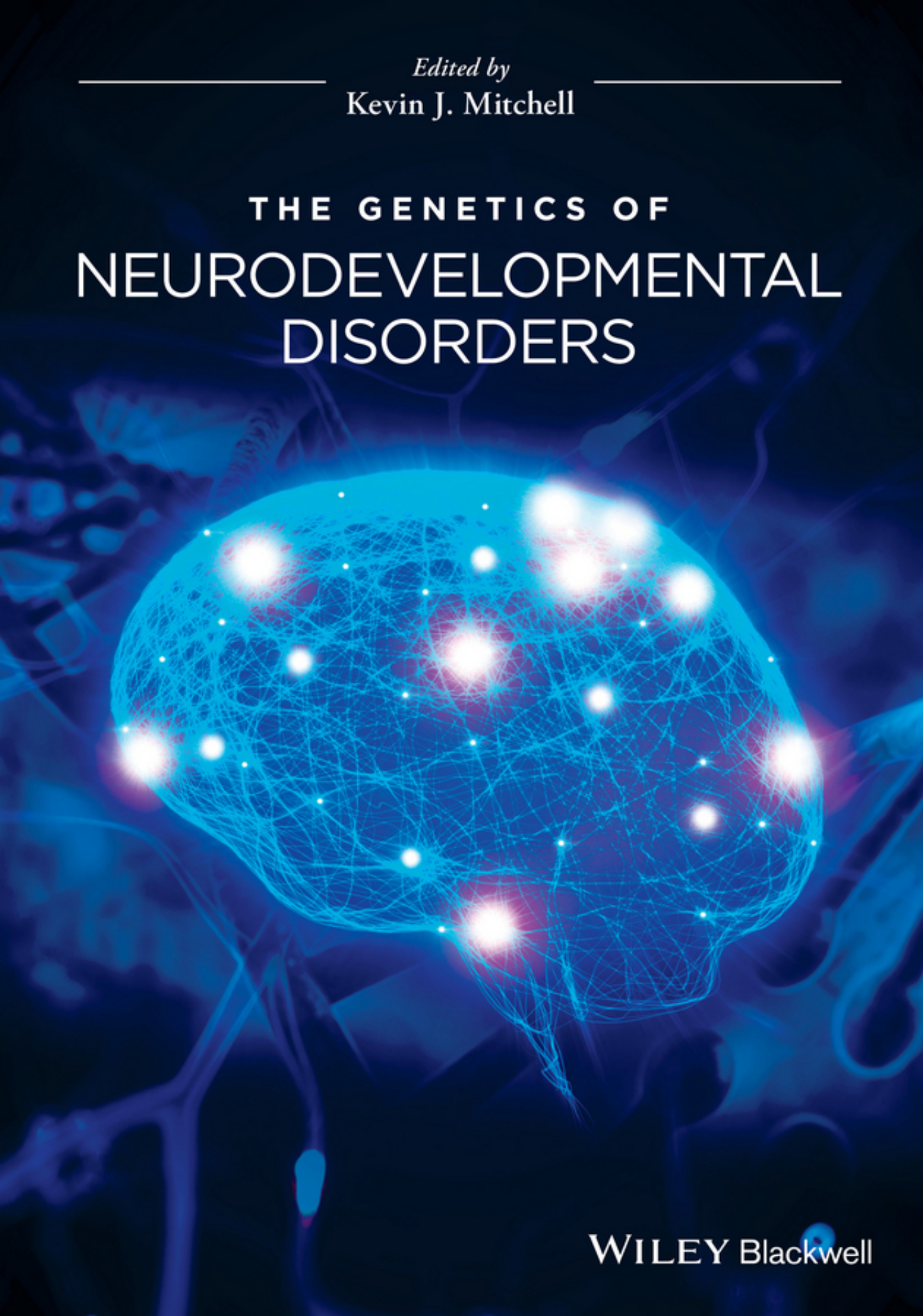
Edited by
Kevin J. Mitchell

THE GENETICS OF NEURODEVELOPMENTAL DISORDERS



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FOREWORD

Kevin J. Mitchell

The term "neurodevelopmental disorders" is clinically defined in psychiatry as "*a group of conditions with onset in the developmental period … characterized by developmental deficits that produce impairments of personal, social, academic, or occupational functioning*".[1] This term encompasses the clinical categories of intellectual disability (ID), developmental delay (DD), autism spectrum disorders (ASD), attention-deficit hyperactivity disorder (ADHD), speech and language disorders, specific learning disorders, tic disorders, and others.

However, the term can be defined differently, not based on age of onset or clinical presentation, but by an etiological criterion, to mean disorders arising from aberrant neural development. This definition includes many forms of epilepsy (considered either as a distinct disorder or as a comorbid symptom) as well as disorders such as schizophrenia (SZ), which have later onset but which can still be traced back to neurodevelopmental origins. Though the symptoms of SZ itself typically arise only in late teens or early twenties, convergent evidence of epidemiological risk factors during fetal development and very early deficits apparent in longitudinal studies strongly indicate that SZ is a disorder of neural development, though its clinical consequences may remain latent for many years.

Collectively, severe neurodevelopmental disorders affect ~5% of the population (though exact numbers are almost impossible to obtain, due to changing diagnostic criteria and substantial comorbidity between clinical categories). These disorders impact on the most fundamental aspects of human experience: cognition, language, social interaction, perception, mood, motor control, and sense of self. They impair function, often severely, and restrict opportunities for sufferers, as well as placing a heavy burden on families and caregivers. As lifelong illnesses, they also give rise to a substantial economic burden, both in direct health-care costs and indirect costs due to lost opportunity.

The treatments currently available for neurodevelopmental disorders are very limited and problematic. Intensive educational interventions may help ameliorate some cognitive or behavioral difficulties, such as those associated with ID or ASD, but to a limited extent and without addressing the underlying pathology. With respect to psychiatric symptoms, the mainstays of pharmacotherapy (antipsychotic medication, mood stabilizers, antidepressants, and anxiolytics) all emerged between the 1940s and 1960s

[1] Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

with almost no new drugs being developed since. Most of these treatments were discovered serendipitously, and their mechanisms of action remain poorly understood. In most cases, the existing treatments are only partially effective and can induce serious side effects. This is also true for the range of anticonvulsants, and, for all these drugs, it is typically impossible to predict from symptom profiles alone whether individual patients will benefit from a particular drug or possibly be harmed by it. These difficulties and the attendant poor outcomes for many patients arise from not knowing the causes of disease in particular patients and not understanding the underlying pathogenic mechanisms. Genetic research promises to address both these issues.

Neurodevelopmental disorders are predominantly genetic in origin and have often been thought of as falling into two groups. The first includes a very large number of individually rare syndromes with known genetic causes. Examples include Fragile X syndrome, Down syndrome, Rett syndrome, and Angelman syndrome but there are literally hundreds of others. Each of these is clearly caused by a single genetic lesion, sometimes involving an entire chromosome or a section of chromosome, sometimes affecting a single gene. Most are characterized by ID, but many also show high rates of epilepsy, ASD or other neuropsychiatric symptoms.

The second group comprises idiopathic cases of ID, ASD, SZ, or epilepsy – those with no currently known cause. Despite the lack of an identified genetic lesion, there is still very strong evidence of a genetic etiology across these categories. All of these conditions are highly heritable, showing high levels of twin concordance, much higher in monozygotic than in dizygotic twins, substantially increased risk to relatives and typically zero effect of a shared family environment, indicating strong genetic causation.

What has not been clear is whether these so-called "common disorders" are simply collections of rare genetic syndromes that we cannot yet discriminate, or whether they have a very different genetic architecture. The dominant paradigm in the field has held that the idiopathic, non-syndromic cases of common disorders such as ASD or SZ reflect the extreme end of a continuum of risk across the population. This is based on a model involving the segregation of a very large number of genetic variants, each of small effect alone, which can, above a collective threshold of burden in individuals, result in frank disease.

Recent genetic discoveries are prompting a re-evaluation of this model, as well as casting doubt on the biological validity of clinical diagnostic categories. After decades of frustration, the genetic secrets of these conditions are finally yielding to new genomic microarray and sequencing technologies. These are revealing a growing list of rare, single mutations that confer high risk of ASD, ID, SZ, or epilepsy, particularly epileptic encephalopathies.

These findings strongly reinforce a model of genetic heterogeneity, whereby common clinical categories do not represent singular biological entities, but rather are umbrella terms for a large number of distinct genetic conditions. These conditions are individually rare but collectively common. Strikingly, almost all of the identified mutations are associated with variable clinical manifestations, conferring risk across traditional diagnostic boundaries. These findings fit with large-scale epidemiological studies that also show shared risk across these disorders. Thus, while current diagnostic categories may reflect more or less distinct clinical states or outcomes, they do not reflect distinct etiologies.

The "genetics of autism" is thus neither singular nor separable from the "genetics of intellectual disability," the "genetics of schizophrenia," or the "genetics of epilepsy." The more general term of "*developmental brain dysfunction*" has been proposed to encompass disorders arising from altered neural development, which can manifest clinically in diverse ways. This book is about the genetics of developmental brain dysfunction.

A lot can go wrong in the development of a human brain. The right numbers of hundreds of distinct types of nerve cells have to be generated in the right places, they have to migrate to form highly organized structures, and they

must extend nerve fibers, which navigate their way through the brain to ultimately find and connect with their appropriate partners, avoiding wrong turns and illicit interactions. Once they find their partners they must form synapses, the incredibly complex and diverse cellular structures that mediate communication between nerve cells. These synapses are also highly dynamic, responding to patterns of activity by strengthening or weakening the connection.

The instructions to carry out these processes are encoded in the genome of the developing embryo. Each of these aspects of neural development requires the concerted action of the protein products of thousands of distinct genes. Mutations in any one of them (or sometimes in several at the same time) can lead to developmental brain dysfunction.

The identification of numerous causal mutations has focused attention on the roles of the genes affected, with a number of prominent classes of neurodevelopmental genes emerging. These include genes involved in early brain patterning and proliferation, those mediating later events of cell migration and axon guidance, and a major class involved in synapse formation and subsequent activity-dependent synaptic refinement, pruning, and plasticity. Also highlighted are a number of biochemical pathways and networks that appear especially sensitive to perturbation.

Genetic discoveries thus allow an alternate means to classify disorders, based on the underlying neurodevelopmental processes affected. This provides more etiologically valid and arguably more biologically coherent categories than those based on clinical outcome. For individual patients, the application of microarray and sequencing technologies is already changing clinical practice in diagnosis and management of neurodevelopmental disorders. This will only increase as more and more pathogenic mutations are identified.

Such discoveries also provide entry points to enable the elucidation of pathogenic mechanisms, where exciting progress is being made using cellular and animal models. For any given mutation, this involves defining the defects at a cellular level (in the right cells), and working out how such defects propagate to the levels of neural circuits and systems, ultimately producing pathophysiological states that underlie neuropsychiatric symptoms. Definition of these pathways will hopefully lead to a detailed enough understanding of the molecular or circuit-level defects to rationally devise new therapeutics.

The elucidation of the heterogeneous genetic and neurobiological bases of neurodevelopmental disorders should thus enable a much more personalized approach to diagnosis and treatment for individual patients, and a shift in clinical care for these disorders from an approach based on superficial symptoms and generic medicines, to one based on detailed knowledge of specific causes and mechanisms.

The book is organized into several sections:

Chapters 1–6 cover broad conceptual issues relevant to neurodevelopmental disorders in general. These are informed by recent advances in genomic technologies, which have transformed our view of the genetic architecture of both rare and so-called "common" neurodevelopmental disorders. These chapters will consider the genetic heterogeneity of clinical categories such as ASD or SZ, the relative importance of different types of mutations (common vs rare; single-gene vs large deletions or duplications; inherited vs *de novo*), etiological overlap between clinical categories and complex interactions between two or more mutations or between genetic and environmental factors.

Chapters 7–11 present our current understanding of several different types of disorder, grouped by the neurodevelopmental process impacted. Consideration of disorders from this angle provides a more rational and biologically valid approach than consideration from the point of view of clinical symptoms, which can be arrived at through various routes.

Chapters 12–14 deal with the elucidation of pathogenic mechanisms, following genetic discoveries. They include chapters on cellular models (using induced pluripotent stem cells derived from patients) and animal models (recapitulating pathogenic mutations in mice),

which are revealing the routes of pathogenesis, from defects in diverse cellular neurodevelopmental processes to resultant alterations in neural circuits and brain systems, which ultimately impinge on behavior. The manifestation of these defects in humans also depends on processes of learning and experience-dependent development that proceed for many years after birth. Taking this aspect of development seriously is essential as it is a critical period where symptoms can be exacerbated if neglected or potentially improved by intensive interventions.

Chapters 15–16 consider the clinical implications of recent discoveries and of the general principles described in earlier chapters. Foremost among these is the recognition of extreme genetic heterogeneity, meaning that understanding what is going on in any particular patient requires knowledge of the specific underlying genetic cause. The dramatic reductions in cost for whole-genome sequencing mean such diagnoses will become far easier to make, with important implications for clinical genetic practice (including preimplantation or prenatal screening or diagnosis). Finally, the study of cellular and animal models of specific disorders is already suggesting potential therapeutic avenues for some conditions. These advances illustrate a general principle – to treat these conditions we need to identify and understand the underlying biology and design therapies to treat the specific cause in each patient and not just the generic symptoms.

1

THE GENETIC ARCHITECTURE OF NEURODEVELOPMENTAL DISORDERS

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1.1 INTRODUCTION

There are several hundred known genetic syndromes that affect neural development and result in intellectual disability (ID), epilepsy, or other neurological or psychiatric symptoms. These include recognized syndromes that often manifest with symptoms of autism spectrum disorders (ASD) or schizophrenia (SZ), such as Fragile X syndrome, Rett syndrome, tuberous sclerosis, velocardio-facial syndrome, and many others. For ASD, it has been known for many years that these syndromes account for a significant but still small fraction (5–10%) of all cases (Miles, 2011). What has not been clear is whether such cases, associated with single mutations, represent a typical mode by which such conditions arise or are, alternatively, exceptional and quite distinct from the general etiology of idiopathic ASD, epilepsy, SZ, or ID (Wray and Visscher, 2010). Other common disorders including dyslexia, specific language impairment, obessive-compulsive disorder, and so on, will not be considered here in detail, though the general principles probably apply.

In general, the genetic architecture of common NDDs has been considered to be "complex" or multifactorial (Plomin et al., 2009; Sullivan et al., 2003). This is usually taken to mean that many causal factors, both genetic and non-genetic, are involved in each affected individual. Under this view, the large group of currently idiopathic cases have a very different genetic architecture from the small number of known monogenic cases. An alternative view is that the vast majority of cases of these conditions are caused by independent mutations in any one of a very large number of genes. According to this model, these diagnostic categories of idiopathic cases represent artificial groupings reflecting our current ignorance, rather than natural kinds.

Here, I consider the theoretical underpinnings and empirical evidence relating to the genetic architecture of NDDs. These have been greatly influenced by technological advancements which have allowed various types of

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