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Risk genes for schizophrenia: Translational opportunities for drug discovery

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ABSTRACT

Despite intensive research over many years, the treatment of schizophrenia remains a major health issue. Current and emerging treatments for schizophrenia are based upon the classical dopamine and glutamate hypotheses of disease. Existing first and second generation antipsychotic drugs based upon the dopamine hypothesis are limited by their inability to treat all symptom domains and their undesirable side effect profiles. Third generation drugs based upon the glutamate hypothesis of disease are currently under evaluation but are more likely to be used as add on treatments. Hence there is a large unmet clinical need. A major challenge in neuropsychiatric disease research is the relatively limited knowledge of disease mechanisms. However, as our understanding of the genetic causes of the disease evolves, novel strategies for the development of improved therapeutic agents will become apparent. In this review we consider the current status of knowledge of the genetic basis of schizophrenia, including methods for identifying genetic variants associated with the disorder and how they impact on gene function. Although the genetic architecture of schizophrenia is complex, some targets amenable to pharmacological intervention can be discerned. We conclude that many challenges lie ahead but the stratification of patients according to biobehavioural constructs that cross existing disease classifications but with common genetic and neurobiological bases, offer opportunities for new approaches to effective drug discovery.

Contents

Abbreviations: ADRA, alpha adrenoreceptors; CATIE, Clinical Antipsychotic Trials in Intervention Effectiveness; CNVs, copy number variants; D2, dopamine receptor subtype 2; DRD, dopamine receptors; DSMV, The Diagnostic and Statistical Manual of Mental Disorders V; EPS, extrapyramidal side effects; FDA, United States of America food and drug administration; GlyT1, glycine transporter 1; GRIA, AMPA (alphaamino-3-hydroxy-5 methyl-4-isoxazolepropionic acid) receptors; GRIN, NMDA receptors; GWAS, genome wide association studies; HRH, histamine receptors; HTR/5-HT, serotonin (5 hydroxytryptamine) receptors; Indels, small DNA insertions or deletions; MARTAs, Multi-affinity receptor target agents; mGlu2/3, metabotropic glutamate receptors 2 and 3; MHC, major histocompatibility complex; NET, norepinephrine transporter; NGS, next generation sequencing; NMDA, N-methyl D-aspartate; O.R., odd's ratio; PCR, polymerase chain reaction; SERT, serotonin transporter; SNPs, single nucleotide polymorphisms; SNVs, single nucleotide variants.

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1. Introduction

Schizophrenia is a severely debilitating form of mental illness that affects 1% of the population globally and along with depression and bipolar disorder is amongst the top 10 diseases in terms of disability affected life years (WHO, 2001; Rossler et al., 2005). The disease is complex clinically and is categorised according to DSMV rather than from a neurobiological causal perspective. The heterogeneous range of symptoms includes hallucinations and delusions (known as 'positive' symptoms), avolition and reduced affect (known as 'negative' symptoms) and cognitive deficits (including deficits in working memory, attention and cognitive flexibility). These symptoms overlap with other forms of mental illness including bipolar disorder and there is an ongoing debate about the future classification and diagnosis of neuropsychiatric disorders (Craddock & Owen, 2010; Kapur et al., 2012). In general, diagnosis is usually made in late adolescence or early adulthood and patients require lifelong medication.

From a biological perspective, schizophrenia is increasingly viewed as a disorder of disrupted brain networks arguably arising through genetic and environmental factors which impact on brain development. This disruption in brain networks is manifested as abnormal circuit formation and consequently aberrant neurotransmitter and synaptic function and ultimately abnormal behaviour. Increased knowledge of the causes of schizophrenia in the past decade is not yet sufficiently secure to diagnose schizophrenia, based upon 'biomarkers'. Nevertheless, new initiatives, such as the National Institute of Mental Health supported, Research Domain Criteria (RDoC) project are developing a research-based classification system for mental disorders informed by the genetics, physiology and neural circuits that underpin defined biobehavioural constructs, which cut across current disorder categories. The aim is that this approach will inform future versions of diagnostic systems, thereby moving away from the current systems based upon symptoms and signs (Cuthbert & Insel, 2013).

Antipsychotic drugs have been used to treat schizophrenia for several decades. The introduction of chlorpromazine in the 1950s was a major clinical advance despite the lack of knowledge of the mechanism of drug action. Some twenty years later it was determined that the binding affinity of antipsychotic drugs to the dopamine (D2) receptor subtype correlated with their clinical efficacy in alleviating the hallucinations and delusions (Creese et al., 1976). At the neuronal level, the drugs block dopamine receptors in the mesolimbic/mesocortical dopaminergic system and this is thought to alleviate the psychotic (positive) symptoms. However, dopamine receptor blockade in the nigrostriatal and hypothalamic–pituitary systems results in unwanted effects resembling Parkinson's disease (extrapyramidal side effects; EPS) and hyperprolactineamia, respectively. This profile of first generation drugs ('typical' antipsychotics), such as haloperidol led to the search for newer compounds, with an improved side-effect profile and with efficacy against a wider range of symptoms. A range of compounds were developed including drugs that target specific dopamine receptor subtypes, those that target a diverse range of receptors (multi-affinity receptor target agents; MARTAs), and those with a balance of activity against 5-HT versus D2 receptors. The term 'atypical' (second generation drug) was introduced to suggest that these newer compounds, which include clozapine, risperidone, olanzapine, and quetiapine, were a significant improvement over the first generation drugs. However, this distinction has not been realised in the clinic. It has been argued by Lieberman and colleagues (Lieberman et al., 2005) that there have been no major breakthroughs in drug discovery for schizophrenia in the last 50 years. This is supported by findings from the CATIE (Clinical Antipsychotic Trials in Intervention Effectiveness) studies (Lieberman & Stroup, 2011) which demonstrated similar efficacy and EPS side effect profiles for both first and second generation antipsychotic drugs. Despite the abundance of proposed receptor mechanisms, existing drugs all target dopamine receptors to varying degrees. Indeed the drugs approved by the FDA in the last 12 years are largely based on targeting dopamine receptors, as well as 5-HT (serotonin) and alpha adrenoceptors. Although these drugs have not been developed on the basis of the genetic understanding of schizophrenia, there is some genetic based support for variants in these receptors, albeit very weak (Table 1) (SZGene database, Allen et al., 2008). The commonality of drug action on dopamine receptors has contributed to the dopamine hypothesis of schizophrenia. This hypothesis was originally developed in the 1960s and 1970s and was based upon several lines of evidence; i) antipsychotic drugs increase dopamine metabolism ii) amphetamine, which enhances synaptic dopamine can produce symptoms of schizophrenia and iii) that D2 receptor antagonism correlates with clinical efficacy against psychosis (see Howes & Kapur, 2009). A body of evidence supports the view that the 'positive' symptoms are related, at least in part, to aberrant mesolimbic dopamine transmission which can be improved through antipsychotic drugs blocking dopamine receptors (Howes & Kapur, 2009). Nevertheless the hallucinations and delusions experienced by a substantial proportion of patients (up to 30%) do not respond to medication and overall the current drugs have limited ability to improve the negative symptoms and cognitive deficits. Whilst clozapine is helpful to some degree in such treatment resistant patients there remains a large unmet clinical need and this has resulted in significant activity by the pharmaceutical industry to develop new compounds.

The development of new drugs to treat schizophrenia is dependent upon developing new models that tap into the underlying causes of the disease and which are integrated with end point assessments that are translationally relevant (Pratt et al., 2012). Recent advances in genetic and genomic research have significantly enhanced our understanding of genetic risk factors for schizophrenia and offer promise for drug discovery by targeting molecules known to be dysfunctional in schizophrenia that correlate with specific symptom domains. To date drugs for schizophrenia have not been based on genetics or dysfunctional molecular pathways. There is some genetic evidence to support the genes encoding dopamine receptors but these are not the strongest genetic risk factors for schizophrenia (Allen et al., 2008).

A few novel therapeutical strategies are emerging, targeting other neurotransmitter systems such as glycine, glutamate and acetylcholine, as well as second messenger degradation (Medtrack, 2012). Several novel compounds are based upon the glutamate NMDA receptor hypofunction hypothesis of schizophrenia which was formulated in the 1990s from the observations that NMDA-receptor antagonists such as ketamine and PCP can induce negative symptoms, cognitive deficits and paranoia in normal subjects and exacerbate psychosis in schizophrenia patients (see Pratt et al., 2012).

The activation of the NMDA receptor can be modulated by synaptic glutamate levels which in turn can be modulated by compounds such as GlyT1 inhibitors and mGlu2/3 modulators. It is too early to assess the impact of these third generation drugs (Pratt et al., 2012). Although mGlu2/3 compounds have not lived up to early clinical trial results (Hopkins, 2013), GlyT1 inhibitors are showing promise in Phase 2 studies for improving negative symptoms (Chue, 2012). To date no evidence has been found to support *SLC6A9*, the gene encoding this glycine transporter, as a risk factor for schizophrenia (Tsai et al., 2006; Deng et al., 2008). However there is some genetic evidence for the genes encoding other targets in the drug development pipeline, although pharmacology rather than genetics has been the reason for the development of these drugs (Table 2) (SZGene database, Allen et al., 2008).

Understanding the genetic basis of schizophrenia offers the potential for rational drug design based on knowledge of how the genetic variants impact on protein function in biological pathways and consequently brain circuitry, leading to the many symptoms of schizophrenia.

2. Genetics of schizophrenia

Schizophrenia has a complex genetic basis. Family, twin and adoption studies have shown that there is a strong genetic influence on the development of the disorder, with genetic factors estimated to account