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Neurobiology of Schizophrenia

Review

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With its hallucinations, delusions, thought disorder, and cognitive deficits, schizophrenia affects the most basic human processes of perception, emotion, and judgment. Evidence increasingly suggests that schizophrenia is a subtle disorder of brain development and plasticity. Genetic studies are beginning to identify proteins of candidate genetic risk factors for schizophrenia, including *dysbindin*, *neuregulin 1*, *DAOA*, *COMT*, and *DISC1*, and neurobiological studies of the normal and variant forms of these genes are now well justified. We suggest that *DISC1* may offer especially valuable insights. Mechanistic studies of the properties of these candidate genes and their protein products should clarify the molecular, cellular, and systems-level pathogenesis of schizophrenia. This can help redefine the schizophrenia phenotype and shed light on the relationship between schizophrenia and other major psychiatric disorders. Understanding these basic pathologic processes may yield novel targets for the development of more effective treatments.

Introduction

Schizophrenia, affecting about 0.5 to 1.0 percent of the population worldwide with devastating consequences for affected individuals and their families, is the seventh most costly medical illness to our society (Freedman, 2003). The available symptomatic treatment is only partially successful, and therefore the development of rational therapeutics, based on an understanding of the etiology and pathogenesis of schizophrenia, is imperative. However, until recently, progress in schizophrenia has been painfully slow and limited by a number of factors, including the heterogeneity of the schizophrenia phenotype and the lack of clear pathological lesions like those that have provided reference points in the study of Alzheimer's disease (AD), Parkinson's disease (PD), and other neurodegenerative disorders (Ross and Margolis, 2005). Investigation into the mechanism of action of the drugs used to treat schizophrenia has not provided clear understanding of the pathogenesis of the disease. While schizophrenia is highly heritable (it has a heritability score of approximately 0.8), the genetics are complex and the interpretation of genetic data has proven difficult. Now, however, advances in phenotypic analysis, neuroimaging, genetics, and molecular pathology provide the basis for optimism. Schizophrenia can be understood, at least in part, as a subtle disorder of brain development (Arnold et al., 2005; Harrison and Weinberger, 2005; Rapoport et al., 2005). Evidence now supports an etiologic role for mutations or polymorphisms in a number of genes (Chen et al., 2006; Craddock et al., 2006; Owen et al., 2005; Riley and Kendler, 2006), as well as obstetrical and premorbid abnormalities of development and cognition. We argue in this review that a definitive study of the neurobiology of schizophrenia is now possible.

Lessons from Neurodegenerative Diseases

The success in understanding etiology and pathogenesis of neurodegenerative disorders such as AD, PD, and Huntington's disease and related polyglutamine diseases suggests some potential lessons for schizophrenia. First, even for complex diseases, there can be tremendous benefit from understanding rare familial variants (Ross and Margolis, 2005). Schizophrenia is likely to be more complicated than the neurodegenerative disorders, since the search for Mendelian variants has been less rewarding. But possibly other chromosomal translocations (see below), as well as the identification of *DISC1*, suggests that this approach may yet be fruitful. Second, identification of more than one causative gene may help define a pathogenic pathway, and therapeutic targets, via the interaction of gene products. For instance, *presenilin 1* and *presenilin 2* mutations both cause familial AD through aberrant cleavage of the APP protein. Similarly, understanding the interactions of gene products mutated in genetic PD is beginning to elucidate the pathogenesis of familial, and potentially sporadic, PD (Smith et al., 2005). Third, with the identification of the genetic causes of neurodegenerative diseases, commonalities among the different disorders are now emerging, such as the presence of inclusion bodies and other deposits of aggregated protein (Ross and Poirier, 2005). Fourth, mutations that increase the risk of developing a disease but are not by themselves causative can also be illuminating. For instance, *ApoE* polymorphisms, which influence the risk for AD, appear to alter the metabolism of the A-Beta peptide, providing additional insight into AD pathogenesis. Finally, genetic changes need not be point mutations, frame shifts, or deletions. RNA as well as protein can be neurotoxic (Margolis et al., 2006). Diseases can also be caused by alterations in the dosage of genes, such as the duplications and triplications of α-synuclein that cause familial PD (Singleton et al., 2004). More subtle alterations in levels of expression may also increase susceptibility to PD (Singleton et al., 2004) and AD.

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Lessons from Developmental Diseases

Schizophrenia is increasingly viewed as a subtle disorder of neurodevelopment. A chromosome 22 microdeletion syndrome termed Velocardio Facial Syndrome (VCFS) is associated with schizophrenia. As described below, it may offer clues to schizophrenia's pathogenesis.

We suggest that the severe disorders of cortical development, grouped together as the lissencephalies, may also provide clues to the etiology and pathogenesis of schizophrenia. Lissencephaly involves severe abnormalities of the normal "inside out" development of the cerebral cortex. Neurons migrate from the ventricular zone toward the pial surface, guided by radial glia, directed in part by secretion of Reelin by Cajal-Retzius or subpial granular layer cells. Migration of the neuronal cell body is mediated via microtubule-based transport organized by the centrosome. First the centrosome moves up the microtubules, followed by the nucleus and the cell body (D'Arcangelo, 2006; Hatten, 2002; Kato and Dobyns, 2003; Olson and Walsh, 2002; Tsai and Gleeson, 2005).

Reelin is believed to have a key role in directing cortical neuronal migration. Mutations in *Reelin* are one cause of lissencephaly. Other major genes whose mutations can cause lissencephaly are *Lis1* and *doublecortin* (*DCX*), both of which are involved in regulation of microtubule-based transport. The potential roles of these molecules in the more subtle abnormalities of neuronal migration and positioning detected in schizophrenia and in models of *DISC1* mutation are described below. Furthermore, the example of lissencephaly is another example, like that of familial AD, of the utility of knowing several genes, which, when mutated, lead to similar phenotypes. Also, the N-methyl-D-aspartate (NMDA) receptor has been shown to stimulate neuronal migration, so that impaired function of this receptor could contribute to the developmental phenotype. With mutations in several genes leading to the same phenotype, it becomes possible to identify relationships among their protein products and ultimately piece together the framework of a pathogenic pathway.

Schizophrenia Clinical Features and Therapeutics

Schizophrenia is a heterogeneous syndrome without any single defining symptom or sign and is unidentifiable with any known diagnostic laboratory tests. The diagnosis is applied to individuals with psychotic phenomena (hallucinations, delusions, and thought disorder) after other causes of psychosis, such as affective disorder or delirium, have been excluded. Many individuals with schizophrenia exhibit negative symptoms, including diminished emotional expression and reaction, diminished participation in interpersonal relationships, diminished production of speech, and apathy, with loss of energy, drive, and interests. While less striking than positive symptoms, negative symptoms may be more impairing and less responsive to treatment. The symptom profiles of bipolar disorder (which involves dramatic alterations of mood, with psychotic phenomena as a frequent accompaniment) and schizophrenia frequently overlap.

The success of genetic and neurobiological investigations of schizophrenia is likely to be dependent on understanding the heterogeneity of schizophrenia. One approach has been to divide patients into subtypes based on their predominant clinical manifestations. For instance, the 25%–30% of individuals with chronic schizophrenia who have predominantly negative symptoms (Kirkpatrick et al., 2001) have been defined as having "deficit" schizophrenia. However, other attempts to subtype schizophrenia in the past have not been very fruitful, so caution should be exercised. The use of dimensionally distinctive features, such as negative symptoms or cognitive abnormalities, as quantitative traits may be more productive.

The onset of schizophrenia most commonly occurs in the second or third decade of life, though onset age may vary from childhood to old age. Subtle abnormalities of cognition, social interaction, motor function, and physical morphology are frequently observed in individuals who later develop schizophrenia (Niemi et al., 2003), which is suggestive of a developmental vulnerability.

Clinical Features: Endophenotypes

An alternative approach to classification of heterogeneous disorders is to define endophenotypes (or intermediate phenotypes) (Cannon, 2005; Gottesman and Gould, 2003). These are heritable, and often quantitative, traits that may not be readily apparent in routine clinical examinations of affected individuals, yet may reflect neurobiological features underlying the disease and may be useful in genetic linkage studies. Ideally, endophenotypes in schizophrenia will reflect abnormalities of specific neural systems under relatively simple genetic control. Valid endophenotypes will associate with schizophrenia in population studies, will be present (though less prominent) in the first degree family members of probands with schizophrenia, and will be found at similar levels in both members of twins discordant for schizophrenia.

A variety of potential endophenotypes have been associated with schizophrenia, though none has yet been confirmed in large, unselected samples of at-risk individuals. For instance, disordered eye movements, which can be measured using quantitative methods, include antisaccade performance (associated with frontal-striatal function) (Ettinger et al., 2006) and abnormal smooth pursuit eye movements, especially the predictive pursuit component of this function (Hong et al., 2006). Attenuated inhibition of the P50 auditory event-related potential, a sensory motor gating task, may reflect deficits in attention and vigilance (Erwin et al., 1998). The P300 event-related potential, a measurement of cortical activity taken during stimuli discrimination tasks that also reflects attention and working memory, is attenuated both in individuals with schizophrenia and, to an intermediate extent, in their relatives (Bramon et al., 2006). Structural and functional neuroanatomic deficits, as revealed by imaging studies, have also been proposed as endophenotypes.

Clinical Features: Neuropsychology

While the psychotic phenomena of schizophrenia are striking, more subtle cognitive problems are increasingly recognized as central to the disease. Impairments in cognition include attention, working memory, learning, verbal fluency, motor speed, and executive functions. While positive and negative symptoms of schizophrenia can fluctuate, cognitive deficits remain relatively

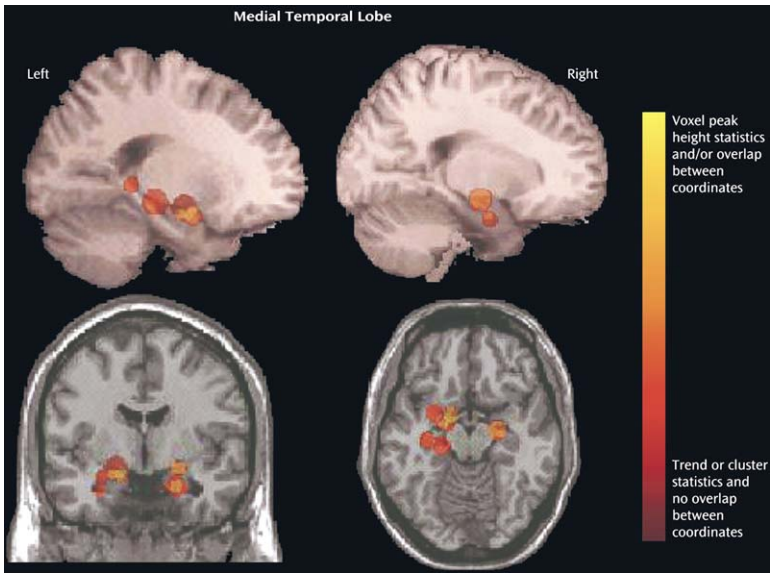

Figure 1. Structural Abnormalities Identified by MRI Scan in Schizophrenia

Location of voxel-based morphometry findings of significant volume deficits in the medial temporal lobe (including the amygdala and hippocampus) in patients with schizophrenia. The top images are left and right 3D images, respectively; the bottom left image is a coronal view, and the bottom right image is an axial view. The color scale depicts the stringency of the statistics used in the studies. From Honea et al. (2005), with permission of the publisher.

stable, and are already apparent in first-episode patients who have never received antipsychotic medicines (Harvey et al., 2003). Cognitive deficits are found in the biological relatives of subjects with schizophrenia (Snitz et al., 2006), suggesting that aspects of cognition impaired in schizophrenia may be under specific genetic control, and therefore, serve as informative endophenotypes in the genetic analysis of schizophrenia. Cognitive dysfunction has been recognized as a core feature of schizophrenia (Antonova et al., 2004; Gold, 2004), leading to impairment of skills and diminished functional capacity (Bowie and Harvey, 2005).

The National Institute of Mental Health (NIMH)-sponsored Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative (Nuechterlein et al., 2004) is developing a consensus around a cognitive battery for use in clinical trials in schizophrenia. It incorporates seven cognitive domains, including Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning and Memory, Visual Learning and Memory, Reasoning and Problem Solving, and Social Cognition.

Working memory dysfunction in schizophrenia has been linked to dysfunction of the dorsolateral prefrontal cortex (DLPFC) (Goldman-Rakic, 1999). Even schizophrenia patients with good performance on working memory tasks are inefficient in their use of prefrontal networks. Behavioral strategies for cognitive improvement can be effective in improving neurocognitive deficits.

Clinical Features: Neuroimaging

Recent advances in imaging technology (such as fMRI and diffusion tensor imaging, or DTI) have enabled investigators to move beyond measures of isolated regional abnormalities and instead begin the exploration of the function and structure of the interconnected neural networks that are implicated in schizophrenia.

The most consistent structural abnormalities found in schizophrenia include lateral and third ventricular enlargement; medial temporal lobe (hippocampal formation, subiculum, parahippocampal gyrus) volume reductions; and superior temporal gyrus (STG) volume reductions, particularly on the left (Figure 1). There is also moderate evidence for frontal lobe volume reduction, particularly of prefrontal and orbitofrontal regions, and parietal lobe abnormalities. Enlarged cavum septi pellucidi, basal ganglia abnormalities, corpus callosum abnormalities, thalamus abnormalities, and cerebellar abnormalities are also evident (Antonova et al., 2004; Honea et al., 2005; Niznikiewicz et al., 2003). Some, but not all, studies have suggested that structural changes may be progressive (Rapoport et al., 2005).

Structural neuroimaging suggests that abnormal processes in schizophrenia occur at different stages of neurodevelopment. There is evidence for an early neurodevelopmental lesion (pre- or perinatal) that may render the brain vulnerable to anomalous late neurodevelopmental processes (particularly postpubertal); these anomalous late neurodevelopmental processes may interact with other environmental factors associated with the onset of psychosis (e.g., stress, substance use), which together have neuroprogressive sequelae that may be neurodegenerative (Pantelis et al., 2005; Rapoport et al., 2005). Abnormal brain structure may be detectible via MRI prior to the onset of psychotic symptoms (Lymer et al., 2006).

Studies of executive function and memory using fMRI have reported abnormalities of the DLPFC, medial temporal lobe, hippocampus, parahippocampal gyrus, anterior cingulate, medial frontal and posterior parietal cortex, striatum, thalamus, and cerebellum (Niznikiewicz et al., 2003). Recent fMRI studies have focused on the integration of genetic and neuroimaging data (for review see Turner et al., 2006). The fMRI studies suggest that for any given task that is performed poorly by individuals with schizophrenia, there is a network of affected brain regions related to the abnormal function, rather than a single abnormal brain region, raising the issue of the state of the interconnections between regions.

DTI, a technique based on the direction of water diffusion, can probe white matter abnormalities in the brain.

Early studies with the technique, which is still under development, have raised the possibility of white matter disorganization in brain regions such as prefrontal and temporal white matter, corpus callosum, and uncinate fasciculus (Kanaan et al., 2005; Kubicki et al., 2005). More systematic and detailed confirmatory studies are now necessary. A potentially powerful approach may be to combine fMRI and DTI to probe potential brain circuit abnormalities in schizophrenia.

Neuropathology

Neuropathological investigations of schizophrenia (Arnold et al., 1998) have not found any evidence of the usual features of neurodegenerative diseases, such as inclusion bodies, dystrophic neuritis, or reactive gliosis. There is intriguing, though not always consistent, evidence of subtle cytoarchitectural anomalies in entorhinal gray matter (Arnold et al., 1997) and in other corticolimbic regions, and an abnormally high frequency of aberrant neurons in the white matter underlying prefrontal cortex (e.g, Akbarian et al., 1996), temporal, and parahippocampal regions (Arnold et al., 2005). While these findings remain open to various interpretations (Arnold et al., 2005), together they provide suggestive evidence for subtle abnormalities in neurodevelopment in schizophrenia, such as disordered cortical neuronal migration, consistent with the observation of subtle behavioral, neurological, and morphologic abnormalities.

Another line of evidence suggestive of neurodevelopment abnormality derives from findings of a reduction in the volume of cortical neuropil without comparable neuronal loss (Selemon et al., 1995; Selemon and Goldman-Rakic, 1999). Many (though not all) ultrastructural, immunohistochemical, and other quantitative neuropathological studies suggest quantitative and qualitative deficits in neuronal processes and synaptic connectivity in schizophrenia (Honer et al., 2000). A summary of neuronal connections implicated in the pathology of the neuropil in schizophrenia is shown in Figure 2.

Gene expression array studies have compared the expression profiles, in a number of different brain regions, of schizophrenias and controls (Katsel et al., 2005). These studies have yielded inconsistent results and still need to overcome the difficulties inherent in the usage of postmortem brain tissue. Genes related to GABA neurotransmission, synaptic transmission, and metabolism have been implicated, though the significance remains uncertain. Several studies have identified abnormal expression of genes related to myelination, suggesting the possibility of glial and white matter abnormalities, which could be fundamental to the disease, given the imaging indications of white matter abnormalities noted above.

Pharmacology

Treatment for schizophrenia remains far from optimal. While psychosocial programs and various forms of reality-based therapy are helpful, the mainstays of treatment are medications tautologically termed "antipsychotics." The antipsychotics, first introduced over 50 years ago with the serendipitous discovery that chloropromazine was effective in reducing the "positive" symptoms of schizophrenia, all have as their primary mechanism of action blockade of dopamine D2 receptors (Snyder, 2006). This "first" generation of antipsychotics included chlorpromazine, haloperidol, and perphenazine, and, while clearly more effective than placebo, they had a propensity to cause acute and chronic neurologic symptoms, including tremor, rigidity, dystonia, and dyskinesia.

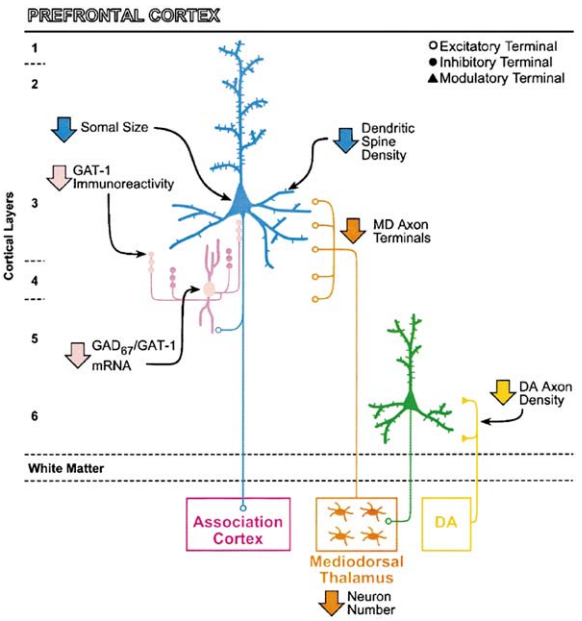

Figure 2. Cortical Circuitry in Schizophrenia

Schematic diagram summarizing disturbances in the connectivity between the mediodorsal (MD) thalamic nucleus and the dorsal prefrontal cortex (PFC) in schizophrenia. From Lewis and Lieberman (2000).

More recently, a "second" generation of antipsychotics, such as clozapine and olanzapine, have been developed that have reduced risk for these acute and chronic neurologic side effects, possibly because of their additional blockade of serotonin 5HT2A receptors. However, it is now apparent that these newer antipsychotics confer a much greater risk for obesity, hyperlipidemia, and type II diabetes. Furthermore, recent head-to-head comparisons between the older, off-patent perphenazine and the newer atypical antipsychotics did not disclose major differences in efficacy or tolerability by patients with schizophrenia (CATIE, 2005).

While the antipsycotics generally reduce positive symptoms, poor compliance and the lack of impact on negative and cognitive symptoms mean that most individuals with schizophrenia remain substantially disabled and unemployed, and require supervised housing arrangements for the rest of their lives. The one exception appears to be clozapine, which is significantly more effective, causes improvement in a subgroup of patients unresponsive to other antipsychotics, and can reduce negative symptoms (McEvoy et al., 2006).

Clinical trials (Coyle, 2006; Heresco-Levy et al., 2002; Lane et al., 2005; Tsai and Gleeson, 2005) with agents which modulate NMDA receptors, including glycine, D-Serine, D-cyclosperine, sarcosine, or D-alanine, have suggested improvement in negative and cognitive symptoms when these agents are added to either typical or atypical antipsychotics. However, the doses and

agents have not been consistent among the different trials, and larger, more definitive trials may be indicated. Other agents under investigation to enhance NMDA receptor function indirectly, thereby treating the negative and cognitive symptoms unresponsive to antipsychotics, include AMPAkines, which prolong AMPA receptor open time, positive modulators of the metabotropic mGluR5 receptors, and mGlu2/3 receptor agonists (Moghaddam, 2003).

Pathophysiology

Hypotheses regarding pathophysiology of schizophrenia originated from pharmacology (Snyder, 2006). The "dopamine hypothesis" derived, in part, from the identification of D2 receptor blockade as the mechanism for the action of antipsychotics, and was supported by the observation that stimulants acting via dopamine, such as amphetamines, can cause psychosis in normal individuals and can exacerbate psychosis in individuals with schizophrenia. Pharmacological and physiological studies indicate that dopamine modulates cognitive function in the prefrontal cortex, a finding of potential relevance to schizophrenia.

Evidence for a role of glutamate in schizophrenia also originated from pharmacology (Coyle, 2006). NMDA receptor antagonists, such as ketamine and phencyclidine (PCP), can cause psychotic and cognitive abnormalities reminiscent of schizophrenia. In addition, subjects with schizophrenia appear to be especially sensitive to the psychotomimetic effects of these drugs. The extent to which these effects recapitulate schizophrenic pathophysiology remains uncertain. As noted above, treatment of schizophrenia with D-Serine, glycine, and sarcosine, which modulate NMDA receptors, has therapeutic benefit, particularly with regard to negative symptoms. Thus, hypofunction of the NMDA receptor, possibly on critical GABA interneurons, may contribute to the pathophysiology of schizophrenia (Coyle, 2006).

The potential role for GABA in the pathogenesis of schizophrenia derives mostly from neuropathologic studies (Lewis et al., 2005). A particular subtype of GABA interneurons, chandelier neurons, have decreased immunostaining for the GABA transporter (GAT), possibly related to reduced BDNF signaling or NMDA receptor hypofunction. Consistent with the inferred reduced GABAergic neurotransmission, ligand binding and immunocytochemical studies have revealed upregulation of the postsynaptic GABA-A receptors in these sectors. The extent to which these changes represent primary pathogenesis has yet to be determined.

Mouse Models of Pathogenesis

Functional hypotheses of schizophrenia can now be addressed using mouse models, aided by the recognition that observation of some aspects of the schizophrenia phenotype and endophenotype do not require the self-reports of affected individuals (Chen et al., 2006). Behaviors that have been used as outcome measures in mice, with varying resemblance to the clinical features of schizophrenia, include social interaction, prepulse inhibition, aggression, and locomotor activity. Mouse models associated with selected candidate genes are discussed below.

For instance, knock out of the dopamine transporter or overexpression of D2 dopamine receptors causes behavioral abnormalities, and overexpression of the D2 receptor in the forebrain causes cognitive changes reminiscent of those observed in schizophrenia (Kellendonk et al., 2006). Similarly, mice with alterations in molecules downstream of dopamine signaling such as DARPP-32 (dopamine and cyclic adenosine monophosphate-regulated phosphoproteins of 32 kDa) have behavioral phenotypes that may be relevant to schizophrenia. Targeted deletion of the *calcineurin* gene yields abnormal locomotion, decreased social interactions, and altered cognition, consistent with evidence of decreased cortical calcineurin. Caron's group developed a mutant mouse line that expressed only 5% of normal levels of the NMDA receptor subunit NR1 (Mohn et al., 1999). These mice exhibited hyperactivity that responded to the typical antipsychotic haloperidol, but they also exhibited impaired social behaviors and mating that were partially reversed by the atypical antipsychotic clozapine.

These studies of candidate genes, based on functional hypotheses, provide interesting behavioral and pathophysiologic information, which is in many cases relevant to understanding the pharmacology of schizophrenia treatment, and in some cases of potential relevance to disease pathogenesis. However, we believe that the development of mouse models based on etiologic risk factors, such as the genes discussed below, will ultimately provide the most powerful tools for understanding the neurobiology of schizophrenia.

Genetic Etiologies: Genes Identified in Linkage or Association Studies

Linkage and association studies have now implicated several loci in the genome that appear likely to harbor genes conferring risk for schizophrenia (Figure 3, Table 1). Candidate genes identified by a genetic approach have the advantage over candidate genes chosen based on pharmacotherapies or pathological studies in that they are of necessity involved in the disease process, at least for the populations in which the genetic results were obtained. It should be kept in mind that schizophrenia genetics are complex, with multiple genes of modest effect interacting to produce the phenotype. Relative risk at the loci identified so far range between 1.5 to 2.0, indicating modest effect sizes. Simple mutations with Mendelian inheritance and complete penetrance have not yet been found using standard linkage and association methods, though study of chromosomal translocations provides a useful alternative.

Neuregulin 1

Neuregulin 1 was identified as a candidate gene via fine-mapping of a locus on chromosome 8p linked to schizophrenia (Harrison and Law, 2006; Stefansson et al., 2002). A number of studies have found association with schizophrenia within the *neuregulin 1* region. The *neuregulin 1* gene is very complex, with at least 25 exons spread over almost a megabase, with extensive alternative promoter usage and alternative splicing, resulting in multiple possible protein products. A region in the 5′ end of the gene appears to most consistently associate with disease. Unfortunately, no functional polymorphisms have been identified. Most *neuregulin 1* isoforms

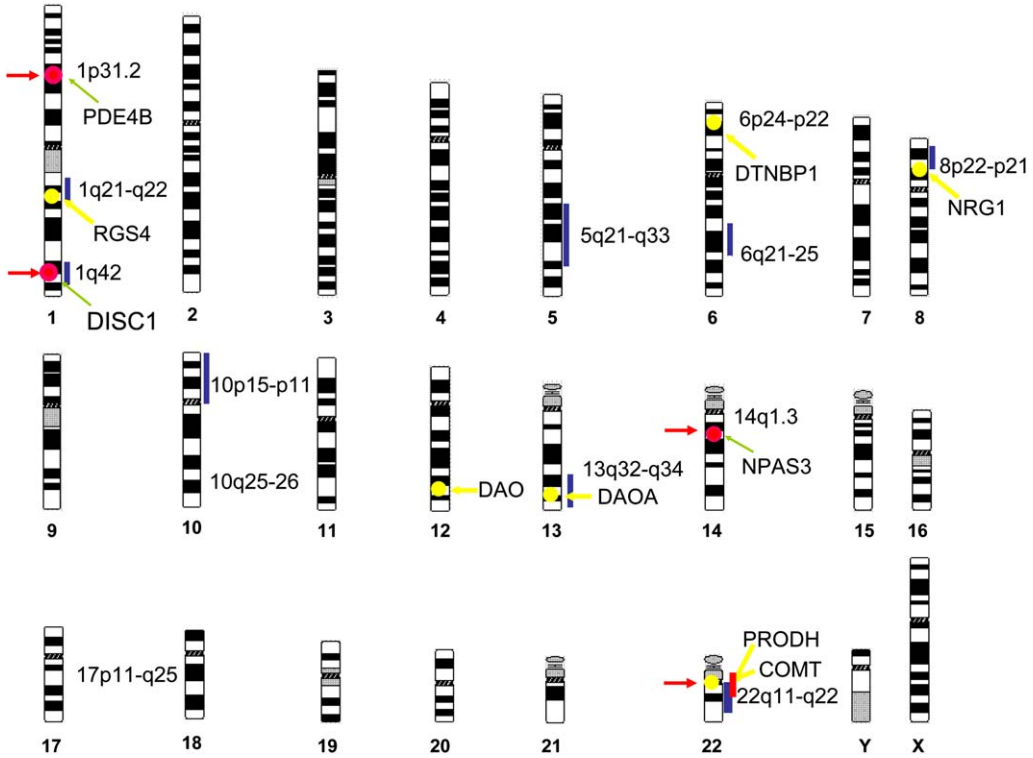

Figure 3. Locations of Linkage Findings and Genes

Chromosomal regions with significant linkage to schizophrenia are indicated by vertical blue lines. Chromosomal deletions are shown with vertical red lines. The red arrows refer to the location of chromosomal abnormalities associated with schizophrenia. The yellow arrows and circles show the locations of the genes identified by linkage and association. The red arrows circles indicate genes identified via translocations. Adapted from Owen et al. (2005).

are transmembrane proteins, which can undergo proteolytic cleavage to release extracellular fragments, intracellular fragments, transmembrane receptors, or membrane-bound signaling proteins.

Neuregulin 1 signaling, via ErbB receptors and regulation of both NMDA receptors and postsynaptic density 95 (PSD-95), has been implicated in neuronal differentiation and migration. In addition, a C-terminal fragment

Table 1. Candidate Schizophrenia Susceptibility Genes and the Strength of Evidence in Four Domains

		Strength of evidence (0 to 5+)			
		Association with schizophrenia	Linkage to gene locus	Biological plausibility	Altered expression in schizophrenia
COMT	22q11	++	++++	+++	yes, +
DTNBP1	6p22	+++++	++++	++	yes, ++
NRG1	8p12-21	+++++	++++	+++	yes, +
RGS4	1q21-22	+++	+++	++	yes, ++
GRM3	7q21-22	+++	+	++	no, ++
DISC1	1q42	++++	++	++++	not known
DAOA (G72/G30)	13q32-34	+++	++	++	not known
DAAO	12q24	++	+	++++	not known
PPP3CC	8p21	+	++++	++++	yes, +
CHRNA7	15q13-14	+	++	+++	yes, +++
PRODH2	22q11	+	++++	++	no, +
AKT1	14q22-32	+	+	++	yes, ++
GAD1	2q31.1	++		++	yes, +++
ERBB4	2q34	++			yes, ++
FEZ1	11q24.2	++		+++	yes, ++
MUTED	6p24.3	++++	++++	+++	yes
MRDS1 (OFCC1)	6p24.3	++	++++	+	not known
NPAS3	9q34	++		++	not known
GRIK4	11q23	++	+	++	not known

Adapted from Straub and Weinberger (2006).

of Neuregulin 1 can translocate to the nucleus and interact with transcription factors to enhance expression of genes, including *PSD-95*. The functional role of *neuregulin 1* in schizophrenia is still uncertain, particularly since many different alleles and haplotypes have been implicated. However, recent biochemical experiments in human postmortem tissue suggest that *neuregulin 1* signaling may be enhanced in schizophrenia, leading to suppression of NMDA receptor function (Hahn et al., 2006). This would be consistent with the glutamate hypofunction hypothesis of schizophrenia (see above). No consistent changes in the expression level of Neuregulin 1 itself have been detected in schizophrenia, and, in the absence of mutations changing protein sequence, it is unclear how this increased activation would come about. One possibility is the existence of polymorphisms that lead to alternative splice variants that encode protein products with enhanced function.

Mouse models with heterozygous deletions of the transmembrane domain of neuregulin 1 have altered activity and prepulse inhibition (Chen et al., 2006). However, the relation of the deletion in this model to changes in human schizophrenia is unclear. No coding mutations have been detected in schizophrenia. The region implicated in schizophrenia by haplotype analysis is upstream from the transmembrane domain, and includes the initial exon of the type II isoform (Falls, 2003), and mouse models with alterations in this region have not yet been described.

Dysbindin

Dysbindin (dystrobrevin binding protein I) was identified as a gene associated with schizophrenia through linkage to chromosome 6p (Straub et al., 2002). The association between this locus and schizophrenia has been replicated in several subsequent studies. Dysbindin colocalizes with dystrobrevin in both muscle and brain. It is widely distributed in brain, and has been detected both pre- and postsynaptically, including in synaptic terminals in the hippocampus (Benson et al., 2001). The function of dysbindin in brain is not well understood. It has been reported to influence glutamate neurotransmission (Numakawa et al., 2004). Mutations in *dysbindin* also cause Hermansky-Pudlak syndrome type 7 (Li et al., 2003), a complex genetic disorder related to lysosome biogenesis, which is not known to have a psychiatric phenotype. A deletion within the homologous gene in mice accounts for the phenotype known as "Sandy," with albinism and bleeding disorders.

While the association of *dysbindin* with schizophrenia has been fairly well replicated, no protein coding mutations contributing to the risk for schizophrenia have been identified. Furthermore, many different alleles and haplotypes have been implicated in different studies (e.g., Burdick et al., 2006; Gornick et al., 2005). Reduced levels of expression of *dysbindin* message or protein have been found in schizophrenic brains (Bray et al., 2005), raising the possibility that polymorphisms in *dysbindin* associated with schizophrenia may modulate dysbindin expression level. In addition, knockdown of endogenous dysbindin with siRNA resulted in reduction of glutamate levels in neurons in culture, suggesting a possible synaptic consequence for reductions in dysbindin levels (Numakawa et al., 2004; Talbot et al., 2004) and connecting dysbindin with the glutamate hypofunction hypothesis of schizophrenia.

Two studies have independently described an association between *dysbindin* risk haplotypes and high levels of negative symptoms in schizophrenia (Fanous et al., 2005; DeRosse et al., 2006), supporting the importance of careful delineation of different domains of schizophrenia symptoms. This finding is consistent with other evidence that *dysbindin* haplotypes may influence prefrontal brain function (Fallgatter et al., 2006). Thus, further study of *dysbindin* genotypes in relationship to specific subtypes of schizophrenia and to cognitive endophenotypes appears warranted, as does detailed investigation of the role of dysbindin in glutamate neurotransmission and other neuronal functions. Further mouse models of *dysbindin* alterations would be very valuable.

D Amino Acid Oxidase Activator

The chromosome 13 locus has strong linkage regions to schizophrenia. Among other genes, this locus contains *G72*, now called *D amino acid oxidase activator* (*DAOA*). Several individual replication studies and a meta-analysis have supported the association of *DAOA* with schizophrenia, though as with other loci, the associated alleles and haplotypes are not identical across studies, and some variants are located outside of the gene (Detera-Wadleigh and McMahon, 2006). Functionally, DAOA activates D amino acid oxidase (DAO). DAO oxidizes D-Serine, which is a coagonist at NMDA glutamate receptors. Thus, there is some biologic plausibility for *DAOA* as a candidate gene, based on the glutamate hypothesis. *DAOA* does not have a homolog in mice, so no knockout model has been made. Further explorations of this system may be of considerable interest, especially given the potential efficacy of D-Serine in therapeutic trials and reports of reduced D-Serine in blood and CSF in individuals with schizophrenia.

COMT and Chromosome 22 Region

Another linkage region is on chromosome 22 (Harrison and Weinberger, 2005; Owen et al., 2005). It has been supported in many, though not all, linkage and association studies. In addition, strong genetic association between schizophrenia and the chromosomal microdeletion syndrome VCFS (Mendelian Inheritance in Man, MIM 192430), which is caused by deletion of approximately 1.5 to 3 Mb in chromosome 22q11, supplies strong evidence for a genetic contribution to schizophrenia from this region. Approximately 20% to 30% of patients with VCFS have schizophrenia or other major psychiatric disorders with psychosis (Murphy et al., 1999). Furthermore, patients with schizophrenia have increased frequency of the microdeletion compared with the general population (Karayiorgou et al., 1995). VCFS includes facial dysmorphism and other features, and presumably is caused by loss of one copy of several or many genes in this region. The VCSF region includes at least 27 genes. The *Tbx1* gene may account for many of the physical features of VCSF (Li et al., 2003; Long et al., 2006). It is expressed in microvasculature in brain. Inactivating mutations in *Tbx1* have been found in one small family with VCSF or Asberger's syndrome (Li et al., 2003), but the relation of this gene to schizophrenia is still incompletely explored.

The gene on chromosome 22q11 that has received the most attention is *catechol-O-methyltransferase* (*COMT*). The protein product is an enzyme that participates in the clearance of dopamine from synapses, and thus could be involved in regulation of neurotransmission related to schizophrenia (Craddock et al., 2006; Tunbridge et al., 2006). A functional polymorphism, involving the presence of either valine or methione at codon 108 (in the soluble isoform of COMT, equivalent to codon 158 in the membrane-bound isoform of COMT) alters enzyme activity. The methione allele is less stable and thus has lower activity, suggesting the hypothesis that individuals with two copies of the methione allele, or with a deletion of one copy of COMT, would be expected to have higher dopamine levels in critical central synapses, perhaps especially in the prefrontal cortex.

In a seminal study combining genetics of the COMT valine/methione polymorphism with imaging methods, the valine allele, which would have lower synaptic dopamine, was reported to confer risk for schizophrenia via variation in cognitive function in contradiction to the dopamine hypothesis, which proposes increased synaptic dopamine as the risk mechanism (Egan et al., 2001). The relationship appears to be complicated (Craddock et al., 2006; Tunbridge et al., 2006), and the association between *COMT* alleles and schizophrenia appears to be less striking than the association between *COMT* and cognitive function. For instance, a relationship between the valine/methione polymorphism and longitudinal cognitive decline in patients with the 22q11.2 deletion syndrome has recently been reported, though not yet replicated (Gothelf et al., 2005). Variation at the *COMT* locus may provide the best studied example of the relationship between variation at a genetic locus and an endophenotype closely related to schizophrenia.

Other genes in the deletion syndrome region may also contribute to the risk for schizophrenia. For instance, genetic variation of the *proline dehydrogenase* (*PRODH*) influences the availability of glutamate, and mutant mice with a PRODH loss-of-function exhibit some behavioral abnormalities. A recent report has postulated an interaction between COMT and PRODH (Paterlini et al., 2005). However, association and follow-up linkage studies have not been strongly positive. *ZDHHC8*, also in the 22q deletion region, encodes a zinc finger domain protein. However, strong evidence in favor of this gene has not yet emerged (Harrison and Weinberger, 2005; Owen et al., 2005).

Other Candidate Genes Based on Linkage Studies

Other candidate genes are listed in Table 1 and described in recent reviews (e.g. Harrison and Weinberger, 2005; Owen et al., 2005; Straub and Weinberger, 2006).

Genes Disrupted by Chromosomal Translocations

Genes interrupted by chromosomal translocations so far appear to be very rare causes of schizophrenia. However, the advantage is that since translocations produce a definable genetic lesion, it may be possible to determine the effects of the mutation on the function of the gene product.

The *Neuronal PAS Domain Protein 3* (*NPAS3*) gene codes for a transcription factor containing a basic helix-loop-helix (HLH) PAS domain involved in transcriptional regulation. *NPAS3* was found to be disrupted by chromosomal translocation in two related individuals with schizophrenia (Pickard et al., 2005). Since HLH domain-containing proteins function as dimers, and because the translocation could produce a truncated protein without the transcriptional activation domains, the truncation might act via a dominant-negative mechanism. Since the family is so small, it is premature to conclude that there is a relationship between this gene and schizophrenia. However, deletions of *NPAS* transcription factors in mice cause behavioral phenotypes and altered hippocampal neurogenesis (Pieper et al., 2005), providing additional support for a role of NPAS in schizophrenia.

A translocation through *GRIK4*, which codes for one of the glutamate kainaite receptors, has also been detected in an individual with schizophrenia (Pickard et al., 2006). Subsequent case control studies suggested an association of a haplotype within this gene to schizophrenia. A translocation through *PDE4B*, as discussed below, has also been detected in a small family with schizophrenia.

DISC1: Interrupted by a Chromosome 1,11 Translocation

DISC1, in our view, is emerging as the best supported candidate gene for schizophrenia (Hennah et al., 2006; Ishizuka et al., 2006; Porteous and Millar, 2006), with a great potential for future research. *DISC1* was identified via a balanced (1:11) chromosomal translocation, segregating with schizophrenia, bipolar disorder, and other major mental illness in a large pedigree in Scotland, with LOD scores of 7 using a broad phenotype. The translocation is between exons 8 and 9 of the *DISC1* gene on chromosome 1. No genes have been found at the chromosome 11 site.

The translocation has not been found in any other families. Another small family (Sachs et al., 2005), identified via a proband with schizophrenia, has a four-base deletion resulting in a frame shift and predicted C-terminal truncation of the DISC1 protein. However, the family is too small to clearly demonstrate segregation with disease, and the deletion has also been found in two presumably unaffected blood donors (Green et al., 2006).

A locus on chromosome 1 within the *DISC1* gene was linked to schizophrenia in a Finnish population (Ekelund et al., 2001), and the *DISC1* locus has emerged as a potential risk factor for both schizophrenia and affective disorder in different populations (Craddock et al., 2005; Hennah et al., 2006; Millar et al., 2003; Thomson et al., 2005; Porteous and Millar, 2006).

Study of the original Scottish phenotype suggested two distinctive features of the clinical phenotype. First, affected individuals have either schizophrenia or affective disorder. Consistent with this, recent linkage studies have implicated the *DISC1* locus, especially for schizoaffective disorder (Hamshere et al., 2005). Second, reduced P300 amplitude and latency, an endophenotype, was associated with the translocation in both affected and unaffected translocation carriers (Blackwood et al., 2001). More recent imaging and neuropsychological studies have suggested that *DISC1* haplotypes, including a putative functional polymorphism (S704C), are associated with altered hippocampal function, altered

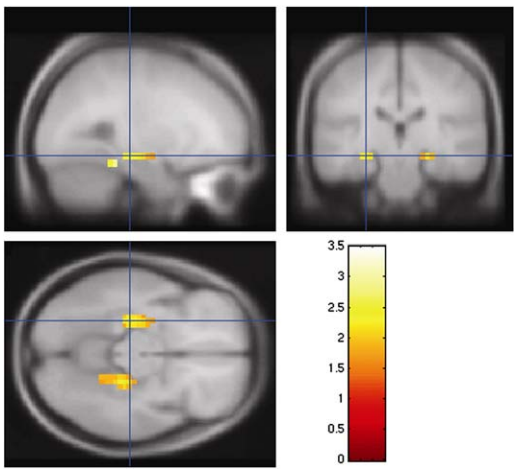

Figure 4. Influence of *DISC1* Polymorphisms on Functional Brain Activation

BOLD fMRI and SNP10 (Ser704Cys). DISC1 SNP10 affects hippocampal formation activation during working memory tasks in healthy subjects. For the N-back task, Healthy Ser homozygotes (n = 18) showed an apparent atypical increase in HF activation, indicated as yellow-red signal, during the N-back working memory task relative to Cys carriers (n = 24). From Calicott et al. (2005), with permission of the publisher.

fMRI signals, and altered working memory and cognition in individuals with and without schizophrenia or affective disorder (Figure 4), consistent with an influence of *DISC1* on cognitive endophenotypes (Callicott et al., 2005; Cannon et al., 2005; Porteous et al., 2006).

Variation at the *DISC1* locus, via a deletion in exon 6, may also contribute to phenotypes in mouse substrain 129. The effects of this have not been conclusively demonstrated, but it appears to abrogate expression. On transfer of the *DISC1* deletion allele to the BL/6 background, the deletion mice, but not littermate controls, have selective impairment in working memory (Koike et al., 2006).

The molecular mechanism of the *DISC1* translocation mutation is uncertain. Most of the evidence points to loss-of-function effects, but the exact mechanism is controversial. Loss of function could result from loss of expression, and thus haploinsufficiency. Alternatively, it is conceivable that a truncated mutant protein is produced. No mutant protein expression was detected in lymphoblasts from the patients with the Scottish translocation (Millar et al., 2005), though techniques might not have been sensitive enough to identify low levels of expression, and expression of transcripts from the mutant allele could be detected. Biochemical studies have indicated that DISC1 protein has a self interaction domain and likely functions as a dimer. DISC1 protein with a C-terminal truncation, corresponding to the protein that would be produced from the translocation allele, disrupts the normal function and cellular localization of the full-length protein (Kamiya et al., 2005), suggesting the possibility of a dominant-negative mechanism. Future mouse model studies may resolve some of these issues in vivo. Whether via haploinsufficiency or dominant-negative interactions, loss-of-function mechanisms imply that understanding the normal function of DISC1 will be critical for understanding DISC1-related disease.

DISC1 appears to have roles in both brain development and adult neuronal functioning. Developmental roles include regulation of neuronal migration, neurite outgrowth, and neuronal maturation. Roles in the adult appear to include modulation of cytoskeletal function, synaptic transmission, and plasticity. The expression of DISC1 is increased during neuronal development, with peaks at E13.5 during late fetal development and at P35 in early postnatal periods (Schurov et al., 2004). Expression continues into adulthood, with the highest expression in hippocampus, olfactory bulb, lateral septum, cerebral cortex, and hypothalamus and other brainstem regions (Austin et al., 2003). DISC1 protein can be detected in many regions within cortical neurons, including presynaptic and postsynaptic locations (Kirkpatrick et al., 2001).

Studies of the protein interaction partners of DISC1, and the cell biology of these interactions, have greatly illuminated DISC1 functions and provided strong support for roles of DISC1 in brain development and adult neuronal function. Table 2 shows some of the protein interaction partners of DISC1 and their potential cellular roles. As indicated in Figure 5, the molecular and cellular interactions of DISC1 are critical for normal neuronal development and in the adult are implicated in normal neuronal signal transduction and plasticity.

DISC1 interacts with several proteins which themselves are implicated in neuropsychiatric diseases. For

Table 2. DISC1 Interactors

DISC1 interactor	Interactor function	DISC1 binding site	Reference
NudEL	neuronal migration	727–854	Brandon et al., 2004; Morris et al., 2003; Ozeki et al., 2003
Lis1	neuronal migration	727–854	Brandon et al., 2004
PDE4B	cAMP hydrolysis	219-283	Millar et al., 2005
Citron	synaptic function	347–600	Ozeki et al., 2003
α-tubulin	cytoskeleton	181–157	Brandon et al., 2004
ATF4/5	transcription factors	598–854	Morris et al., 2003
DISC1		403–504	Kamiya et al., 2005
FEZ1	neurite extension	446–633	Miyoshi et al., 2004
Kendrin	centrosome, microtubule	446–633	Miyoshi et al., 2004
eIF3	translation initiation factor	2–231	Ogawa et al., 2005
MAP1A	microtubule associated	1–292	Morris et al., 2003
MIPT3	microtubule associated	293–696	Morris et al., 2003

Adapted from Porteous et al. (2006).

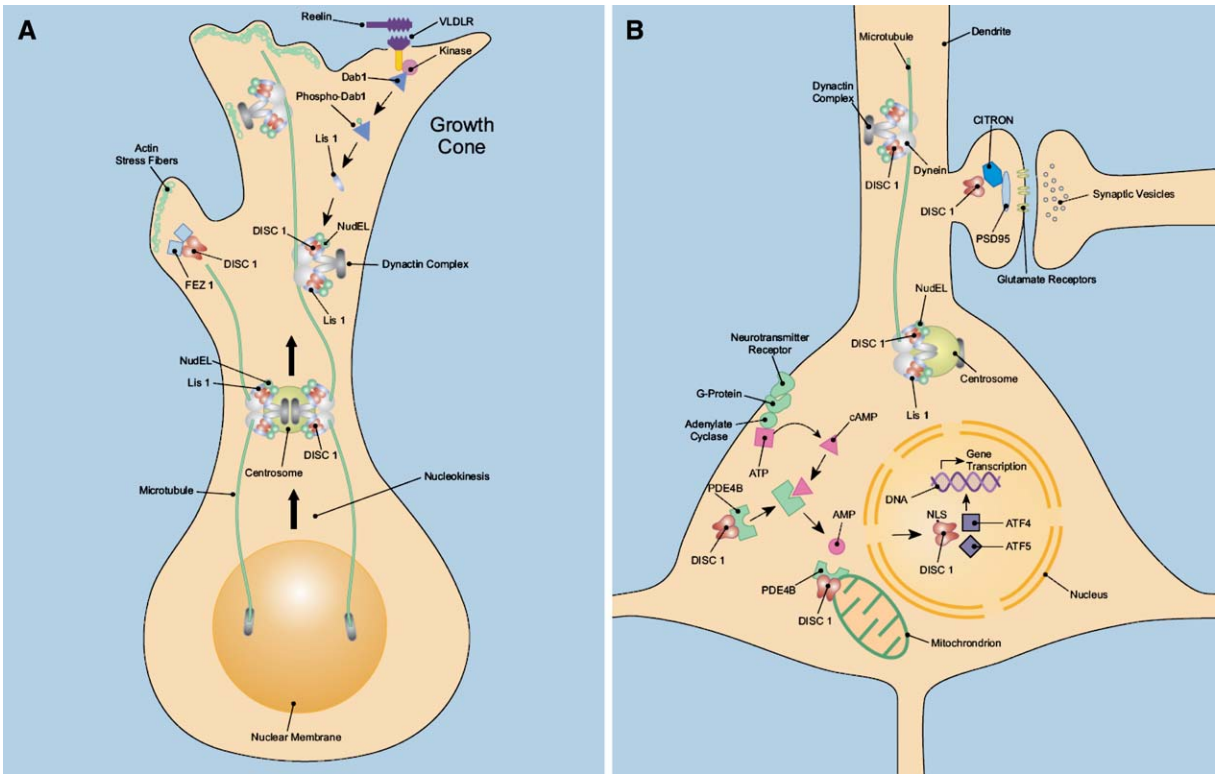

Figure 5. DISC1 Roles in Developing Cortical Neurons and Adult Neuronal Functioning

(A) In the developing neuron, DISC1 is part of a complex with NudEL and Lis1, interacting with the dynein/dynactin motor complex, which is involved with microtubule transport and organization of microtubules at the centrosome. This complex is critical for nucleokinesis, and thus, cortical neuronal migration, and is downstream from Reelin signaling via Dab1. DISC1 also has a key role in neurite outgrowth and organization via its interaction with FEZ1 and actin stress fibers.

(B) In the adult neuron, DISC1 continues to have a role in microtubule-based transport. DISC1 also interacts with Citron, and thus presumably has functions in postsynaptic responses. DISC1 presumably can modulate neurotransmission (and potentially neuroplasticity) by regulating the ability of PDE4B to hydrolyze cAMP, a role which may be localized in part to mitochondrial outer membranes. In the nucleus, DISC1 interacts with transcription factors to modulate stress-induced transcriptional regulation.

example, DISC1 interacts with NudEL. Its close homolog NudE may be genetically related to schizophrenia (Hennah et al., 2006). NudEL is part of a protein complex with Lis1, downstream of Reelin signaling (Brandon et al., 2004). As noted above, mutations of Lis1 cause lissencephaly, and the presence of DISC1 in the same complex as Lis1 is consistent with the idea that schizophrenia, as a relatively mild disorder of cortical development, is pathophysiologically related to more severe disorders of cortical development. Reelin mutations also cause lissencephaly. The interaction between DISC1 and both NudEL and Lis1 would be disrupted by truncated protein expressed from the putative message produced by the chromosomal translocation. Finally, *DISC1* interacts with PDE4B, which is itself interrupted by balanced chromosomal translocation in two individuals with schizophrenia or chronic psychiatric illness (Millar et al., 2005).

These interactions are relevant for the cellular functions of DISC1. DISC1 is part of a protein complex including, in addition to Lis1 and NudEL, dynein and dynactin, which is critical for neuronal migration (Hatten, 2002; Olson and Walsh, 2002; Tsai and Gleeson, 2005). Neuronal migration in the cerebral cortex involves movement along radial glial toward Cajal-Retzius cells and subpial granular layer cells, which secrete Reelin. Migration is driven by nucleokinesis, for which microtubule-based transport is critical. The DISC1 protein complex appears to have several important functions in this process. It appears to be critical for assembly of the centrosome and the organization of the cellular microtubule network. The nucleus is moved by microtubule-based transport toward the centrosome, and neurites extend distally from the centrosome, which is also based in part on microtubule-based transport. Cell biological studies in the Sawa laboratory indicate that DISC1 is important for maintaining a protein complex at the centrosome that is critical for these functions (Kamiya et al., 2005).

DISC1 also modulates neurite outgrowth (Miyoshi et al., 2003) (Ozeki et al., 2003). Either loss of normal DISC1 function or expression of the mutant allele caused abnormal neurite outgrowth in PC12 cells and cortical neurons. Furthermore, elegant in vivo studies in the Nakajima laboratory using in utero electroporation found delayed migration of cortical neurons expressing DISC1 siRNA or mutant truncated DISC1. In the adult cortex, affected neurons continued to have subtle disturbances of neurite orientation (Kamiya et al., 2005).

In addition to microtubules, the actin cytoskeleton is important for neuronal migration and neurite outgrowth. DISC1 associates with FEZ1, an actin binding protein that may have a critical role in anchoring microtubules

near the cell membrane. Neurite outgrowth also appears to involve the DISC1/FEZ1 complex (Miyoshi et al., 2003). DISC1 also interacts with several transcription factors, including ATF4 and ATF5, suggesting that DISC1 mutations could potentially alter gene transcription (Morris et al., 2003). DISC1 also binds to Citron, a postsynaptic protein that interacts with PSD-95, suggesting a role for DISC1 in the regulation of synaptic function and synaptic plasticity.

Finally, as noted above, DISC1 has recently been shown to interact with PDE4B, with functional consequences for cAMP signaling. Release of PDE4B by DISC1 activates PDE4B, causing conversion of cAMP to adenosine monophosphate. cAMP is critical for regulation of protein kinase A, which in turn has many functions in neuronal signaling and plasticity in the cell. Furthermore, PDE4B is a target of the antidepressant Rolipram, consistent with the postulated involvement of DISC1 in affective disorder as well as schizophrenia.

Etiology: Environmental Interactions

Environmental and genetic etiologies are both important in psychiatry (Caspi and Moffitt, 2006) and are believed to interact in most cases of schizophrenia. Recent immunologic, epidemiologic, and neuropsychiatric studies suggest infectious etiologies of several major neuropsychiatric diseases (Yolken et al., 2000). Infections that have been associated with schizophrenia include rubella, influenza, Herpes Simplex Virus-1 and -2, cytomegalovirus, poliovirus, and *Toxoplasma gondii* (Brown and Susser, 2002). Patterson (2002) has developed evidence that it is not the virus itself that adversely affects fetal brain development, but rather the cytokine response mounted by the infected mother. Infections during pregnancy can affect brain development by releasing stress hormones, producing hypoxia, hyperthermia, or malnutrition, or by triggering proinflammatory cytokine responses of the mother, the placenta, or the fetus (Gilmore and Jarskog, 1997; Verdoux, 2004). The effects of infection in the perinatal and postnatal period can differ. There can be substantial individual difference in the response to infectious agents. Among other environmental insults implicated as risk factors for schizophrenia are obstetric complications, including premature birth, low birth weight, preeclampsia, rhesus incompatibility, resuscitation at birth, emergency Cesarean delivery, and prenatal nutritional deficiency (Cannon et al., 2002; Kyle and Pichard, 2006; St Clair et al., 2005).

Conclusions and Possibilities for Future Research

In conclusion, we now believe that the molecular genetics of schizophrenia are sufficiently advanced such that etiology-based studies of the neurobiology of schizophrenia are both justified and feasible. The field is still in its infancy, and we must struggle to integrate our rudimentary knowledge of schizophrenia genetics with our scarcely better developed understanding of normal human brain function. Additional genetic studies are indispensable in this effort, and will now be facilitated by genome-wide methods for study of association and methods to systematically investigate variations in genomic copy number. Epigenetic modification, such as methylation, may also prove relevant (Abdolmaleky et al., 2005). Mouse models will make it possible to test pathogenic hypotheses.

How to address the nature and contribution of environmental factors is more uncertain. One possibility may be to introduce proposed environmental factors, such as viral infections, to mouse models of identified mutations in genes such as DISC1 or NPAS3.

The mouse models generated to date have been based on the study of Mendelian disorders (Chen et al., 2006). The more subtle etiologies of schizophrenia and other psychiatric disorders may make more complex genetic models important. For instance, it may be important to generate models with splicing alterations in *neuregulin 1* or with amino acid polymorphisms in COMT or DISC1. In addition, it may be important to use inducible or other conditional systems in order to mimic the effect of activation of the genetic lesion in particular tissues at particular times.

In addition to mouse models, genetic models in other organisms may be very useful. Unlike in neurodegenerative diseases, it may be difficult to use *Drosophila* or other invertebrates as models for the complexities of human psychiatric disorders. For understanding alterations of cortical development, zebrafish, in which development can be directly visualized, may prove suitable. Other species with more complex social behaviors and more complex cognition may ultimately be necessary. Perhaps genetically modified primates may become an important source of models. However, human patients must remain the gold standard. Studies of genetics and clinical and imaging phenotypes can increasingly be integrated. Future imaging studies may be able to combine fMRI with DTI to trace functionally identified circuits.

We propose that study of DISC1 may offer unique opportunities for inroads into understanding the biology of schizophrenia. DISC1 appears to act as a scaffold for protein interactions, and some of these interacting proteins have altered expression in schizophrenia (Lipska et al., 2006). These interactors will be helpful for understanding pathogenesis, and can themselves serve as potential candidate genes to test for mutations. Thus, a neurogenetic approach based on candidate genes (Ross and Pearlson, 1996) may now become possible. The DISC1 interacting protein Lis1 is related to lissencephaly, highlighting the idea that schizophrenia, as a subtle disorder of cerebral cortical development, is related to more severe disorders of cerebral cortical development.

Study of the different genetic etiologies of schizophrenia will also improve understanding of the schizophrenia phenotype, and also understanding of affective disorder and potentially other related major psychiatric illnesses, just as study of the different genes causing lissencephaly has allowed a more careful classification of the phenotypes of lissencephaly (Kato and Dobyns, 2003). Some of the genes, such as *dysbindin*, appear to be related more specifically to schizophrenia, perhaps especially deficit schizophrenia, while others such as *DISC1* and *neuregulin 1* can relate to both schizophrenia and affective disorder.

The genes associated with schizophrenia may have a spectrum of different pathogenic effects, altering neuronal development, neuronal plasticity, and signal

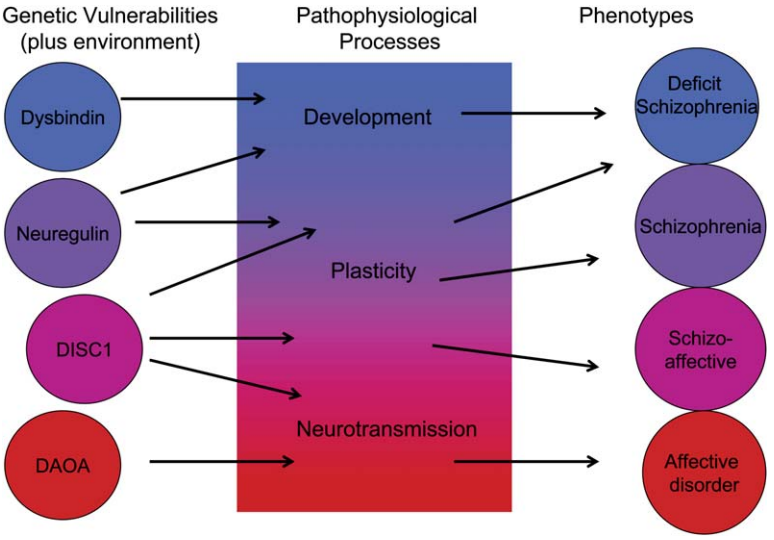

Figure 6. Hypothetical Genotype-Phenotype Relationships via Neurobiological Processes

Based on the very incomplete knowledge available at present, we hypothesize that genetic vulnerabilities associated more closely with schizophrenia, and especially deficit schizophrenia, will involve developmental pathogenesis, while genes associated with affective phenotypes will involve pathophysiology more closely linked to neuromodulation. Intermediate phenotypes may involve plasticity. *DISC1* (and *neuregulin 1*) mutations may involve a range of phenotypes, and the molecular interactions, as shown in Figure 5, could potentially impact a range of cellular effects. This scheme is undoubtedly a great oversimplification. The details of the genotype-phenotype relationships will have to be modified as more studies are done. Since the genetics are complex, several different genetic vulnerabilities act together with environmental factors to cause the phenotype, except in the case of the *DISC1* translocation, which may be sufficient on its own.

transduction. While undoubtedly a great oversimplification, it may be of heuristic value to postulate that variations in particular genes can affect particular neurobiological processes (Figure 6), in turn causing specific phenotypes. For instance, effects on neurodevelopment may be more closely associated with schizophrenia, while effects on signal transduction may be more likely to cause affective disorder. We suggest that DISC1 may serve as a kind of Rosetta Stone for schizophrenia research, helping to connect disparate domains. Testing these broader hypotheses will require integration of research in biochemistry and cell biology, mouse genetics, neuroimaging, and human genotype-phenotype correlations. These studies may allow us to reconceptualize our definitions of the psychiatric disorders, including schizophrenia, based on a better understanding of etiology and pathogenesis.

Ultimately, neurobiological study of schizophrenia, a remarkable disorder of brain function, may help illuminate the nature of normal thought, perception, and emotion. Thus, understanding of this most human disorder may help us better understand human nature itself.

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References

Abdolmaleky, H.M., Cheng, K.H., Russo, A., Smith, C.L., Faraone, S.V., Wilcox, M., Shafa, R., Glatt, S.J., Nguyen, G., Ponte, J.F., et al. (2005). Hypermethylation of the reelin (RELN) promoter in the brain of schizophrenic patients: a preliminary report. Am. J. Med. Genet. B. Neuropsychiatr. Genet. *134*, 60–66.

Akbarian, S., Kim, J.J., Potkin, S.G., Hetrick, W.P., Bunney, W.E., Jr., and Jones, E.G. (1996). Maldistribution of interstitial neurons in prefrontal white matter of the brains of schizophrenic patients. Arch. Gen. Psychiatry *53*, 425–436.

Antonova, E., Sharma, T., Morris, R., and Kumari, V. (2004). The relationship between brain structure and neurocognition in schizophrenia: a selective review. Schizophr. Res. *70*, 117–145.

Arnold, S.E., Ruscheinsky, D.D., and Han, L.Y. (1997). Further evidence of abnormal cytoarchitecture of the entorhinal cortex in schizophrenia using spatial point pattern analyses. Biol. Psychiatry *42*, 639–647.

Arnold, S.E., Trojanowski, J.Q., Gur, R.E., Blackwell, P., Han, L.Y., and Choi, C. (1998). Absence of neurodegeneration and neural injury in the cerebral cortex in a sample of elderly patients with schizophrenia. Arch. Gen. Psychiatry *55*, 225–232.

Arnold, S.E., Talbot, K., and Hahn, C.G. (2005). Neurodevelopment, neuroplasticity, and new genes for schizophrenia. Prog. Brain Res. *147*, 319–345.

Austin, C.P., Ma, L., Ky, B., Morris, J.A., and Shughrue, P.J. (2003). DISC1 (Disrupted in Schizophrenia-1) is expressed in limbic regions of the primate brain. Neuroreport *14*, 951–954.

Benson, M.A., Newey, S.E., Martin-Rendon, E., Hawkes, R., and Blake, D.J. (2001). Dysbindin, a novel coiled-coil-containing protein that interacts with the dystrobrevins in muscle and brain. J. Biol. Chem. *276*, 24232–24241.

Blackwood, D.H., Fordyce, A., Walker, M.T., St Clair, D.M., Porteous, D.J., and Muir, W.J. (2001). Schizophrenia and affective disorders–cosegregation with a translocation at chromosome 1q42 that directly disrupts brain-expressed genes: clinical and P300 findings in a family. Am. J. Hum. Genet. *69*, 428–433.

Bowie, C.R., and Harvey, P.D. (2005). Cognition in schizophrenia: impairments, determinants, and functional importance. Psychiatr. Clin. North. Am. *28*, 613–633, 626.

Bramon, E., Dempster, E., Frangou, S., McDonald, C., Schoenberg, P., MacCabe, J.H., Walshe, M., Sham, P., Collier, D., and Murray, R.M. (2006). Is there an association between the COMT gene and P300 endophenotypes? Eur. Psychiatry *21*, 70–73.

Brandon, N.J., Handford, E.J., Schurov, I., Rain, J.C., Pelling, M., Duran-Jimeniz, B., Camargo, L.M., Oliver, K.R., Beher, D., Shearman, M.S., and Whiting, P.J. (2004). Disrupted in Schizophrenia 1 and Nudel form a neurodevelopmentally regulated protein complex: implications for schizophrenia and other major neurological disorders. Mol. Cell. Neurosci. *25*, 42–55.

Bray, N.J., Preece, A., Williams, N.M., Moskvina, V., Buckland, P.R., Owen, M.J., and O'Donovan, M.C. (2005). Haplotypes at the dystrobrevin binding protein 1 (DTNBP1) gene locus mediate risk for

schizophrenia through reduced DTNBP1 expression. Hum. Mol. Genet. *14*, 1947–1954.

Brown, A.S., and Susser, E.S. (2002). In utero infection and adult schizophrenia. Ment. Retard. Dev. Disabil. Res. Rev. *8*, 51–57.

Burdick, K.E., Lencz, T., Funke, B., Finn, C.T., Szeszko, P.R., Kane, J.M., Kucherlapati, R., and Malhotra, A.K. (2006). Genetic variation in DTNBP1 influences general cognitive ability. Hum. Mol. Genet. *15*, 1563–1568.

Callicott, J.H., Straub, R.E., Pezawas, L., Egan, M.F., Mattay, V.S., Hariri, A.R., Verchinski, B.A., Meyer-Lindenberg, A., Balkissoon, R., Kolachana, B., et al. (2005). Variation in DISC1 affects hippocampal structure and function and increases risk for schizophrenia. Proc. Natl. Acad. Sci. USA *102*, 8627–8632.

Cannon, M., Jones, P.B., and Murray, R.M. (2002). Obstetric complications and schizophrenia: historical and meta-analytic review. Am. J. Psychiatry *159*, 1080–1092.

Cannon, T.D. (2005). The inheritance of intermediate phenotypes for schizophrenia. Curr. Opin. Psychiatry *18*, 135–140.

Cannon, T.D., Hennah, W., van Erp, T.G., Thompson, P.M., Lonnqvist, J., Huttunen, M., Gasperoni, T., Tuulio-Henriksson, A., Pirkola, T., Toga, A.W., et al. (2005). Association of DISC1/TRAX haplotypes with schizophrenia, reduced prefrontal gray matter, and impaired short- and long-term memory. Arch. Gen. Psychiatry *62*, 1205–1213.

Caspi, A., and Moffitt, T.E. (2006). Gene-environment interactions in psychiatry: joining forces with neuroscience. Nat. Rev. Neurosci. *7*, 583–590.

CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N. Engl. J. Med. *353*, 1209–1223.

Chen, J., Lipska, B.K., and Weinberger, D.R. (2006). Genetic mouse models of schizophrenia: from hypothesis-based to susceptibility gene-based models. Biol. Psychiatry *59*, 1180–1188.

Coyle, J.T. (2006). Glutamate and schizophrenia: Beyond the dopamine hypothesis. Cell. Mol. Neurobiol., in press. Published online June 14, 2006. 10.1007/s10571-006-9062-8.

Craddock, N., O'Donovan, M.C., and Owen, M.J. (2005). The genetics of schizophrenia and bipolar disorder: dissecting psychosis. J. Med. Genet. *42*, 193–204.

Craddock, N., Owen, M.J., and O'Donovan, M.C. (2006). The catechol-O-methyl transferase (COMT) gene as a candidate for psychiatric phenotypes: evidence and lessons. Mol. Psychiatry *11*, 446–458.

D'Arcangelo, G. (2006). Reelin mouse mutants as models of cortical development disorders. Epilepsy Behav. *8*, 81–90.

DeRosse, P., Funke, B., Burdick, K.E., Lencz, T., Ekholm, J.M., Kane, J.M., Kucherlapati, R., and Malhotra, A.K. (2006). Dysbindin genotype and negative symptoms in schizophrenia. Am. J. Psychiatry *163*, 532–534.

Detera-Wadleigh, S.D., and McMahon, F.J. (2006). G72/G30 in schizophrenia and bipolar disorder: review and meta-analysis. Biol. Psychiatry *60*, 106–114.

Egan, M.F., Goldberg, T.E., Kolachana, B.S., Callicott, J.H., Mazzanti, C.M., Straub, R.E., Goldman, D., and Weinberger, D.R. (2001). Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc. Natl. Acad. Sci. USA *98*, 6917–6922.

Ekelund, J., Hovatta, I., Parker, A., Paunio, T., Varilo, T., Martin, R., Suhonen, J., Ellonen, P., Chan, G., Sinsheimer, J.S., et al. (2001). Chromosome 1 loci in Finnish schizophrenia families. Hum. Mol. Genet. *10*, 1611–1617.

Erwin, R.J., Turetsky, B.I., Moberg, P., Gur, R.C., and Gur, R.E. (1998). P50 abnormalities in schizophrenia: relationship to clinical and neuropsychological indices of attention. Schizophr. Res. *33*, 157–167.

Ettinger, U., Picchioni, M., Hall, M.H., Schulze, K., Toulopoulou, T., Landau, S., Crawford, T.J., and Murray, R.M. (2006). Antisaccade performance in monozygotic twins discordant for schizophrenia: the Maudsley twin study. Am. J. Psychiatry *163*, 543–545.

Fallgatter, A.J., Herrmann, M.J., Hohoff, C., Ehlis, A.C., Jarczok, T.A., Freitag, C.M., and Deckert, J. (2006). DTNBP1 (Dysbindin) gene variants modulate prefrontal brain function in healthy individuals. Neuropsychopharmacology *31*, 2002–2010. Published online January 11, 2006. 10.1038/sj.npp.1301003.

Falls, D.L. (2003). Neuregulins: functions, forms, and signaling strategies. Exp. Cell Res. *284*, 14–30.

Fanous, A.H., van den Oord, E.J., Riley, B.P., Aggen, S.H., Neale, M.C., O'Neill, F.A., Walsh, D., and Kendler, K.S. (2005). Relationship between a high-risk haplotype in the DTNBP1 (dysbindin) gene and clinical features of schizophrenia. Am. J. Psychiatry *162*, 1824–1832.

Freedman, R. (2003). Schizophrenia. N. Engl. J. Med. *349*, 1738–1749.

Gilmore, J.H., and Jarskog, L.F. (1997). Exposure to infection and brain development: cytokines in the pathogenesis of schizophrenia. Schizophr. Res. *24*, 365–367.

Gold, J.M. (2004). Cognitive deficits as treatment targets in schizophrenia. Schizophr. Res. *72*, 21–28.

Goldman-Rakic, P.S. (1999). The physiological approach: functional architecture of working memory and disordered cognition in schizophrenia. Biol. Psychiatry *46*, 650–661.

Gornick, M.C., Addington, A.M., Sporn, A., Gogtay, N., Greenstein, D., Lenane, M., Gochman, P., Ordonez, A., Balkissoon, R., Vakkalanka, R., et al. (2005). Dysbindin (DTNBP1, 6p22.3) is associated with childhood-onset psychosis and endophenotypes measured by the Premorbid Adjustment Scale (PAS). J. Autism Dev. Disord. *35*, 831–838.

Gothelf, D., Eliez, S., Thompson, T., Hinard, C., Penniman, L., Feinstein, C., Kwon, H., Jin, S., Jo, B., Antonarakis, S.E., et al. (2005). COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome. Nat. Neurosci. *8*, 1500–1502.

Gottesman, I.I., and Gould, T.D. (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. Am. J. Psychiatry *160*, 636–645.

Green, E.K., Norton, N., Peirce, T., Grozeva, D., Kirov, G., Owen, M.J., O'Donovan, M.C., and Craddock, N. (2006). Evidence that a DISC1 frame-shift deletion associated with psychosis in a single family may not be a pathogenic mutation. Mol. Psychiatry *11*, 798–799.

Hahn, C.G., Wang, H.Y., Cho, D.S., Talbot, K., Gur, R.E., Berrettini, W.H., Bakshi, K., Kamins, J., Borgmann-Winter, K.E., Siegel, S.J., et al. (2006). Altered neuregulin 1-erbB4 signaling contributes to NMDA> receptor hypofunction in schizophrenia. Nat. Med. *12*, 824–828.

Hamshere, M.L., Bennett, P., Williams, N., Segurado, R., Cardno, A., Norton, N., Lambert, D., Williams, H., Kirov, G., Corvin, A., et al. (2005). Genomewide linkage scan in schizoaffective disorder: significant evidence for linkage at 1q42 close to DISC1, and suggestive evidence at 22q11 and 19p13. Arch. Gen. Psychiatry *62*, 1081–1088.

Harrison, P.J., and Law, A.J. (2006). Neuregulin 1 and Schizophrenia: Genetics, Gene Expression, and Neurobiology. Biol. Psychiatry. *60*, 132–140. Published online January 25, 2006. 10.1016/j.biopsych.2005.11.002.

Harrison, P.J., and Weinberger, D.R. (2005). Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol. Psychiatry *10*, 40–68.

Harvey, P.D., Green, M.F., McGurk, S.R., and Meltzer, H.Y. (2003). Changes in cognitive functioning with risperidone and olanzapine treatment: a large-scale, double-blind, randomized study. Psychopharmacology (Berl.) *169*, 404–411.

Hatten, M.E. (2002). New directions in neuronal migration. Science *297*, 1660–1663.

Hennah, W., Thomson, P., Peltonen, L., and Porteous, D. (2006). Genes and schizophrenia: beyond schizophrenia: The role of DISC1 in major mental illness. Schizophr. Bull. *32*, 409–416.

Heresco-Levy, U., Ermilov, M., Shimoni, J., Shapira, B., Silipo, G., and Javitt, D.C. (2002). Placebo-controlled trial of D-cycloserine added to conventional neuroleptics, olanzapine, or risperidone in schizophrenia. Am. J. Psychiatry *159*, 480–482.

Honea, R., Crow, T.J., Passingham, D., and Mackay, C.E. (2005). Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. Am. J. Psychiatry *162*, 2233–2245.

Honer, W.G., Young, C., and Falkai, P. (2000). Synaptic pathology. In The Neuropathology of Schizophrenia, P.J. Harrison and G.W. Roberts, eds. (New York: Oxford University Press), pp. 105–136.

Hong, L.E., Mitchell, B.D., Avila, M.T., Adami, H., McMahon, R.P., and Thaker, G.K. (2006). Familial aggregation of eye-tracking endophenotypes in families of schizophrenic patients. Arch. Gen. Psychiatry *63*, 259–264.

Ishizuka, K., Paek, M., Kamiya, A., and Sawa, A. (2006). A review of Disrupted-In-Schizophrenia-1 (DISC1): neurodevelopment, cognition, and mental conditions. Biol. Psychiatry *59*, 1189–1197.

Kamiya, A., Kubo, K., Tomoda, T., Takaki, M., Youn, R., Ozeki, Y., Sawamura, N., Park, U., Kudo, C., Okawa, M., et al. (2005). A schizophrenia-associated mutation of DISC1 perturbs cerebral cortex development. Nat. Cell Biol. *7*, 1167–1178.

Kanaan, R.A., Kim, J.S., Kaufmann, W.E., Pearlson, G.D., Barker, G.J., and McGuire, P.K. (2005). Diffusion tensor imaging in schizophrenia. Biol. Psychiatry *58*, 921–929.

Karayiorgou, M., Morris, M.A., Morrow, B., Shprintzen, R.J., Goldberg, R., Borrow, J., Gos, A., Nestadt, G., Wolyniec, P.S., Lasseter, V.K., et al. (1995). Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. Proc. Natl. Acad. Sci. USA *92*, 7612–7616.

Kato, M., and Dobyns, W.B. (2003). Lissencephaly and the molecular basis of neuronal migration. Hum. Mol. Genet. *12* (Spec No 1), R89–R96.

Katsel, P.L., Davis, K.L., and Haroutunian, V. (2005). Large-scale microarray studies of gene expression in multiple regions of the brain in schizophrenia and Alzheimer's disease. Int. Rev. Neurobiol. *63*, 41–82.

Kellendonk, C., Simpson, E.H., Polan, H.J., Malleret, G., Vronskaya, S., Winiger, V., Moore, H., and Kandel, E.R. (2006). Transient and selective overexpression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. Neuron *49*, 603–615.

Kirkpatrick, B., Buchanan, R.W., Ross, D.E., and Carpenter, W.T., Jr. (2001). A separate disease within the syndrome of schizophrenia. Arch. Gen. Psychiatry *58*, 165–171.

Koike, H., Arguello, P.A., Kvajo, M., Karayiorgou, M., and Gogos, J.A. (2006). Disc1 is mutated in the 129S6/SvEv strain and modulates working memory in mice. Proc. Natl. Acad. Sci. USA *103*, 3693–3697.

Kubicki, M., Westin, C.F., McCarley, R.W., and Shenton, M.E. (2005). The application of DTI to investigate white matter abnormalities in schizophrenia. Ann. N Y Acad. Sci. *1064*, 134–148.

Kyle, U.G., and Pichard, C. (2006). The Dutch Famine of 1944-1945: a pathophysiological model of long-term consequences of wasting disease. Curr. Opin. Clin. Nutr. Metab. Care *9*, 388–394.

Lane, H.Y., Chang, Y.C., Liu, Y.C., Chiu, C.C., and Tsai, G.E. (2005). Sarcosine or D-serine add-on treatment for acute exacerbation of schizophrenia: a randomized, double-blind, placebo-controlled study. Arch. Gen. Psychiatry *62*, 1196–1204.

Lewis, D.A., and Lieberman, J.A. (2000). Catching up on schizophrenia: natural history and neurobiology. Neuron *28*, 325–334.

Lewis, D.A., Hashimoto, T., and Volk, D.W. (2005). Cortical inhibitory neurons and schizophrenia. Nat. Rev. Neurosci. *6*, 312–324.

Li, W., Zhang, Q., Oiso, N., Novak, E.K., Gautam, R., O'Brien, E.P., Tinsley, C.L., Blake, D.J., Spritz, R.A., Copeland, N.G., et al. (2003). Hermansky-Pudlak syndrome type 7 (HPS-7) results from mutant dysbindin, a member of the biogenesis of lysosome-related organelles complex 1 (BLOC-1). Nat. Genet. *35*, 84–89.

Lipska, B.K., Peters, T., Hyde, T.M., Halim, N., Horowitz, C., Mitkus, S., Weickert, C.S., Matsumoto, M., Sawa, A., Straub, R.E., et al. (2006). Expression of DISC1 binding partners is reduced in schizophrenia and associated with DISC1 SNPs. Hum. Mol. Genet. *15*, 1245–1258.

Long, J.M., Laporte, P., Merscher, S., Funke, B., Saint-Jore, B., Puech, A., Kucherlapati, R., Morrow, B.E., Skoultchi, A.I., and Wynshaw-Boris, A. (2006). Behavior of mice with mutations in the conserved region deleted in velocardiofacial/DiGeorge syndrome. Neurogenetics, in press. Published online August 10, 2006. 10.1007/s10048-006-0054-0.

Lymer, G.K., Job, D.E., William, T., Moorhead, J., McIntosh, A.M., Owens, D.G., Johnstone, E.C., and Lawrie, S.M. (2006). Brain-behaviour relationships in people at high genetic risk of schizophrenia. NeuroImage, in press. Published online August 18, 2006. 10.1016/j.neuroimage.2006.06.031.

Margolis, R.L., Holmes, S.E., Rudnicki, D., O'Hearn, E., Ross, C.A., Pletnikova, O., and Troncoso, J.C. (2006). Huntington's disease-like 2. In Genetic Instabilities in Human Disease, R. Wells and T. Ashizawa, eds. (Amsterdam: Academic Press), pp. 261–273.

McEvoy, J.P., Lieberman, J.A., Stroup, T.S., Davis, S.M., Meltzer, H.Y., Rosenheck, R.A., Swartz, M.S., Perkins, D.O., Keefe, R.S., Davis, C.E., et al. (2006). Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am. J. Psychiatry *163*, 600–610.

Millar, J.K., Christie, S., and Porteous, D.J. (2003). Yeast two-hybrid screens implicate DISC1 in brain development and function. Biochem. Biophys. Res. Commun. *311*, 1019–1025.

Millar, J.K., Pickard, B.S., Mackie, S., James, R., Christie, S., Buchanan, S.R., Malloy, M.P., Chubb, J.E., Huston, E., Baillie, G.S., et al. (2005). DISC1 and PDE4B are interacting genetic factors in schizophrenia that regulate cAMP signaling. Science *310*, 1187–1191.

Miyoshi, K., Honda, A., Baba, K., Taniguchi, M., Oono, K., Fujita, T., Kuroda, S., Katayama, T., and Tohyama, M. (2003). Disrupted-In-Schizophrenia *1*, a candidate gene for schizophrenia, participates in neurite outgrowth. Mol. Psychiatry *8*, 685–694.

Miyoshi, K., Asanuma, M., Miyazaki, I., Diaz-Corrales, F.J., Katayama, T., Tohyama, M., and Ogawa, N. (2004). DISC1 localizes to the centrosome by binding to kendrin. Biochem. Biophys. Res. Commun. *317*, 1195–1199.

Moghaddam, B. (2003). Bringing order to the glutamate chaos in schizophrenia. Neuron *40*, 881–884.

Mohn, A.R., Gainetdinov, R.R., Caron, M.G., and Koller, B.H. (1999). Mice with reduced NMDA receptor expression display behaviors related to schizophrenia. Cell *98*, 427–436.

Morris, J.A., Kandpal, G., Ma, L., and Austin, C.P. (2003). DISC1 (Disrupted-In-Schizophrenia 1) is a centrosome-associated protein that interacts with MAP1A, MIPT3, ATF4/5 and NUDEL: regulation and loss of interaction with mutation. Hum. Mol. Genet. *12*, 1591–1608.

Murphy, K.C., Jones, L.A., and Owen, M.J. (1999). High rates of schizophrenia in adults with velo-cardio-facial syndrome. Arch. Gen. Psychiatry *56*, 940–945.

Niemi, L.T., Suvisaari, J.M., Tuulio-Henriksson, A., and Lonnqvist, J.K. (2003). Childhood developmental abnormalities in schizophrenia: evidence from high-risk studies. Schizophr. Res. *60*, 239–258.

Niznikiewicz, M.A., Kubicke, M., and Shenton, M.E. (2003). Recent structural and functional imaging findings in schizophrenia. Curr. Opin. Psych. *16*, 123–147.

Nuechterlein, K.H., Barch, D.M., Gold, J.M., Goldberg, T.E., Green, M.F., and Heaton, R.K. (2004). Identification of separable cognitive factors in schizophrenia. Schizophr. Res. *72*, 29–39.

Numakawa, T., Yagasaki, Y., Ishimoto, T., Okada, T., Suzuki, T., Iwata, N., Ozaki, N., Taguchi, T., Tatsumi, M., Kamijima, K., et al. (2004). Evidence of novel neuronal functions of dysbindin, a susceptibility gene for schizophrenia. Hum. Mol. Genet. *13*, 2699–2708.

Ogawa, F., Kasai, M., and Akiyama, T. (2005). A functional link between Disrupted-In-Schizophrenia 1 and the eukaryotic translation initiation factor 3. Biochem. Biophys. Res. Commun. *338*, 771–776.

Olson, E.C., and Walsh, C.A. (2002). Smooth, rough and upside-down neocortical development. Curr. Opin. Genet. Dev. *12*, 320–327.

Owen, M.J., Craddock, N., and O'Donovan, M.C. (2005). Schizophrenia: genes at last? Trends Genet. *21*, 518–525.

Ozeki, Y., Tomoda, T., Kleiderlein, J., Kamiya, A., Bord, L., Fujii, K., Okawa, M., Yamada, N., Hatten, M.E., Snyder, S.H., et al. (2003). Disrupted-in-Schizophrenia-1 (DISC-1): mutant truncation prevents binding to NudE-like (NUDEL) and inhibits neurite outgrowth. Proc. Natl. Acad. Sci. USA *100*, 289–294.

Pantelis, C., Yucel, M., Wood, S.J., Velakoulis, D., Sun, D., Berger, G., Stuart, G.W., Yung, A., Phillips, L., and McGorry, P.D. (2005).

Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. Schizophr. Bull. *31*, 672–696.

Paterlini, M., Zakharenko, S.S., Lai, W.S., Qin, J., Zhang, H., Mukai, J., Westphal, K.G., Olivier, B., Sulzer, D., Pavlidis, P., et al. (2005). Transcriptional and behavioral interaction between 22q11.2 orthologs modulates schizophrenia-related phenotypes in mice. Nat. Neurosci. *8*, 1586–1594.

Patterson, P.H. (2002). Maternal infection: window on neuroimmune interactions in fetal brain development and mental illness. Curr. Opin. Neurobiol. *12*, 115–118.

Pickard, B.S., Malloy, M.P., Porteous, D.J., Blackwood, D.H., and Muir, W.J. (2005). Disruption of a brain transcription factor, NPAS3, is associated with schizophrenia and learning disability. Am. J. Med. Genet. B. Neuropsychiatr. Genet. *136*, 26–32.

Pickard, B.S., Malloy, M.P., Christoforou, A., Thomson, P.A., Evans, K.L., Morris, S.W., Hampson, M., Porteous, D.J., Blackwood, D.H., and Muir, W.J. (2006). Cytogenetic and genetic evidence supports a role for the kainate-type glutamate receptor gene, GRIK4, in schizophrenia and bipolar disorder. Mol Psychiatry *11*, 847–857. Published online July 4, 2006. 10.1038/sj.mp.4001867.

Pieper, A.A., Wu, X., Han, T.W., Estill, S.J., Dang, Q., Wu, L.C., Reece-Fincanon, S., Dudley, C.A., Richardson, J.A., Brat, D.J., and McKnight, S.L. (2005). The neuronal PAS domain protein 3 transcription factor controls FGF-mediated adult hippocampal neurogenesis in mice. Proc. Natl. Acad. Sci. USA *102*, 14052–14057.

Porteous, D.J., and Millar, J.K. (2006). Disrupted in schizophrenia 1: building brains and memories. Trends Mol. Med. *12*, 255–261.

Porteous, D.J., Thomson, P., Brandon, N.J., and Millar, J.K. (2006). The genetics and biology of disc1-an emerging role in psychosis and cognition. Biol. Psychiatry *60*, 123–131.

Rapoport, J.L., Addington, A.M., Frangou, S., and Psych, M.R. (2005). The neurodevelopmental model of schizophrenia: update 2005. Mol. Psychiatry *10*, 434–449.

Riley, B., and Kendler, K.S. (2006). Molecular genetic studies of schizophrenia. Eur. J. Hum. Genet. *14*, 669–680.

Ross, C.A., and Pearlson, G.D. (1996). Schizophrenia, the heteromodal association neocortex and development: potential for a neurogenetic approach. Trends Neurosci. *19*, 171–176.

Ross, C.A., and Poirier, M.A. (2005). Opinion: What is the role of protein aggregation in neurodegeneration? Nat. Rev. Mol. Cell Biol. *6*, 891–898.

Ross, D.E., and Margolis, R.L. (2005). Neurogenetics: insights into degenerative diseases and approaches to schizophrenia. Clin. Neurosci. Res. *5*, 3–14.

Sachs, N.A., Sawa, A., Holmes, S.E., Ross, C.A., DeLisi, L.E., and Margolis, R.L. (2005). A frameshift mutation in Disrupted in Schizophrenia 1 in an American family with schizophrenia and schizoaffective disorder. Mol. Psychiatry *10*, 758–764.

Schurov, I.L., Handford, E.J., Brandon, N.J., and Whiting, P.J. (2004). Expression of disrupted in schizophrenia 1 (DISC1) protein in the adult and developing mouse brain indicates its role in neurodevelopment. Mol. Psychiatry *9*, 1100–1110.

Selemon, L.D., and Goldman-Rakic, P.S. (1999). The reduced neuropil hypothesis: a circuit based model of schizophrenia. Biol. Psychiatry *45*, 17–25.

Selemon, L.D., Rajkowska, G., and Goldman-Rakic, P.S. (1995). Abnormally high neuronal density in the schizophrenic cortex. A morphometric analysis of prefrontal area 9 and occipital area 17. Arch. Gen. Psychiatry *52*, 805–818.

Singleton, A., Myers, A., and Hardy, J. (2004). The law of mass action applied to neurodegenerative disease: a hypothesis concerning the etiology and pathogenesis of complex diseases. Hum. Mol. Genet. *13* (Spec No 1), R123–R126.

Smith, W.W., Pei, Z., Jiang, H., Moore, D.J., Liang, Y., West, A.B., Dawson, V.L., Dawson, T.M., and Ross, C.A. (2005). Leucine-rich repeat kinase 2 (LRRK2) interacts with parkin, and mutant LRRK2 induces neuronal degeneration. Proc. Natl. Acad. Sci. USA *102*, 18676–18681.

Snitz, B.E., Macdonald, A.W., III, and Carter, C.S. (2006). Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. Schizophr. Bull. *32*, 179–194.

Snyder, S.H. (2006). Dopamine receptor excess and mouse madness. Neuron *49*, 484–485.

St Clair, D., Xu, M., Wang, P., Yu, Y., Fang, Y., Zhang, F., Zheng, X., Gu, N., Feng, G., Sham, P., and He, L. (2005). Rates of adult schizophrenia following prenatal exposure to the Chinese famine of 1959-1961. JAMA *294*, 557–562.

Stefansson, H., Sigurdsson, E., Steinthorsdottir, V., Bjornsdottir, S., Sigmundsson, T., Ghosh, S., Brynjolfsson, J., Gunnarsdottir, S., Ivarsson, O., Chou, T.T., et al. (2002). Neuregulin 1 and susceptibility to schizophrenia. Am. J. Hum. Genet. *71*, 877–892.

Straub, R.E., and Weinberger, D.R. (2006). Schizophrenia genes - famine to feast. Biol. Psychiatry *60*, 81–83.

Straub, R.E., Jiang, Y., MacLean, C.J., Ma, Y., Webb, B.T., Myakishev, M.V., Harris-Kerr, C., Wormley, B., Sadek, H., Kadambi, B., et al. (2002). Genetic variation in the 6p22.3 gene DTNBP1, the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. Am. J. Hum. Genet. *71*, 337–348.

Talbot, K., Eidem, W.L., Tinsley, C.L., Benson, M.A., Thompson, E.W., Smith, R.J., Hahn, C.G., Siegel, S.J., Trojanowski, J.Q., Gur, R.E., et al. (2004). Dysbindin-1 is reduced in intrinsic, glutamatergic terminals of the hippocampal formation in schizophrenia. J. Clin. Invest. *113*, 1353–1363.

Thomson, P.A., Wray, N.R., Millar, J.K., Evans, K.L., Hellard, S.L., Condie, A., Muir, W.J., Blackwood, D.H., and Porteous, D.J. (2005). Association between the TRAX/DISC locus and both bipolar disorder and schizophrenia in the Scottish population. Mol. Psychiatry *10*, 616, 657–668.

Tsai, L.H., and Gleeson, J.G. (2005). Nucleokinesis in neuronal migration. Neuron *46*, 383–388.

Tunbridge, E.M., Harrison, P.J., and Weinberger, D.R. (2006). Catechol-o-methyltransferase, cognition, and psychosis: Val(158)Met and beyond. Biol. Psychiatry *60*, 141–151.

Turner, J.A., Smyth, P., Macciardi, F., Fallon, J.H., Kennedy, J.L., and Potkin, S.G. (2006). Imaging phenotypes and genotypes in schizophrenia. Neuroinformatics *4*, 21–49.

Verdoux, H. (2004). Perinatal risk factors for schizophrenia: how specific are they? Curr. Psychiatry Rep. *6*, 162–167.

Yolken, R.H., Karlsson, H., Yee, F., Johnston-Wilson, N.L., and Torrey, E.F. (2000). Endogenous retroviruses and schizophrenia. Brain Res. Brain Res. Rev. *31*, 193–199.