Principles of Psychiatric Genetics
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The major psychiatric disorders are common illnesses with complex origins in gene–environment interactions. As is the case with most medical diseases, such as diabetes and hypertension, genetic factors for psychiatric disorders are composed of many common alleles, each with a small effect on risk. Additionally, there are many rare alleles, including copy number variants (CNVs), with larger effects on risk.

Despite this complex picture, substantial progress has been made in identification of individual risk alleles, through various molecular approaches, including linkage and association, studies of epigenetic factors, and recently direct sequencing of DNA from affected persons. It is the intent of the contributors and editors to describe these recent molecular advances, in the context of the genetic epidemiology (population, family and twin studies) and our knowledge of the phenomenology and course of illness of psychiatric disorders.

This book is organized in chapters according to the current nosology of psychiatric disorders, but the reader should not conclude that this nomenclature is based on genetic, epigenetic, neurobiologic, or environmental influences. The current nosology is based primarily on acute signs and symptoms, few of which are “pathognomonic”. Individuals with patterns of these signs and symptoms are categorized as “having” schizophrenia, for example, but the term “schizophrenia” undoubtedly refers to a very heterogeneous group of brain disorders which share some acute signs and symptoms and course of illness variables. In the future, it is expected that the current nosology will be transformed into one which reflects knowledge of the neurobiological and experiential origins of these groups of heterogeneous disorders. It is anticipated that new diagnostic tools and therapeutic agents will result from this expanded molecular knowledge.

While this book is, by necessity, a picture in time of current knowledge, the rapidly advancing technology of DNA sequencing is likely to produce a multitude of new discoveries in the near future. During the past decade, the cost of sequencing a human genome has fallen from ~ $1 000 000 000 USD to ~ $5000 USD, and the “thousand dollar genome” is widely predicted. This will allow for the sequencing of thousands of affected individuals within each category of psychiatric disorder. Analysis of this sequence information will permit the development of a catalogue of common and rare genetic variants that increase risk for these diseases. Studies of gene expression in post-mortem brain samples and in living blood and skin tissue from affected persons will enable catalogues of epigenetic events to be developed as well. These advances in genetics and epigenetics should permit an explosion of knowledge concerning the genetic and environmental risks for psychiatric disorders.

It is now possible to develop and culture neurons in the laboratory, from easily obtained skin or blood cells of persons with a psychiatric disorder. This should allow for an unprecedented correlation of neuronal phenotype to genotype on a scale we can only imagine. There will be the potential to characterize in beautiful detail the electrophysiologic, morphologic, and neurochemical characteristics of these neurons from genetically defined origins. This should permit discovery of specific neuronal abnormalities. That would enable the targeting of therapeutic agents to pathophysiology, even if that pathophysiology is unique to an individual person or family.

The book you have before you should be seen as a window to that day in the future when such targeted, individualized therapies are used by doctors and patients around the world. We have designed Principles of Psychiatric Genetics to be useful to investigators in related areas, including Psychiatry, Human Genetics, and Neurobiology. However we also expect that it will be of value to practicing clinicians who
Preface

Wish to understand the sometimes confusing and contradictory reports of discoveries in the media. Is there a blood test for bipolar disorder? Has “a gene” been identified for alcohol addiction? Is there a genetic test for the proper treatment for a patient with schizophrenia? What new drugs may we expect for Alzheimer’s disease?

Implicit in the foregoing discussion is a critical message for every reader of this book: genetic abnormalities are not immutable; they are treatable. Each genome represents a program for the body and the brain, but it is not destiny. In fact genetic programs are altered in their expression by the food we eat, the medicine we take, and by everyday experience. The finished product of a human life is a massively complex combination of the genetic program (which in itself does not change, except for mutation) and the effects of our experience, beginning with the intrauterine environment. Given this complexity, it is remarkable that genetic signals are even detectable in behavioral disorders, and yet they are. But one should never expect them to be constant, or unchangeable.

Principles of Psychiatric Genetics should be of interest to every mental health professional in training. All those who wish to become psychiatrists, psychologists, and counselors during the twenty-first century should know about the field that we describe, because it will affect your practice profoundly. Do we have a blood test for bipolar disorder? No, not today (despite what you may read on the internet). But such tests are not far in the future. When they arrive, they will likely be based on arrays that examine multiple gene variants and biological pathways in a single test. Those of you beginning practice today will likely send your patients for such tests. They will be designed based on some of the Principles in this book. The other questions above may be answered similarly.

There are clues to the answers in the appropriate chapters in this book.

Because the genetic and epigenetic variants responsible for these disorders are not fully available today, we are titling this book with the term Principles. The details of this expanding field will change daily over the coming years. The pace of discovery in the laboratory is daunting, and to remain current requires monitoring several hundred journals in print and/or online (consult the bibliographies in this book for examples). However, the core areas of psychiatry and human genetics are somewhat more constant.

You will notice that each chapter on a disease refers to epidemiology, twin and family studies, and linkage and association. Some disease-centered chapters also refer to epigenetic studies, bioinformatic studies, and drug development. There are special chapters in the first section of the book on each of these methodological areas. These have been prepared by subspecialty experts in psychiatric genetics and will be useful in interpreting the disease-centered chapters and also the journal literature in these areas.

Each disease chapter utilizes the methods described and then provides an up-to-date summary of where we stand now in identifying specific genetic influences on that trait or traits. Disease chapters also generally provide an overview of the symptoms, signs, and life course of the condition described. We have concentrated on those conditions usually treated by psychiatrists and other mental health professionals, but we are aware of the similarities in origin and course of other neuropsychiatric conditions that may be more frequently seen by pediatricians or neurologists (i.e. tuberous sclerosis, seizure disorders, or vascular dementia). For a more general reference on medical genetics in clinical practice, we would refer the reader to the online Mendelian Inheritance in Man by McKusick and collaborators.

As editors of this volume, we are humbled by the contributions of those who have gone before us in defining the field of Psychiatric Genetics. We would like to thank our mentor and longtime collaborator Elliot Gershon, who decades ago taught us the Principles in this volume. Others who influenced our approach to the issues in this book include Theodore Reich, Seymour Kety, George Winokur, Irving Gottesmann, Ming Tsuang, and Robert Cloninger, among others. We thank our contributing authors for their insight, their industry, their patience, and their trust that our shared effort would result in a book that they and others would admire. We appreciate the indulgence of our colleagues and families with the time this task took away from other activities. In this regard we thank Patricia Nurnberger and Christine Berrettini most of all. Finally we thank the patients and families who continue to teach us in our clinics every day. By this book, may we provide a stepping stone to better and more productive lives for you . . .