REVIEW

Schizophrenia: Diverse Approaches to a Complex Disease

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Schizophrenia is a debilitating mental illness that affects 1% of the population. Despite intensive study, its molecular etiology remains enigmatic. Like many common diseases, schizophrenia is multifactorial in origin, with both genetic and environmental contributions likely playing an important role in the manifestation of symptoms. Recent advances based on pharmacological studies, brain imaging analyses, and genetic research are now converging on tantalizing leads that point to a central role for several neurotransmitters, including dopamine, glutamate, and serotonin, that may interface with neurodevelopmental defects reflecting disease-related genetic aberrations. Here, we provide a brief overview of the parallel approaches being used to identify the molecular causes of schizophrenia and discuss possible directions for future research.

Most psychiatric disorders are classified as complex in origin—that is, they cannot be easily explained by a single genetic or environmental component. One of the most debilitating of these disorders is schizophrenia (SZ), which affects about 1% of the population. Once the symptoms of SZ occur (usually in young adulthood), they persist for the entire lifetime of the patient and are almost totally disabling.

How do we define SZ? In the absence of a known molecular abnormality, the diagnosis is based on the simultaneous presentation of two types of symptoms that reflect a psychotic disturbance: "positive" symptoms that include delusions, hallucinations, and bizarre thoughts, and negative symptoms that include social withdrawal with affective flattening, poor motivation, and apathy. Patients with affective disorders such as bipolar disorder may exhibit a subset of the psychotic symptoms associated with SZ, such as hallucinations, but these disorders generally have a distinct constellation of symptoms and familial incidence (*1*).

Efforts to identify the underlying disturbances in SZ are currently focused on three general lines of inquiry: (i) examination of the mechanism of action of the drugs that alleviate the symptoms of SZ, (ii) examination of neuroanatomical abnormalities in the brains of SZ patients, and (iii) examination of candidate genes that confer susceptibility to SZ. Here, we review these diverse approaches and attempt a conceptual synthesis.

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Drugs and Neurotransmitters

There was no truly efficacious treatment for SZ until the early 1950s, when the beneficial effects of chlorpromazine were discovered. This drug revolutionized patient treatment: Besides calming down hyperactive patients, it ameliorated the positive symptoms of the disorder, enabling patients to leave mental hospitals and function moderately well in society at large. Chlorpromazine and its successor drugs were designated "neuroleptics," from the Greek term meaning "to clasp the neuron." This designation was based on the pioneering work of Jean Delay and Pierre Deniker, who observed that the effective dose of chlorpromazine varied widely among patients. Beneficial responses generally occurred at doses that elicited neurologic side effects resembling Parkinson's disease. Parkinson's disease is associated with degeneration of dopamine neurons that project to the caudate putamen of the brain. Through studies of dopamine turnover and direct measurements of dopamine receptors, it was established that neuroleptics block the D2 subtype of dopamine receptor (*2, 3*). Blockade of receptors in the caudate putamen was found to cause the neurologic side effects of the neuroleptics, and blockade of receptors in limbic areas such as the nucleus accumbens and prefrontal cerebral cortex of the brain—which regulate emotional behavior—was found to account for the drugs' antipsychotic effects. Administration of amphetamines, which act by releasing dopamine, was found to exacerbate SZ symptoms. These drug effects led to a "dopamine hypothesis" for the modulation of SZ symptoms, with excess dopamine accentuating and decreased dopamine alleviating the symptoms (*2–4*).

Although the great majority of neuroleptics relieve only the positive symptoms of SZ, clozapine also relieves the negative symptoms and can cause substantial improvement in patients who fail to respond to other neuroleptics (*5*). The great success of clozapine led to the development of several "atypical" neuroleptics whose pharmacologic profile resembled that of clozapine. These drugs, such as olanzepine, risperidone, and quetiapine, share several properties with clozapine. They display a lower incidence of neurologic side effects relative to classical neuroleptics. They relieve negative as well as positive symptoms. However, there is an emerging consensus that they are not as effective overall as clozapine and thus may lack the ability of clozapine to alleviate symptoms in patients who are unimproved by classic neuroleptics.

The unique therapeutic efficacy of clozapine prompted researchers to examine how its actions on various neurotransmitter receptors differ from those of "typical" neuroleptics. One notable feature is the considerable potency of clozapine at the 5-HT2 subtype of serotonin receptor, greater than its potency in blocking dopamine receptors. The new atypical neuroleptics have been sculpted by chemists to exert greater potency at 5-HT2 receptors than at dopamine D2 receptors. This has led to speculation about a role for serotonin in the pathophysiology of SZ.

The difficulty in designing anti-SZ drugs stems from our ignorance as to the molecular causes of the disease and the absence of reliable animal models. For a disease such as depression, which is characterized by hopelessness, one can create a model in which a rat is trained to carry out a task for a reward that is hopelessly inaccessible. No such common-sense approach is feasible for SZ. Some researchers have tried to model SZ by administering psychotomimetic drugs such as amphetamine, LSD, or phencyclidine (PCP); however, there is much debate as to how well these drugs can mimic SZ.

Phencyclidine, a widely abused illicit drug, causes a psychosis that is often indistinguishable from *SZ* (*6*). The phencyclidine psychosis mimics SZ far better than do other drug-induced psychoses such as those associated with amphetamine or LSD. Phencyclidine acts by blocking the *N*-methyl-D-aspartate (NMDA) subtype receptor for the excitatory neurotransmitter glutamate. Partial deletion of the gene encoding a form of the NMDA receptor causes the same behavioral abnormalities as phencyclidine (*7*). If SZ involves diminished NMDA receptor activity, then one would predict that drugs activating the receptor

might be therapeutic. For a variety of reasons, it is difficult to administer glutamate to patients, but there is an alternative approach. The NMDA receptor is unique among neurotransmitter receptors in that it requires activation by two transmitter-like molecules. Besides the recognition site for glutamate, the NMDA receptor has a distinct site that recognizes glycine as well as the D-isomer of serine (*6, 8*). In most parts of the brain, D-serine appears to be the endogenous ligand for this site, while in some areas glycine fills this role (*8*). The glutamate theory of SZ has been bolstered by several studies establishing that treatment of SZ patients with glycine, D-serine, or cycloserine (which also activates the D-serine site) causes symptomatic improvement (*9*) (Table 1).

Neurodevelopmental Alterations

Neuropathologists have looked for abnormalities in SZ brains repeatedly over the past century. Many of these studies failed, however, because the disordered lives of SZ patients involve extensive drug treatment and dietary abnormalities that may themselves alter brain anatomy. More recently, sophisticated clinical studies, advanced imaging techniques such as magnetic resonance imaging (MRI), and novel neuroanatomical markers have provided reliable evidence that SZ is a neurodevelopmental disorder.

SZ brains display consistent increases in ventricular size at the onset of the disease, with notable alterations in the prefrontal cerebral cortex and hippocampus (*1, 10–12*). These brain areas participate in emotional regulation and cognitive functions that are impaired in SZ. The existence of abnormalities early in the disease process indicates that they are not mere artifacts of drug treatment, trauma, or dietary alterations. Some studies indicate that there is no overall loss in neuronal number, but each neuron is smaller in size (*10, 13–15*). In contrast to neurodegenerative diseases in which glial proliferation typically accompanies neuronal degeneration, SZ brains show no signs of glial proliferation (*10*). This indicates that the primary disorder in SZ is neurodevelopmental rather than neurodegenerative.

It is likely, then, that abnormalities in proteins with key roles in brain development may contribute to SZ pathogenesis. One such molecule, Reelin, is a large secreted matrix protein that acts as a "stop" signal for neuronal migration, thereby facilitating normal brain patterning during development. SZ brains display a 30 to 50% reduction in Reelin expression in the prefrontal cerebral cortex (*16*) and hippocampus (*17*). Patients with bipolar disorder who manifest psychotic symptoms also display loss of Reelin expression (*16, 17*). During development, the first cells to produce Reelin are Cajal-Retzius neurons, transient cells that act as pathfinders in the developing cerebral cortex and cerebellum. In the cerebral cortex Reelin is particularly concentrated in interneurons that produce the neurotransmitter γ-aminobutyric acid (GABA). Interestingly, the level of a major enzyme in GABA biosynthesis, glutamic acid decarboxylase, is diminished in SZ brains (*16, 18*).

Genetic, Neurotransmitter, and Neuroanatomic Associations

Twin and adoption studies have revealed that SZ has a genetic component (*19*). However, most investigators feel that SZ is not a single disease entity but may reflect common symptomatology caused by several distinct genetic abnormalities. Also, as with many cancers, SZ may require more than one genetic "hit" to become symptomatically manifest. Not surprisingly, different researchers have reported widely varying chromosomal abnormalities, and no highly reliable candidate SZ gene has yet emerged (Table 2). Genetic loci that appear to confer susceptibility to SZ have been mapped to several chromosomes, including 1q21-22, 1q32-43, 6p24, 8p21, 10p14, 13q32, 18p11, and 22q11-13 (*20–24*). A subset of these genetic loci also shows linkage with bipolar affective illness. These findings suggest that in some forms SZ and affective illness have similar causation. Similarly, Reelin deficits occur in both SZ and depression (*16, 17*). The existence of multiple loci conferring susceptibility to SZ suggests that the disease is caused by the interaction of many different genetic components.

By analogy with approaches used for Alzheimer's disease (AD), the genetic complexity of SZ may be simplified by focusing on rare, inherited forms of the disorder. In the case of AD, specific genes regulating formation of the amyloid β peptide, which constitutes the disease's characteristic senile plaques, are mutated in rare forms of familial AD. The involvement of these genes in the familial forms of AD suggests that they also have a pathophysiologic role in the much larger population of sporadic AD. One of the susceptibility loci for SZ is at chromosome 22q11 (*20*). Children with a deletion of 22q11 [once known as velocardiofacial syndrome and DiGeorge syndrome and now des-

Table 1. Drugs, neurotransmitters, and schizophrenia. Some of the best clues to neurotransmitters relevant to the pathophysiology of schizophrenia come from drug effects. Thus, therapeutic actions of antipsychotic neuroleptic drugs derive from blockade of dopamine and serotonin receptors. Amphetamines, which increase dopamine release, worsen symptoms. Phencyclidine, which can mimic schizophrenic symptoms, blocks the NMDA subtype of glutamate receptors; agents that stimulate the glycine/D-serine site on the receptor alleviate symptoms.

Neurotransmitter	Drug	Mechanism of action	SZ symptom	Ref.
Dopamine	Neuroleptics	Antagonists of D2 receptor	↓	
	Amphetamine	Increase dopamine in synaptic cleft	↑	(*2–4*)
Glutamate	Phencyclidine	Antagonist of NMDA receptor	↑	(*6*)
	D-serine, D-cycloserine, glycine	Agonist of NMDA receptor	↓	(*8, 9*)
Serotonin	Atypical antipsychotics (clozapine)	Binding to 5-HT2 receptor	↓	(*5*)

Table 2. The genetics of schizophrenia. The chromosomal loci cited represent the principal sites identified but are not an exhaustive compilation. In linkage studies, investigators seek genetic markers selectively linked to a disease. Association studies compare the occurrence of specific molecular elements in disease and control populations.

Genetics			Affected systems	Ref.
Method	Chromosomal locus	Candidate gene		
Linkage studies	1q21-22, 1q32-42, 6p24, 8p21, 10p14, 13q32, 18p11, 22q11-13	None		(*20–24*)
Chromosomal abnormalities	22q11 deletion (22qDS)	*COMT*	Dopamine; working memory	(*25–28*)
	Balanced translocation	*DISC-1*		(*29*)
Association studies		*5HT2A*	Serotonin	(*31, 32*)
Microarray technology		Synapsin II, NSF	Synaptic vesicle dynamics	(*33*)

ignated 22q deletion syndrome (22qDS) (*25*)] display learning disabilities, cardiac defects, a peculiar hypernasal speech associated with abnormalities in the palate, and characteristic facial features. Adults with 22qDS display an extraordinarily high incidence of SZ, about 25 to 30% (*26*). Furthermore, deletion of 22q11 has been detected in 2% of diagnosed schizophrenics.

The exact gene causing the symptoms of 22qDS has not been definitively established, but there are several interesting candidates, such as the gene encoding catechol-*O*-methyltransferase (COMT). COMT is one of the two principal enzymes that degrade catecholamines such as dopamine. The synaptic activity of dopamine is normally terminated by reuptake of the neurotransmitter via a dopamine transporter protein. Interestingly, in the prefrontal cerebral cortex, the levels of the dopamine transporter are low, suggesting that COMT is primarily responsible for the inactivation of dopamine in this region of the brain. Mice with a targeted deletion of COMT exhibit elevated dopamine levels only in the prefrontal cortex (*27*). Weinberger and associates (*28*) examined a common genetic polymorphism of COMT that results in replacement of valine (Val) with methionine (Met) at codon 108 in the short form of COMT and codon 158 in the long form. The Met form of COMT has only 25% the enzyme activity of the Val form; thus, individuals with Val-COMT would be expected to have less dopamine in their prefrontal cortex. SZ patients and their unaffected siblings with the Val-COMT allele performed poorly on a neuropsychological test of working memory, a brain function that maps to the prefrontal cortex. Subjects with the Val-COMT allele also displayed inefficient brain activation, as assessed by functional MRI, while performing the task (Fig. 1). Moreover, the Val-COMT allele occurred somewhat more often in SZ patients than in age-matched normal controls. It is remarkable that COMT, which regulates dopamine, is localized to 22q11, where a microdeletion is associated with a profound increase in susceptibility to SZ.

The *DISC-1* gene is another promising candidate gene. In a Scottish family with a 47% prevalence of major mental illnesses including SZ, a balanced translocation led to disruption of a gene at 1q42, which was designated *DISC-1* (Disrupted in Schizophrenia) (*29*). A recent linkage report also indicated 1q42 as a possible locus for SZ in a study of Finnish families (*24*). The DISC-1 protein has not yet been well characterized. It is expressed throughout the body and has no motifs that would suggest a unique role in signaling or protein-protein interactions. Although a study in this issue of *Science* fails to find a major SZ locus on chromosome 1q (*30*), this is not incompatible with *DISC-1* being associated with schizophreniform illness in selected families.

A third candidate gene identified in association studies occurs on chromosome 13 and encodes the serotonin receptor 5-HT_{2A} (*31*). It is this receptor that appears to mediate the activity of atypical antipsychotics such as clozapine (*5*). A meta-analysis confirmed the association between SZ and a polymorphism of thymidine-102 to cytidine (T102C) in the gene for the 5-HT_{2A} receptor (*32*). No functional correlate of this mutation has yet been established.

Microarray technology for gene expression analysis may also provide a useful tool for studying the pathogenesis of SZ. For example, a study of the SZ prefrontal cortex has revealed selective declines in the transcripts encoding proteins that regulate presynaptic function, such as synapsin II and *N*-ethylmaleimide–sensitive factor (NSF) (*33*).

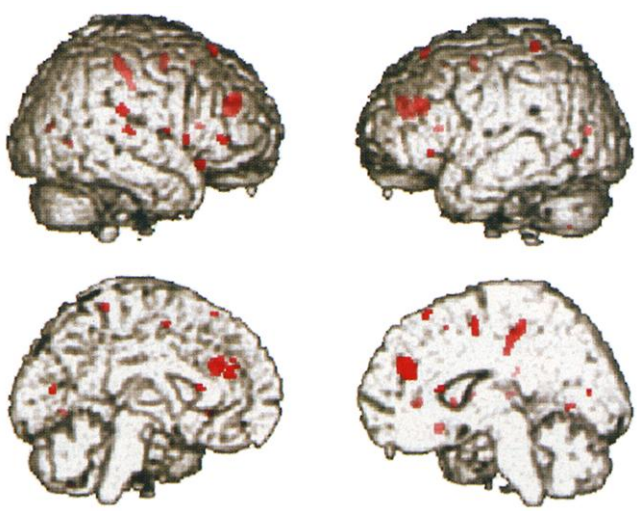

Fig. 1. COMT subtypes influence the activation of discrete brain regions during a memory task. Functional MRI studies were conducted on siblings of schizophrenic patients. Subjects were subtyped as to the Val/Val, Met/Met, or Val/Met genotype of COMT. The Val isoform has four times the COMT activity of the Met isoform, which should lead to lower dopamine levels in the prefrontal cortex. Areas in red showed a significant effect of genotype on activation (shown clockwise from upper left in right lateral, left lateral, right medial, and left medial views). Val/Val individuals showed greater activation than Val/Met subtypes, who in turn showed more activation than Met/Met subjects. Greater activation reflects inefficiency in information processing and correlates with poorer performance on the memory task. The prefrontal cortex, where dopamine has been linked to cognitive performance, is a prominent site for Val-COMT–associated enhanced activation. [Image from Egan *et al.* (*28*), © National Academy of Sciences, USA.]

Future Directions

The recent convergence of neuropathologic, neurotransmitter, and genetic studies indicates that we may be coming much closer to understanding the molecular causes of SZ. Although our focus here was on genetic contributions, it is clear that environmental factors also play an important role, as among identical twins the concordance rate for SZ is only 40 to 50%. It had long been thought that the key environmental factors predisposing to SZ are psychological stresses exerted by emotionally distant or manipulative parents, especially mothers. Abundant literature characterized "schizophrenogenic" mothers who place their children in emotional "double binds." However, familial studies have not supported such notions. Thus, in studies of schizophrenics adopted at birth, the incidence of behavioral disturbance is greater in biologic than in adoptive parents. Studies of identical twins discordant for SZ have identified relevant environmental factors. For instance, the schizophrenic twin is more likely to have suffered birth trauma or experienced a neonatal viral infection. Interestingly, a recent study of cerebrospinal fluid showed sequences homologous to retroviral *pol* genes in 29% of recent-onset SZ or schizoaffective patients. These sequences were not detected in subjects with noninflammatory neurological diseases or in normal control subjects (*34*).

The difficulties in pinning down specific abnormalities in SZ are not unique. Other common diseases that similarly derive from multigenic influences, such as cancer, diabetes, and various cardiovascular disorders, present similar challenges. SZ and other diseases of the central nervous system are particularly well suited to attack by the multiple tools of modern neuroscience with a confluence of imaging, neuroanatomy, genetic analysis, and psychopharmacology. As genetic linkage studies proliferate, highly reproducible defects are emerging that mesh with hints from research on neurotransmitters and neuroanatomy. For instance, two excellent candidate genes, those encoding COMT and the 5-HT_{2A} serotonin receptor, are related to neurotransmitters that mediate the therapeutic effects of antipsychotic drugs.

The inexorable "walking" along chromosomal sequences will likely lead to the identification of causal genes within a decade. Once causal genes are identified, showing how defects in them give rise to disease symptoms may be challenging. Huntingtin,

the protein that is mutated in Huntington's disease, was discovered almost 10 years ago. Yet its normal function remains elusive, and it is still unclear how polyglutamine repeats in huntingtin cause selective pathology in discrete parts of the brain. Similarly, we already know that DISC-1 abnormalities are responsible for psychotic disturbances, but we have no idea as to the actions of normal or abnormal DISC-1. The combination of animal models and imaging technology may prove useful in resolving these dilemmas.

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VIEWPOINT

Balancing Life-Style and Genomics Research for Disease Prevention

Walter C. Willett

Genetic and environmental factors, including diet and life-style, both contribute to cardiovascular disease, cancers, and other major causes of mortality, but various lines of evidence indicate that environmental factors are most important. Overly enthusiastic expectations regarding the benefits of genetic research for disease prevention have the potential to distort research priorities and spending for health. However, integration of new genetic information into epidemiologic studies can help clarify causal relations between both life-style and genetic factors and risks of disease. Thus, a balanced approach should provide the best data to make informed choices about the most effective means to prevent disease.

The elucidation of the human genome sequence was an enormous achievement in biomedical research and will certainly lead to more effective disease prevention and treatment strategies. Among the anticipated advances are improved abilities to predict disease through identification of specific biochemical abnormalities that put individuals at risk. In principle, this information could more effectively focus screening and prevention strategies and also lead to "designer" interventions targeted at specific biochemical defects. However, overly enthusiastic expectations regarding the benefits of genetic research for disease prevention have the potential to distort research priorities and spending for health, resulting in both increased costs and suboptimal health. I argue here that the most effective strategies for disease prevention will be based on a balanced integration of new genetic information into epidemiologic studies.

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Environmental and Genetic Contributions to Complex Human Disease

The relative contributions of genetic variation and nongenetic factors, here considered as "environmental" in the broadest sense, to common diseases such as cancer, heart disease, and psychiatric disorders have been the topic of much research and discussion for decades. These contributions can be expressed as the population-attributable risk percent, meaning the percentage of disease incidence that would be eliminated if the risk factor were removed. Often not appreciated in these discussions is that attributable risks for a complex disease can add to well over 100% because the disease can be avoided in more than one way. Statistically, this can be described as interactions among the various risk factors. As an extreme example, a genetic aberration may be necessary for a disease to occur, but the disease would not be manifest without the presence of an environmental risk factor. Thus, the attributable risks for the genetic aberration and the environmental factor would both be 100%. Phenylketonuria is a classic case: the clinical disease can be avoided either by not having the genetic mutation or by eliminating phenylalanine from the diet.

For most diseases contributing importantly to mortality in Western populations, epidemiologists have long known that nongenetic factors have high attributable risks, often at least 80 or 90%, even when the specific etiologic factors are not clear. This follows from observations that rates of cardiovascular diseases and major cancers differ 5- to 100-fold among various populations and that when groups migrate from low- to high-risk countries, their disease rates almost always change to those of the new environment (*1*, *2*). Dramatic changes in disease rates within a country over time also highlight the importance of environmental factors. For example, in the 1950s age-adjusted colon cancer mortality rates in Japan were less than one-fifth