Drug Discovery for Schizophrenia

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Drug Discovery for Schizophrenia

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Preface

We wish to thank our friends, family members, and colleagues who encouraged us to create this book, "Drug Discovery for Schizophrenia". We have carefully included some of the most important directions in the field of schizophrenia, and are thankful to all contributors, who generously dedicated their time to create their chapters.

This book was motivated by our desire – and that of all the contributors – to further understand the mechanisms of schizophrenia and envision future research on this mental disorder at multiple levels; from epigenetics, genetics, neurochemistry, neuroimmunology, and animal models to opto-/chemo-genetics or protein–protein interactions. Personally, the main motivation was the wish to help Dr John Roder's son, Nathan, who suffers from this mental disorder and who was diagnosed in his final year of secondary school.

Hopefully, our scientific attempts will ultimately lead to effective treatments for this complex brain disorder. We believe that consistent analyses of new findings in the field of schizophrenia will benefit psychiatric neuroscience to unlock this complex brain puzzle.

Tatiana V. Lipina and John C. Roder

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CHAPTER 1

The Genetics of Schizophrenia

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1.1 Introduction

If you know the enemy and know yourself, you need not fear the result of a hundred battles. If you know yourself but not the enemy, for every victory gained you will also suffer a defeat. If you know neither the enemy nor yourself, you will succumb in every battle.

Sun Tzu, *The Art of War*

The greatest difficulty in finding treatments for schizophrenia is that we do not know the enemy well enough. Revealing the complex etiology and pathophysiology of schizophrenia has posed a considerable challenge for researchers, but improving technology is now enhancing our ability to use the wellspring of information present in the genome to help find these answers. It is more than three decades since the first development of genome sequencing technology,[1] and we have come to appreciate the intricate way in which variations in the genome can influence disease. Genetic research has provided insights into elucidating the pathophysiology of many diseases,[2,3] and also promises to improve clinical outcomes through personalized treatments and targeted therapeutics.[4–6] Studying the genetics of schizophrenia is important

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to discover genes and pathways that contribute to its development. The hope is that the symptoms of schizophrenia can be prevented or resolved by targeting therapeutics at these pathways. Still, treatment is most likely to be administered late in the development of the disorder, after diagnosable symptoms have already presented. By this time, the processes leading to the development of schizophrenia may have caused permanent changes; for example, alterations in brain morphology. Genetics can also help us to understand the underlying pathophysiology of the individual symptoms of schizophrenia, allowing for the development of targeted therapeutics to improve the lives of patients by treating symptoms after developmental pathways have become fixed. Whether to understand developmental processes or symptom pathophysiology, the study of the genetics of schizophrenia has great potential in helping us to understand the enemy, and hopefully, eventually, to conquer schizophrenia.

1.2 What Genetics Can Tell Us about Schizophrenia

It is now understood that genes and environment work together to influence the development of disease. The power of genetics to enable us to understand a disease is dependent upon how much of the variance in liability is contributed by genes compared to other factors. It is also important to consider the manner in which genes affect phenotype. The heritability and genetic architecture of schizophrenia tell us how genetic information can be used to understand the disorder.

1.2.1 The Heritability of Schizophrenia

The contribution of genes in determining a given phenotype can be quantified by estimating heritability. Heritability is a mathematical expression of the amount of variance in phenotype that is explained by genetic variation. This does not measure how much phenotypic variation is *caused* by genes; rather, it reflects the relative contribution of genetic *vs*. non-genetic factors in determining phenotype. Heritability is estimated by comparing the liability of developing a trait (schizophrenia, for example) between related and unrelated individuals.[7,8] Twin studies have been invaluable for estimating heritability, as it is easier to differentiate between genetics and shared *vs.* differential environment in such studies.[9] The concordance in phenotype between monozygotic (MZ) and dizygotic (DZ) twins gives a measure of the correlation between genotypic variation and presence of a trait. MZ concordance rates for schizophrenia have been reported between 41% and 65%, with DZ concordance ranging from 0% to 28%.[10,11] Since DZ twins have approximately half the genetic variance of unrelated individuals, and MZ twins have identical genomes, heritability can be crudely calculated as twice the difference in concordance (r) between MZ and DZ twins (see eqn 1.1).[8]

$$\text{Heritability}(h^2) = 2(r(MZ) - r(DZ)) \tag{1.1}$$