ROSENBERG'S MOLECULAR AND GENETIC BASIS OF NEUROLOGICAL AND PSYCHIATRIC DISEASE

FIFTH EDITION

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Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease, 5e
Roger N. Rosenberg, Juan M. Pascual Editors

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FIFTH EDITION

Edited by

ROGER N. ROSENBERG
The Abe (Brunky), Morris and William Zale Distinguished Chair in Neurology
Department of Neurology and Neurotherapeutics
Department of Physiology
Head, Section of Cognitive and Memory Disorders
Director, Alzheimer's Disease Center
The University of Texas Southwestern Medical Center
Dallas, TX
USA

JUAN M. PASCUAL
The Once Upon a Time Foundation Professorship in Pediatric Neurologic Diseases
Director, Rare Brain Disorders Program
Department of Neurology and Neurotherapeutics
Department of Physiology
Department of Pediatrics
Eugene McDermott Center for Human Growth & Development/Center for Human Genetics
Division of Pediatric Neurology
The University of Texas Southwestern Medical Center
Dallas, TX
USA

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Dedications

We dedicate this text to our colleagues, who, by perseverance and dedication, have provided essential new scientific knowledge about the molecular and genetic basis of neurologic and psychiatric disorders, and, in so doing, have conceptualized important insights into disease causation and therapies for the future.

Roger N. Rosenberg and Juan M. Pascual

I wish to dedicate this work to my parents, Cora and Sol Rosenberg, and to my wife, Adrienne. They have been an inspiration to me and have provided me with their care and love to maintain my focus and resilience throughout my life and career, for which I will forever be grateful.

Roger N. Rosenberg

Juan M. Pascual dedicates this work to the memory of his father, Juan Pascual Toledo, magister, who traversed his life and ours loyal, unswerving, and serene, and awaits:

"Venisti tandem, tuaque exspectata parenti
vicit iter durum pietas?
datur ora tueri,
nate, tua et notas audire et reddere voces?"

Preface to the Fifth Edition

We are publishing the fifth edition of the *Molecular and Genetic Basis of Neurological and Psychiatric Disease*. The first edition appeared in 1993 followed by editions in 1997, 2003, and 2008. We are most grateful for the foresight, dedication, and authorship of our former editors for the success of the first four editions. They are Stanley B. Prusiner, Salvatore DiMauro, Robert L. Barchi, Louis M. Kunkel, Henry L. Paulson, Louis Ptáček and Eric J. Nestler. The fifth edition is edited by Roger N. Rosenberg and Juan M. Pascual.

There are several major new aspects to the fifth edition: The text now includes well over 100 chapters and 200 contributors. Every chapter has been thoroughly updated either by previous contributors or by new experts in the field, all of which are of international renown. A standard, unified chapter format has been followed as much as possible. Most illustrations are new or have been newly drawn, and color has been used wherever helpful throughout the text. The book is available both in print and in up-to-date electronic format. Additional new chapters in this edition cover the following topics: DNA sequencing and other methods of exonic and genomic analysis; pharmacogenomics; causation and association; stem cells and therapeutic development; neuroimaging; genetic counseling; the ethics of cognitive enhancement and mental impairment; cerebral malformations; global developmental delay and intellectual disability; neurodegeneration with brain iron accumulation; pantothenate kinase deficiency; Wilson disease; Menkes disease and other ATP7A disorders; disorders of manganese transport; aceruloplasminemia; neurotransmitter disorders; frontotemporal dementias; dystonia; glioblastoma; tuberous sclerosis; von Hippel–Lindau disease; Sturge–Weber syndrome; incontinentia pigmenti; channelopathies; vanishing white matter disease; pyruvate metabolism and Krebs cycle disorders; pain; vasculopathies; coagulopathies; sickle cell disease; and autism. Clearly, neurogenics/neurogenomics has advanced rapidly and is now poised to develop in the next decade effective targeted neurotherapeutics.

In the 21 years spanning the five editions of our book, molecular genomic analyses of the human genome have been implemented seeking the genetic basis for natural selection providing biological fitness and also risk of developing disease. Genome-wide association studies (GWAS) seeking gene variations, single nucleotide polymorphisms (SNP), causal of several human diseases have been conducted in recent years including autism, schizophrenia, obesity, diabetes and heart disease.

Several GWAS for risk association with neurological diseases, neuromic studies, have been reported. An increased risk for amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), restless leg syndrome (RLS), and multiple sclerosis have been associated with polymorphisms in specific genes. These observations have advanced an understanding of the causation of inherited, complex polygenetic, multifactorial neurological diseases. They have been made possible by the publication of the human genome and haplotype studies (HapMap analyses).

The hope with neurome-wide association studies has been that the complete complement of variant genes will be identified causal of the major neurodegenerative diseases. Then, pharmaconeuromic therapy would not be far behind. GWAS has provided new and important data of the major genes responsible for major human traits and common diseases. GWAS has provided insights into gene variations in low penetrant genes causal for polygenetic, multifactorial neurological disease, such as Alzheimer disease. Overall, about 400 genetic variants have been identified that contribute to human traits and diseases including neurological diseases.

Sequencing candidate genes for disease including their surrounding regions in thousands of people will be needed to discover more associations with disease. SNPs are turning out not to be a stringent enough level of analysis seeking genetic risks for disease. The change in mindset is going from seeking analyses of common, low-penetrance variants causal of common diseases to seeking rare low- or moderate-penetrance variants that have been missed by GWAS. It may be necessary to move beyond sequencing candidate genes and surrounding regions for disease association and begin sequencing whole genomes to find the missing heritability. Francis Collins, Director of the National Institutes of Health, has suggested that the 1000 genomes project, designed to sequence the genomes of at least 1000 people from all over the world, would provide a powerful approach to finding the hidden heritability.

The genetic explanations that would be of primary interest to find the missing heritability for genetic neurological disease missed by GWAS include copy-number variation (CNV), epistatic effects, and epigenetics. CNV refers to regions of DNA that are up to hundreds of base pairs long that are deleted or duplicated between individuals.

There are strong CNV associations between schizophrenics compared to normals and they may arise *de novo* in persons without a family history of the mutation. Epistasis, where one or more modifying genes reduce or enhance the effect of another gene, may be an important genetic mechanism at work to explain heritability not found by GWAS. Epigenetics is another vital area to be explored. It refers to changes in gene expression that are inherited but not caused by alteration in the sequence of the gene. We now know that gene expression is altered by methylation or acetylation, and also by inhibition of messenger RNA expression by iRNA or microRNA binding.

The 21,000 protein-coding genes in the human genome make up less than 1.2% of the human genome. Analysis of the remaining 98.8% of the human genome and its role in the causation of human neurological diseases, both inherited and acquired, is a formidable challenge yet unexplored to any degree. RNA transcripts and their effects on regulation and levels of gene expression is one of the next frontiers for neuromics.

Then there is the issue that natural selection only functions before or during the reproductive years and not afterwards, when Alzheimer disease and Parkinson disease occur. Natural selection has as its major biological function to select for fitness allowing for reproduction and maintenance of a lineage or species. Aging and neurodegenerative diseases seem to have escaped the forces of natural selection by occurring after the reproductive years. On the other hand, perhaps evolution has actually selected for aging and neurodegenerative diseases as a means to maintain the limits of a finite lifespan. Clearly, neuromics must address the molecular basis of brain aging and why the aging process provides a permissive environment to allow the opportunistic neuromic program causal of late-onset neurodegenerative diseases to be expressed.

The cause of Alzheimer disease is due both to genetic polymorphisms and environmental stimuli. In this view, environmental stimuli, to be determined, influence the production of an abnormal pattern of gene expression causal of Alzheimer disease. So, we will have to understand the process of natural selection in the context of the selection pressures from the environments that we inhabit. Darwin emphasized adaptation to a changing environment as the principal selective influence for evolution. This principle is valid studying the interaction of environmental stimuli and the genetic factors causal of neurodegenerative diseases.

Deriving induced pluripotential stem cells from late-onset Alzheimer disease patients and differentiating them into neuroblasts would be one way to screen compounds to see if an abnormal pattern of gene expression is produced compared to derived neuroblasts from normal controls. Here would be a method to link environment to the genetic program causal of Alzheimer disease. It would also be a means to screen potential therapeutic agents that correct an abnormal pattern of gene expression seen in AD patients as a prelude to a clinical trial.

The 200 years since Charles Darwin's birth, 150 years since the publication of *On the Origin of Species,* and the 20 years of the publication of the four editions of this book, is a brief time in human experience. The fifth edition builds on the development of neurogenetics during the past 20 years and documents the advances in genome sequencing, CNV, epistasis, epigenetics, RNA regulation of gene expression, and stem cell applications to decipher how mutations in these genetic functions are causal of neurological diseases.

We look forward to future editions of the book and wish to express our gratitude to our many loyal colleagues who have participated in all five editions, and thank our new authors for their contributions to maintain the book's scientific rigor and excellence. Whereas we have made every effort towards comprehensiveness and clarity, many omissions and imprecisions are bound to remain. To that effect, we will welcome comments and suggestions at Rosenberg5ed@gmail.com. We have retained the names of Hugo W. Moser and John H. Menkes through the kindness of their families to honor their memory. The outstanding editorial contributions of Kristi Anderson, project manager, Mica Haley, publisher for neuroscience, and Julia Haynes, book production project manager, are most gratefully acknowledged. We are also thankful to our families, patients, colleagues and trainees both for interactions and for lost time while we were working on the fifth edition. While a textbook on the human experience of neurological or psychiatric patients has not yet been written, we hope that ours will assist in the understanding of one important dimension of their existence.

Roger N. Rosenberg
Juan M. Pascual
Editors

Contributors

Nicholas Ah Mew The Center for Neuroscience and Behavioral Medicine, Department of Genetics and Metabolism, Children's National Medical Center, Washington, DC, USA

Wado Akamatsu Department of Physiology, School of Medicine, Keio University, Tokyo, Japan

Hasan Orhan Akman Department of Neurology, Columbia University Medical Center, New York, NY, USA

Koji Aoyama Department of Pharmacology, Teikyo University School of Medicine, Tokyo, Japan

W. David Arnold Deparment of Neurology, The Ohio State University, Wexner Medical Center, Columbus, OH, USA

Rafael Artuch Hospital Sant Joan de Déu, Barcelona, Spain; CIBERER (Network for Research in Rare Diseases), Instituto de Salud Carlos III, Madrid, Spain

Robert M. Bachoo Departments of Internal Medicine and Neurology & Neurotherapeutics, Annette G. Strauss Center for Neuro-Oncology, Simmons Cancer Center, The University of Texas Southwestern Medical Center, Dallas, TX, USA

Sergio E. Baranzini Department of Neurology, University of California, San Francisco, CA, USA

Michael Beck Children's Hospital, University Medical Center, University of Mainz, Mainz, Germany

Merrill D. Benson Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

Vladimir M. Berginer Department of Neurology, Soroka Medical Center, Beer Sheva, Israel

Gerard T. Berry Boston Children's Hospital, Division of Genetics and Genomics, Harvard Medical School, Boston, MA, USA

Kevin M. Biglan Department of Neurology, University of Rochester, Rochester, NY, USA

Thomas D. Bird Departments of Neurology and Medicine, University of Washington and VA Medical Center, Seattle, WA, USA

D. Montgomery Bissell National Institutes of Health (NIH)-supported Liver Center, Division of Gastroenterology, UCSF Medical Center, San Francisco, CA, USA

Michael H. Bloch Child Study Center, Yale University School of Medicine, New Haven, CT, USA

Aldobrando Broccolini Institute of Neurology, Department of Geriatrics, Neurosciences and Orthopedics, Catholic University, Rome, Italy

Robert H. Brown, Jr. Department of Neurology, University of Massachusetts Medical School, Worcester, MA, USA

Allison Caban-Holt Department of Behavioral Science, Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA

Brenda Canine McLaughlin Research Institute, Great Falls, MT, USA

C. Thomas Caskey Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

Patrick F. Chinnery Department of Neurology, Institute of Genetic Medicine, Newcastle University, Newcastle NIHR Biomedical Research Centre, Newcastle upon Tyne, UK

David T. Chuang Departments of Biochemistry and Internal Medicine, The University of Texas Southwestern Medical Center, Dallas, TX, USA

Jacinta L. Chuang Department of Biochemistry, The University of Texas Southwestern Medical Center, Dallas, TX, USA

Bernard A. Cohen Dermatology and Pediatrics, Johns Hopkins Children's Center, Baltimore, MD, USA

Anne M. Comi Neurology and Pediatrics, Kennedy Krieger Institute, Johns Hopkins School of Medicine, Hunter Nelson Sturge-Weber Center, Baltimore, MD, USA

Rody P. Cox Department of Internal Medicine, The University of Texas Southwestern Medical Center, Dallas, TX, USA

John C. Crabbe Department of Behavioral Neuroscience, Department of Veterans Affairs Medical Center Director, Portland Alcohol Research Center, Oregon Health & Science University, Portland, OR, USA

Marie Y. Davis Department of Neurology, University of Washington, Seattle, WA, USA

Darryl C. De Vivo SMA Clinical Research Center, Motor Neuron Center, Colleen Giblin Laboratories for Pediatric Neurology, Columbia University Medical Center, New York, NY, USA

Robert J. Desnick Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Stefano Di Donato Fondazione IRCCS Istituto Neurologico "Carlo Besta," Milan, Italy

Salvatore DiMauro Department of Neurology, Columbia University Medical Center, The Neurological Institute of New York, New York, NY, USA

Michael M. Dowling Departments of Pediatrics, Neurology and Neurotherapeutics, The University of Texas Southwestern Medical Center, Dallas, TX, USA

David A. Dyment Children's Hospital of Eastern Ontario Research Institute, University of Ottawa, Ottawa, ON, Canada

Florian S. Eichler Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Ramyiadarsini Elangovan Functional Genomics Unit, Department of Physiology, Anatomy and Genetics and Medical Research Council, University of Oxford, Oxford, UK

Bernice Elger Institute of Biomedical Ethics, University of Basel, Basel, Switzerland

Sara Elrefai Department of Medical Genetics, Henry Ford Hospital, Detroit, MI, USA

Orna Elroy-Stein Department of Cell Research and Immunology, Faculty of Life Sciences, Tel Aviv University, Tel Aviv, Israel

Bakri H. Elsheikh Saudi Aramco, Dhahran, Saudi Arabia

Andrew G. Engel Mayo Clinic College of Medicine, Department of Neurology, Mayo Clinic, Rochester, MN, USA

Patricia Evans Department of Neurology and Pediatrics, The University of Texas Southwestern School of Medicine, Dallas, TX, USA

Stanley Fahn Movement Disorder Division, Department of Neurology, Neurological Institute, Columbia University Medical Center, New York, NY, USA

Scott C. Fears Ronald Reagan UCLA Medical Center, Stewart and Lynda Resnick Neuropsychiatric Hospital at UCLA, Los Angeles, CA, USA

John K. Fink Department of Neurology, University of Michigan, Geriatric Research Education and Care Center, Ann Arbor Veterans Affairs Medical Center, Ann Arbor, MI, USA

Theodore Friedmann Department of Pediatrics, UCSD School of Medicine, La Jolla, CA, USA

Martin J. Gallagher Department of Neurology, Vanderbilt University, Nashville, TN, USA

Àngels García-Cazorla Department of Neurology, Hospital Sant Joan de Déu, Barcelona, Spain; CIBERER (Network for Research in Rare Diseases); Instituto de Salud Carlos III, Madrid, Spain

Jill S. Goldman Taub Institute, Columbia University Medical Center, New York, NY, USA

Sailaja Golla Neurodevelopmental Pediatrics, Division Of Pediatric Neurology, The University of Texas Southwestern Medical Center, Children's Medical Center, Dallas TX, USA

Sidney M. Gospe, Jr. Departments of Neurology and Pediatrics, University of Washington, and Seattle Children's Hospital, Seattle, WA, USA

William D. Graf Department of Pediatrics, Department of Neurology, Yale School of Medicine, New Haven, CT, USA

Robert C. Griggs Departments of Neurology, Pathology and Laboratory Medicine and Pediatrics, University of Rochester Medical Center, Rochester, NY, USA

Andrea L. Gropman Division of Neurogenetics and Developmental Pediatrics, Department of Neurology and Pediatrics, Children's National Medical Center and the George Washington University of the Health Sciences, Washington, DC, USA

Yian Gu Taub Institute on Alzheimer's Disease and the Aging Brain, Department of Neurology, Columbia University Medical Center, New York, NY, USA

Teresa M. Gunn McLaughlin Research Institute, Great Falls, MT, USA

David H. Gutmann Department of Neurology, Washington University Neurofibromatosis Center, Washington University School of Medicine, St. Louis, MO, USA

Richard Haas Departments of Neurosciences and Pediatrics, University of California, San Diego, La Jolla, CA, USA

Randi J. Hagerman MIND Institute, UC Davis Health System, Sacramento, CA, USA

Matti J. Haltia Department of Pathology, Children's Hospital, University of Helsinki, Helsinki, Finland

Emma B. Hare MIND Institute, UC Davis Medical Center, Sacramento, CA, USA

Tamar Harel Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

Stephen L. Hauser Department of Neurology, University of California, San Francisco, CA, USA

Elizabeth Head Department of Molecular and Biomedical Pharmacology, Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA

James E. Hilbert Department of Neurology, Neuromuscular Disease Center, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

Eric P. Hoffman Research Center for Genetic Medicine, Children's Research Institute, Department of Integrative Systems Biology, George Washington University, Washington, DC, USA

Othon Iliopoulos Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, MA, USA

Hiroyuki Ishiura Department of Neurology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Monica P. Islam Department of Clinical Pediatrics, The Ohio State University College of Medicine, Department of Pediatric Neurology, Nationwide Children's Hospital, Columbus, OH, USA

Clifford R. Jack, Jr. Aging and Dementia Imaging Laboratory, Department of Radiology, Mayo Clinic, Rochester, MN, USA

William G. Johnson Laboratory of Molecular Neurogenetics, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Fabrice Jotterand Department of Health Care Ethics, Regis University, Denver, CO, USA; Institute of Biomedical Ethics, University of Basel, Basel, Switzerland

Heinz Jungbluth Department of Clinical Neuroscience, King's College London, Guy's & St. Thomas' Hospital NHS Foundation Trust, London, UK

John P. Kane Departments of Medicine, Biochemistry and Biophysics, Cardiovascular Research Institute, UCSF Medical Center, San Francisco, CA, USA

Clara van Karnebeek Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada

Saima N. Kayani Department of Neurology and Neurotherapeutics, and Pathology, The University of Texas Southwestern Medical Center, Dallas, TX, USA

Pravin Khemani Department of Neurology and Neurotherapeutics, The University of Texas Southwestern Medical Center, Dallas, TX, USA

Fenella J. Kirkham Department of Paediatric Neurology, Neurosciences Unit, Institute of Child Health, University College London, London, UK

A. Yasmine Kirkorian Division of Pediatric Dermatology, Department of Dermatology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

John T. Kissel Department of Neurology and Pediatrics, Wexner Medical Center, The Ohio State University, Columbus, OH, USA

Christine Klein Institute of Neurogenetics and, Department of Neurology, University of Lübeck, Lübeck, Germany

Kleopas A. Kleopa Department of Clinical Neurosciences, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus

Satoshi Kono First Department of Medicine, Hamamatsu University School of Medicine, Handayama, Hamamatsu, Japan

Michael C. Kruer University of South Dakota Sanford School of Medicine, Sanford Children's Specialty Clinic, Sanford Children's Research Center, Sioux Falls, SD, USA

Walter A. Kukull Department of Epidemiology, University of Washington, Seattle, WA, USA

Jessica B. Lennington Child Study Center, Yale University School of Medicine, New Haven, CT, USA

David A. Lewis Department of Psychiatry, University of Pittsburgh, Western Psychiatric Institute and Clinic, Pittsburgh, PA, USA

Wen-Chen Liang Department of Pediatrics, Kaohsiung Medical University Hospital, Department of Pediatrics, School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

Katja Lohmann Institute of Neurogenetics, University of Lübeck, Lübeck, Germany

Paul J. Lombroso Child Study Center, Yale University School of Medicine, New Haven, CT, USA

Reymundo Lozano MIND Institute, UC Davis Medical Center, Sacramento, CA, USA

James R. Lupski Department of Pediatrics, Department of Molecular and Human Genetics, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA

Paola Luzi Department of Neurology, Assistant Director, Lysosomal Diseases Testing Laboratory, Jefferson Medical College, Philadelphia, PA, USA

Qian Ma Rare Brain Disorders Program, Department of Neurology and Neurotherapeutics, The University of Texas Southwestern Medical Center, Dallas, TX, USA

Robert L. Macdonald Department of Neurology, Vanderbilt University, Nashville, TN, USA

Gustavo H.B. Maegawa McKusick-Nathans Institute of Genetic Medicine, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Elizabeth A. Maher Departments of Internal Medicine and Neurology & Neurotherapeutics, Annette G. Strauss Center for Neuro-Oncology, Simmons Cancer Center, The University of Texas Southwestern Medical Center, Dallas, TX, USA

Mary J. Malloy* Departments of Medicine and Pediatrics, Cardiovascular Research Institute, UCSF Medical Center, San Francisco, CA, USA

*Deceased

Ami K. Mankodi Neurogenetics Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA

Douglas A. Marchek Department of Molecular Genetics and Microbiology, Duke University School of Medicine, Durham, NC, USA

Isaac Marin-Valencia Rare Brain Disorders Program, Department of Neurology and Neurotherapeutics, Department of Pediatrics, Division of Pediatric Neurology, The University of Texas Southwestern Medical Center, Dallas, TX, USA

Frederick J. Marshall Geriatric Neurology Unit, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

James A. Mastrianni Center for Comprehensive Care and Research on Memory Disorders, Department of Neurology, The University of Chicago, Chicago, IL, USA

Reuben Matalon Department of Pediatrics, The University of Texas Medical Branch (UTMB), Galveston, TX, USA

Richard Mayeux Gertrude H. Sergievsky Center, Taub Institute on Alzheimer's Disease and the Aging Brain, Columbia University Medical Center, New York, NY, USA

Jennifer L. McCurdy Department of Health Care Ethics, Rueckert-Hartman College of Health Professions, Regis University, Denver, CO, USA

Andrew J. McGarry Department of Neurology, Cooper University Health Care, Cherry Hill, NJ, USA

John H. Menkes* Cedars-Sinai Medical Center, Los Angeles, CA, USA

Giovanni Meola Department of Neurology, University of Milan, IRCCS Policlinico San Donato, Milan, Italy

Ana Metelo Faculty of Science and Technology, Coimbra University, Coimbra; Portugal; Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, MA, USA

Kimberlee Michals Matalon Health and Human Performance, The University of Houston, Houston, TX, USA

Bruce L. Miller Neurology, Memory and Aging Center, University of California, San Francisco, CA, USA

Massimiliano Mirabella Institute of Neurology, Department of Geriatrics, Neurosciences and Orthopedics, Catholic University, Rome, Italy

Justin Miron Department of Neuroscience, McGill University, Montreal, QC, Canada

Jun Mitsui Department of Neurology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Hiroaki Miyajima First Department of Medicine, Hamamatsu University School of Medicine, Handayama, Hamamatsu, Japan

Shuki Mizutani Department of Pediatrics and Developmental Biology, Tokyo Medical and Dental University, Graduate School of Medicine, Yushima, Tokyo, Japan

Sara E. Mole MRC Laboratory for Molecular Cell Biology, UCL Institute of Child Health, University College London, London, UK

Lisa M. Monteggia Department of Neuroscience, The University of Texas Southwestern Medical Center, Dallas, TX, USA

Hugo W. Moser Department of Neurogenetics, Johns Hopkins University, Kennedy Krieger Institute, Baltimore, MD, USA

Mary Ann Morris Department of Neurology and Neurotherapeutics, The University of Texas Southwestern School of Medicine, Dallas, TX, USA

Richard T. Moxley, III Department of Neurology and Pediatrics, Neuromuscular Disease Center, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

Jennifer M. Mueller Division of Genetics and Metabolism, Department of Pediatrics, University of Florida, Gainesville, FL, USA

Francesco Muntoni Department of Paediatric Neurology, Dubowitz Neuromuscular Centre, UCL Institute of Child Health, London, UK

Melissa E. Murray Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA

Toshio Nakaki Department of Pharmacology, Teikyo University School of Medicine, Tokyo, Japan

Charles B. Nemeroff Department of Psychiatry and Behavioral Sciences, Leonard M. Miller School of Medicine, University of Miami, Miami, FL, USA

Ichizo Nishino Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP), Tokyo, Japan

William L. Nyhan Department of Pediatrics, University of California, San Diego, La Jolla, CA, USA

Hideyuki Okano Department of Physiology, School of Medicine, Keio University, Tokyo, Japan

Jorge R. Oksenberg Department of Neurology, University of California, San Francisco, CA, USA

Adam P. Ostendorf Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA

Massimo Pandolfo Université Libre de Bruxelles, ULB Institute of Neurosciences (UNI), Department of Neurology, Hôpital Erasme, Brussels, Belgium

Maria Belen Pappa Division of Neurogenetics and Developmental Pediatrics, Department of Neurology and Pediatrics, Children's National Medical Center and the George Washington University of the Health Sciences, Washington, DC, USA

Carmen Paradas Unidad de Enfermedades Neuromusculares, Servicio de Neurologia, Hospital Universitario Virgen del Rocio/Instituto de Biomedicina de Sevilla, Universidad de Sevilla, Seville, Spain

Juan M. Pascual Rare Brain Disorders Program, Departments of Neurology and Neurotherapeutics, Physiology and Pediatrics and Eugene McDermott Center for Human Growth & Development/ Center for Human Genetics. Division of Pediatric Neurology, The University of Texas Southwestern Medical Center, Dallas, TX, USA

Gregory M. Pastores Adult Metabolic Service, Department of Medicine, National Centre for Inherited Metabolic Disorders Mater Misericordiae University Hospital, Dublin, Ireland

Shailendra B. Patel Division of Endocrinology, Metabolism and Clinical Nutrition, Clement J Zablocki Veterans Medical Center, Medical College of Wisconsin, Milwaukee, WI, USA

Marc C. Patterson Division of Child and Adolescent Neurology, Departments of Neurology, Pediatrics and Medical Genetics, Mayo Clinic Children's Center, Rochester, MN, USA

Davut Pehlivan Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

Scott D. Philibin Department of Psychiatry, The University of Texas Southwestern Medical Center, Dallas, TX, USA

Cynthia Picard Department of Neuroscience, McGill University, Montreal, QC, Canada

Judes Poirier Centre for Studies on the Prevention of Alzheimer's Disease, Douglas Mental Health University Institute, Montreal, QC, Canada

Louis J. Ptáček Department of Neurology, Howard Hughes Medical Institute, University of California, San Francisco, San Francisco, CA, USA

Geetha L. Radhakrishnan Department of Pediatrics, The University of Texas Medical Branch (UTMB), Galveston, TX, USA

Jeffrey W. Ralph Department of Neurology, University of California, San Francisco, CA, USA

Sreeram V. Ramagopalan Functional Genomics Unit, Department of Physiology, Anatomy and Genetics and Medical Research Council, University of Oxford, Oxford, UK

Gerald V. Raymond Department of Neurology, University of Minnesota, Minneapolis, MN, USA

William Renthal Department of Neurology and Neurotherapeutics, The University of Texas Southwestern Medical Center, Dallas, TX, USA

Victor I. Reus Department of Psychiatry, University of California San Francisco School of Medicine, San Francisco, CA, USA

E. Steve Roach Department of Pediatrics and Neurology, The Ohio State University College of Medicine, Nationwide Children's Hospital, Columbus, OH, USA

Roger N. Rosenberg Department of Neurology and Neurotherapeutics, Department of Physiology, Section of Cognitive and Memory Disorders, Alzheimer's Disease Center, The University of Texas Southwestern Medical Center, Dallas, TX, USA

David S. Rosenblatt Departments of Human Genetics, Medicine, Pediatrics and Biology, McGill University, Montreal, QC, Canada

Gerald Salen Division of Gastroenterology, Rutgers, New Jersey Medical School, Newark, NJ, USA

Konrad Sandhoff LIMES, Kekulé-Institut, Bonn University, Bonn, Germany

Lawrence D. Scahill Department of Pediatrics, Marcus Autism Center, Emory University School of Medicine, Atlanta, GA, USA

Steven S. Scherer Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Raphael Schiffmann Institute of Metabolic Disease, Baylor Research Institute, Dallas, TX, USA

Detlev Schindler Department of Human Genetics, University of Würzburg, Würzburg, Germany

Frederick Schmitt Department of Neurology, Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA

Susanne A. Schneider Department of Neurology, University of Kiel, Kiel, Germany

Eric A. Schon Department of Neurology, Columbia University Medical Center, The Neurological Institute of New York, New York, NY, USA

Edward H. Schuchman Icahn School of Medicine at Mount Sinai, New York, NY, USA

Nicole Schupf The Gertrude H. Sergievsky Center, Columbia University Medical Center, New York, NY, USA

Margretta Reed Seashore Departments of Genetics, Laboratory Medicine and Pediatrics, Yale University School of Medicine, New Haven, CT, USA

Dennis J. Selkoe Center for Neurologic Diseases, Department of Neurology, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA

Caroline Sewry Dubowitz Neuromuscular Centre, UCL Institute of Child Health and Great Ormond Street Hospital for Children, London, UK; RJAH Orthopaedic Hospital, Oswestry, UK

Michael Shevell Departments of Pediatrics and Neurology/Neurosurgery, McGill University, Montreal Children's Hospital/McGill University Health Centre, Montreal, QC, Canada

Shunichiro Shinagawa Department of Psychiatry, The Jikei University School of Medicine, Tokyo, Japan

Jemeen Sreedharan Babraham Institute, Cambridge, UK

Myriam Srour Departments of Pediatrics and Neurology/Neurosurgery, McGill University, Division of Pediatric Neurology, Montreal Children's Hospital/McGill University Health Centre, Montreal, QC, Canada

Kazuma Sugie Department of Neurology, Nara Medical University School of Medicine, Nara, Japan, Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP), Tokyo, Japan

Kristen L. Szabla Department of Neuroscience, The University of Texas Southwestern Medical Center, Dallas, TX, USA

Steven T. Szabo Department of Psychiatry and Behavioral Sciences, Division of Translational Psychiatry, Duke University Medical Center, Durham, NC, USA

Gábor Szuhay Child Study Center, Yale University School of Medicine, New Haven, CT, USA

Franco Taroni Fondazione IRCCS Istituto Neurologico "Carlo Besta," Milan, Italy

Rabi Tawil Department of Neurology, University of Rochester Medical Center, Rochester, NY, USA

Mireia Tondo Rare Brain Disorders Program, Department of Neurology and Neurotherapeutics, The University of Texas Southwestern Medical Center, Dallas, TX, USA

Shoji Tsuji Department of Neurology, Neuroscience Program, Graduate School of Medicine, Medical Genome Center, The University of Tokyo Hospital, The University of Tokyo, Tokyo, Japan

Bjarne Udd Department of Neurology, Neuromuscular Research Center, University and University Hospital of Tampere, Tampere, Finland, Folkhalsan Institute of Genetics, University of Helsinki, Helsinki, Finland; Vasa Central Hospital, Department of Neurology, Vasa, Finland

Wendy R. Uhlmann Departments of Internal Medicine and Human Genetics, University of Michigan Medical School, Ann Arbor, MI, USA

Flora M. Vaccarino Child Study Center, Program in Neurodevelopment and Regeneration, Yale Kavli Institute for Neuroscience, Yale University School of Medicine, New Haven, CT, USA

Prashanthi Vemuri Aging and Dementia Imaging Laboratory, Department of Radiology, Mayo Clinic, Rochester, MN, USA

Charles P. Venditti Organic Acid Research Section, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA

David W. Volk Department of Psychiatry, University of Pittsburgh, Western Psychiatric Institute and Clinic, Pittsburgh, PA, USA

Dong Wang Department of Neurology, Southern Regional Medical Center, Riverdale, GA, USA

David Watkins Department of Human Genetics, McGill University, Montreal, QC, Canada

David A. Wenger Department of Neurology, Director, Lysosomal Diseases Testing Laboratory, Jefferson Medical College, Philadelphia, PA, USA

Charles A. Williams Division of Genetics and Metabolism, Department of Pediatrics, University of Florida, Gainesville, FL, USA

Kathleen S. Wilson Department of Pathology and the McDermott Center for Human Growth and Development, Cytogenomic Microarray Analysis Laboratory, The University of Texas Southwestern Medical Center, Dallas, TX, USA

Golder N. Wilson Department of Pediatrics, Texas Tech University Health Science Centers, Amarillo and Lubbock (Pediatrics), KinderGenome Genetic Practice, Medical City Hospital, Dallas, TX, USA

Barry Wolf Department of Medical Genetics, Henry Ford Hospital, Center for Molecular Medicine and Genetics, Wayne State University School of Medicine, Detroit, MI, USA

R. Max Wynn Departments of Biochemistry and Internal Medicine, The University of Texas Southwestern Medical Center, Dallas, TX, USA

Shihui Yu Department of Pathology and Laboratory Medicine, Seattle Children's Hospital and University of Washington School of Medicine, Seattle, WA, USA

CHAPTER

1

Mendelian, Non-Mendelian, Multigenic Inheritance, and Epigenetics

Tamar Harel[*], *Davut Pehlivan*[*], *C. Thomas Caskey*[*], *and James R. Lupski*[*,†]

[*]**Baylor College of Medicine, Houston, TX, USA**

[†]**Texas Children's Hospital, Houston, TX, USA**

INTRODUCTION

Genetic influence on neurologic disease expression can include the contribution of a highly penetrant Mendelian variant (HPMV) and be the most prominent and perhaps singular factor required to manifest a disease phenotype, or it can be a genetic modifier and one relatively minor component of many different disease-associated factors. Perhaps the best example of the former is monogenic Mendelian disorders with complete penetrance wherein a mutation in a single disease-causing gene usually results in a relatively uniform disease phenotype. The latter pattern can be observed in many common diseases in which genetic factors contribute a portion of the risk and may play a role in either increasing or decreasing disease susceptibility. Between these extremes of genetic pathophysiology, however, there is a continuum of genetic influence on disease pathophysiology.

Mendelian traits represent the most basic and simple pattern of inheritance. Mutations in a gene encoded on an autosome or sex chromosome result in specific inheritance patterns. Non-Mendelian traits reveal some complexity in their mode of inheritance, in which the classic pattern of inheritance may not always apply, and epigenetic factors are often associated with disease mechanisms. Furthermore, in some diseases one gene is not sufficient to cause the clinical phenotype, but when two or more genes are involved, a particular disease becomes apparent. This latter mechanism is usually referred to as multigenic inheritance, and termed oligogenic inheritance when only a small number of genes are involved and digenic inheritance when variation or mutation in two genes is a prerequisite to disease trait manifestation. Finally, complex traits can involve multiple genes as susceptibility or protective factors but also require internal factors, including other health conditions, as well as external factors such as environment, lifestyle, diet, accident, infection, and drug exposure.

Regardless of the mode of inheritance, defining specific genetic factors that are associated with certain diseases and their functional role in phenotypic manifestations is important for patient management and genetic counseling, as well as for understanding disease mechanisms at the molecular level and ultimately developing new therapeutic approaches. Molecular diagnostics contribute to patient management by establishing an accurate diagnosis, by enabling presymptomatic or prenatal diagnosis, by providing prognostic information, and by further refining or subclassifying more general diagnostic labels. It is estimated that approximately one-third of all human genes are expressed in the nervous system; thus, neurogenetic phenotypes are common.[1] This chapter provides an update to the corresponding chapter by Shiga et al.[2] in the previous edition of this book; here we review the modes of inheritance that can be observed in various human neurologic and psychiatric diseases, and how genetics and more recently genomics is increasing our molecular understanding of neurological disease.

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MENDELIAN TRAITS

Mendel's Laws

The basic rules of inheritance were delineated from first principles by Gregor Mendel based upon his observation of the segregation of traits in the common garden pea, *Pisum sativum*.[3] Mendel's first law, the principle of independent segregation, referred to the ability of genes, which he called factors, to segregate independently during the formation of gametes or sex cells. Mendel's second law, the principle of independent assortment, was derived from his observations using peas that differed by more than one characteristic or trait. Mendel postulated that only one factor from each pair was independently transmitted to the gamete during sex-cell formation and that any one gamete contains only one type of inherited factor from each pair. There is no tendency for genes arising from one parent to stay together. Of course, we now know that this latter principle is true only for unlinked genes. Genes or loci that are linked, or physically located in close proximity on the same chromosome, do not assort independently. The closer these loci are, the more frequently they will cosegregate. Linkage analysis is a quantitative measurement of this cosegregation (expressed as a LOD score or $\log_{10}$ of the odds ratio for cosegregation vs. independent assortment)[4] and has been a powerful tool in human genetics to map genes for disease traits to particular regions in the human genome.

Chromosomes and Genes

The chromosomal theory of heredity expounded by Walter Sutton emphasized that the diploid chromosome group consists of a morphologically similar set, a homolog pair, for each chromosome and that during meiosis every gamete receives only one chromosome of each homolog pair. This observation was used to explain Mendel's results by assuming that genes, or factors, were part of the chromosome. Genes are arranged in a linear order on the chromosome, each having a specific position or locus. There are two copies for each gene at a given locus, one on each chromosome homolog. These two copies, or alleles, may be identical, or homozygous, at the specific autosomal locus. Alternatively, the two gene copies at a particular locus may be different and represent heterozygous alleles. When only one copy is physically present, either because of deletion of a specific genomic region on the other homolog or because of the special circumstances of the X chromosome in XY males, this condition is referred to as hemizygous. The genes are passed to the next generation through parental gametes, which contain only one of the two alternative gene copies. A particular gamete may contain alleles from different chromosome homologs because of chromosome crossover and recombination of alleles that occur during meiosis.

Mendelian Inheritance

Mendelian inheritance refers to an inheritance pattern that follows the laws of segregation and independent assortment in which a gene inherited from either parent segregates into gametes at an equal frequency. Three major patterns of Mendelian inheritance for disease traits are described: autosomal dominant, autosomal recessive, and X-linked (Figure 1.1). Mendelian inheritance patterns refer to observable traits, not to genes. Some alleles at a specific locus may encode a trait that segregates in a dominant manner, whereas another allele may encode the same or a similar trait, but instead it segregates in a recessive manner.

Autosomal dominant alleles exert their effect despite the presence of a corresponding normal allele on the homologous chromosome. A vertical transmission pattern is observed in the pedigree, with the trait manifested in approximately half of the individuals in each generation (Figure 1.1A). An affected individual will have a 50% chance of transmitting the disease to each independent offspring, which is a reflection of whether a mutant or a normal allele is segregated in the gamete involved in fertilization. Usually, unaffected members of the family do not carry the mutant allele; thus they cannot transmit a disease allele to the next generation. If an affected male transmits the disease to his son, this is considered proof of autosomal dominant inheritance. Male-to-male transmission is inconsistent with X-linked inheritance because a father contributes the Y chromosome but no X chromosome to all his sons.

In autosomal recessive inheritance, both alleles must be abnormal for the disease trait to be expressed. The unaffected parents of an affected child are obligate heterozygote carriers for the recessive mutant allele. Affected children may be homozygous for a specific recessive mutant allele, as is more commonly observed with consanguineous matings, or they may be compound heterozygotes for two different mutations. Couples who are heterozygous carriers of a recessive mutant allele have a 25% risk of having an affected child with each pregnancy. The pattern of transmission observed in the pedigree is horizontal, with multiple members of one generation affected (Figure 1.1B). The unaffected siblings have a 67% (two-thirds) chance of being a carrier for the mutant allele.

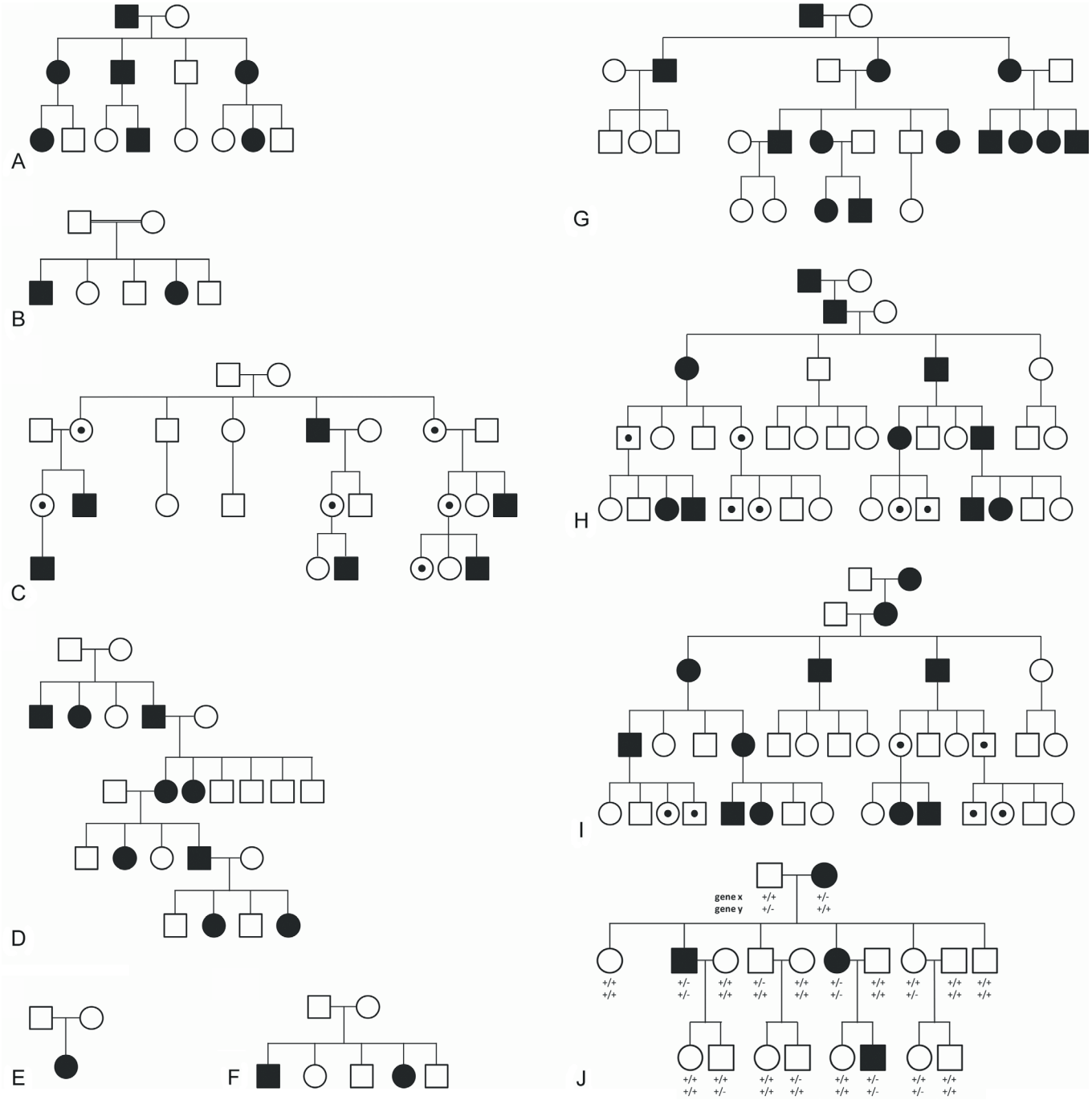

FIGURE 1.1 **Pedigrees representing different patterns of inheritance that can be observed for disease traits in families.** Unaffected males (open squares) and females (open circles) are shown. Filled symbols represent individuals manifesting the trait. Inheritance patterns include (**A**) autosomal dominant; (**B**) autosomal recessive; (**C**) X-linked recessive showing individuals who carry the mutant gene but do not manifest the disease trait (filled-in symbols with large dot in center); (**D**) X-linked dominant; (**E**) sporadic or new mutation or autosomal recessive; (**F**) new mutation with gonadal mosaicism or autosomal recessive; (**G**) maternal or mitochondrial inheritance; (**H**) dominant maternally imprinted showing individuals who carry the mutant imprinted gene on the non-expressing allele and do not manifest the disease trait (filled-in symbols with small dot in center); (**I**) dominant paternally imprinted; and (**J**) digenic inheritance showing wild-type (plus signs) and mutant (minus signs) alleles at disease loci X and Y.

X-linked inheritance patterns reflect special circumstances regarding sex chromosomes. Females have two X chromosomes, while males have one X chromosome and one Y chromosome. In X-linked recessive inheritance, a mutation in a gene located on the X chromosome may not express itself in females because of the normal copy on the other X chromosome. However, all males who inherit the mutant allele will be affected. An important feature of X-linked inheritance is that male-to-male transmission never occurs, but all female offspring of affected males inherit the abnormal gene. Therefore, affected fathers will have genetically normal sons and obligate carrier daughters (Figure 1.1C).

X-linked recessive disorders may sometimes be observed in females because of a skewing in the process of lyonization or X-inactivation.[5] Usually, the expression of one of the two X chromosomes in females is suppressed randomly in each cell early in embryonic development. If nonrandom or skewed X-inactivation occurs, such that the X chromosome carrying a mutant allele for an X-linked recessive trait is predominantly the active X chromosome, then a phenotype will be manifested in a carrier female. In normal females, a "bell-shaped" or gaussian distribution represents X-inactivation patterns with a 50:50 average ratio. Therefore, a skewed inactivation pattern is not rare in normal females. A ratio of 80:20 or greater can be observed in 5–10% of normal females. This skewing may not result in a phenotype unless one has a deleterious mutation in a gene that is subject to X-inactivation. Alternatively, rare conditions such as mutations in *XIST* (a master regulatory gene of X-inactivation) or X-autosome translocation (which separates translocated genes from the regulation by *XIST*) result in skewed X-inactivation. In addition, X-linked recessive traits may be expressed in females with a 45,X karyotype and Turner syndrome phenotype.

In X-linked dominant inheritance, females who carry a mutation in a gene on the X chromosome will express the disease phenotype but usually will have a milder clinical course than males with the mutation. Approximately twice as many females as males will be affected in a multigenerational pedigree. There will be no instance of male-to-male transmission (Figure 1.1D). Whether a trait is considered X-linked recessive or X-linked dominant may sometimes be a matter of how the phenotype is scored. For instance, the X-linked form of Charcot–Marie–Tooth disease may manifest either subtle or no clinical features on neurologic examination of a female patient, but electrophysiologic studies may reveal reduced motor nerve conduction velocities. Some X-linked dominant disorders may be lethal in males and therefore may be observed only in females. Examples of X-linked dominant neurologic disorders that are usually lethal in males include incontinentia pigmenti (MIM# 308300), Aicardi syndrome (MIM# 304050), bilateral periventricular nodular heterotopia (MIM# 300049), and Rett syndrome (MIM# 312750).

Molecular Pathomechanisms of Mutations

Specific mutations in each gene may behave differently in disease pathogenesis and associated phenotypic expression.[6] Mutations may result in an inactive gene product and are thus referred to as *loss-of-function* mutations. Null alleles result from complete absence or loss-of-function of the protein product, whereas mutations resulting in some retention of protein function are considered *hypomorphic alleles*. Loss-of-function mutations explain many recessive traits in which phenotypes become evident only when both alleles are mutated. Heterozygous carriers may have no disease-associated phenotypes but may present with subtle biochemical defects or reduced levels of protein expression that may result in susceptibility to a milder trait. *ABCA4* mutations are identified in recessive Stargardt macular dystrophy (MIM# 248200) patients. Mutations in both alleles can give Stargardt macular dystrophy or the milder and later onset cone–rod dystrophy; if both alleles are null, early onset retinitis pigmentosa (RP) can be seen, and heterozygous *ABCA4* mutations are identified in a fraction of patients with age-related macular degeneration (MIM# 153800). Some genes may require two wild-type alleles for normal function. In such case, heterozygotes for loss-of-function mutations may reveal phenotypes that can transmit as dominant traits because of the insufficient amount of gene products (*haploinsufficiency*).

Two other mutational mechanisms can explain a dominant inheritance pattern. When a translated mutant protein interferes with the function of a normal (wild-type) protein that is produced from the normal allele, a *dominant-negative* effect occurs (*antimorphic mutations*). Dominant-negative alleles occur when the encoded proteins compose a subunit structure (homodimer, heterodimer, or other multimeric complex formation) or when they interact with other proteins (ligand–receptor) or DNA (transcription factors). In contrast, *gain-of-function* is the mechanism in which mutant proteins abnormally enhance the normal function, or acquire novel functions that are toxic to cells without interfering with the wild-type allele function (also referred to as *neomorphic alleles*). Many neurodegenerative disorders with dominant inheritance are likely associated with gain-of-function mutations (e.g., polyglutamine diseases, prion disorders) that may prevent proteins from proper cellular processing, such as folding, transport, or degradation.

The identical or similar trait can often be caused by mutations in different genes at different loci; this is known as *genetic* or *locus heterogeneity*. The molecular basis of genetic heterogeneity is diverse but may be explained by

abnormalities in different genes that function in the same biologic process. This may involve genes that encode various enzymes in the same metabolic pathway (e.g., G_{M2} gangliosidoses), abnormalities in genes that code for discrete subunits of a functional protein complex (e.g., leukodystrophy with vanishing white matter, MIM# 603896), or a macromolecular structure such as myelin (Charcot–Marie–Tooth disease type 1). Different types of mutations in a single gene may result in the same clinical disease phenotypes. This phenomenon is referred to as *allelic heterogeneity*. Generally, disorders within a single family represent neither genetic nor allelic heterogeneity. It has been recognized more recently that different mutations in the same gene may give distinct clinical phenotypes—*allelic affinity* (e.g., Duchenne/Becker muscular dystrophies; PCWH [peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome and Hirschsprung disease]/Waardenburg–Shah syndrome;[7] and Yunis–Varon syndrome/Charcot–Marie–Tooth disease type 4J).[8]

The molecular basis for at least one example of allelic affinity has been clarified by functional determination of the effects of mutations using exogenous mutant gene transfer and endogenous gene silencing *in vitro* and *in vivo*. Mutations in the coding exons can be missense, nonsense, small insertions/deletions, or nonsynonymous alterations, whereas other mutations can be found in noncoding regions, such as intronic splicing junctions, regulatory elements upstream or downstream of exons. Variations in clinical phenotypes conveyed by these mutants have been considered to be a direct result of the function of mutant proteins. However, the *in vivo* consequences of mutations can be complex, and factors other than protein structure/function effects, such as mRNA instability or posttranslational modifications, may be important to ultimate clinical outcome. For example, mutations causing premature termination codons (PTCs) by nonsense, frameshift, or splice-junction mutations can be processed differently during translation depending on the location of PTCs. The nonsense-mediated decay (NMD) surveillance pathway typically degrades transcripts containing PTCs in 5′ exons to prevent translation of aberrant transcripts, resulting in a loss-of-function allele. Evidence suggests a model for NMD in which PTCs in the last exon or distal to 50–55 bp of the penultimate exon can escape NMD, subsequently being translated into truncated mutant proteins, which can act as a dominant-negative, gain-of-function, or hypomorphic allele.[9] Thus, the distribution of PTC mutations can often be correlated with the mode of inheritance.[10] Furthermore, either triggering or escaping NMD can result in distinct neurological disease phenotypes, as shown in *SOX1O* and *MPZ* mutations; PTCs in *SOX1O* that trigger NMD cause a milder disease, WS4 (Waardenburg–Shah syndrome type IV), whereas those escaping NMD result in a severe neurocristopathy, referred to as PCWH. Likewise, PTCs in *MPZ* that trigger NMD result in an adult-onset neuropathy (CMT1B), whereas those escaping NMD cause childhood-onset or congenital neuropathies.[7]

Factors That Modify Classic Mendelian Inheritance Patterns

New Mutations, Mosaicism, and Somatic Mutations

In some dominant diseases, new mutations or *de novo* mutations may occur frequently (e.g., tuberous sclerosis [MIM# 191100], neurofibromatosis type 1 [MIM# 162200], Alexander disease [MIM# 203450], Charcot–Marie–Tooth disease type 1A [MIM# 118220]). Such diseases may present sporadically in families (Figure 1.1E) and may not be recognized as involving hereditary factors if the phenotypes resemble nongenetic diseases. New point mutations result from DNA replication or repair errors and frequently occur in germ cells of men at an advanced age (e.g., paternal age effect observed in achondroplasia [MIM# 100800]). The *de novo* mutation (DNM) rate for single nucleotide variations in the paternal germline is about four times greater than that in the maternal germline, and increases linearly by about two DNMs per year in line with spermatogonial stem cell turnover after puberty.[11] New mutations appear to play a prominent role in intellectual disability[12] and other neurodevelopmental and neuropsychiatric traits such as autism spectrum disorders. This is not unexpected because individuals with these disorders are less likely to bear offspring, placing the disease-causing mutations under strong negative selection. Because affected people rarely transmit the mutation to children, the presence of disease reflects the ongoing appearance of new mutations.[13]

Mosaicism refers to the mixture of two or more different cell populations carrying either heterozygous mutant or homozygous normal alleles in the somatic cells generated by *de novo* mutations during postzygotic mitosis, and is perhaps much more common within multicellular organisms than our limited genomic assays have detected thus far.[14] Our ability to detect a pathogenic somatic mutation by using current clinical methods depends on how abundant it is in the leukocytes. However, in some cases of autism, epilepsy, and perhaps other neuropsychiatric conditions, somatic mutations affecting a specific lineage of neurons may be overlooked by conventional genetic testing of leukocyte-derived DNA.[13]

Somatic mutations are clinically significant when they occur early in organogenesis and the organs comprise a reasonable ratio of mutant cells. Some mutations that are not compatible with embryonic development might be found only as somatic mosaic and not as inherited mutations. Examples include somatic activating mutations in the

GNAQ gene, encoding guanine nucleotide-binding protein q polypeptide, that are associated with Sturge–Weber syndrome; and somatic activating mutations in the gene *AKT3*, encoding PKBγ in the mTOR pathway, which lead to hemimegalencephaly. The latter condition is characterized by enlargement and extensive malformation of an entire cerebral hemisphere with functional preservation of the other hemisphere.[13,15]

In other cases, somatic mosaicism may not result in a phenotype, but its presence in germline cells (gonadal mosaicism) may cause recurrence of affected offspring despite the parents having no detectable mutation in DNA isolated from blood (Figure 1.1F). In the case of Duchenne muscular dystrophy (MIM# 310200), somatic mosaicism, in this case germline mosaicism, can account for a recurrence rate up to approximately 15%. A single somatic mutation may result in a tumor-associated phenotype when it arises in the context of an existing cellular recessive mutation on the other allele ("two-hit" model).[16] *NF1* and *RB1* mutations in neurofibromatosis type 1 (MIM# 162200) and retinoblastoma (MIM# 180200), respectively, are examples of cellular recessive mutations in dominantly inherited disorders that require somatic mutation events to manifest the phenotype.

Penetrance and Expressivity

We often observe differences in the severity of clinical manifestation within a pedigree (intrafamilial variability) or between different pedigrees (interfamilial variability). *Penetrance* describes the proportion of individuals with the disease allele that have any manifestations of the disorder. If one observes individuals who have genotypes that usually result in disease but are present with no sign of disorder over a lifetime, the condition is referred to as nonpenetrant. A family with nonpenetrant individuals may represent reduced penetrance.

The use of these terms is sometimes confusing. *Expressivity* illustrates the range of phenotypic expression in individuals who carry an identical mutation. Variation in age of onset may be included in the expressivity, but it may also be considered as age-dependent penetrance.[2] In the strictest sense, penetrance is qualitative (step function), whereas expressivity is quantitative and reflects variability in degree (continuous function), but when referring to a population of patients/subjects the term variable penetrance has been used.

REPEAT EXPANSION DISORDERS

Repeat expansion disorders are those in which unstable expansion of tandem nucleotide repeats, ranging from tri-, tetra-, penta- to dodecanucleotide repeats, result in distinct diseases. Such a mechanism is currently responsible for more than 40 neurological or neuromuscular phenotypes.[17] Pedigrees segregating repeat expansion disorders reveal a Mendelian inheritance pattern; however, unlike static mutations in Mendelian diseases, the repeat mutation process is dynamic. Repeats continue to expand in subsequent generations and even within tissues of the same individual. Table 1.1 shows several examples of neurological disease that are caused by trinucleotide repeat expansions.

First, repeat expansions show different genetic properties depending on the locations of the repeats. Nucleotide repeats can be found in untranslated regions (UTRs) of genes (3′ distal UTR, 5′ proximal UTR, introns, and antisense

TABLE 1.1 Neurological Diseases Associated with Trinucleotide Repeat Expansions

Disease	MIM #	Gene	Trinucleotide repeat expansion	Phenotype
Myotonic dystrophy	160900	*DMPK*	CTG	Myotonia, muscular dystrophy, cataracts, hypogonadism
Huntington disease	143100	*HTT*	CAG	Chorea, dystonia, incoordination, cognitive decline, behavioral difficulties
Spinocerebellar ataxia 1	164400	*ATXN1*	CAG	Cerebellar ataxia, opthalmoplegia, peripheral neuropathy, dementia
Dentatorubral-pallidoluysian atrophy	125370	*ATN1*	CAG	Myoclonic epilepsy, dementia, ataxia, choreoathetosis
Oculopharyngeal muscular dystrophy	602279	*PABPN1*	GCG	Dysphagia, progressive ptosis of eyelids
Friedreich ataxia	229300	*FXN*	GAA	Ataxia, limb muscle weakness, dysarthria
Fragile X syndrome	300624	*FMR1*	CGG	Mental retardation, macro-orchidism, long face, large ears, prominent jaw

sequence) or in coding sequences, such as CAG polyglutamine repeats observed in Huntington disease and in spinocerebellar ataxias[18] and polyalanine repeats in congenital malformation syndromes.[19] Diseases conveying repeats within untranslated regions usually confer greater repeat instability and multisystemic involvement.

Second, affected individuals in successive generations often present with a more severe disease phenotype and an earlier age of onset compared to their affected predecessors (*anticipation*). The molecular basis for anticipation is an increasing number of repeats in subsequent generations, whereby nucleotide repeats tend to increase in number through the transmission from a parent to offspring. Phenotypic manifestations may dramatically change between generations with anticipation, as observed in myotonic dystrophy type 1 (MIM# 160900) and Huntington disease (MIM# 143100).

Third, in some clinically unaffected individuals, the number of repeats appears to exceed beyond the normal range of the general population in a state called *premutation*. Premutations show both somatic and germline instability and often can be found in the phenotypically normal antecedent of patients in a pedigree. Premutations often develop into full mutations that contain longer repeat expansions, resulting in disease phenotypes in progeny. One example is fragile X syndrome (MIM# 309550), in which a CGG repeat in the 5′ untranslated region of the *FMR1* gene ranges in size from approximately 5 to 40 repeat units in the normal population. The premutation range for *FMR1* is between 55 and 200 repeats, whereas full mutations exceed 230 repeats. A subset of individuals with premutations displays a unique neurologic phenotype showing late-onset progressive intention tremor, ataxia, and cognitive decline.[20]

The fourth facet of nucleotide repeat disorders is parent-of-origin effects on anticipation wherein the repeat instability is influenced by the transmitting parent. Overall, paternal intergenerational instability is common, whereas fragile X syndrome, Friedreich ataxia, and myotonic dystrophy type 1 usually reveal greater repeat instability with maternal transmission.

Finally, in some repeat expansion disorders, repeat alleles often associate with a distinct haplotype on the disease chromosome more frequently than expected by chance, indicating linkage disequilibrium (LD). Myotonic dystrophy type 1 shows complete LD both in white and Japanese individuals, suggesting a common Eurasian founder mutation. Huntington disease reveals multiple founder alleles that result in strong LD in different populations. Many sporadic cases of repeat expansion disease are not new mutations; rather, they are likely new full mutations developed from inherited founder chromosome that conveyed premutations. This feature is in sharp contrast to genomic disorders wherein numerous sporadic cases represent *de novo* mutations and no evidence for founder mutations exist.

NON-MENDELIAN INHERITANCE

Non-Mendelian inheritance refers to an inheritance pattern that does not follow the law of segregation in which a gene inherited from either parent segregates into germline cells at an equal probability. Non-Mendelian inheritance includes *mitochondrial inheritance*, wherein maternal transmission of mitochondrial DNA is the rule; *imprinting*, in which only one parental allele is transcribed due to parental-origin-dependent methylation of CpG dinucleotide sites on DNA; *uniparental disomy*, in which an individual receives both copies of a homologous chromosome pair or of a specific chromosomal region from one parent; and *digenic* and *oligogenic* traits.

Mitochondrial Inheritance

In addition to the nuclear genome, mitochondria contain DNA that transmits genetic information to subsequent generations. Because of the cytoplasmic localization and high copy number of mitochondria, mitochondrial DNA (mtDNA) or the mitochondrial genome has a unique inheritance pattern. Mitochondrial DNA is a circular genome of approximately 16.6 kilobase pairs (kb) located within the mitochondrial matrix in the cytoplasm of the cell. It encodes 13 polypeptides of subunits of the mitochondrial respiratory chain and oxidative phosphorylation system, two rRNAs, and 22 tRNAs. Each human cell contains hundreds of mitochondria, and each mitochondrion contains 5–10 mitochondrial genomes.

Traits that result from mtDNA mutations show a specific segregation pattern in a pedigree referred to as *maternal inheritance* (Figure 1.1G). This is due to the fact that the ovum supplies the total complement of mtDNA, while there are effectively no mitochondria that can be transmitted from sperm. Disorders resulting from mtDNA mutations can have tremendous variability in clinical expression because of *heteroplasmy*, wherein different tissues may have a different percentage of a mutant mitochondrial genome. During mitotic growth, the large number of mtDNA can result in asymmetric distribution of mutant versus normal copies (replicative segregation), leading to a change of the heteroplasmy ratio within a cell or organ over time. Moreover, different tissues have varying requirements for the

energy generated by oxidative phosphorylation, which contributes further to the clinical heterogeneity of mitochondrial disorders. These variant features present a significant challenge for both clinical diagnosis and genetic counseling in such families. Nevertheless, some mitochondrial diseases can be due to mutations in nuclear encoded genes wherein the proteins are either important to mitochondrial function or to nuclear–mitochondrial communication. mtDNA depletion syndromes (MDS) are a group of autosomal recessive disorders characterized by a severe reduction in mtDNA content leading to impaired energy production in affected tissues and organs. They are due to defects in mtDNA maintenance caused by mutations in nuclear genes that function in either mitochondrial nucleotide synthesis or mtDNA replication. Phenotypic presentation may be myopathic, encephalomyopathic, hepatocerebral, or neurogastrointestinal. An example of the latter is mitochondrial neurogastrointestinal encephalopathy (MNGIE; MIM #603041), which presents with progressive gastrointestinal dysmotility and peripheral neuropathy.[21]

Imprinting

Imprinting is an epigenetic marking placed on certain genes or genomic regions as a result of passage through male or female gametogenesis. Imprinting clusters contain 3–12 genes spread over 20–3700 kb of DNA. Each cluster has a discrete *imprinting control region* (ICR) that exhibits parent-of-origin-specific epigenetic modifications including allele-specific DNA methylation at the cytosine residue in CpG dinucleotides and posttranslational histone modifications. Functionally, DNA methylation inhibits the transcriptional machinery from accessing DNA, leading to decreased transcription of genes with high levels of promoter methylation. Deletion of ICRs results in loss of imprinting of multiple genes within the cluster. Recently, long noncoding RNAs (lncRNAs) within the imprinted cluster have emerged as contributing to transcriptional gene silencing in *cis*, by a variety of proposed mechanisms including transcriptional interference of adjacent imprinted genes by a sense–antisense physical overlap or direct recruitment of repressive chromatin proteins to the imprinted cluster.[22,23]

An inheritance pattern in which expression of a disease depends on the specific parent who transmitted the mutant allele (i.e., imprinting) is referred to as a *parent-of-origin effect*. Pedigrees in Figures 1.1H and 1.1I show families with defects in a maternally or paternally imprinted gene, respectively. In the family H, the gene is only expressed when inherited from the father, but silenced when inherited from the mother. Thus, the disease phenotype is only apparent when the mutant allele is inherited from a father. Family I represents the reciprocal situation, where the gene is expressed only when inherited from the mother. Of note, a woman who inherited a paternally imprinted allele will switch this allele to a maternal imprint when she transmits it to her offspring. Likewise, a man who inherits a maternally imprinted allele will switch to the paternal imprint when he transmits it to his offspring. This reflects the fact that although imprinting is strictly maintained through numerous somatic cell divisions, it is reset during gametogenesis, when the imprint from the previous generation is erased and a new gender-appropriate imprint is established. Of concern, children conceived by assisted reproductive technology (ART) have an increased incidence of rare epigenetic disorders such as Angelman syndrome (MIM# 105830) and Beckwith–Wiedemann syndrome (MIM# 130650), with most of these patients exhibiting loss of DNA methylation at ICRs. This disruption of normal epigenetic programming may be due to embryo culture, embryo transfer, or hormonal treatments and is currently under investigation.[22]

Uniparental Disomy

According to Mendel's first law, only one of two factors in a parent is transmitted to the next generation. The laws of chromosome inheritance also state that only one parental chromosome from the homologous pair is transmitted to the offspring. Uniparental disomy (UPD) is an exception to this segregation rule, and it is defined as inheritance of both copies of homologous chromosomes from one parent.[24,25] Because UPD maintains numerical and structural features of diploid chromosomes, it may not always be associated with a clinical phenotype unless additional genetic components (such as a recessive allele or imprinting) occur on the same chromosome. Thus, UPD may be more frequent than observed because it may not produce a recognizable clinical phenotype. Four distinct mechanisms were originally proposed and each recognized to result in UPD:[25] trisomy rescue, monosomy rescue, gamete complementation, and postfertilization errors.

When UPD results from two copies of a single chromosome homolog that was present in one parent, this condition is referred to as *uniparental isodisomy*. In contrast, *heterodisomy* is the inheritance of the two different chromosomes for one homologous pair derived from one parent. Consequently, in the isodisomic condition, a homozygous allele for a recessive mutation can be transmitted from a heterozygous carrier parent, resulting in a non-Mendelian inheritance pattern for a recessive mutation. At least 40 diseases have been reported in which UPD results in reduction