

Preface

Although it seems clichéd to say so, we live in a time of great discovery. With the remarkable advances in molecular genetics and genomics, and the Human Genome Project essentially completed, the feasibility of establishing meaningful genotype–phenotype correlations for complex human neurobehavioral disorders is within our reach.

In recent years, molecular geneticists have cloned, among others, genes producing Huntington’s disease, spinal cerebellar ataxia, myotonic dystrophy, the fragile X syndrome (FXS), FRAXE (the “other” fragile X disorder), α -thalassemia mental retardation (ATR-X syndrome), neurofibromatosis types 1 and 2, tuberous sclerosis 1 and 2, and Rett syndrome. Researchers have also identified many of the genes in regions containing microdeletions that are associated with other neurobehavioral disorders, e.g., Prader–Willi/Angelman syndromes, Williams syndrome, and velo-cardio-facial syndrome (del22q11). Other genes associated with nonsyndromal X-linked mental retardation (MRX) have also been identified.

At the phenotypic end of these disorders, the development, refinement, and standardization of psychometric, clinical, and neuropsychological instruments have led to greater precision in the quantitative assessment and evaluation of cognition deficits and behavioral dysfunction. Among other neuroimaging techniques, functional magnetic resonance imaging (fMRI) now permits noninvasive access to brain function during the performance of various cognitive tasks. The development of animal models to emulate cognitive–behavioral features associated with many human genetic mutations, e.g., α -calcium-calmodulin kinase II, FXS, and Rett syndrome, also permit us to examine neurobiological and neurophysiological functions, as well as neuroanatomical structures that could not have been previously investigated.

The time has come to weave the various molecular genetic, genomic, neurophysiological, and neurobehavioral threads together into a cohesive fabric of human genes, brain, and behavior. The goal of *Genetics and Genomics of Neurobehavioral Disorders* is to provide the reader with a clear and comprehensive account of how genetic abnormalities, neurobiology, and neuropsychology work in concert to manifest cognitive–behavioral dysfunction.

To achieve our objective, we have divided *Genetics and Genomics of Neurobehavioral Disorders* into four distinct parts. In the first we present an

introduction and overview of neurobehavioral disorders. Chapter 1 introduces neurobehavioral disorders from an historical prospective. Chapter 2 considers the neuroanatomical aspects of neurogenetic disorders, and Chapter 3 examines animal model strategies to investigate cognitive–behavioral deficits. The fourth chapter discusses the utility of examining behavioral phenotypes to investigate the pathway between genes and behavior.

The second part of the text is devoted to autosomal disorders that produce neurobehavioral dysfunction. Chapter 5 explores the genetics and pleiotropic phenotype of neurofibromatosis type 1. Chapter 6 is devoted to the cognitive–behavioral phenotype in Prader–Willi syndrome and Angelman syndrome and the genes in the deleted region that seem to affect specific functions in PWS/AS. The seventh chapter examines tuberous sclerosis 1 and 2 and genes recently discovered that cause these disorders. Chapter 8 investigates the behavioral phenotype in del22q11 (velo-cardio-facial syndrome), the psychopathology associated with the disorder, and the genes known to be deleted from the region. In Chapter 9, Williams–Beuren syndrome and genes in the deleted region on chromosome 7 known to be associated with the disorder are presented. The chapter on myotonic dystrophy (Chapter 10) describes the phenotype and the difficulties in teasing out the psychopathology associated with the disorder from what may be produced by the mutation itself.

The third and fourth parts consider X-linked disorders in which syndromal and nonsyndromal forms of XLMR are present. First, the nonsyndromal forms of X-linked mental retardation are presented in Chapters 11 and 12. Chapter 11 is a comprehensive examination of all known genes that produce syndromal and nonsyndromal XLMR (three of which are discussed in Part IV). Chapter 12 is the first comprehensive account of the genotype and phenotype in FRAXE, the “other” fragile X mutation. In Part IV the final three chapters are devoted to the three major syndromal forms of XLMR. In Chapter 13, α -thalassemia mental retardation (ATR-X) syndrome is described and both gene and gene function are reported. Chapter 14 is a comprehensive account of the fragile X syndrome and the fragile X mutation. Chapter 15 discusses Rett syndrome, an X-linked disorder primarily affecting females.

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