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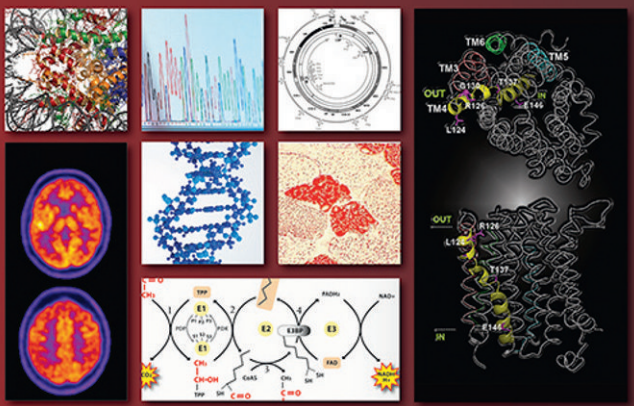
Fifth Edition



Edited by
Roger N. Rosenberg
Juan M. Pascual

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

FIFTH EDITION

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AMSTERDAM • BOSTON • HEIDELBERG • LONDON
NEW YORK • OXFORD • PARIS • SAN DIEGO
SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO
Academic Press is an imprint of Elsevier

Academic Press is an imprint of Elsevier
32 Jamestown Road, London NW1 7BY, UK
225 Wyman Street, Waltham, MA 02451, USA
525 B Street, Suite 1800, San Diego, CA 92101-4495, USA

Fifth edition

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

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN: 978-0-12-410529-4

For information on all Academic Press publications
visit our website at www.store.elsevier.com

Typeset by SPI

Printed and bound in United States of America

15 16 17 18 19 10 9 8 7 6 5 4 3 2 1

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?"

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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.

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SECTION I

GENERAL CONCEPTS AND TOOLS

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CHAPTER

1

Mendelian, Non-Mendelian, Multigenic Inheritance, and Epigenetics

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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.

http://dx.doi.org/10.1016/B978-0-12-410529-4.00001-2

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.