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Review article

Synapse pathology and translational applications for schizophrenia

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ABSTRACT

Schizophrenia is a chronic, severe, and disabling brain disorder, with an estimated lifetime prevalence of 0.7%. Despite its relatively low prevalence, the onset of schizophrenia usually occurs early in life, resulting in a severe lifelong disability for patients and increasing the economic and care burden on their families. This makes schizophrenia one of the most catastrophic mental illnesses. Although the etiology of schizophrenia remains poorly understood, clinical, genetic, and pharmacological studies have indicated that its pathophysiology involves synaptic disturbances. Here, I review the evidence suggesting synaptic disturbance as the causal pathophysiology of schizophrenia and discuss the possible application of synaptic intervention as a novel therapeutic strategy for schizophrenia.

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Contents

1. Introduction

Schizophrenia is a complex disorder characterized by disturbances in multiple brain functions, including cognitive, emotional, and perceptual processes. The diagnosis is based on the core symptoms that are categorized into three symptom dimensions: positive, negative, and disorganization. However, the overall course of the illness, including the profile of clinical signs, disease progression, and response to therapeutic treatment, differs substantially among individual cases (Tsuang et al., 1990; Gottesman, 1991). This heterogeneity has led to the consensus that what we recognize clinically as schizophrenia encompasses a large number of disorders that differ with respect to their underlying pathogenesis and mechanisms of disease. In accordance with this notion, no causal gene for schizophrenia has been identified despite the fact that schizophrenia has a very significant genetic component (Gershon et al., 2011). This "missing heritability" is defined as the inability of single genetic variations to account for the heritability of diseases. This implies that susceptibility to disease may depend on the combined effects of all the genes in an individual's genetic background, resulting in a complicated network of contributory disease-pathways that in aggregate increase the probability of disease. Accumulated genetic evidence suggests that multiple disease susceptibility genes function in a similar biological context (e.g., disease-pathway) (Gandhi et al., 2006). The aim of this review is to summarize the findings of genetic studies on schizophrenia

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and to discuss the potential biological pathways affected by the genetic variations. A comprehensive review of all existing genetic studies on schizophrenia was beyond the scope of this paper. Therefore, the focus is on the current largest exome sequencing studies and genome-wide association studies (GWAS) (Fromer et al., 2014; Purcell et al., 2014; Schizophrenia Working Group of the Psychiatric Genomics, 2014; Pocklington et al., 2015; Sekar et al., 2016; Singh et al., 2016). Because the majority of these studies indicate the significance of synaptic networks as the disease-pathway of interest in schizophrenia, these data are summarized to highlight the synaptic functions of susceptibility genes and their possible therapeutic applications for schizophrenia in the future.

2. Human genetic research on schizophrenia

2.1. General introduction to the genetics of schizophrenia

Results from family, twin, and adoption studies have revealed that schizophrenia is a highly heritable disease. For instance, the lifetime morbidity risk for schizophrenia in the general population is 0.7%. This risk increases with the degree of genetic relationship and becomes approximately 2% in third degree relatives of an individual with schizophrenia, 2–6% in second degree relatives, and 6–17% in first degree relatives, in which approximately 12.5%, 25%, and 50% of the genome is shared, respectively (Gottesman, 1991). In spite of this evidence supporting a strong genetic component in the etiology of schizophrenia, no single gene per se is crucial for the development of schizophrenia.

Human genetic studies of the genome and exome sequences of a large number of individuals have indicated that each genome is extremely diverse, with approximately 3.5 million single nucleotide polymorphisms (SNP) and several hundred thousand structural variations, including copy number variations (CNVs) (Mills et al., 2011). A GWAS successfully provides an unbiased survey of the effects of common genetic variants (the common disease–common variant hypothesis), uncovering SNPs that confer disease susceptibility. However, common alleles account for a relatively limited portion of the heritability of the disease, and the genetic research has expanded the focus to spot rare variants that might impart larger effect sizes (the common disease–rare variant hypothesis). A new repertoire of disease-associated genetic variations has been identified in large-scale exome studies. Based on the overview of 2600 Mendelian diseases in which the genetic component has been elucidated, approximately 85% of the disease-related variations can be found in the coding region or in canonical splice sites (Cooper et al., 1995), which supports the utility of exome studies. However, given the highly heterogeneous and polygenic features of schizophrenia, these two hypotheses are likely not mutually exclusive. Indeed, people with schizophrenia carrying a disease-related CNV also had a higher burden of GWAS-determined risk alleles than healthy controls (Tansey et al., 2015). Thus, an overview of disease-susceptible genes identified by both strategies, GWAS and exome sequencing, may lead to a comprehensive understanding of schizophrenia etiology.

Regarding the sampling method, there are two major strategies of genetic analyses, population-based and family-based, each of which has advantages and disadvantages (Hodge, 1994). Population-based studies, which compare cases to unrelated controls, are commonly performed. For these, sufficiently large study populations can be readily assembled without enrolling other family members of the recruited participants. However, one of the major confounding factors of this approach is population stratification, which is defined as a systematic difference in allele frequencies between subpopulations within a population, possibly due to different ancestry. Population stratification can cause serious problems wherein a case-associated variation may be found because of the underlying structure of the population and not because of a disease-associated locus (Ott et al., 2011). In contrast, family-based trio designs, usually comprising a proband (the affected individual) and his or her parents, are advantageous because of the common genetic background among the family members, which helps bypass the problem of population stratification. Moreover, families tend to be more homogeneous regarding exposure to environmental factors that are possibly associated with the disease etiology. Thus, mutations found in affected individuals but not in their unaffected parents (thus de novo mutations) might provide good evidence for a gene's causal role in disease etiology. The main disadvantage of family-based studies, however, is that it is usually more difficult to recruit adequate numbers of well-characterized families. Given this complementary property, studies from both sampling strategies are considered in this review.

2.2. Schizophrenia-susceptibility genes identified by GWAS

A milestone for recent schizophrenia GWAS study, which consisted of 36,989 cases and 113,075 controls, identified 108 schizophrenia-susceptibility loci that exceed genome-wide significance (Schizophrenia Working Group of the Psychiatric Genomics, 2014). The strongest genetic association involves variation in the major histocompatibility complex locus, and this association arises in part from the Component 4 (*C4*) genes (Sekar et al., 2016). C4 activates C3, leading C3 to covalently attach onto its targets and promote synapse elimination by microglia. Of note, an associated SNP of the *C4* allele generates higher expression of *C4A*, the expression of which significantly increased in schizophrenia patients. Because C4-mediated synapse pruning robustly takes place during postnatal development, these results indicate that excessive complement activity could account for the reduced numbers of synapses in the brains of individuals with schizophrenia. Immunological intervention to ameliorate the exacerbated C4 signaling might be a tailor-made personalized medicine beneficial to C4 risk allele carriers with a family history of schizophrenia. Of other identified loci, some were relevant to the current dominant hypotheses for the etiology and treatment for schizophrenia, such as *GRM3* (Glutamate Receptor, Metabotropic 3), *GRIN2A* (Glutamate Receptor, Ionotropic, *N*-methyl D-aspartate, 2A), *SRR* (Serine Racemase), *GRIA1* (Glutamate Receptor, Ionotropic, AMPA 1) and *DRD2* (Dopamine Receptor D2). *GRM3*, *GRIN2A*, *SRR*, and *GRIA1* encode mGluR3 (metabotropic glutamate receptor-3), GluN2A (glutamate-binding NMDA receptor subunit 2), serine racemase, and GluA1 (glutamate-binding AMPA receptor subunit 1), respectively, all of which are involved in glutamatergic transmission. The so-called glutamate hypothesis of schizophrenia originally stemmed from observations that administration of NMDA receptor antagonists such as phencyclidine induces schizophrenic symptoms in humans. Consistently, phencyclidine elicits an increase in glutamate efflux in several brain regions in rodents, and systemic administration of mGluR3 agonists suppresses phencyclidine-induced behavioral effects and the increase in glutamate efflux. This suggested that mGluR agonists would be beneficial in the treatment of schizophrenia. Thus, several agonists for mGluRs have been used in previous trials of schizophrenia, and the efficiency of this strategy is now intensely debated. Additional support for the glutamate hypothesis of schizophrenia came from the observation that a variety of co-agonists of the NMDA receptor, such as D-serine, significantly reduced negative symptoms and partially improved cognition in schizophrenia patients. Because serine racemase is responsible for the synthesis of D-serine, identification of serine racemase by the GWAS supports NMDA receptor signaling augmentation as a potentially safe and feasible approach for ameliorating persistent negative symptoms of schizophrenia.

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