic representation of somite maturation.

Plate 13 (Fig. 7, Chapter 66). Expression pattern of a myogenin-lacZ transgene in an 11.5-day mouse embryo. The myogenin promoter was linked to a β -galactosidase reporter gene and introduced into transgenic mice.

Plate 14 (Fig. 1, Chapter 84). Global epidemiology of HIV-1 subtypes and estimated number of infected individuals (in millions) at the end of 2002 according to the International AIDS Vaccine Initiative and the Joint United Nations Programme on HIV/AIDS.

Plate 15 (Fig. 1, Chapter 108). Features of the hairless phenotype in humans and mice.

Plate 16 (Fig. 1, Chapter 119). Characteristic neuropathological features of transmissible spongiform encephalopathies.

Plate 17 (Fig. 1, Chapter 129). Key neural circuits of addiction. Dotted lines indicate limbic afferents to the nucleus accumbens. Arrows represent efferents from the nucleus accumbens thought to be involved in drug reward.

GENETICS

*SECTION EDITORS:
TERRY MAGNUSON AND JAMES P. EVANS*

I

Abbreviations

I. MOLECULAR GENETICS

AAV	adeno-associated virus	IGF	insulin-like growth factor
ABGC	American Board of Genetics Counseling	IND	investigational new drug
ADR	adverse drug reaction	LGK	Lander-Green-Kruglyak
AMKL	acute megakaryocytic leukemia	LOD	likelihood of the odds
AS	Angelman syndrome	MCMC	Monte-Carlo Markov Chain
BBS	Bardet-Biedl syndrome	MDR	multidrug resistance
BNSF	Burlington Northern Santa Fe Railroad	MELAS	mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes
BWS	Beckwith-Wiedemann syndrome	MEN	multiple endocrine neoplasia
CD	Crohn's disease	MEN1	multiple endocrine neoplasia type 1
CEERs	Centers of Excellence in ELSI Research	MEN2	multiple endocrine neoplasia type 2
CF	cystic fibrosis	MTC	medullary thyroid carcinoma
cM	centimorgan	mtDNA	mitochondrial DNA
DPD	dihydropyrimidine dehydrogenase	NHGRI	National Human Genome Research Institute
DS	Down syndrome	PKU	phenylketonuria
ELSI	ethical, legal, and social implications	PM	poor metabolizer
EM	extensive metabolizer	PWS	Prader-Willi syndrome
F1	filial 1	RP	retinitis pigmentosa
FAP	familial adenomatous polyposis	SNP	single-nucleotide polymorphism
FDA	Food and Drug Administration	TDT	transmission/disequilibrium test
FISH	fluorescent <i>in situ</i> hybridization	UC	ulcerative colitis
HD	Huntington disease	UPD	uniparental disomy
HER2	human epidermal receptor 2	URM	ultra rapid metabolizer
HGP	Human Genome Project	UV	ultraviolet
HH	hemihyperplasia	WAGR	Wilm's tumor, aniridia, genital-urinary abnormalities, and mental retardation
htSNP	haplotype tagging single-nucleotide polymorphism	XP	xeroderma pigmentosum
IBD	inflammatory bowel disease		

1 Mendelian Inheritance

BRUCE R. KORF

SUMMARY

The basic patterns of genetic transmission in humans have been known for about a century, but are now coming to be understood at the molecular level. In addition to classical dominant, recessive, and sex-linked inheritance, more complex patterns have also been identified. These include maternal transmission of traits encoded in the mitochondrial genome, digenic traits determined by two distinct genes, and genomic imprinting. It is becoming clear that both rare and common genetic traits are determined by a complex interaction of multiple genetic and nongenetic factors.

Key Words: Digenic; dominant; expressivity; imprinting; Mendelian; mitochondrial inheritance; penetrance; recessive; X-linked.

INTRODUCTION

The existence of human traits that are transmitted from generation to generation in accordance with Mendel's laws was first recognized early in the 20th century. Understanding the mechanisms that underlie Mendelian inheritance has unfolded over the ensuing decades, and forms the basis for knowledge of human genetics. With increasing sophistication it has become clear that the seemingly straightforward rules of inheritance—for example, dominance and recessiveness—are in fact complex. With more nuanced understanding, however, comes recognition of genetic principles that have a critical role in diagnosis and counseling. This chapter reviews the basics of Mendelian inheritance and explores how insights in molecular genetics are both explicating and changing views of these fundamental principles.

PATTERNS OF GENETIC TRANSMISSION

The patterns of Mendelian transmission ensue from the fact that humans are diploid organisms, inheriting a complete set of genes from each parent. The two individual copies of a specific gene are referred to as *alleles*. The alleles on homologous chromosomes segregate at meiosis and new combinations are paired together on fertilization. The specific alleles at a locus comprise the genotype; the physical characteristic that results from action of the alleles is the phenotype.

DOMINANT AND RECESSIVE INHERITANCE The first instance of Mendelian transmission in humans was recognized by Archibald Garrod, working in the early years of the 20th century.

He originated the term “inborn errors of metabolism” to describe a set of disorders in which specific biochemical pathways were deranged, leading to accumulation of toxic substrates or deficiency of end products. He recognized that these conditions are familial and behave as Mendelian recessive traits. A recessive trait is only expressed in a homozygous individual who inherits a mutant allele from both parents (Fig. 1-1A). The parents are heterozygous carriers, who are asymptomatic because of the action of the dominant allele. A couple consisting of two carriers faces a 25% risk of transmission of homozygosity to any offspring.

The basis of recessive inheritance of inborn errors of metabolism is that the responsible genes encode enzymes required to catalyze specific biochemical reactions. Enzymes function in a catalytic manner, so the 50% level of activity that may occur in a heterozygote is sufficient to complete the reaction and thereby avoid the phenotype. Only a homozygote will lack sufficient activity to manifest the disorder. An example is the disorder phenylketonuria, which is because of mutation in the gene that encodes the enzyme phenylalanine hydroxylase, required to convert phenylalanine to tyrosine. Homozygotes accumulate phenylalanine to toxic levels, and also have a deficiency of phenylalanine metabolites such as dopamine and melanin. Children with this disorder detected by newborn screening can be spared the severe developmental impairment of this disorder by treatment with a low-phenylalanine diet. Carrier parents are asymptomatic, but have a 25% risk of additional affected children.

Dominant traits are expressed in both homozygous and heterozygous individuals (Fig. 1-1B). If the trait is rare, most affected individuals will be heterozygous. Moreover, many dominantly inherited medical conditions are lethal in the homozygous state, technically indicating that they are not “true” dominants. An individual who is heterozygous for a dominant trait has a 50% chance of passing either allele to any offspring.

A prototypical autosomal-dominant disorder is Marfan syndrome, resulting from mutation in the connective tissue protein fibrillin. Affected individuals are tall, lanky, and experience complications such as joint dislocation, lens subluxation, and aortic aneurysms because of weakness of connective tissue. The disorder is compatible with survival to reproductive age, and affected individuals have a 50% risk of transmitting the mutant allele to any offspring. The molecular basis for dominance is reviewed later.

SEX LINKAGE Sex determination occurs by inheritance of two X chromosomes in females or an X and a Y in males. The Y carries a limited repertoire of genes, including those involved

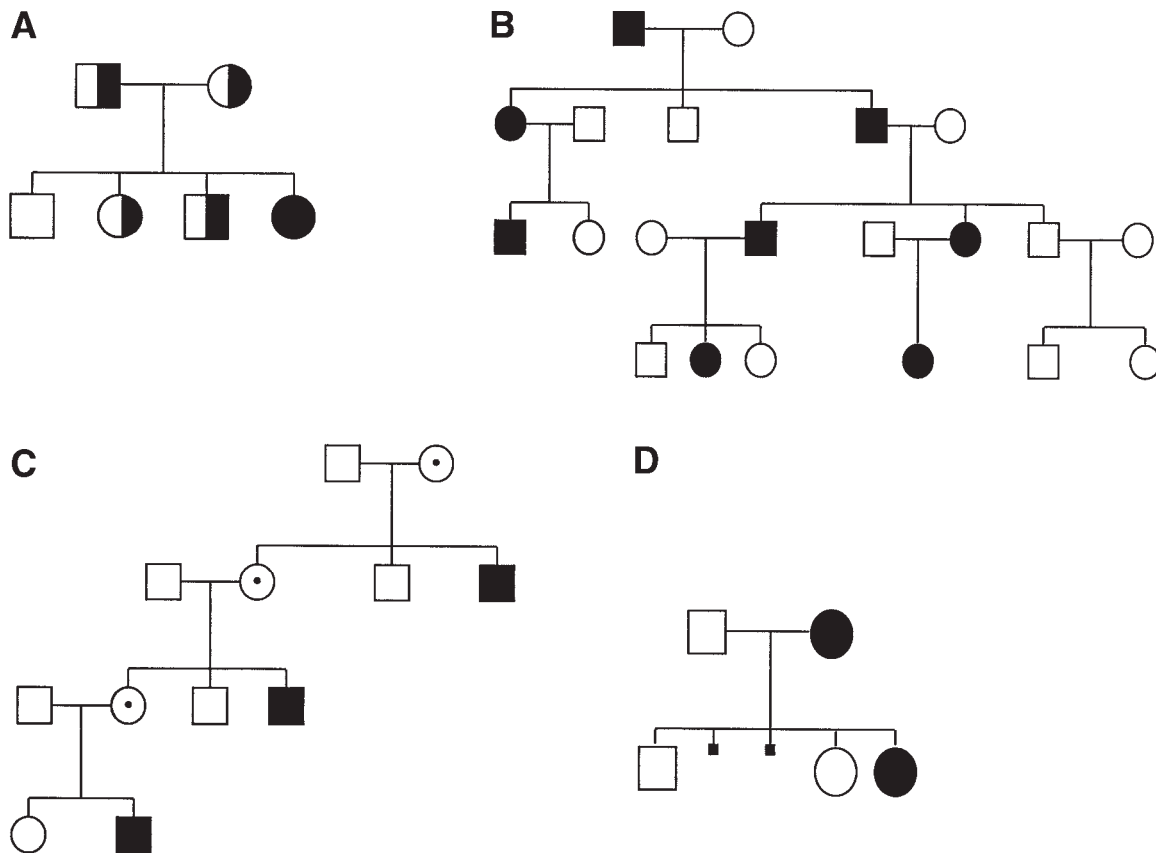


Figure 1-1 Pedigrees depicting autosomal-recessive (A), autosomal-dominant (B), X-linked-recessive (C), and X-linked-dominant with male lethality (D). By convention, squares denote males, circles females, and filled-in symbols are individuals who manifest a phenotype. Half-filled symbols in the recessive pedigree are carriers, and females with dots in the X-linked recessive pedigree are heterozygotes.

in testes determination and spermatogenesis. The X carries a larger set, most of which lack counterparts on the Y. Therefore, for these genes, females have two alleles, but males only one. There are regions at the two ends of the X chromosome where homologous loci exist on the Y. These are referred to as *pseudoautosomal*. For the other loci found only on the X males are said to be *hemizygous*.

Gene dosage is finely controlled, and, therefore, a mechanism exists to compensate for the dosage differences in males and females for X-linked genes. Most genes on the X chromosome are inactivated on one of the two X's in female cells early in development. The choice of X to be inactivated is random, but once an X is "turned off," that chromosome remains off in all descendants of a particular cell. Some genes, especially those in the pseudoautosomal regions escape inactivation. The molecular basis for X chromosome inactivation is becoming understood. It includes selection of the chromosome to be inactivated by an RNA molecule encoded by an X-linked gene called *Xist* and subsequent methylation of DNA on the inactive chromosome.

There are few Y-linked traits of medical significance. A Y-linked gene is transmitted from a male to all his sons and none of his daughters. X-linked traits are transmitted by a heterozygous female to half her offspring; a hemizygous male passes the gene to all his daughters and none of his sons (Fig. 1-1C). The concepts of dominance and recessiveness are meaningless when applied to genes on the X chromosome, which are subject to inactivation, because only one allele is expressed in any cell in either a male or a female.

Whether or not a trait is expressed in a heterozygous female depends on whether expression of the mutant gene in approx 50% of cells is sufficient to cause the phenotype, or whether expression of the wild-type allele in 50% is insufficient. Classic "X-linked-recessive" traits such as Duchenne muscular dystrophy and hemophilia A tends not to lead to a phenotype in heterozygous females, unless X chromosome inactivation has somehow been skewed toward inactivation of the wild-type allele. "X-linked-dominant" traits, such as hypophosphatemic rickets, are expressed in both sexes. X-linked traits such as Rett syndrome or incontinentia pigmenti are lethal in hemizygous males and, therefore, only are seen in heterozygous females (Fig. 1-1D).

MATERNAL TRANSMISSION Although not a "Mendelian" pattern, maternal inheritance is another form of single gene transmission. Maternal inheritance applies to a set of genes found on the 16.5-kb circular double-stranded DNA molecules found within mitochondria. These encode 13 peptides involved in mitochondrial oxidative phosphorylation, as well as a set of transfer RNAs and ribosomal RNAs. There are thousands of DNA molecules within mitochondria in every cell. If there is a mutation in some, the cell is said to be heteroplasmic (Fig. 1-2A). Because mitochondrial DNA molecules segregate at random during cell division, the proportion of mutant and wild-type DNA molecules can vary widely between cells. Mitochondrial DNA mutations tend to interfere with cellular energy production. Because of heteroplasmy there can be a wide range of phenotypic effects, depending on the proportion of mutant mitochondria in different tissues.

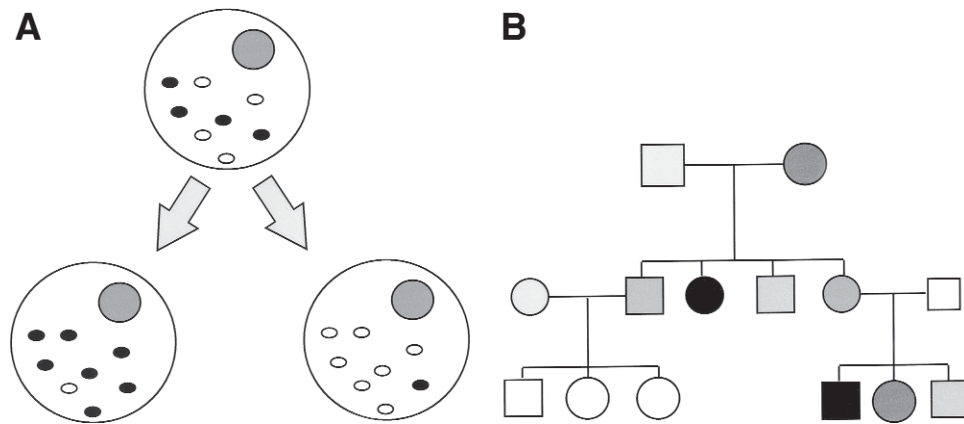


Figure 1-2 (A) Mutant and wild-type mitochondrial DNA may coexist in a cell, referred to as heteroplasmy. Mitochondrial DNA molecules segregate passively when a cell divides, so daughter cells may differ in their proportions of mutant and wild-type mitochondrial DNA. (B) Essentially, all the mitochondrial DNA is maternally transmitted. Hence, a female with a mitochondrial disorder will transmit it to all her offspring, whereas a male will not transmit the trait. Offspring may differ in their degree of expression of the phenotype because of heteroplasmy.

Most, if not all, mitochondria are transmitted through the oocyte. As a result, a female with a mitochondrial mutation will pass it to all of her offspring, whereas a male will not transmit it at all (Fig. 1-2B). Once again, however, heteroplasmy will account for variability, in this case among members of a sibship. This creates a challenge in recurrence risk counseling for mitochondrial disorders, because the likelihood that an offspring will inherit sufficient mutant DNA molecules to produce a phenotype cannot be predicted.

COMPLEXITIES OF MENDELIAN TRAITS

Although single gene traits are transmitted in accordance with Mendel's laws, a number of phenomena may lead to deviation from the expected segregation ratios. These include nonpenetrance, new mutation, mosaicism, anticipation, imprinting, and digenic inheritance.

PENETRANCE AND EXPRESSIVITY Individuals who have the genotype associated with a particular phenotype yet do not display the phenotype are said to be nonpenetrant. For a dominant trait this may lead to a skipped generation (i.e., a trait is seen in a child and a grandparent, but the parent is not affected). Some phenotypes display age-dependent penetrance, so the probability of phenotypic expression increases with age. This is typical of disorders such as Huntington disease or adult polycystic kidney disease. Penetrance is an all-or-none phenomenon for an individual; the phenotype is either present or not at a particular time. Penetrance should not be confused with expressivity, which refers to the degree of phenotypic expression from individual to individual. The possibility of nonpenetrance or of age-dependent penetrance needs to be considered when counseling an individual at risk of a dominant trait. The lack of phenotype does not necessarily preclude one from occurring at a later age or exclude the possibility of transmission of the trait to an offspring.

MUTATION AND MOSAICISM Sporadically affected individuals with a dominant or an X-linked trait may occur because of a new mutation in the sperm or egg cell. Neither parent will be found to carry the trait, and the affected child will be the first affected member of the family. That child, however, will be at risk of transmitting the trait to his or her offspring. Mutation rates vary among different loci, usually hovering in the range of 10^{-4} to 10^{-6} /gamete/generation. Few distinct risk factors have been

identified, although there is a slight increase in the risk of mutation with advancing paternal age.

Mutation may occur in somatic cells as well as in the germline. Somatic mutation during early development results in somatic mosaicism, in which an individual has a mixture of mutant and nonmutant cells. This may manifest as milder expression of a phenotype, or as expression of the phenotype in a limited region of the body. A dramatic example is segmental neurofibromatosis, where *café-au-lait* spots and neurofibromas may be restricted to part of the body. Germline mosaicism results in multiple sperm or egg cells carrying a new mutation. A parent with germline mosaicism can have multiple affected children despite not carrying the mutation in somatic cells.

ANTICIPATION It has long been noted that in some families with particular dominant traits, severity increases, and age of onset decreases, from generation to generation. This phenomenon is referred to as anticipation. Although initially thought to be an artifact owing to bias of ascertainment, it is now known to be a real event that is the signature of a specific type of mutation, the triplet repeat expansion (Fig. 1-3). A number of genes include repeated triplets of bases, such as CAGCAGCAG. The exact number of repeats is a heritable polymorphism, as there is no phenotypic impact regardless of the number, up to a point. Individuals with mutations, however, have expanded numbers of repeats that lead to aberrant gene expression. Anticipation results from two characteristics of repeat expansion mutations. First, the larger the number of repeats, the more severe and earlier is the onset of the disorder. Second, the larger the repeat size, the more unstable it is, creating risk of further expansion in the next generation. The expansion, therefore, increases from generation to generation, leading to anticipation. Disorders associated with triplet repeat expansion tend to affect the nervous system, and include Huntington disease, fragile X syndrome, myotonic dystrophy, spinocerebellar ataxia, and others.

IMPRINTING A subset of genes is expressed only from the maternal or paternal allele, but not both, and is referred to as imprinting. The "imprint" that identifies an allele as being of maternal or paternal origin is "erased" each generation. For example, if it is the maternally derived allele that is expressed, a maternally inherited allele will be turned on in a male, but will be turned off when he transmits it to the next generation. It appears that only

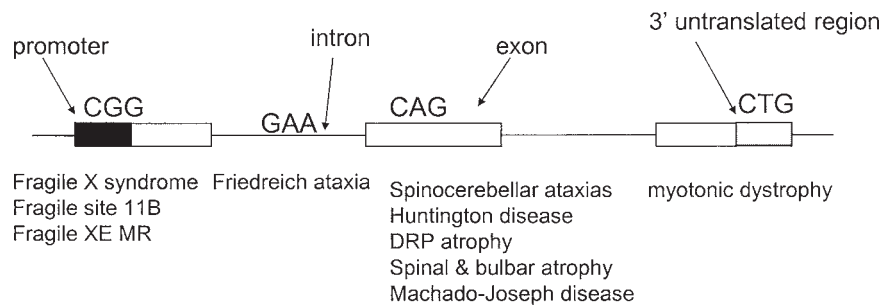


Figure 1-3 A prototypical gene, showing sites of triplet repeats that are prone to expansion, and examples of resultant disorders.

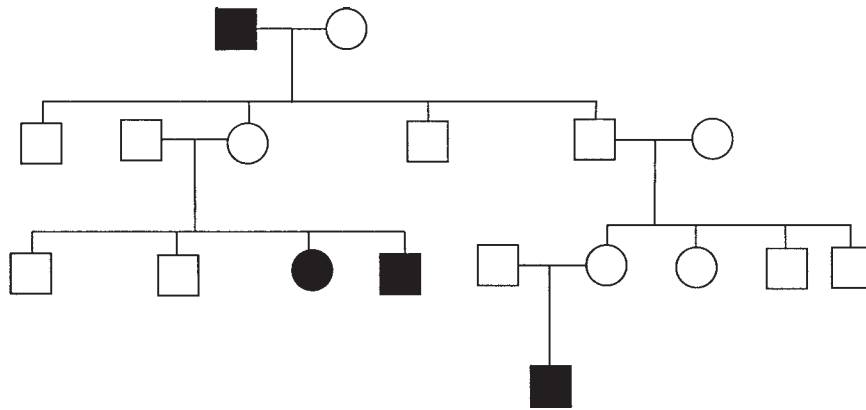


Figure 1-4 In this autosomal-dominant trait, an imprinted gene is only expressed when inherited from a female. Hence, only females can have affected offspring. Individuals who inherit the mutation from their fathers will not express the phenotype, but their daughters who carry the mutation can have affected children.

a relatively small number of genes are subject to imprinting, but these account for some distinct phenotypes and unusual patterns of transmission. A dominant trait because of an imprinted gene will only result in a phenotype when the transmitting parent is the one who transmits the expressed allele (Fig. 1-4). This gives rise to multiple examples of nonpenetrance. For example, this is the case in familial glomus tumors. Prader–Willi and Angelman syndromes result from deletions on chromosome 15 from a region that contains imprinted genes. The gene involved in Angelman syndrome is expressed from the maternal allele, so deletion of this allele results in the disorder. In contrast, paternal deletion of the same region produces Prader–Willi syndrome, reflecting the presence of one or more paternally expressed genes in the region. The same phenotypes can result from the inheritance of both copies of chromosome 15 from the same parent, referred to as uniparental disomy. In this case there will be absence of either maternally or paternally expressed genes, depending on whether there are two copies of mother's or father's chromosomes. Uniparental disomy results when a trisomic zygote produces an embryo in which disomy is restored by a second nondisjunction event. If the chromosomes that remain are from the parent in whom nondisjunction occurred, uniparental disomy will result. Aside from accounting for some cases of Prader–Willi or Angelman syndromes, uniparental disomy for several other chromosomes has been associated with a phenotype.

DIGENIC INHERITANCE In rare instances, it has been found that individuals who are doubly heterozygous for two recessive alleles may manifest a phenotype (Fig. 1-5). This has been

found, for example, in some cases of the eye disorder retinitis pigmentosum. Parents who are heterozygous for two different genes can have doubly heterozygous offspring. If the genes are on different chromosomes, an affected child can transmit both mutant alleles to an offspring, producing apparent dominant transmission. Genes that are subject to digenic inheritance tend to encode proteins that interact with one another in the same pathway.

MOLECULAR BASIS OF MENDELIAN INHERITANCE

The patterns of single gene transmission have been known for a long time, but only recently the phenomena have begun to be understood at the molecular level. The bases for the Mendelian patterns as well as the complexities noted in the previous section are gradually emerging.

RECESSIVE VS DOMINANT ALLELES Recessive alleles, by definition, only exert a phenotypic effect in a homozygous state. In general, this implies that a mutation has resulted in loss of function of the gene product, and that partial loss of function is not sufficient to result in a phenotype. As noted, this is the case for most enzyme deficiencies. The mutations responsible for such disorders tend to be those that cause premature termination of translation, such as frame shifts or stop mutations, nonsense mutations, deletions, or splicing mutations, which significantly disrupt the coding sequence. Missense mutations may also cause a phenotype if they significantly disrupt the function of the gene product.

The basis for dominance can be a diverse set of genetic changes. Some mutations lead to gain of function, for example,

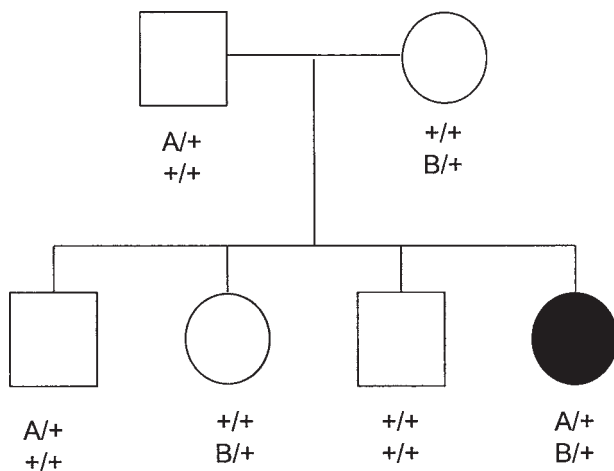


Figure 1-5 Pedigree illustrating digenic inheritance. Each parent is heterozygous for a different gene. The child who is heterozygous for both expresses the phenotype.

constitutive activation of a cell membrane receptor as occurs in the *FGFR3* gene in achondroplasia. Activation of just one allele is sufficient to alter the behavior of a cell. Another mechanism is referred to as dominant negative. Here, a single mutant allele produces sufficient abnormal product to disrupt cellular function. This is the hallmark of mutations in genes that encode products of multimeric proteins. Although only 50% of the protein may be abnormal, abnormal subunits may contribute to a higher proportion of proteins, resulting in a heterozygous phenotype. This is the case for some types of collagen mutations responsible for osteogenesis imperfecta. Dominant transmission may also occur with loss-of-function mutations if 50% levels of gene product are insufficient for normal function. This occurs in mild forms of Marfan syndrome because of loss-of-function fibrillin gene mutations. Interestingly, dominant negative mutations in this gene cause more severe disease, because the presence of abnormal fibrillin molecules has a more pervasive effect on connective tissue integrity than does 50% reduction of quantity.

A special case of dominant inheritance is accounted for by tumor suppressor genes. These genes account for familial susceptibility to cancers such as retinoblastoma, colon cancer, and breast or ovarian cancer. In families with an inherited susceptibility, the risk is transmitted as a dominant trait. Within a tumor cell, however, both alleles of the tumor suppressor are mutated, usually with a loss of function type mutation (Fig. 1-6). The mutation of one allele in such families is transmitted from generation to generation. An individual with heterozygous mutation faces an increased risk of cancer because somatic mutation of the remaining wild-type allele is all that is required to start a cell on the path to malignancy.

GENETIC HETEROGENEITY There is a wide diversity of different mutation types, with a range of effects on gene function, including mutations that increase or decrease levels of gene product expression, or change the functional properties of the protein. Different mutations in the same gene may have differing impacts on phenotype. The consequence is that different individuals with a dominant trait may have distinct mutations. Furthermore, the two mutant alleles in an individual who is homozygous for a recessive mutation may differ. There are exceptions; in some cases only a very specific mutation will cause a specified phenotype. This is true for the *FGFR3* mutation in achondroplasia. In other instances,

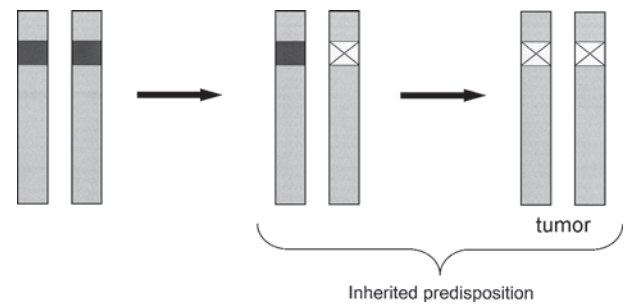


Figure 1-6 Tumor suppressor concept. A tumor suppressor gene is homozygously mutated in a tumor cell. Those who inherit a heterozygous mutation as a dominant trait are at increased risk of cancer if the remaining wild-type allele is mutated.

a specific mutation may have arisen in an isolated population and remain relatively common there. This is called the founder effect, and accounts, for example, for the high prevalence of specific mutations responsible for Tay-Sachs disease in the Ashkenazi Jewish population.

Other than these instances, allelic heterogeneity is more a rule than an exception. In some cases, variable expressivity is explained by the occurrence of different mutations causing slightly different phenotypes. Study of genotype–phenotype correlations can sometimes provide information predictive of disease severity useful in genetic counseling. The difference between severe Duchenne muscular dystrophy and the milder Becker form can be predicted from whether the mutation causes complete loss of the gene product, dystrophin (Duchenne), or production of an aberrant protein (Becker). In still other cases, the different mutations result in phenotypes that would not have been regarded as the same disease. For example, different mutations in the *CFTR* gene can cause cystic fibrosis, chronic sinusitis, or male infertility resulting from congenital bilateral absence of the vas deferens.

Genetic heterogeneity extends not only to different alleles, but also to different loci. Studies to identify genes responsible for disease often reveal multiple distinct genes that are associated with the same phenotype in different individuals. In some instances, such as congenital deafness, this locus heterogeneity reflects that a large number of genes contribute to normal hearing. Many of these genes can be disrupted by mutation, all leading to deafness. In other cases, genes that encode proteins that interact with one another in the same pathway result in an indistinguishable phenotype when mutated. This is the case in tuberous sclerosis, associated with mutation in either the *TSC1* or *TSC2* genes. The protein products, hamartin and tuberin, interact with one another to form a complex that is involved in the control of cell growth. Locus heterogeneity is important in clinical genetics, because testing of the incorrect gene will fail to reveal an underlying mutation and could lead to incorrect exclusion of a diagnosis. For a recessive disorder, locus heterogeneity explains why two affected parents may have unaffected children. This is a common occurrence in hereditary deafness.

MODIFYING GENES Although some phenotypes are reliably associated with specific genotypes, such as sickle cell anemia with the substitution of valine for glutamic acid at position 6 β -globin mutation, mutations should not be thought of as totally deterministic of any specific phenotype. All mutations act within a context that is specified by factors including genetic background and the

environment. Although a distinction is often made between monogenic and multilateral phenotypes, in a sense all phenotypes are multifactorial. In some instances, a single gene exerts a major effect and in others many genes exert a more modest effect, but in virtually all cases genetic background and environment play some role.

Modifying loci may be intragenic or may occur as interactions between different gene loci. The poly T polymorphism with the *CFTR* gene exerts a modifying effect in the expression of mutations within this gene. Individuals may have an allele with 5, 7, or 9T's with this polymorphic site, which resides within the interval between exons 7 and 8. The 5T allele is associated with skipping of exon 9, whereas the 9T allele leads to normal splicing. Genotype at the poly T site influences phenotype associated with another *CFTR* mutation, R117H. This mutation is associated with CBAVD when in *cis* with 9T and opposite another *CFTR* mutation, but with mild cystic fibrosis if in *cis* with a 5T allele.

A dramatic example of gene–gene interaction is the phenomenon of epistasis, wherein the phenotype of one gene masks that of another. Individuals will only secrete A or B blood group antigens into saliva if they have at least one dominant *Se* alleles at the secretor locus. Someone with the *se/se* genotype will not have A or B antigen in saliva regardless of ABO genotype. Modifier loci with more subtle effects are likely to play a role in a large number of phenotypes. At least some degree of variable expression is probably the consequence of interactions between genes. Any single locus can be visualized as a node in a network. Changing the state of a single node will influence, and be influenced by, a large number of other nodes. In rare and common disorders, expression of a phenotype is a consequence of a complex web of interactions, and genetic analysis will increasingly require such complex systems.

CONCLUSIONS

The rules of Mendelian inheritance have provided the basis for the study of human genetics for a century. Studies at the molecular level have provided an understanding of the basis for single gene inheritance and have uncovered some unexpected mechanisms. With new tools of genomics, exploration is beginning of the complexities of gene interactions as they relate to rare and

common phenotypes, and knowledge of the elements of genetics is being integrated into a broader picture of biology.

SELECTED REFERENCES

- Augarten A, Kerem BS, Kerem E, Gazit E, Yahav Y. Correlation between genotype and phenotype in patients with cystic fibrosis. *N Engl J Med* 1993;329:1308–1313.
- Cassidy SB, Dykens E, Williams CA. Prader-Willi and Angelman syndromes: sister imprinted disorders. *Am J Med Genet* 2000;97(2):136–146.
- DiMauro S, Schon EA. Mitochondrial DNA mutations in human disease. *Am J Med Genet* 2001;106(1):18–26.
- Kajiwara K, Berson EL, Dryja TP. Digenic retinitis pigmentosa due to mutations at the unlinked peripherin/RDS and ROM1 loci. *Science* 1994;264(5165):1604–1608.
- Kiesewetter S, Macek M Jr, Davis C, et al. A mutation in *CFTR* produces different phenotypes depending on chromosomal background. *Nat Genet* 1993;5:274–278.
- Levy HL, Albers S. Genetic screening of newborns. *Annu Rev Genomics Hum Genet* 2000;1:139–177.
- Lieberman AP, Fischbeck KH. Triplet repeat expansion in neuromuscular disease. *Muscle Nerve* 2000;23(6):843–850.
- McIntosh GC, Olshan AF, Baird PA. Paternal age and the risk of birth defects in offspring. *Epidemiology* 1995;6:282–288.
- Monaco AP, Bertelson CJ, Liechti-Gallati S, Moser H, Kunkel LM. An explanation for the phenotypic differences between patients bearing partial deletions of the DMD locus. *Genomics* 1989;2:90–95.
- Plath K, Mlynarczyk-Evans S, Nusinow DA, Panning B. Xist RNA and the mechanism of X chromosome inactivation. *Annu Rev Genet* 2002;36:233–278.
- Prockop DJ, Baldwin CT, Constantinou CD. Mutations in type I procollagen genes that cause osteogenesis imperfecta. *Adv Hum Genet* 1990;19:105–132.
- Robinson PN, Booms P, Katzke S, et al. Mutations of *FBN1* and genotype-phenotype correlations in Marfan syndrome and related fibrillinopathies. *Hum Mutat* 2002;20(3):153–161.
- Ruggieri M, Huson SM. The clinical and diagnostic implications of mosaicism in the neurofibromatoses. *Neurology* 2001;56(11):1433–1443.
- Sampson JR. *TSC1* and *TSC2*: genes that are mutated in the human genetic disorder tuberous sclerosis. *Biochem Soc Trans* 2003;31(Pt 3):592–596.
- Shiang R, Thompson LM, Zhu Y-Z, et al. Mutations in the transmembrane domain of *FGFR3* cause the most common genetic form of dwarfism, achondroplasia. *Cell* 1994;78:335–342.
- Walter J, Paulsen M. Imprinting and disease. *Semin Cell Dev Biol* 2003;14(1):101–110.

2 Nontraditional Inheritance

SHAWN E. MCCANDLESS AND SUZANNE B. CASSIDY

SUMMARY

The “rules” of segregation of alleles originally defined by Gregor Mendel explained much of the phenomena associated with inheritance and have been dogmatically applied in the field of genetics. However, there are situations in which the rules of Mendelian inheritance cannot explain observed phenomena. A variety of molecular mechanisms have been identified that explain certain phenomena that are not easily explained by traditional Mendelian patterns of inheritance. These non-Mendelian mechanisms differ on a molecular basis, but can be described as a group by the term “nontraditional mechanisms of inheritance” or “nontraditional inheritance.” Stated simply, nontraditional inheritance refers to the pattern of inheritance of a trait or phenotype that occurs predictably, recurrently, and in some cases familiarly, but does not follow the rules of typical Mendelian autosomal or sex chromosome inheritance. Examples discussed in this chapter are the triplet repeat expansion mutations, and genomic disorders including genetic imprinting, mitochondrial inheritance, and multi-allelic inheritance.

Key Words: Angelman syndrome (AS); fragile X; Mendelian; mitochondrial inheritance; multifactorial inheritance; non-Mendelian; Prader–Willi syndrome (PWS).

INTRODUCTION

The “rules” of segregation of alleles originally defined by Gregor Mendel explained much of the phenomena associated with inheritance and have been dogmatically applied in the field of genetics. However, there are situations in which the rules of Mendelian inheritance cannot explain observed phenomena. A variety of concepts have been suggested to explain such phenomena, including the idea that individual genes may function in cooperation with each other and with environmental factors to produce a given phenotype. This concept of multifactorial inheritance is well accepted; however, specific examples for which the various factors can be well defined have been difficult to identify. Other natural phenomena, such as anticipation, in which genetic traits or disorders become more severe or pronounced in successive generations, or genetically determined conditions that appear to depend on the sex of the parent of origin of the involved chromosome, have been difficult to explain, even using concepts of multifactorial inheritance.

A variety of molecular mechanisms have been identified, which explain certain phenomena that are not easily explained by traditional Mendelian patterns of inheritance. These non-Mendelian mechanisms differ on a molecular basis, but can be described as a group by the term “nontraditional mechanisms of inheritance” or “nontraditional inheritance.” Stated simply, nontraditional inheritance refers to the pattern of inheritance of a trait or phenotype that occurs predictably, recurrently, and in some cases familiarly, but does not follow the rules of typical Mendelian autosomal or sex chromosome inheritance. Examples discussed in this chapter are the triplet repeat expansion mutations and genomic disorders including genetic imprinting, mitochondrial inheritance, and multi-allelic inheritance.

TRIPLET REPEAT EXPANSION

The first disorder identified as resulting from this form of nontraditional inheritance is fragile X syndrome (FRAXA). FRAXA is a well-recognized disorder that causes mental retardation, autistic-like behaviors, and a subtle, but characteristic, external phenotype in all males and many females possessing the mutation. Early studies confirmed that the locus of interest was on the X chromosome, and that in some cases the trait was associated with a cytogenetically visible fragile site on the X chromosome, seen only when cells were grown in a folic acid-deficient medium. The mental retardation syndrome was inherited in a classic pattern of X-linked inheritance, with carrier mothers who might have affected brothers or uncles passing the trait on to half of their male offspring. However, some unusual families caused confusion because of a pedigree pattern demonstrating what came to be known as the Sherman paradox. Specifically, there were families identified in which a male appeared to have passed the trait on to his daughters, but he himself was not affected, even though he might have affected brothers or uncles. This pattern could not be explained by typical X-linked inheritance.

The solution to the Sherman paradox became apparent when the molecular basis of the FRAXA was found to be a unique type of mutation that occurs in a region of repeated nucleotides in the genetic sequence. Specifically, in the FMR1 gene (*Xq27.3*) there is a repeated sequence of CGG nucleotides, a “triplet repeat” (Fig. 2-1). In normal individuals this sequence is repeated 5–44 times, but in an affected individual the sequence is repeated more than 200 times. Even more interesting, the mothers of the affected individuals were found to have triplet repeats with 60–200 copies. The normal allele is stably copied during the process of meiosis,