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Animal models of gene–environment interaction in schizophrenia: A dimensional perspective

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ABSTRACT

Schizophrenia has long been considered as a disorder with multifactorial origins. Recent discoveries have advanced our understanding of the genetic architecture of the disease. However, even with the increase of identified risk variants, heritability estimates suggest an important contribution of non-genetic factors. Various environmental risk factors have been proposed to play a role in the etiopathogenesis of schizophrenia. These include season of birth, maternal infections, obstetric complications, adverse events at early childhood, and drug abuse. Despite the progress in identification of genetic and environmental risk factors, we still have a limited understanding of the mechanisms whereby gene–environment interactions (G × E) operate in schizophrenia and psychoses at large. In this review we provide a critical analysis of current animal models of G × E relevant to psychotic disorders and propose that dimensional perspective will advance our understanding of the complex mechanisms of these disorders.

Contents

Abbreviations: GEI, gene–environment interaction; DSM-V, the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders; GWAS, genome-wide-association studies; SNP, single nucleotide polymorphism; PGC, Psychiatric Genomics Consortium; MHC, the major histocompatibility complex; CNV, copy number variations; DISC1, Disrupted-In-Schizophrenia 1; LOD, logarithm of odds; MIA, maternal immune activation; HSV, herpes simplex virus; CMV, cytomegalovirus; HLA, the human leukocyte antigen; HERV, human endogenous retroviruses; *FOX2P*, the Forkhead box protein P2 gene; MRI, magnetic resonance imaging; METH, methamphetamine; ADHD, attention deficit hyperactivity disorder; TLR, toll-like receptor; DOX, doxycycline; GD, gestation day; mPFC, the medial prefrontal cortex; Nurr1, The nuclear receptor related 1 protein.

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1. Introduction

Awareness of the burden of psychiatric disorders is growing, as is the body of research on the causes of mental illnesses. With 0.5% of the total human population affected by schizophrenia over their lifetime (Saha et al., 2005), it represents a major public health concern, having an overall disability burden exceeding that of many infectious diseases (Murray et al., 2012). Schizophrenia is a debilitating psychiatric disorder characterized by positive (e.g., hallucinations and delusion), negative (e.g., social withdrawal and flat affect) and cognitive impairments. These abnormalities usually lead to a lifetime disability for affected patients. The disease is commonly diagnosed in the early 20s, with the diagnosis being made on average 5 years earlier in males than females (Tandon et al., 2008).

The heterogeneous symptoms and clinical manifestations of schizophrenia overlap with those of other major mental illnesses (i.e., bipolar disorders). Prompted by the growing genetic evidence, the conceptual scope of the disorder has been questioned (Berrios et al., 2003), leading to the development of perspectives for psychotic disorders that are independent of diagnosis category, including dimensional approaches and the Research Domain Criteria (RDoC) matrix. In their influential review, van Os and Kapur (2009) propose that symptoms of psychotic disorders be grouped into five dimensions, including psychosis (“the positive-symptom dimension”), avolition and social withdrawal (“the negative-symptom dimension”), cognitive impairments (“the cognitive-symptom dimension”); and affective disorders clustered into depressive and manic symptoms. Another indication of the shifting diagnostic landscape within psychotic disorders can be seen in the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). This latest edition now includes dimensional assessments, with the classification of domains being expanded over those described above, but based on the same principles (Heckers, 2013).

Concurrent with these changes, research in psychiatry has worked to identify genetic variants and environmental adversities that may be significant risk factors for schizophrenia. However, there is a growing consensus that the pathogenesis of the disorder may rely on a constellation of causative factors that lead to disease. Collectively, the interplay of these factors is referred to as gene–environment interaction or G × E (van Os and Kapur, 2009; Uher, 2014).

Recently, there have been published a number of reviews of human and animal studies of G × E in schizophrenia (Ayhan et al., 2009; van Winkel et al., 2010; Kannan et al., 2013; Réthelyi et al., 2013; Hida et al., 2013; Cash-Padgett and Jaaro-Peled, 2013; Karl, 2013). The novel feature of this review is to propose dimensional approach to animal models instead of recapitulating the entire disorder by adhering to the clinical diagnostic criteria. We argue that dimensional perspective will be more successful in addressing the molecular mechanisms underlying G × E in order to facilitate search for new therapeutic interventions of this complex disorder.

2. Genes and environment in schizophrenia

2.1. Genetic bases

The etiology of schizophrenia is poorly understood, and the disease defies any single definition of where risk may originate. A genetic component of risk is well established with twin studies showing an estimated heritability of schizophrenia in the range of 70–80% (Neale and Sklar, 2015). With regards to genetics of the disease, the greatest progress has come from the large sample-sized genome-wide-association studies (GWAS). The Psychiatric Genomics Consortium (PGC), established in 2007, includes more than 500 investigators from 25+ countries and deserves strong consideration in this field (Sullivan, 2010). The Consortium has been collecting genome wide single nucleotide polymorphism (SNP) data worldwide to establish meta-analyses that highlight common disease causing polymorphisms. The leading hypothesis resulting from this work is that the genetic architecture of schizophrenia is similar to that of height, Crohn’s disease or diabetes and relies on common variants of small effects (Sullivan et al., 2012).

The latest PGC paper describes the genotyping data of 36,989 cases and 113,075 controls (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). With this sample size, 108 loci of genome wide significance were identified, with 83 being newly described. More than 80% of these loci were found in or near known gene regions, including haplotypes with polymorphisms coding for dopaminergic receptors, glutamatergic transmission proteins and calcium gated voltage channels. When the causal sequences were mapped with epigenetic markers of specific tissues, the risk variants were found to be enriched in the brain, particularly in the cortex and the striatum, compared to other organs. This study identified genes that encode for the proteins involved in the pathophysiological mechanisms of schizophrenia, including dopaminergic and glutamatergic systems. In addition, this work reported single nucleotide polymorphisms on chromosome 6, where the major histocompatibility complex (MHC) genes are located. Although this region contains genetic elements beyond those involved in immunity, the MHC locus variants suggest etiological relevance of immune genes and inflammatory pathways (Anon, 1999; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). GWAS share concerns about the population stratification, clinical and genetic heterogeneity, the absence/presence of marginal effects, and the multiple testing problem as reviewed in (Price et al., 2010).

Another development in schizophrenia genetics is the demonstration of the role of structural variations (Walsh et al., 2008; Purcell et al., 2014). Some of these mutations are rare and have a