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REVIEW

AVOIDING MOUSE TRAPS IN SCHIZOPHRENIA GENETICS: LESSONS AND PROMISES FROM CURRENT AND EMERGING MOUSE MODELS

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Abstract—Schizophrenia is one of the most common psychiatric disorders, but despite progress in identifying the genetic factors implicated in its development, the mechanisms underlying its etiology and pathogenesis remain poorly understood. Development of mouse models is critical for expanding our understanding of the causes of schizophrenia. However, translation of disease pathology into mouse models has proven to be challenging, primarily due to the complex genetic architecture of schizophrenia and the difficulties in the re-creation of susceptibility alleles in the mouse genome. In this review we highlight current research on models of major susceptibility loci and the information accrued from their analysis. We describe and compare the different approaches that are necessitated by diverse susceptibility alleles, and discuss their advantages and drawbacks. Finally, we discuss emerging mouse models, such as second-generation pathophysiology models based on innovative approaches that are facilitated by the information gathered from the current genetic mouse models.

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Key words: schizophrenia, mouse models, candidate genes, rare mutations, common variants, disease models.

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Abbreviations: cAMP, cyclic AMP; CDCA, common disease/common allele; CDRA, common disease/rare variant; CNVs, copy number variations; *DGCR6*, DiGeorge syndrome critical region 6; *DISC1*, Disrupted in Schizophrenia-1; GWAS, genome-wide association studies; HPC, hippocampus; Mb, megabases; mPFC, medial prefrontal cortex; MWM, Morris Water Maze; NRG1, neuregulin; PDE4b, phosphodiasterase 4b; PPI, prepulse inhibition; SCZ, schizophrenia; WM, working memory.

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SCHIZOPHRENIA

Schizophrenia (SCZ) is a debilitating mental disorder that affects nearly 1% of the world's population. Onset of behavioral symptoms occurs in the late teens and early twenties for most patients. These are defined as positive symptoms (hallucinations, delusions, disordered thoughts and behaviors), negative symptoms (flattened affect, asociality, avolition) and cognitive deficits such as impaired working memory (WM) and executive function. There are also structural brain abnormalities, which have been identified in patients who suffer from SCZ, such as enlargement of the ventricles and a reduction in cortical gray matter (Tandon et al., 2008). However, SCZ is a heterogeneous disease with no single defining symptom or any consistent diagnostic biological marker. Pharmacological interventions have limited effectiveness in the treatment of negative symptoms and cognitive deficits, and this poor response is further complicated by the wide array of side effects associated with antipsychotics and the need for a chronic course of treatment (Webber and Marder, 2008). Results from twin and family studies show that SCZ has a high degree of heritability at around 80% (Sullivan et al., 2003). However, identical twins are only about 50% concordant for the disease suggesting that epigenetic, environmental and very likely stochastic factors also play a substantial role.

MOUSE MODELS OF SCZ

To date, a number of animal models of psychiatric diseases have been developed to address the different aspects of these disorders (Arguello and Gogos, 2006; Nestler and Hyman, 2010). The most proximal brain dysfunc-

tion representing the clinically observed psychopathology has been recapitulated through *pathophysiology models*. These include primarily models that test the hypothesis that because psychoactive drugs produce a psychopathology similar to that seen in individuals with a certain psychiatric disease, the neurotransmitter system affected by the drug is dysfunctional in the disorder (Svenningsson et al., 2003). Examples of these include models of dopaminergic and glutamatergic dysregulation that can be modeled through pharmacological (Dawe et al., 2009) and genetic interventions (Mohn et al., 1999; Kellendonk et al., 2006). Models that attempt to recapitulate the processes that lead to the pathophysiology of a disorder are *models of pathogenesis* (Weinberger, 1995). In this paradigm, prenatal or postnatal perturbations that interfere with normal brain maturation are assessed for their capacity to produce the pathophysiological deficits later in development. Examples are hippocampal lesion models (Lipska and Weinberger, 2000) or exposure to a methylating agent that introduces various neuroanatomical and behavioral abnormalities (Moore et al., 2006). There are a number of challenges for interpreting such pathophysiology and pathogenesis-oriented approaches in the absence of accompanying human genetic evidence, and the question whether they represent legitimate disease models remains a matter of debate (Nestler and Hyman, 2010). Finally, models designed on experimentally proven risk factors or casuative agents of human disease are referred to as *etiological models*. This review will exclusively focus on this last approach, exemplified by specific genetic mouse models. In the last section of this paper we will also discuss the potential of generating novel pathophysiology models based on knowledge accrued by analysis of genetic models.

GENETIC ARCHITECTURE OF SCZ

Two principle theories have been proposed to explain the genetic etiology of the disorder. The *common disease/common allele (CDCA) hypothesis* (Pritchard and Cox, 2002) proposes that the presence of common mutations with low penetrance in many genes acting in concert leads to the disease. Conversely, the *common disease/rare allele (CDRA) hypothesis* assumes an association with rare, but highly penetrant mutations that increase vulnerability for the disease (Cirulli and Goldstein, 2010). Evidence suggests that with SCZ, as with many other diseases, these scenarios are not mutually exclusive and that both common and rare mutations are likely involved in the etiology of the disease.

Genetic association studies provide a powerful approach for identifying risk genes in feasible sample sizes. These studies are based primarily on the CDCA hypothesis and typically examine if common genetic variants are associated with a certain trait or disorder. The simplest design compares the frequencies of genetic variants between groups of non-related cases and controls. Family-based studies that compare the frequencies of the transmitted alleles to non-transmitted alleles from parents to affected offspring are also used to examine the relationship of genetic variants to the disease. Candidate genes in this type of studies are typically identified based on *a priori* evidence, by focusing on candidates derived from neurobiological hypotheses (functional candidate genes) or by attempting to identify positional candidate genes either through systematic follow-up of linkage signals or based on possible biological functions (Gogos and Gerber, 2006). More recently, genome-wide association studies (GWAS) have allowed for an unbiased investigation of polymorphisms throughout the entire genome (Owen et al., 2010). GWAS have opened a window into the biology of common complex diseases and yielded several genes of small effect showing strong association with a number of complex diseases or traits (McCarthy et al., 2008). Results from GWAS in SCZ have been promising but remain controversial (McClellan and King, 2010). Moreover, support for all previously identified top candidate genes has not been found in such agnostic GWAS (Sanders et al., 2008). Overall, although common variants of small effect almost certainly contribute to the genetic risk of psychiatric disorders, genetic association studies have had only limited success so far in identifying them in an unequivocal manner. This is likely due to the complexity of the affected organ (the brain) as well as a number of technical confounds that limit the power of such assays. In that respect, it is worth noting that the Schizophrenia Research Forum (szgene.org) (Allen et al., 2008) lists 1008 susceptibility genes and 8788 polymorphisms as genetic risk loci identified primarily by candidate genetic association studies. Many of these are considered strong susceptibility genes, but none have unequivocal support.

One interesting irony of recent psychiatric genetics is that when these large GWAS data sets, collected initially to test the CDCA hypothesis, were used to determine the prevalence of large structural variations (chromosomal microdeletions and microduplications, also named copy number variations or CNVs) in the genome, new evidence emerged demonstrating the importance of rare large-effect variants in the genetic etiology of the disease in both familial and sporadic cases (Sebat et al., 2009). Specifically, several studies found an enrichment of CNVs in patients with SCZ (Xu et al., 2008; International Schizophrenia Consortium, 2008; Walsh et al., 2008; Stefansson et al., 2008), providing strong empiric evidence supporting the notion that multiple rare genetic variants contribute to the genetic risk of the disease. Notably, several rare variants with large effects on the development of SCZ have been known for a long time. In particular, the association between recurrent 22q11.2 microdeletions and SCZ, described over fifteen years ago (Karayiorgou et al., 1995), represented a shift in our understanding of the genetic architecture of SCZ, highlighting the role that rare and highly penetrant mutations play in the disease risk. This view is further strengthened by the recent identification of a widespread role of CNVs in determining susceptibility to SCZ as well as other psychiatric and neurodevelopmental disorder.