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Review

Susceptibility genes for schizophrenia: Characterisation of mutant mouse models at the level of phenotypic behaviour

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Abstract

A wealth of evidence indicates that schizophrenia is heritable. However, the genetic mechanisms involved are poorly understood. Furthermore, it may be that genes conferring susceptibility interact with one another and with non-genetic factors to modulate risk status and/or the expression of symptoms. Genome-wide scanning and the mapping of several regions linked with risk for schizophrenia have led to the identification of several putative susceptibility genes including *neuregulin-1* (*NRG1*), *dysbindin* (*DTNBP1*), *regulator of G-protein signalling 4* (*RGS4*), *catechol-o-methyltransferase* (*COMT*), *proline dehydrogenase* (*PRODH*) and *disrupted-in-schizophrenia 1* (*DISC1*). Genetic animal models involving targeted mutation via gene knockout or transgenesis have the potential to inform on the role of a given susceptibility gene on the development and behaviour of the whole organism and on whether disruption of gene function is associated with schizophrenia-related structural and functional deficits. This review focuses on data regarding the behavioural phenotype of mice mutant for schizophrenia susceptibility genes identified by positional candidate analysis and the study of chromosomal abnormalities. We also consider methodological issues that are likely to influence phenotypic effects, as well as the limitations associated with existing molecular techniques.

Keywords: Schizophrenia; Animal models; Susceptibility genes; Linkage; Association; Behaviour; Knockouts; Transgenics; Phenotype

Contents

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1. Schizophrenia: psychopathology

Schizophrenia is a chronic and debilitating psychiatric disorder with a lifetime prevalence estimated to range between 0.5% and 1%. This illness has been proposed to consist of several broad domains of psychopathology, including positive, psychotic symptoms (reality distortion), thought disorder (disorganisation) and negative symptoms (psychomotor poverty and impaired social functioning), together with cognitive abnormalities (Thaker and Carpenter, 2001; Freedman, 2003). Psychotic symptoms commonly involve delusions, i.e. false beliefs, and hallucinations, i.e. perceptual experiences which are not based in reality; auditory hallucinations of control are most common, while the content of delusions is often persecutory. Patients with schizophrenia show impairment in numerous neuropsychological tasks probing a variety of cognitive functions such as working memory, attention and executive function (Gold, 2004; Bowie and Harvey, 2005). These cognitive deficits are suggested to better predict functional status and outcome than do observed symptoms (Green, 1996; Gold, 2004; Bowie and Harvey, 2005).

2. Schizophrenia: genetics

If it is true that schizophrenia has proved to be the "graveyard of neuropathologists" (Plum, 1972), it has proved no less problematic for molecular geneticists searching for chromosomal loci and genes associated with the disorder. Schizophrenia is a complex illness whose mode of transmission is either polygenic or oligogenic, with the influence of any single gene on susceptibility to develop the disorder appearing relatively small. Genetic epidemiological data from family, twin and adoption studies have consistently implicated genetic factors in the development of schizophrenia (Thaker and Carpenter, 2001; Freedman, 2003; Owen et al., 2005). However, the lack of complete concordance among monozygotic twins highlights the contribution of nongenetic factors towards risk. Identifying susceptibility genes has proven difficult due to the imprecise clinical phenotype and a presumed significant effect of environmental risk factors. Variations on a polygenic-multifactorial model of gene–environment interaction in schizophrenia have been proposed whereby genetic and/or early environmental risk factors confer vulnerability to develop psychosis, while full blown expression of the disorder later in life is subject to the influence of environmental triggers (Maynard et al., 2001; Lewis and Levitt, 2002; Kennedy et al., 2003).

The observed heterogeneity in the clinical presentation of schizophrenia has lead some to suggest that it represents a combination of distinct disorders rather than a unitary disorder, and that this may be reflected in heterogeneity at both genetic and pathological levels (Thaker and Carpenter, 2001; Freedman, 2003). One approach to dealing with clinical heterogeneity has been the search for cognitive or neurophysiological endophenotypes specific for psychosis such that individual susceptibility genes can be assessed in relation to quantitative phenotypic measures (Thaker and Carpenter, 2001; Freedman, 2003; Harrison and Weinberger, 2005). The importance of precise selection of "cases" that are included in association studies is also highlighted by reports of overlap of candidate genes for schizophrenia with those for illnesses such as bipolar disorder (Green et al., 2005; Maziade et al., 2005).

3. Candidate gene approaches

A number of lines of evidence have suggested a role for dopaminergic and glutamatergic dysfunction in the pathogenesis of schizophrenia and/or the mechanisms of antipsychotic drug action (Schiffer, 2002; Collier and Li, 2003; Laruelle et al., 2005). A recent meta-analyis of studies examining candidate gene associations with schizophrenia revealed that the dopamine (DA) *D3* receptor gene and the *5-HT$_{2a}$* receptor gene displayed a modest effect on risk (Lohmueller et al., 2003). However, other authors have suggested that substantial or reliable associations have not been found between schizophrenia and polymorphisms in genes related to DA or glutamate function (O'Donovan et al., 2003). Given the diversity and inconsistency of findings and the limited contribution of mutant models to the debate they engender, these issues are not considered further here.

4. Evidence from linkage and association studies

Linkage analysis involves the search for chromosomal regions within families that tend to be shared by affected family members but not by unaffected individuals. Until recently, research implicating specific loci for schizophrenia susceptibility has been confounded by difficulties in replicating previous findings as well as frequent contradictory results; these are likely attributable to a combination of