Biochemical Pharmacology 81 (2011) 1367–1373

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Review

Schizophrenia risk genes: Implications for future drug development and discovery

Garret O'Connell *, Stephen M. Lawrie, Andrew M. McIntosh, Jeremy Hall

Division of Psychiatry, University of Edinburgh, Scotland, United Kingdom

ARTICLE INFO

Article history:
Received 8 October 2010
Accepted 8 November 2010
Available online 18 November 2010

Keywords:
Risk genes
Schizophrenia
Drugs
Pharmacogenomics
Transgenic animal models

ABSTRACT

Present-day development of improved treatments for schizophrenia is hindered by uncertain models of disease, inter-individual response variability in clinical trials and a paucity of sensitive measures of treatment effects. Findings from genetic research emphasize the potential for schizophrenia risk genes to help develop focused treatments, discover new drug targets and provide markers of clinical subtypes. Advances in genetic technologies also provide novel modes of drug discovery in schizophrenia such as transcriptomics, epigenetics and transgenic animal models. In this review, we discuss proven and proposed ways risk genes can be used to enhance the development and discovery of treatments for schizophrenia and highlight key studies in these approaches.

Contents

1. Introduction

The discovery of the antipsychotic clozapine which improved prognoses for treatment resistant patients marked the last major improvement in treatments for patients with schizophrenia [1,2]. A wave of medications was engineered based on this compound attempting to replicate its apparently superior efficacy. However, efforts to develop a new generation of antipsychotics without the side-effects of clozapine have failed to improve on the previous 'typical' compounds [3].

Responses to clozapine are highly variable with individual side-effect profiles and just over half of patients being responsive [4]. Even with a good therapeutic response, cognitive impairments and negative symptoms often remain. In addition to the shortcomings of existing antipsychotic treatments, their mode of action in treating the symptoms of schizophrenia remains unclear. For these reasons, the current viewpoint from within psychiatry is that treatment discovery in schizophrenia has not progressed appreciably in a long time and new modes of investigation are needed to edify research on how to identify targets and develop treatments of greater efficacy [5].

A widely cited reason for the ineffectiveness of present-day treatments for schizophrenia is the poorly understood pathophysiology of the disorder [6]. Knowledge of disease pathways is

* Corresponding author at: School of Psychology and Clinical Language Sciences, University of Reading, RG6 6AL, United Kingdom. Tel.: +44 07523652248.
E-mail address: G.OConnell-2@sms.ed.ac.uk (G. O'Connell).

0006-2952/$ – see front matter.
doi:10.1016/j.bcp.2010.11.009

required to identify treatment targets and design accurate animal models in which to examine drug effects. The field of psychiatric molecular genetics provides new avenues for clinical research to explore mechanistic aspects of pathology and new foci for treatments. Studies of schizophrenia risk genes could also shed light on diagnostic ambiguities resulting from the clinical heterogeneity of the disorder, a problem that has been purported to slow the progress of clinical trials [7].

For the purposes of this review, the term risk genes includes not only risk conferred by variation in the genome code such as single nucleotide polymorphisms (SNP), but also encompasses structural chromosomal aberrations and genetic processes (transcription/methylation) which are implicated in schizophrenia. In separate sections, key examples are used to describe the benefits and limitations schizophrenia risk genes offer for: (1) finding sensitive biomarkers of disease states and treatment effects to enhance the strength of clinical testing, and; (2) provide new targets and animal models for the discovery of drugs.

2. Genetic biomarkers of schizophrenia

In the research phase, sporadic or weak results during clinical trials may arise from the inclusion of patients with different pathologic profiles [8]. As a result, accurate diagnostic tools are an emphasized need in schizophrenia to identify "the right patient for the right drug" [9]. Biomarkers are correlates of disease or drug properties that enable researcher to create pathologically uniform samples, establish clinically meaningful dosages and permit earlier detection of clinical improvements—all of which enhance the strength of clinical testing. Such benefits have, however, hitherto rarely been apparent in pharmacological research of schizophrenia or other psychiatric disorders. Growing evidence indicates that risk genes associate with specific features of schizophrenia pathology. Studies suggest that neuregulin 1 [*NRG1*] variation is associated with abnormal cortical function and white-matter integrity in patients [10–12]. In this sense, risk genes have the potential to serve as biomarkers by providing an index of an individual's pathologic profile, and thence their suitability for validating specific pharmacological targets.

2.1. Genome wide association studies of schizophrenia

Fulfilling certain criteria, genome wide association studies (GWAS) are sufficiently powered to detect pathogenic variants of moderate to large risk effects for psychiatric disorders [13]. GWAS over the last decade have shed light on the complex etiology of psychiatric disorders by suggesting the contribution of thousands of commonly found genetic variants of very small effects—none of which are sufficient or necessary to confer disease (*ZNF804A*, *MHC*, *NRGN*, and *TCF4* being the strongest reported). Evidence over the last five years has also identified a class of rare and penetrant genetic risk in the form of structural duplications and deletions, referred to as copy number variations (CNVs), as significant contributors to both individual variation and risk for psychiatric illnesses.

CNVs commonly occur in the healthy population [14], but accumulating evidence indicates an increased burden of large (>100 kb) and rare CNVs in schizophrenia [15–17]. The functional role of specific disease-related CNVs remains obscure. Identified deletions in *NRXN1* suggest the disruption of synaptic development [18]. In addition to schizophrenia, this variation has been associated with risk for autism [19], mental retardation [20] and attention-deficit/hyperactivity disorder [21,22]. That psychiatric disorders share genetic risk has become an intrinsic feature of the GWAS era and has led to the argument that current DSM-IV/ICD-10 classifications used to guide clinical studies are insufficient to annotate the complex etiopathology of psychiatric disorders such as schizophrenia [23].

2.1.1. GWAS and the classification of psychiatric disorders

Ambiguities in the diagnostic dichotomy between bipolar disorder and schizophrenia illustrate how existing classifications used in the drug development conflict with the GWAS depicted nosology of neuropsychiatric disorders. The *ZNF804A* polymorphism has been the most consistently replicated schizophrenia risk gene to date [24]. However, this SNP has also been shown to have an association with bipolar disorder, as has the 22q11 deletion implicated in the genetic risk for schizophrenia [25]. Evidence of a common etiology for these disorders is not unexpected from a clinical viewpoint given their psychotic dimension and similar treatment strategy. However, GWAS evidence highlights the shortcomings of the schizophrenia/bipolar dichotomy in instances of less prototypical psychiatric disorders.

Schizoaffective disorder is the clinical terminology for cases that demonstrate intermediary symptoms of bipolar and schizophrenia. However, definitions of this term vary substantially, expectedly along with clinical application [25]. The viewpoint that schizoaffective disorder is a form of "mixed psychosis" – and therefore a nonunique disease entity comprised of overlapping affective and psychotic symptoms – has resulted in the perception that research into schizoaffective specific treatments is unwarranted. In contrast, GWAS provide strong support for the etiological discontiguity of schizoaffective disorder with bipolar disorder and schizophrenia.

A GWAS by Craddock et al. [26] found that genes associated with schizoaffective disorder were not present in cases of either bipolar-I disorder or schizophrenia, suggesting the presence of disease processes specific to schizoaffective disorder. Furthermore, a large-scale GWAS found that bipolar cases meeting the criteria for schizoaffective disorder had a substantially greater genetic risk than other forms of bipolar [27]. As the majority of clinical cases are estimated to fall between prototypical classifications of schizophrenia and bipolar, these findings have major implications for the utility of DSM-IV/ICD-10 criteria in pharmacological studies of schizophrenia.

The lack of correspondence between traditional measures and the pathophysiology of neuropsychiatric diseases highlights the need for more complex, biological-based approaches to the classifications of psychiatric disorders that reflect both categorical and dimensional aspects of their pathology [28]. In this view, psychiatric disorders are conceptualised as heterogeneous sets of distinct and overlapping pathologies along a spectrum of severity dictated by the burden of genetic risk. Although it may be too early in the field of psychiatric genetic research to develop frameworks for classification along these lines, a move towards using finer detailed descriptions of traits in psychiatric disorder afford more biologically plausible clinical labels [29].

The National Institute of Mental Health (NIMH) has recently launched the Research Domain Criteria (RDoC) project to guide genetic and neuroscience research and help align future classification schemes with the rapidly growing evidence base for the pathophysiology of psychiatric disorders [30]. Abating the widely cited challenges to obtaining pathologically uniform samples and tractable animal models of psychiatric disorders is an exciting prospect of this effort [5]. It can thus be tentatively concluded that classification initiatives based on the progress of psychiatric molecular genetics have the potential to profoundly impact future clinical research.

2.2. Peripheral-blood transcriptomic biomarkers of schizophrenia

An additional benefit of enhancing the resolution of disease phenotypes is the improved predictability of dynamic physiological and pharmacological effects of treatments. Advances in mRNA profiling techniques make it now possible to quickly perform analyses of expression across the entire transcriptome and detect changes related to disease or treatment response [31]. These molecular signatures could provide biomarkers in clinical testing. However, as such abnormalities are usually localised in specific tissues, these methods are often dependent on invasive biopsies. This is a major obstacle in CNS drug development where brain tissues are less easily accessible. An alternative approach stems from the finding that pharmacologically induced changes expressional changes in certain tissues correlate with those in readily obtainable peripheral-blood samples [31,32]. The use of these 'surrogate' measures is expected to have a major impact on clinical research in schizophrenia.

Transcriptomic evidence has gathered in support of a peripheral-blood biomarker of positive 'psychotic' symptoms of schizophrenia. Glatt et al. [33] examined gene expression profiles in both brain and peripheral-blood samples of schizophrenia and healthy subject groups. In comparison to healthy controls, they found that six genes were differentially expressed in the patient group. Of these, they suggested *SELENBP1*, the gene that codes for the selenium-binding protein 1, as a promising biomarker of schizophrenia. Expression of this gene is upregulated in both blood and brain samples in patients with schizophrenia and selenium deficiency has been found to regulate glutamate-induced neurotoxicity in the brain [34].

Kanazawa et al. [35] tested the proposed utility of *SELENBP1* expression as a biomarker in schizophrenia across multiple criteria. They found that upregulation of this gene strongly correlated with presence of psychosis and was unaffected by medication status or duration of illness, all of which indicate that *SELENBP1* expression is a consistent feature of positive symptoms in schizophrenia. Future studies are needed to verify these claims, explore the causal links between *SELENBP1* and psychosis and to localize its effects in the brain before it can be translated into an effective biomarker for clinical trials. A report of a *de novo* deletion in the *SELENBP1* locus in a schizophrenia population raises the possibility of its involvement in the etiology of the disorder [36].

A recent study in this area deserves brief mention: Glatt and colleagues [37] have pioneered a methodological approach for identifying blood-based transcriptomic biomarkers of major psychoses called 'spliceome-profiling'. In addition to querying the transcriptome, this technique profiles subfeatures of the "exome" (all exons) and "spliceome" (all alternatively spliced variants). A test of its effectiveness provided evidence of fifteen genes across schizophrenia and bipolar samples that were differentially spliced, several of which converge on prior supported disease pathways. If replicated this may provide valuable biomarkers of schizophrenia subtypes of therapeutic response variability.

In summary, there is a pressing need for biomarkers of schizophrenia to provide a translational bridge between basic and clinical research. Although biomarker testing is inexpensive, the inherent costs in their discovery and development are considerable so it is important to explore search optimization possibilities offered by risk genes. The 'omic' technologies therefore facilitate the search for biomarkers by providing new ways of characterising abnormalities in biological pathways.

3. Risk genes and schizophrenia drug discovery

The expanding range of gene-linked abnormalities in schizophrenia has intensified the search for new treatment targets. Risk genes potentially provide a functional annotation for target validation by specifying anatomical targets or pathways vulnerable to their dysfunction [38]. The following section provides examples of how risk genes have been used to develop techniques for identifying novel antipsychotic targets.

3.1. Glutamate hypofunction hypothesis of schizophrenia

Glutamate hypofunction has received increasing support as a primary pathological cause of schizophrenia. The reduced signalling of the N-methyl-D-aspartic acid (NMDA) glutamate receptor is proposed as the primary pathogenic process in this approach [39]. Effective NMDA receptor activity is a prerequisite of modulating activity-dependent changes in synaptic plasticity underpinning learning and memory. The disrupted in schizophrenia 1 gene [*DISC1*], *NRG1*, dysbindin [*DTNBP1*] and the glutamate coding gene *GRM3* are among the highest reported risk genes of schizophrenia, all of which are functionally involved in NMDA receptor signalling [40,41]. In addition, associations between the expression of NMDA receptor coding genes *NMDAR1* and *GRIN2B* and clozapine dosage suggests that clinical benefits are mediated via these receptors [42].

An attractive prospect of targeting glutamate is the possibility of alleviating cognitive and negative symptoms that are difficult to treat with present antipsychotic drugs. Initial evidence that modulating NMDA function can confer these benefits comes from numerous clinical trials indicating that the addition of D-serine – a partial coagonist of NMDA receptors – to conventional antipsychotics improved these symptoms [43,44]. A novel glutamate-based treatment of psychosis has been designed that activates group II metabotropic glutamate receptors (mGluR2/mGluR3) [45]. If these results survive pending phase three trials, it would present the first evidence of an effective antipsychotic drug that does not target dopamine [46,47].

3.2. Targets from genetic studies of glutamate in schizophrenia

Aside from providing supportive evidence for the pharmacological focus on glutamate hypofunction in schizophrenia, genetic association studies have identified a novel target for antipsychotic modulation of NMDA function [48]. A linkage study first identified the 13q22 region containing *G72* in the genetic risk for schizophrenia [49]. Molecular evidence supports a functional role of *G72* in the metabolism of D-amino acids [49]. This interactive partner, D-amino acid oxidase (DAAO), pertains to schizophrenia pathology in its role as an oxidative agent of D-serine. Findings of reduced prefrontal D-serine in schizophrenia supports *G72* modulated overactivity of DAAO as a causal mechanism of NMDA receptor hypofunction [50].

Extensive evidence from animal studies has since gathered for the potential of DAAO inhibition as an antipsychotic target. DAAO inhibitors have been found to normalise prepulse-inhibition (PPI) responses in PCP mice models of reduced NMDA functioning in schizophrenia to levels comparable to clozapine [51]. The authors of this study also report that subchronic administration of this novel compound attenuated the psychomotor impact of PCP. Moderate efficacy reported in subsequent studies motivated investigations of the combined effect of D-serine and DAAO inhibitors. Three studies have since reported on the resulting increases in cortical and cerebrospinal D-serine and reduced PPI deficits following co-administration than when either D-serine and DAAO inhibitors were used separately [52–54]. As has been suggested, the combined use of these drugs could have dual benefits both in terms of enhanced antipsychotic activity and in reducing the side-effects associated with the high dosages of D-serine needed for clinical effect [55].

The association of D-amino acid oxidase activator [*DAOA*] – as *G72* is now known – and schizophrenia has been replicated in independent samples [56,57]. In addition, fMRI evidence reports *DAOA* variation impact on prefrontal and hippocampal function in subjects with high familial risk for schizophrenia [58]. However, the emergence of conflicting evidence from subsequent schizophrenia gene-association studies has led to the perception that this association is weaker than previously considered [59–61]. In the context of the recently proposed therapeutic potential of DAAO inhibition, the inconsistency of findings may serve as a caveat to future genetic research: the fluctuating importance of this risk gene exemplifies the difficulty in replicating and drawing definitive conclusions from gene association studies of psychiatric disorders in the absence of supporting pharmacologic evidence [48].

3.3. GABA deficit hypothesis of schizophrenia

Compelling evidence indicates the importance of neural inhibition to abnormal synaptic plasticity in schizophrenia. Gamma aminobutyric acid (GABA) ergic interneurons are responsible for mediating fast synaptic inhibition in the brain, essential for effective signalling in neural circuits [62]. Studies indicate that defective GABAergic transmission disrupts neural synchronization in cortical and hippocampal networks that underlie prefrontal information processing and sensory gating [63], features repeatedly reported as impaired in schizophrenia. Pharmacologic evidence also suggests that vulnerable NMDA receptors in schizophrenia are highly concentrated on $GABA_A$ interneurons [64,65]. GABAergic function in corticolimbic circuits may therefore be crucial to understanding neural and cognitive defects in schizophrenia.

The antipsychotic action of existing drugs has indicated to be partly mediated via GABAergic receptors. Benzodiazepines, efficient in equilibrating $GABA_A$ transmission, are used adjunctively with antipsychotic treatments to reduce morbidity in schizophrenia patients [66]. Studies have examined the effects of benzodiazepine receptor binding ligand imidazenil to normalise PPI and social deficits (both reported to be disrupted in schizophrenia) in mice models [67,68]. Pharmacologic evidence of the efficacy of a $GABA_A$ targeting compounds to improve cognitive deficits exhibited in schizophrenia provides preliminary support for the antipsychotic potential of indirect $GABA_A$ receptor agonists [69]. A related line of investigation to the GABA deficit hypothesis has proposed a drug-reversible process thought to be a core etiopathogenic cause of schizophrenic GABAergic defects.

3.3.1. Targets from epigenetic events in GABAergic systems

Molecular genetic studies provide robust evidence that reelin and GAD67 transcripts in GABAergic neurons are downregulated in schizophrenia [70–72]. Reelin has been implicated in dendritic spine growth and the modulation of neural plasticity by influencing the function of NMDA receptors located on GABAergic interneurons [73], while GAD_{67} is reportedly involved in GABA synthesis with the gene encoding for this isoform also having been linked to abnormal neurodevelopment [74]. Decreased expression of these and other mRNAs are unrelated to medication status, suggesting the possibility of undiscovered treatment targets [75]. To explain the consistency of abnormal reelin and GAD_{67} expression findings, increasing evidence has implicated hypermythelation in schizophrenia.

Research over the last five years has increased the focus of epigenetic mechanisms in the risk for schizophrenia independent of genomic variation. DNA methylation in the promoter region of a gene is associated with a loss of that gene's expression [76]. DNA methyltransferase 1 (DNMT1) is considered to maintain methylation in the cell throughout development [77]. However, increased levels in human prefrontal GABAergic interneurons suggest additional roles besides maintenance [78]. In the brains of schizophrenia patients, an upregulation of DNMT1 has been found to compliment GAD_{67} and reelin downregulation [79]. The origin of these increases is not yet known, but their simultaneous onset with schizophrenic symptoms following puberty strengthens this association [80].

Evidence suggests that valproic acid (VPA), prescribed to psychotic patients as a mood stabilizer, normalizes the expression of GAD_{67} and reelin [81]. VPA is a histone deacetylase inhibitor (HDAC) that downregulates DNMT1 activity, thereby reducing neuronal DNA methylation. Drugs in this class are known to be beneficial when combined with atypical antipsychotics in treatment resistant patients [82,83]. However, existing HDACs have limited pharmacokinetic potential to cross the blood-brain barrier. To examine the physiological effects of downregulated reelin and GAD_{67}, epigenetic mice models have been developed through prolonged administration of L-methionine (MET) [67,68].

MET mouse models can be used to examine how both epigenetic events and pharmacological agents affect the expression of these mRNAs and schizophrenia-related behavioural alterations. In the former case, the schizophrenia symptoms found in $reelin^{+/-}$ mice have also been described in MET mice, suggesting the involvement of convergent disease pathways such as cortical DNMT1 overexpression [84]. In the latter case, reelin and GAD_{67} promoters undergo rapid demethylation in the cortex and hippocampus of these mice when treated with valproic acid [85]. Another important corollary of MET induced changes in methylation patterns is the advent of a neurobiological account of how environmental insults such as drugs and toxins that have been heavily implicated in increased susceptibility to schizophrenia disrupt neural processes in the disease [86].

Epigenetic evidence indicates that following full neurodevelopmental maturation, environmental factors have an amplified impact on modulatory mechanisms of methylation. Post-translational changes in specific loci of the histone structure modify the restrictiveness of chromotin to DNA methylation enzymes. For example, one of the most consistent histone modifications is the acetylation of histone 3 (H3) lysine residues in positions 9 and 14 (H3Lys9 and H3Lys14) [86]. To examine whether enhanced demethylation of reelin and GAD_{67} promoters is mediated by chromatin remodeling, Dong et al. [87] examined the molecular impact of VPA in MET mice. VPA was found to increase the amount of nuclear acetylated H3Lys9 or H3Lys14 bound to the reelin and GAD_{67} promoters in the presence of accelerated reelin and GAD_{67} promoter demethylation, supporting the involvement of histone modification in modulating the methylation of GABAergic gene promoters. However, it remains uncertain whether HDAC inhibitors induce demethylation via DNMT1 inhibition or indirectly by histone code remodeling [86].

Further support for the therapeutic potential of HDAC inhibitors comes from evidence of a similar demethylation effect of antipsychotics. A study by Huang and others [88] found that methylation of a histone modification thought to activate chromatin transcription is increased at GABAergic gene promoters in the PFC neurons of clozapine, but not halipridone, treated mice. Another study has found that hypermethylated reelin and GAD_{67} promoters undergo demethylation in MET mice when treated with clozapine and sulpiride but not halopideral or olanzapine, an effect that was accentuated with conjunct VPA administration [89]. Together these studies strongly suggest that the superior efficacy of clozapine in alleviating positive symptoms of schizophrenia may be mediated by histone modifications that normalize GABAergic gene promoter expression.

The precise role of DNA methylation on chromatin plasticity remains to be clarified, indicating that successful translation into drug therapies is dependent on elucidating these mechanisms in the neurobiology of schizophrenia. Existing research also suggests that different subclasses of HDACs have dissociable roles in moderating the neurodevelopmental pathology of brain disorders [90], emphasizing the need for studies into the impact of individual HDAC inhibitors to improve the specificity of these targets. In conclusion, epigenetic events in the GABAergic system are thought to play a significant role in synaptic plasticity, neural synchonization and the timing of structural brain changes—the major foci of findings from research into the neuropathology of schizophrenia. Their influence across the life-span also introduces the possibility of pharmacological intervention to shift the trajectory of neurodevelopment away from psychiatric illness and avoid disease states altogether [91].

3.4. *DISC1* and animal models of schizophrenia

A final implication of risk genes in clinical schizophrenia research is illustrated by the contribution of *DISC1* studies to developing transgenic animal models in the validation and search of schizophrenia drug targets [92].

DISC1 was identified following the discovery of a single Scottish family with a balanced translocation in chromosomes 1 and 11 disrupting the gene. Although no other family has been identified with a similar translocation, common and rare variants in *DISC1* have been shown to confer risk for schizophrenia across a number of studies. The complexity of *DISC1* biology, as well as the lack of direct access to brain tissue from the *t*(1:11) family, has made the mechanisms of risk difficult to elucidate [93]. A 'DISC1 Interactome' has been identified which details the protein-protein interactions and provides a framework for estimating and understanding the risk-associated mechanisms. Studies have begun using this approach to put forward potential therapeutic targets for treatments, in particular PDE4B and NDEL1 interactors [94–97]. The linking of these respective proteins to cAMP (which functions in cognition, memory, and mood) and NMDA-receptor signalling has provided a clinical framework for explaining how symptoms are elicited via faulty neurotransmitter signalling.

In psychopharmacological research, animal models of sufficiently detailed disease substrates are needed to explore new drug targets. As mentioned, this presents a problem in schizophrenia drug discovery [5]. One major concern comes from evidence suggesting that developmental physiological changes that vastly differ between humans and other species are a fundamental aspect of the disorder's etiopathology. Advancements in transgenic animal models have been used to circumvent this problem by modifying the endogenous *DISC1* promoter to regulate expression [98].

A study by Ayhan et al. [99] found evidence that inducible expression of a mutant human *DISC1* in the forebrain during early-stage development can lead to schizophrenia like symptoms, and that increased expression at any stage led to decreased levels of cortical dopamine and reduced neuronal density. Studies of human development support the role of *DISC1* in neurite growth and neuronal migration [100,95]. In considering the construct validity of animal models of psychiatric disorders, it is bear in mind that clinically characterised phenomena of the disorder may have little biological relatedness to ostensibly similar phenotypes in animals [5]. By shifting focus towards modelling the underlying pathophysiology of disease phenotypes, animal models become more exact and tenable for treatment development. The enhanced ability to simulate pathognomic mechanisms in lab species is thus a valuable addition to the array of research tools in the clinical study of schizophrenia [101].

DISC1 lab species have helped model disorders that are similar even on the level of putative genetic risk. Clapcote and colleagues [102] found dissociable roles for two independent missense polymorphisms in *DISC1* for increasing the risk of depressive-like and schizophrenia-like phenotypes in mice. Identified abnormalities in grey matter volume and the selective pharmacological responses of antipsychotic and antidepressant drugs support the pleiotropic effect of *DISC1*. Further imputes for elucidating the effect of variation in *DISC1* comes from the recent association of a missense variant in *DISC1* with ultra antipsychotic-resistant forms of schizophrenia [103].

While the evidence from these studies is preliminary, findings from *DISC1* have encouraged the development of new ways to model core pathognomic features of schizophrenia in lab species [104]. It has been suggested that models based on highly penetrant genetic mutations such as *DISC1* are among the highest in terms of construct validity of neuropsychiatric disorders [5]. As proteins encoded by schizophrenia risk genes are likely to interact along similar pathways, the *DISC1* interactome also provides a ready

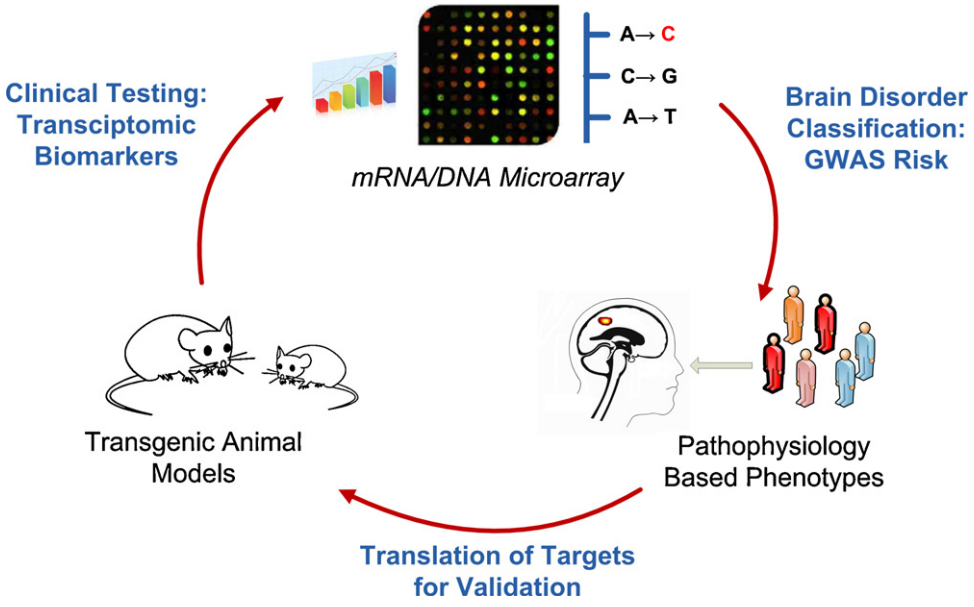

Fig. 1. Overview of gene-based drug development process of neuropsychiatric diseases.

framework for exploring the molecular impact of epistatic gene effects and the subsequent identification of pharmacological targets, which can in turn be systematically validated in schizophrenia phenotypes afforded by *DISC1* mice (Fig. 1).

4. Future directions and conclusion

While genes have fallen in and out of association with schizophrenia over short time spans throughout the GWAS era, definite patterns of the genetic basis of the disorder have emerged. Presently, future studies are focussed on the testing of larger and better phenotyped samples via international consortia to ensure progress. It has been acknowledged that a point may soon be reached where the motivation for GWAS investigations is outweighed by the need to characterise identified risk genes through biological experimentation [105]. A target of present intense focus is identifying the pathogenic function of the *ZNF804A*—the first gene to meet the criteria for genome wide significance in schizophrenia [106]. Pharmacological and systems biology studies of risk genes will be imperative to translating findings into clinical benefits and ensuring that the expectations generated by psychiatric genetic research are realised.

References

[1] Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psych 1988;45:789–96.
[2] Hippius H. History of clozapine. Psychopharmacol 1989;99:53–5.
[3] Owens DC. What CATIE did: some thoughts on implications deep and wide. Psychiatr Serv 2008;59:530–3.
[4] Arranz MJ, Munro J, Birkett J, Bolonna A, Mancama D, Sodhi M, et al. Pharmacogenetic prediction of clozapine response. Lancet 2000;355:1615–6.
[5] Nestler EJ, Hyman SE. Animal models of neuropsychiatric disorders. Nat Neurosci 2010;13:1161–9.
[6] Insel TR. Disruptive insights in psychiatry: transforming a clinical discipline. J Clin Invest 2009;119:700–5.
[7] Arranz MJ, de Leon J. Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research. Mol Psychiatry 2007;12:707–47.
[8] Breier A. Developing drugs for cognitive impairment in schizophrenia. Schizophr Bull 2005;31:816–22.
[9] Hüsing B, Jäncke L, Tag B. Impact assessment of neuroimaging. Amsterdam, Netherlands: IOS Press; 2006.
[10] Hall J, Whalley HC, Job DE, Baig BJ, McIntosh AM, Evans KL, et al. A neuregulin 1 variant associated with abnormal cortical function and psychotic symptoms. Nat Neurosci 2006;9:1477–8.
[11] McIntosh AM, Moorhead TW, Job D, Lymer GK, Muñoz Maniega S, McKirdy J, et al. The effects of a neuregulin 1 variant on white matter density and integrity. Mol Psychiatry 2008;13:1054–9.
[12] Sprooten E, Lymer GK, Maniega SM, McKirdy J, Clayden JD, Bastin ME, et al. The relationship of anterior thalamic radiation integrity to psychosis risk associated neuregulin-1 variants. Mol Psychiatry 2009;14:237–8.
[13] Owen MJ, Craddock N, O'Donovan MC. Suggestion of roles for both common and rare risk variants in genome-wide studies of schizophrenia. Arch Gen Psychiatry 2010;67:667–73.
[14] McCarroll SA, Kuruvilla FG, Korn JM, Cawley S, Nemesh J, Wysoker A, et al. Integrated detection and population-genetic analysis of SNPs and copy number variation. Nat Genet 2008;40:1166–74.
[15] Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, Cooper GM, et al. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. Science 2008;320:539–43.
[16] Stefansson H, Rujescu D, Cichon S, Pietiläinen OP, Ingason A, Steinberg S, et al. Large recurrent microdeletions associated with schizophrenia. Nature 2008;455:232–6.
[17] International Schizophrenia Consortium. Rare chromosomal deletions and duplications increase risk of schizophrenia. Nature 2008;455:237–41.
[18] Kirov G, Rujescu D, Ingason A, Collier DA, O'Donovan MC, Owen MJ. Neurexin 1 (NRXN1) deletions in schizophrenia. Recurrent rearrangements of chromosome 1q21. 1 and variable pediatric phenotypes. Schizophr Bull 2009;35: 851–4.
[19] Autism Genome Project Consortium. Mapping autism risk loci using genetic linkage and chromosomal rearrangements. Nat Genet 2007;39: 319–28.
[20] Friedman JM, Baross A, Delaney AD, Ally A, Arbour L, Armstrong L, et al. Oligonucleotide microarray analysis of genomic imbalance in children with mental retardation. Am J Hum Genet 2006;79:500–13.
[21] Mefford HC, Sharp AJ, Baker C, Itsara A, Jiang Z, Buysse K, et al. Recurrent rearrangements of chromosome 1q21.1 and variable pediatric phenotypes. N Engl J Med 2008;359:1685–99.
[22] Williams NM, Zaharieva I, Martin A, Langley K, Mantripragada K, Fossdal R, et al. Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: a genome-wide analysis. Lancet 2010;376:1401–8.
[23] Craddock N, O'Donovan MC, Owen MJ. Genes for schizophrenia and bipolar disorder? Implications for psychiatric nosology. Schizophr Bull 2006;32: 9–16.
[24] O'Donovan MC, Craddock N, Norton N, Williams H, Peirce T, Moskvina V, et al. Identification of loci associated with schizophrenia by genome-wide association and follow-up. Nat Genet 2008;40:1053–5.
[25] Williams HJ, Norton N, Dwyer S, Moskvina V, Nikolov I, Carroll L, et al. Fine mapping of ZNF804A and genome-wide significant evidence for its involvement in schizophrenia and bipolar disorder. Mol Psychiatry 2010; in press.
[26] Craddock N, O'Donovan MC, Owen MJ. Psychosis genetics: modeling the relationship between schizophrenia, bipolar disorder, and mixed (or "'schizoaffective'') psychoses. Schizophr Bull 2009;35:482–90.
[27] Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447:661–678.
[28] Hamshere ML, Green EK, Jones IR, Jones L, Moskvina V, Kirov G, et al. Genetic utility of broadly defined bipolar schizoaffective disorder as a diagnostic concept. Br J Psychiatry 2009;195:23–9.
[29] Cross-Disorder Phenotype Group of the Psychiatric GWAS Consortium, Craddock N, Kendler K, Neale M, Nurnberger J, et al. Dissecting the phenotype in genome-wide association studies of psychiatric illness. Br J Psychiatry 2009;195:97–9.
[30] Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry 2010;167:748–51.
[31] Iwamoto K, Kato T. Gene expression profiling in schizophrenia and related mental disorders. Neuroscientist 2006;12:349–61.
[32] Mohr S, Liew CC. The peripheral-blood transcriptome: new insights into disease and risk assessment. Trends Mol Med 2007;13(10):422–32.
[33] Glatt SJ, Everall IP, Kremen WS, Corbeil J, Sásik R, Khanlou N, et al. Comparative gene expression analysis of blood and brain provides concurrent validation of SELENBP1 up-regulation in schizophrenia. Proc Natl Acad Sci USA 2005;102: 15533–8.
[34] Savaskan NE, Bräuer AU, Kühbacher M, Eyüpoglu IY, Kyriakopoulos A, Ninnemann. et al. Selenium deficiency increases susceptibility to glutamate-induced excitotoxicity. FASEB J 2003;17:112–4.
[35] Kanazawa T, Chana G, Glatt SJ, Mizuno H, Masliah E, Yoneda H, et al. The utility of SELENBP1 gene expression as a biomarker for major psychotic disorders: replication in schizophrenia and extension to bipolar disorder with psychosis. Am J Med Genet B Neuropsychiatr Genet 2008;147B:686–9.
[36] Amar S, Ovadia O, Maier W, Ebstein R, Belmaker RH, Mishmar D, et al. Copy number variation of the SELENBP1 gene in schizophrenia. Behav Brain Funct 2010;6:40.
[37] Glatt SJ, Chandler SD, Bousman CA, Chana G, Lucero GR, Tatro E, et al. Alternatively spliced genes as biomarkers for schizophrenia. Bipolar disorder and psychosis: a blood-based spliceome-profiling exploratory study. Curr Pharmacogenomics Person Med 2009;7:164–88.
[38] Crowther DJ. Applications of microarrays in the pharmaceutical industry. Curr Opin Pharmacol 2002;2:551–4.
[39] Stephan KE, Friston KJ, Frith CD. Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophr Bull 2009;35: 509–27.
[40] Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol Psychiatry 2005;10:40–68.
[41] Hall J, Romaniuk L, McIntosh AM, Steele JD, Johnstone EC, Lawrie SM. Associative learning and the genetics of schizophrenia. Trends Neurosci 2009;32: 359–65.
[42] Chiu HJ, Wang YC, Liou YJ, Lai IC, Chen JY. Association analysis of the genetic variants of the N-methyl D-aspartate receptor subunit 2b (NR2b) and treatment-refractory schizophrenia in the Chinese. Neuropsychobiology 2003;47: 178–81.
[43] Goff DC, Tsai G, Manoach DS, Coyle JT. Dose-finding trial of D-cycloserine added to neuroleptics for negative symptoms in schizophrenia. Am J Psychiatry 1995;152:1213–5.
[44] Coyle JT, Tsai G. The NMDA receptor glycine modulatory site: a therapeutic target for improving cognition and reducing negative symptoms in schizophrenia. Psychopharmacology (Berl) 2003;174:32–8.
[45] Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV, et al. Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized phase 2 clinical trial. Nat Med 2007;13:1102–7.
[46] Weinberger DR. Schizophrenia drug says goodbye to dopamine. Nat Med 2007;13:1018–9.
[47] Inta D, Monyer H, Sprengel R, Meyer-Lindenberg A, Gass P. Mice with genetically altered glutamate receptors as models of schizophrenia: a comprehensive review. Neurosci Biobehav Rev 2010;34:285–94.
[48] Williams M. Commentary: genome-based CNS drug discovery: D-amino acid oxidase (DAAO) as a novel target for antipsychotic medications: progress and challenges. Biochem Pharmacol 2009;78:1360–5.
[49] Chumakov I, Blumenfeld M, Guerassimenko O, Cavarec L, Palicio M, Abderrahim H, et al. Genetic and physiological data implicating the new human gene G72 and the gene for D-amino acid oxidase in schizophrenia. Proc Natl Acad Sci USA 2002;99:13675–80.

[50] Abou Jamra R, Schmael C, Cichon S, Rietschel M, Schumacher J, Nöthen MM. The G72/G30 gene locus in psychiatric disorders: a challenge to diagnostic boundaries? Schizophr Bull 2006;32:599–608.
[51] Adage T, Trillat AC, Quattropani A, Perrin D, Cavarec L, Shaw J, et al. In vitro and in vivo pharmacological profile of AS057278, a selective d-amino acid oxidase inhibitor with potential anti-psychotic properties. Eur Neuropsychopharmacol 2008;18:200–14.
[52] Smith SM, Uslaner JM, Yao L, Mullins CM, Surles NO, Huszar SL, et al. The behavioral and neurochemical effects of a novel D-amino acid oxidase inhibitor compound 8 [4H-thieno [3,2-b] pyrrole-5-carboxylic acid] and D-serine. J Pharmacol Exp Ther 2009;328:921–30.
[53] Hashimoto K, Fujita Y, Horio M, Kunitachi S, Iyo M, Ferraris D, et al. Co-administration of a D-amino acid oxidase inhibitor potentiates the efficacy of D-serine in attenuating prepulse inhibition deficits after administration of dizocilpine. Biol Psychiatry 2009;65:1103–6.
[54] Ferraris D, Duvall B, Ko YS, Thomas AG, Rojas C, Majer P, et al. Synthesis and biological evaluation of D-amino acid oxidase inhibitors. J Med Chem 2008;51:3357–9.
[55] Smith SM, Uslaner JM, Hutson PH. The therapeutic potential of D-amino acid oxidase (DAAO) Inhibitors. Open Med Chem J 2010;4:3–9.
[56] Shi J, Badner JA, Gershon ES, Chunyu L, Willour VL, Potash JB. Further evidence for an association of G72/G30 with schizophrenia in Chinese. Schizophr Res 2009;107:324–6.
[57] Corvin A, McGhee KA, Murphy K, Donohoe G, Nangle JM, Schwaiger S, et al. Evidence for association and epistasis at the DAOA/G30 and D-amino acid oxidase loci in an Irish schizophrenia sample. Am J Med Genet B Neuropsychiatr Genet 2007;144B:949–53.
[58] Hall J, Whalley HC, Moorhead TW, Baig BJ, McIntosh AM, Job DE, et al. Genetic variation in the DAOA (G72) gene modulates hippocampal function in subjects at high risk of schizophrenia. Biol Psychiatry 2008;64:428–33.
[59] Mulle JG, Chowdari KV, Nimgaonkar V, Chakravarti A. No evidence for association to the G72/G30 locus in an independent sample of schizophrenia families. Mol Psychiatry 2005;10:431–3.
[60] Ohi K, Hashimoto R, Yasuda Y, Yoshida T, Takahashi H, Iike N, et al. Association study of the G72 gene with schizophrenia in a Japanese population: a multicenter study. Schizophr Res 2009;109:80–5.
[61] Williams NM, Green EK, Macgregor S, Dwyer S, Norton N, Williams H, et al. Variation at the DAOA/G30 locus influences susceptibility to major mood episodes but not psychosis in schizophrenia and bipolar disorder. Arch Gen Psychiatry 2006;63:366–73.
[62] Benes FM, Berretta S. GABAergic interneurons: implications for understanding schizophrenia and bipolar disorder. Neuropsychopharmacology 2001;25: 1–27.
[63] Roa SG, Williams GV, Goldman-Rakic PS. Isodirectional tuning of pyramidal cells by somatic feed-forward inhibition. Science 1999;81:1903–16.
[64] Coyle JT. The GABA-glutamate connection in schizophrenia: which is the proximate cause? Biochem Pharmacol 2004;68:1507–14.
[65] Bodarky CL, Halene TB, Ehrlichman RS, Banerjee A, Ray R, Hahn CG, et al. Novel environment and GABA agonists alter event-related potentials in N-methyl-D-aspartate NR1 hypomorphic and wild-type mice. J Pharmacol Exp Ther 2009;331:308–18.
[66] Carpenter Jr WT, Buchanan RW, Kirkpatric B, Breier AF. Diazepam treatment of early signs of exacerbation in schizophrenia. Am J Psychiatry 1999;156: 299–303.
[67] Tremolizzo L, Carboni G, Ruzicka WB, Mitchell CO, Sugaya I, Tueting P, et al. An epigenetic mouse model for epigenetic molecular and behavioral neuropathologies related to schizophrenia vulnerability. Proc Natl Acad Sci USA 2002;99:17095–100.
[68] Tremolizzo L, Doueiri MS, Dong E, Grayson DR, Pinna G, Tueting P, et al. Valproate corrects the schizophrenia-like epigenetic behavioral modifications induced by methionine in mice. Biol Psychiatry 2005;57:500–9.
[69] Bodarky CL, Halene TB, Ehrlichman RS, Banerjee A, Ray R, Hahn CG, et al. Novel environment and GABA agonists alter event-related potentials in N-methyl-D-aspartate NR1 hypomorphic and wild-type mice. J Pharmacol Exp Ther 2009;331:308–18.
[70] Eastwood SL, Harrison PJ. Cellular basis of reduced reelin expression in schizophrenia. Am J Psych 2006;163:540–2.
[71] Guidotti A, Auta J, Davis JM, Di Giorgi-Gerevini V, Dwivedi Y, Grayson DR, et al. Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: a postmortem brain study. Arch Gen Psych 2000;57:1061–9.
[72] Ruzicka WB, Zhubi A, Veldic M, Grayson DR, Costa E, Guidotti A. Selective epigenetic alteration of layer I GABAergic neurons isolated from prefrontal cortex of schizophrenia patients using laser-assisted microdissection. Mol Psych 2007;12:285–97.
[73] Chen Y, Beffert U, Ertunc M, Tang TS, Kavalali ET, Bezprozvanny I, et al. Reelin modulates NMDA receptor activity in cortical neurons. J Neurosci 2005;25: 8209–16.
[74] Addington AM, et al. GAD1 (2q31.1), which encodes glutamic acid decarboxylase (GAD67), is associated with childhood-onset schizophrenia and cortical gray matter volume loss. Mol Psychiatry 2005;10:581–8.
[75] Robertson KD. DNA methylation and human disease. Nat Rev Genet 2005;6: 597–610.
[76] Bird A. DNA methylation patterns and epigenetic memory. Genes Dev 2002;16:6–21.
[77] Veldic M, Caruncho HJ, Liu WS, Davis J, Satta R, Grayson DR, et al. DNA-methyltransferase 1 mRNA is selectively overexpressed in telencephalic GABAergic interneurons of schizophrenia brains. Proc Natl Acad Sci USA 2004;101:348–53.
[78] Veldic M, Guidotti A, Maloku E, Davis JM, Costa E. In psychosis, cortical interneurons overexpress DNA-methyltransferase 1. Proc Natl Acad Sci USA 2005;102:2152–7.
[79] Grayson DR, Chen Y, Dong E, Kundakovic M, Guidotti A. From trans-methylation to cytosine methylation. Evolution of the methylation hypothesis of schizophrenia. Epigenetics 2009;4:144–9.
[80] Brueckner B, Lyko F. DNA methyltransferase inhibitors: old and new drugs for an epigenetic cancer therapy. Trends Pharmacol Sci 2004;25:551–4.
[81] Wassef A, Baker J, Kochan LD. GABA and schizophrenia: a review of basic science and clinical studies. J Clin Psychopharmacol 2003;23:601–40.
[82] Munro J, Matthiasson P, Osborne S, Travis M, Purcell S, Cobb AM, et al. Amisulpride augmentation of clozapine: an open non-randomized study in patients with schizophrenia partially responsive to clozapine. Acta Psychiatr Scand 2004;110:292–8.
[83] Dong E, Agis-Balboa RC, Simonini MV, Grayson DR, Costa E, Guidotti A. Reelin and glutamic acid decarboxylase67 promoter remodeling in an epigenetic methionine induced mouse model of schizophrenia. Proc Natl Acad Sci USA 2005;102:12578–83.
[84] Costa E, Davis J, Pesold C, Tueting P, Guidotti A. The heterozygote reeler mouse as a model for the development of a new generation of antipsychotics. Curr Opin Pharmacol 2002;2:56–62.
[85] Simonini MV, Camargo LM, Dong E, Maloku E, Veldic M, Costa E, et al. The benzamide MS-275 is a potent, long-lasting brain region-selective inhibitor of histone deacetylases. Proc Natl Acad Sci USA 2006;103:1587–92.
[86] Guidotti A, Dong E, Kundakovic M, Satta R, Grayson DR, Costa E. Characterization of the action of antipsychotic subtypes on valproate-induced chromatin remodeling. Trends Pharmacol Sci 2009;30:55–60.
[87] Dong E, Guidotti A, Grayson DR, Costa E. Histone hyperacetylation induces demethylation of reelin and 67-kDa glutamic acid decarboxylase promoters. Proc Natl Acad Sci USA 2007;104:4676–81.
[88] Huang HS, Matevossian A, Whittle C, Kim SY, Schumacher A, Baker SP, et al. Prefrontal dysfunction in schizophrenia involves mixed-lineage leukemia 1-regulated histone methylation at GABAergic gene promoters. J Neurosci 2007;27:11254–62.
[89] Dong E, Nelson M, Grayson DR, Costa E, Guidotti A. Clozapine and sulpiride but not haloperidol or olanzapine activate brain DNA demethylation. Proc Natl Acad Sci USA 2008;105:13614–9.
[90] Fischer A, Sananbenesi F, Mungenast A, Tsai LH. Targeting the correct HDAC(s) to treat cognitive disorders. Trends Pharmacol Sci 2010;31:605–17.
[91] Akbarian S, Huang H. Epigenetic regulation in human brain—focus on histone lysine methylation. Biol Psychiatry 2009;65:198–203.
[92] Wang Q, Jaaro-Peled H, Sawa A, Brandon NJ. How has DISC1 enabled drug discovery? Mol Cell Neurosci 2008;37:187–95.
[93] Blackwood DH, Muir WJ. Clinical phenotypes associated with DISC1, a candidate gene for schizophrenia. Neurotox Res 2004;6:35–41.
[94] Millar JK, Mackie S, Clapcote SJ, Murdoch H, Pickard BS, Christie S, et al. Disrupted in schizophrenia 1 and phosphodiesterase 4B: towards an understanding of psychiatric illness. J Physiol 2007;584:401–5.
[95] Kamiya A, Tomoda T, Chang J, Takaki M, Zhan C, Morita M, et al. DISC1–NDEL1/NUDEL protein interaction, an essential component for neurite outgrowth, is modulated by genetic variations of DISC1. Hum Mol Genet 2006;15:3313–23.
[96] Millar JK, Pickard BS, Mackie S, James R, Christie S, Buchanan SR, et al. DISC1 and PDE4B are interacting genetic factors in schizophrenia that regulate cAMP signaling. Science 2005;310:1187–91.
[97] Camargo LM, Collura V, Rain JC, Mizuguchi K, Hermjakob H, Kerrien S, et al. Disrupted in Schizophrenia 1 Interactome: evidence for the close connectivity of risk genes and a potential synaptic basis for schizophrenia. Mol Psychiatry 2007;12:74–86.
[98] Kellendonk C, Simpson EH, Kandel ER. Modeling cognitive endophenotypes of schizophrenia in mice. Trends Neurosci 2009;32:347–58.
[99] Ayhan Y, Abazyan B, Nomura J, Kim R, Ladenheim B, Krasnova IN, et al. Differential effects of prenatal and postnatal expressions of mutant human DISC1 on neurobehavioral phenotypes in transgenic mice: evidence for neurodevelopmental origin of major psychiatric disorders. Mol Psychiatry 2010; in press.
[100] Duan X, Chaung JH, Ge S, Faulkner RL, Kim JY, Kitabatake Y, et al. Disrupted-in-schizophrenia 1 regulates integration of newly generated neurons in the adult brain. Cell 2007;130:1146–58.
[101] Pletnikov MV, Ayhan Y, Xu Y, Nikolskaia O, Ovanesov M, Huang H, et al. Enlargement of the lateral ventricles in mutant DISC1 transgenic mice. Mol Psychiatry 2008;13:115.
[102] Clapcote SJ, Lipina TV, Millar JK, Mackie S, Christie S, Ogawa F, et al. Behavioral phenotypes of Disc1 missense mutations in mice. Neuron 2007;54: 387–402.
[103] Mouaffak F, Kebir O, Chayet M, Tordjman S, Vacheron MN, Millet B, et al. Association of Disrupted in Schizophrenia 1 (DISC1) missense variants with ultra-resistant schizophrenia. Pharmacogenomics J 2010; in press.
[104] Wanga Q, Jaaro-Peledb H, Sawab A, Brandon NJ. How has DISC1 enabled drug discovery? Mol Cell Neurosci 2008;37:187–95.
[105] Porteous D. Genetic causality in schizophrenia and bipolar disorder: out with the old and in with the new. Curr Opin Genet Dev 2008;18:229–34.
[106] Donohoe G, Morris DW, Corvin A. The psychosis susceptibility gene ZNF804A: associations, functions, and phenotypes. Schizophr Bull 2010;36:904–9.