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REVIEW ARTICLE
Genetics of Schizophrenia and the New Millennium: Progress and Pitfalls

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Introduction

Schizophrenia (MIM 181500) is a severe and common psychiatric disorder afflicting 1% of the world population. The disease is characterized by psychotic symptoms and by cognitive, affective, and psychosocial impairment. As a leading cause of psychiatric admissions, schizophrenia accounts for a considerable portion of health-care expenditures and is viewed as a major public health concern.

Despite extensive research, our knowledge of the structural or functional pathology of schizophrenia is limited. The only etiological factor with a reasonably firm foundation is inheritance, as evidenced by family, twin, and adoption studies that point to substantial heritability (Gottesman and Shields 1982; Gottesman 1991; Kendler and Diehl 1993).

In the premolecular era, attempts to discern the underlying genetic mechanism consisted of (1) segregation analysis, testing the fit of observed familial patterns to specific genetic formulations (e.g., single–major-locus, oligogenic, and multifactorial-polygenic models); (2) searching for genetic susceptibility traits, also known as "biological markers," that segregate with the disorder in families (e.g., neurotransmitter enzymes, receptor proteins, or metabolites; attentional and electroencephalographic measures; and indices based on brain imaging); and (3) linkage studies that used classical gene markers (e.g., leukocyte antigens, blood groups, or serum proteins). However, in spite of numerous studies, the genetic underpinnings of schizophrenia remain elusive. The disorder, which is confounded by a host of factors (e.g., phenotypic diversity, etiologic heterogeneity, incomplete penetrance, unknown mode of inheritance, uncertainty about the number of loci involved and about their interactions, and the existence of nongenetic cases or phenocopies), was consigned to a complex multifactorial etiology, with no firmly established biological correlates (Baron 1986*a* and 1986*b;* Risch 1990*b;* Kendler and Diehl 1993). A single major locus is unlikely as a common mode of inheritance. Oligogenic or polygenic models are plausible alternatives.

The advent of molecular genetics was a turning point in schizophrenia research, enabling the systematic application of both reverse genetics (studying random, anonymous DNA markers spanning the genome) and forward-genetics (testing candidate-gene polymorphisms with presumed functional relevance for the disease) (Martin 1987; Baron and Rainer 1988; Owen and Craddock 1996). In this article I review molecular genetic findings about schizophrenia, with an eye toward methodological issues and future research.

Findings

The search for schizophrenia genes appeared to be off to an auspicious start when Sherrington et al. (1988) reported strong statistical evidence of linkage to DNA markers on chromosome 5q11-13, in British and Icelandic pedigrees (a LOD score of 6.49, under a dominant model of inheritance and a broad disease definition). However, failure to replicate this finding in independent samples, coupled with heightened awareness of phenotypic and genetic complexities, dimmed the initial optimism, and the disease was dubbed a "graveyard for molecular geneticists" (Owen 1992). The initial finding was eventually retracted after a more extensive analysis of the original sample and consideration of additional data (Kalsi et al. 1999).

Conflicting results may arise because of complex inheritance that leads to reduced power and to difficulties in distinguishing a true-positive result from a false-positive one (type 1 error) and in distinguishing a true-negative result from a false-negative one (type 2 error). But a host of other factors must be considered, including diagnostic uncertainties, variability among studies in methods of data collection and interpretation, selection bias, incomplete genotypic information, and statistical artifacts. Several methodological advances have occurred to counter these problems (Baron 1990, 1995; Baron et al. 1990; Risch 1990*a;* Pauls 1993; Spence et al. 1993; Cloninger 1994; Lander and Kruglyak 1995; Owen and Craddock 1996). These include operation-

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alized diagnostic constructs and practices, which enhance diagnostic reliability and consensus among researchers; focus on conservative definitions of the phenotype, to diminish phenotypic ambiguities; maintainenance of scrupulous "blindness" between those conducting diagnostic procedures and those performing genotyping, to avert systematic errors; systematic ascertainment of subjects and pedigrees, to counter selection bias; power simulations, to assess the suitability of clinical samples; a range of analytical models for gene detection; dense genetic maps that allow genomewide searches; and statistical guidelines for the prudent interpretation of results (e.g., adjusting for multiple testing and performing simulations to determine power and levels of significance).

Coupled with advances in other complex disorders (e.g., Alzheimer disease, diabetes, and certain types of cancer), the improved methodology has rekindled interest in the genetics of schizophrenia. A new harvest of findings has been reported, including results of genome searches using linkage mapping and results of studies of candidate genes and chromosomal aberrations. Findings are compiled in the World Congress on Psychiatric Genetics chromosome workshops (Crow and DeLisi 1998; DeLisi and Crow 1998; DeLisi et al. 1999). To narrow the scope of this review, I focus on findings that seem promising by virtue of statistical significance or some consistency across studies. It must be stressed, however, that criteria for significance in the genetic analysis of complex disease are not well established and that positive results are often followed by attempts at replication that yield negative or equivocal findings.

Linkage Studies

Linkage studies are the mainstay of gene-finding strategies in psychiatric genetics. Significant or suggestive evidence of linkage (Lander and Kruglyak 1995) (see the "Linkage Methods" subsection, below) has been reported in several chromosomal regions: 1q21-22, 1q32-41, 4q31, 5p13-14, 5q22-31, 6p22-24, 6q21-22, 8p21-22, 9q21-22, 10p11-15, 13q14-32, 15q15, 22q11-13, and Xp11. There are preliminary results from other genome scans or candidate regions, but evaluation must await the full published reports.

Chromosome 1q21-22.—Brzustowicz et al. (2000) reported a genomewide scan in 22 Canadian pedigrees, which showed pronounced linkage to 1q21-22. A maximum heterogeneity LOD score of 6.50 was found between markers D1S1653 and D1S1679, under a recessive model and a narrow disease definition, and ~75% of the families were linked to this locus. The strength of the evidence is unusual for a complex disorder such as schizophrenia, especially given an outbred population and a relatively small sample. The authors attributed their apparent success to the dense pedigrees selected for study and to a fortuitous sample variation. Marginal support for linkage to 1q22-23 was noted in an earlier study (Shaw et al. 1998). A potassium-channel gene (hKCa3/KCNN3) mapped to 1q21 was reportedly associated with schizophrenia in one study (Dror et al. 1999), although linkage analysis in an independent sample found no evidence for the involvement of hKCa3/KCNN3 in the disease (Austin et al. 1999).

Chromosome 1q32-41.—Hovatta et al. (1999) reported a three-stage genomewide scan in 69 families from a Finnish population isolate. They observed a maximum LOD score of 3.82 at marker D1S2891, under a dominant model and a narrow disease definition, with no evidence of locus heterogeneity. A putative haplotype, which might narrow the chromosomal region implicated, was observed in some core families.

Chromosome 4q31.—Hovatta et al. (1999) also observed a maximum LOD score of 2.74 at marker D4S1586, under a dominant model and a narrow diagnostic model. Positive LOD scores occurred on a fairly large region, and the evidence was supported by affected sib-pair analysis with the same marker (LOD score of 2.09; $P = .00097$).

Chromosome 5p13-14.—Silverman et al. (1996) reported a maximum LOD score of 4.37 at locus D5S111, under dominant inheritance and a broad disease definition (including putative schizophrenia-related phenotypes), in one large Puerto Rican pedigree. However, the LOD score was not robust to sensitivity analysis (testing the impact of diagnostic misclassifications on the evidence for linkage), and 23 other families examined concurrently showed no evidence of linkage to this region, suggesting that the putative disease gene is rare.

Chromosome 5q22-31.—After a genome scan of 265 Irish pedigrees, Straub et al. (1997) reported a maximum heterogeneity LOD score of 3.35 ($P = .0002$) at marker D5S804, under a recessive genetic model and a narrow diagnostic model, and ~10%–25% of the families linked to this locus. D5S804 is mapped to 5q22, but positive LOD scores were in evidence across the entire 5q22-31 region. Schwab et al. (1997) reported additional support, albeit at a lower level of significance, for linkage to this region (marker D5S399 at 5q31), in German and Israeli families.

Chromosome 6p22-24.—Straub et al. (1995), following up on a report on a subset of the data in the same German and Israeli families (Wang et al. 1995), studied 265 Irish families for linkage to 6p22-24. They reported a maximum LOD score of 3.51 ($P = .0002$) at marker D6S296, under an additive genetic model and a broad definition of schizophrenia (including putative schizophrenia-related disorders). An estimated 15%–30% of

the families were presumed linked to this region. The evidence of linkage declined substantially when the narrow disease definition was used. Additional, support for linkage to this region was reported by Schwab et al. (1995 and 2000) in German and Israeli families, by Moises et al. (1995) in 65 European, Canadian, U.S., and Taiwanese families, and by Antonarakis et al. (1995) in 57 U.S. families.

Chromosome 6q21-22.—Cao et al. (1997) reported possible linkage to 6q21-22 in two independent U.S. samples: $P = .00018$ at locus D6S474 using sib-pair analysis in 63 independent sib pairs, and $P = .00095$ at D6S424 (~14 cM proximal to D6S474) in a second sample of 87 independent sib pairs. The same group of researchers reported modest support for linkage to D6S424 in a third sample consisting of 54 U.S. and Australian sib pairs; when these researchers combined samples (141 independent sib pairs), they observed a nonparametric LOD score of 3.82 ($P = .000014$) (Martinez et al. 1999).

Chromosome 8p21-22.—Using a narrow disease definition in a genome scan of 54 U.S. pedigrees, Blouin et al. (1998) observed a nonparametric LOD score of 3.64 ($P = .0001$) at D8S1771. They obtained additional support from a dominant-model analysis (dominant heterogeneity LOD score of 4.54, assuming 70% of the families are linked) and from a follow-up sample of 51 pedigrees. When a broad disease definition was used in this sample, support for linkage increased, yielding a nonparametric LOD score of 6.17 ($P = .0000008$) (Pulver et al. 2000). Previously, Pulver et al. (1995) published preliminary evidence of linkage to this region. Some additional support came from Kendler et al. (1996), who found a maximum LOD score of 2.34, using a dominant genetic model and a broad disease definition, in 265 Irish pedigrees. Further support for linkage to 8p21 was reported by Brzustowicz et al. (1999), with a maximum LOD score of 3.49 at marker D8S136, under a dominant model and narrow disease phenotype, in 21 Canadian families.

Chromosome 9q21-22.—In their Finnish study (see the "Chromosome 1q32-41" subsection, above), Hovatta et al. (1999) also observed a maximum LOD score of 1.95 at marker D9S922, under a dominant model. Other investigators (Moises et al. 1995; Levinson et al. 1998) reported some support for linkage to this region, although at marginal statistical significance.

Chromosome 10p11-15.—Faraone et al. (1998) reported a genome scan of 43 U.S. nuclear families, with suggestive linkage in 50 independent sib pairs using a narrow disease definition. The nonparametric LOD scores at markers D10S1423 and D10S582 were 3.4 ($P = .0004$) and 3.2 ($P = .0006$), respectively. Supportive evidence was provided by Schwab et al. (1998a), with a nonparametric LOD score of 3.2 ($P = .0007$) at marker D10S1714, in 72 German and Israeli families. Straub et al. (1998) observed a multipoint heterogeneity LOD score of 1.91 ($P = .006$) at with markers D10S1426 and D10S674 in 265 Irish pedigrees.

Chromosome 13q14-32.—Blouin et al. (1998) reported a nonparametric LOD score of 4.18 ($P = .00002$), near D13S174 on 13q32, using a narrow disease phenotype in a genome scan of 54 U.S. pedigrees. The maximum heterogeneity LOD score for this region, under a dominant genetic model, was 4.5. This finding was supported in a follow-up sample of 51 families, with a nonparametric LOD score of 2.36 ($P = .007$) at D13S779, ~7 cM distal to the peak obtained in the first sample. Further support for this finding was furnished by Brzustowicz et al. (1999), with a maximum heterogeneity LOD score of 4.42 at D13S793 (~10 cM distal to D13S779), under a recessive model and a broad disease definition, in 21 Canadian pedigrees. Other work (Lin et al. 1997; Shaw et al. 1998) also supported this finding, although at lower significance levels.

Chromosome 15q13-15.—Stober et al. (2000) reported linkage to 15q15 in a genome scan of 12 German pedigrees, segregating the periodic catatonia subtype of schizophrenia. They found a nonparametric LOD score of 3.57 ($P = .000026$) and a maximum LOD score of 2.75 at marker D15S1012, under a dominant model. Marginal support for linkage to15q13-15 in U.S. schizophrenia pedigrees was suggested by Coon et al. (1994*b*) and Leonard et al. (1998). The 15q-candidate region overlaps with a putative schizophrenia locus defined by a neurophysiological impairment in the P50 auditory sensory gating (Freedman et al. 1997). It also contains the $\alpha 7$ nicotinic acetylcholine receptor gene (CHRNA7), a potential candidate gene.

Chromosome 22q11-13.—Pulver et al. (1994*a*) observed a maximum LOD score of 2.82 at marker locus IL2RB, in 39 U.S. pedigrees. Affected sib-pair analysis in an expanded sample of 57 U.S. pedigrees was consistent with linkage to the same general region ($P = .009$) (Lasseter et al. 1995). Other investigators (Polymeropoulos et al. 1994; Coon et al. 1994*a;* Stober et al. 2000) also reported modest support for linkage. The implicated region is near the velocardiofacial syndrome (VCFS) deletion, which is reportedly associated with psychotic features (see the "Chromosomal aberrations" subsection, below). It also harbors a putative candidate gene, which may influence two neurophysiological functions, P50 auditory sensory gating and antisaccade ocular motor performance (Myles-Worsley et al. 1999).

Chromosome Xp11.—This region is of interest, because it harbors the monoamine oxidase B (MAOB) gene, a potential candidate gene for neuropsychiatric disease. The Finnish isolate study (Hovatta et al. 1999; see the "Chromosome 1q32-41" subsection, above) reported a maximum LOD score of 2.01 at the MAOB

locus, using a recessive model and a narrow disease definition. Earlier reports found positive LOD scores in the close vicinity of MAOB, at marker DXS7 (DeLisi et al. 1994*a;* Dann et al. 1997).

Candidate Genes and Chromosomal Aberrations

In contrast to most linkage studies (which typically involve genomewide searches), studies of candidate genes and chromosomal aberrations target specific genomic sites.

Candidate genes.—Candidate genes for schizophrenia (genes that encode products with neurobiological function such as neurotransmitter receptors or enzymes) are commonly studied by way of association studies. Whereas linkage analysis tests for cosegregation of a gene marker and disease phenotype in families, association studies examine the co-occurrence of a marker and disease at the population level, using a case-control design (unrelated cases and population-based controls). Family-based controls can also be studied using a trio consisting of an affected child (case) and two parents (controls).

Most association studies have focused on genes involved in dopaminergic or serotonergic neurotransmission. Disturbances in dopaminergic or serotonergic systems have long been implicated in the pathogenesis of schizophrenia, primarily because of their role as sites for antipsychotic drug action. Numerous association studies have been reported, with conflicting results. Because association studies are largely concerned with genes of minor effect, studies of large, statistically powerful samples may produce more compelling results than the more typical small-scale studies have done. Two such studies, which aimed to pursue previously reported suggestive results, warrant attention and are described below.

Spurlock et al. (1998) examined polymorphisms in the dopamine DRD2 and DRD3 receptor genes in a large European multicenter sample. They studied two polymorphisms: Ser311Cys (in exon 7 of DRD2) and Ser9gly (in exon 1 of DRD3) in samples of 373 and 413, and 311 and 306 patients and controls, respectively. They found no evidence of allelic association with the DRD2 polymorphism and no homozygotes for this variant. However, an excess of homozygotes for both alleles of the DRD3 polymorphism was noted in the patient group ($P = .003$), as well as a significant excess of the 1:1 (Ser9Ser) genotype ($P = .004$), with no allelic association. They concluded that an association exists between increased homozygosity of the DRD3 variant and the disease.

Williams et al. (1996) studied the serotonin polymorphism T102C of the gene for 5-hydroxytryptamine type 2a (5-H2Ta) receptor, in a large European multicenter sample of 571 patients and 631 matched controls. They observed significant association between the disease and allele 2 ($P = .003$), as well as a significant excess of the ½:½ genotype in patients ($P = .008$). They concluded that the 5-HT2a receptor gene—or a locus in linkage disequilibrium with it—confers susceptibility to schizophrenia.

Association studies with specific genes that may be involved in genetic anticipation (progressively earlier age at onset or increased severity in successive generations) have also been of interest (1) because these genes, which are characterized by trinucleotide repeat expansions, are common in human brain, and (2) because anticipation has been reported in schizophrenia. However, the search for such genes has yielded conflicting results, with no evidence for a clear-cut relationship between the trinucleotide-repeat size and age at onset of the disease (Sasaki et al. 1996; Morris et al. 1995; O'Donovan et al. 1995). Also, the evidence for anticipation in schizophrenia may be fraught with ascertainment bias (Asherson et al. 1994).

Chromosomal aberrations.—Chromosomal aberrations have been instrumental in identifying disease genes. There are numerous accounts of associations between schizophrenia and chromosomal aberrations, including the partial trisomy of 5q11-13 (Bassett et al. 1988) which led to the claimed linkage to DNA markers in this region (see the "Linkage Studies" subsection, above). In a separate publication, Bassett (1992) reviewed earlier reports. Later accounts include translocations such as t(2;18)(p11.2;p11.2) (Maziade et al. 1993) and t(1;7)(p22;q22) (Gordon et al. 1994), inversions such as 9p11-9q13 (Nanko et al. 1993) and 4p15.2-q21.3 (Palmour et al. 1994), trisomies of 5p14.1 (Malaspina et al. 1992) and 8 (Ong and Robertson 1995), fragile sites at 8q24 and 10q24 (Garofalo et al. 1993), deletions at 22q11.1 (Karayiorgou et al. 1995) and 5q21-23.1 (Bennett et al. 1997), and sex aneuploidies (reviewed in DeLisi et al. 1994*b*).

Because of the high prevalence of schizophrenia, and the fact that most of the reported chromosomal aberrations are confined to isolated cases, it is likely that the great majority of these associations are spurious. Confidence in the potential relevance of a particular finding can be enhanced by (1) increasing the rate of the chromosomal anomaly in the patient population, (2) increasing the rate of the disease among patients with the chromosomal anomaly, or (3) finding independent evidence of linkage between the disease and the specific genomic region. One of the reported aberrations—the deletion at 22q11, which overlaps the region involved in VCFS (Karayiorgou et al. 1995; also see the "Linkage Studies" subsection, above)—appears to meet these criteria and warrants further study.

Methodological Issues

Although some of the aforementioned results show promise, the failure of attempts to replicate results and the limited power to detect and replicate gene effects, as well as limited power to distinguish true-positive results from false-positive ones, continue to mar the search for susceptibility genes in schizophrenia. Methodological refinements that may expedite this search involve new perspectives on phenotype definition and new analytical approaches.

The Phenotype

The lack of external validating criteria and the considerable variability in clinical manifestations present a challenge to genetic studies. Strategies that attempt to redress this problem include (1) dissecting the phenotype to clinical subtypes that cluster in families and that may have distinct underlying genetic bases and (2) supplanting discrete phenotypes by quantitative measures, such as symptom-based algorithms and biological endophenotypes, that may be more closely related to the underlying genetic vulnerability. The use of quantitative measures may also provide a greater power to detect linkage than the power provided by use of discrete phenotypes. Another strategy to overcome the challenges of genetic studies is to blur the diagnostic boundaries between schizophrenia and other major psychiatric disorders, such as bipolar disorder, to examine genetic commonality. Several investigators have recently applied these strategies, with varying degrees of success.

Clinical Subtypes

As mentioned (see the "Linkage Studies" subsection, above), Stober et al. (2000) found evidence for a major locus for the periodic catatonia subtype of schizophrenia on chromosome15q15. Elsewhere they reported high familial aggregation of this syndrome, with an estimated prevalence of 0.1% in the general population (Stober et al. 1995). Their finding suggests that periodic catatonia is a genetically homogeneous subtype of schizophrenia that is linked to a major locus on 15q15.

It should be noted, however, that catatonic schizophrenia is uncommon and that other recent attempts to determine whether schizophrenia subtypes cluster in families produced negative results (Leboyer et al. 1992; Kendler et al. 1994). This suggests that the finding reported by Stober et al. (2000), although potentially relevant for a subset of schizophrenia, may not have general applicability.

Symptom-Based Analysis

Brzustowicz et al. (1997) studied quantitative clinical traits, using positive-symptom (psychotic), negative-symptom (deficit), and general-psychopathology-symptom scales for schizophrenia. Using categorical phenotypes, they found evidence of linkage between the positive-symptom trait and marker D6S1960 ($P = .0000054$) on chromosome 6p11-21, slightly proximal to the 6p21-24 region previously implicated in schizophrenia (see the "Linkage Studies" subsection, above). The somewhat different localization may result from differences in phenotypic classification and marker coverage or from the presence of two distinct susceptibility loci. Interestingly, there was no evidence of linkage when categorical diagnoses were used. This supports the notions that (1) the use of a quantitative trait may, indeed, have increased the power to detect linkage and (2) positive symptoms show more pronounced correlation with genetic vulnerability at the 6p putative locus.

A different symptom-based approach was taken by Kendler et al. (2000), who tested for linkage of symptom and outcome variables to chromosomes 5q21-31, 6p22-24, 8p21-22, and 10p11-15, all of which are regions implicated in previous linkage studies using discrete diagnoses (see the "Linkage Studies" subsection, above). There was no evidence of linkage to 5q, 6p, or 10p, but affected individuals from families with prior evidence of linkage to 8p21-22 had more affective deterioration, more thought disorder, fewer depressive symptoms, and poorer outcome than did affected individuals from other families. These clinical features are characteristic of the core, poor-outcome form of schizophrenia. Notwithstanding methodological limitations (Kendler et al. 2000), the study suggests that a locus on 8p21-22 confers susceptibility to this syndrome.

Biological Endophenotypes

Much attention has focused on two neurobiological dysfunctions associated with familial schizophrenia: impaired gating of the auditory evoked response (Judd et al. 1992; Freedman et al. 1997) and ocular motor dysfunctions (Holzman et al. 1988; Levy et al. 1993). Impaired sensory gating, commonly measured by recording the P50 wave of the auditory evoked response, reflects a dysfunction in the brain's processing of sensory stimuli. Ocular motor dysfunctions include impaired smooth-pursuit eye movement and deficient antisaccade ocular motor performance. The P50 auditory sensory gating and antisaccade ocular performance are specific measures of inhibitory neurophysiological functioning. Physiological deficits in these measures occur in most schizophrenics and in many of their unaffected relatives, an observation consistent with the hypothesis that vulnerability to the disease is inherited.

Both putative endophenotypes were tested for linkage to schizophrenia (see the "Linkage Studies" subsection, above). Freedman et al. (1997) reported linkage of the

P50 sensory gating deficit to chromosome 15q13-14, the site of the α7-nicotinic receptor locus, in nine U.S. schizophrenia pedigrees (LOD score of 5.3, using a dominant model). Their neurobiological studies suggest that decreased function of the α7-nicotinic receptor could underlie the P50 sensory gating defect, a finding that suggests this gene may have a role in the pathophysiology of schizophrenia. In a follow-up study of eight of these families, Myles-Worsley et al. (1999) reported linkage between a composite biological phenotype— combining the P50 sensory gating and antisaccade ocular motor performance—and marker D22S315 on chromosome 22q11-12 (LOD of 3.55, using a dominant model). This composite endophenotype appeared to identify nearly 80% of nonschizophrenic relatives as abnormal in at least one inhibitory processing domain.

It must be emphasized, however, that the evidence of linkage between the clinical phenotype and the two chromosomal regions, in this sample and in samples reported by others (see the "Linkage Studies" subsection, above), is less pronounced than the linkage reported for the endophenotypes. Also, the endophenotypes appeared to be governed by dominant major genes, a genetic model unlikely for schizophrenia generally.

Diagnostic Boundaries

Ordinarily, the disease phenotype can range from schizophrenia proper (a narrow definition) to broader phenotype definitions that include what are known as "spectrum" disorders (disease states that aggregate in families of schizophrenic patients but do not meet the criteria for schizophrenia). However, recent data suggest a broader perspective on this matter. Specifically, although schizophrenia and bipolar affective disorder do not show significant coaggregation in families and are generally considered distinct nosological entities, there is evidence for some overlap (Baron et al. 1982; Gershon et al. 1988; Maier et al. 1993). In particular, families both of schizophrenic and of bipolar patients are at increased risk for schizoaffective disorder (a syndrome combining schizophrenic and affective features) and unipolar depression. Also, relatives of schizoaffective patients show increased rates of schizophrenia, bipolar illness, and unipolar depression. There is, additionally, some resemblance in epidemiological and clinical features: the two disorders have similar prevalence and age at onset, show no gender preference, are lifelong conditions, and have some common psychotic features.

The apparent partial overlap of schizophrenia and bipolar disorder has drawn attention to the notion of shared susceptibility loci. Indeed, examination of recent linkage studies shows several chromosomal regions that are implicated in both disorders. In particular, 1q32, 10p11-15, 13q32, and 22q11-13, which were linked to schizophrenia in some studies (see the "Linkage Studies" subsection, above), have also been implicated in bipolar disorder. For example, Detera-Wadleigh et al. (1999) observed evidence of linkage at 1q32 (LOD score of 2.67; $P = .00022$), 13q32 (LOD score of 3.5; $P = .000028$), and 22q11-13 (LOD score of 2.1; $P = .00094$) in 22 U.S. pedigrees with bipolar illness. Foroud et al. (2000) reported a LOD score of 2.5 ($P = .001$) at 10p14, in 97 U.S. pedigrees with bipolar illness. Another region of potential interest is 18p11, where Schwab et al. (1998b) reported modest evidence of linkage to schizophrenia (LOD score of 1.76 at marker D18S53) in 59 German and Israeli families. The LOD score increased to 3.1 when the phenotype definition was broadened to include bipolar disorder and unipolar depression. Possible linkage of bipolar disorder to 18p11 was reported in an independent sample of 22 U.S. pedigrees (Berrettini et al. 1994), although the status of this linkage is unclear (Baron and Knowles 2000). Evidence of shared genetic susceptibility between schizophrenia and affective disorders may provide cross-validation of genetic findings and a rationale for some latitude in phenotype definition.

Analytical Approaches

There is an ongoing debate as to the optimal study design and analytical methods for complex traits such as schizophrenia. Issues that warrant attention include linkage and association methods, meta-analyses, and novel analytical models.

Linkage Methods

Linkage analysis examines familial cosegregation of a gene marker and a disease phenotype, to determine whether the marker and the disease are physically linked. Controversial issues include sample configuration (sib pairs in nuclear families vs. extended high-density pedigrees), type of analysis (model-free [nonparametric] methods, e.g., sib-pair analysis, vs. model-based [parametric] methods, e.g., LOD scores in pedigrees), and definition of significant findings.

The advantages and disadvantages of various sample configurations and types of analysis have been discussed elsewhere (Vieland et al. 1992; Greenberg et al. 1997 and 1998; Goldgar and Easton 1997; Kruglyak 1997; Terwilliger 1998; Ott and Hoh 2000) and can be summarized as follows:

Sample configuration.—Proponents of the sib-pair approach argue that extended pedigrees may be error-prone for two main reasons: (1) reduced power for linkage detection may result from intrafamilial heterogeneity caused by "extraneous" genes entering the pedigree through marrying-in spouses and (2) selection bias in favor of a particular form of familial disease with a dominantlike, single-gene effect may accompany a fail-

ure to consider more representative mechanisms for complex traits, such as oligogenic inheritance and multiple genes of modest effect. It may be argued, however, that (1) extended pedigrees can be divided into component nuclear families to account for intrafamilial heterogeneity; (2) sib pairs in small families are also susceptible to intrafamilial heterogeneity (phenocopies may be more common because of low illness density); (3) extended pedigrees contain more genetic information than small families do, and this results in increased statistical power, especially when heterogeneity is accounted for; and (4) although the dominantlike appearance of some extended pedigrees may favor the detection of rarer, large-effect genes, such genes can be more easily traceable, and their biological impact may be greater than that of genes of minor effect.

Type of analysis.—Advocates of model-free methods argue that these methods are more suitable for complex disorders whose mode of inheritance is uncertain, because such methods make no assumptions about the underlying genetic transmission. It may be argued, however, that (1) model-based LOD score analysis has greater power and is largely robust to model misspecification, if more than one model is tested; (2) with model-based methods, several different models can be used, covering a range of genetic hypotheses with adequate power and with little risk of missing a true linkage; (3) there is no systematic evidence that model-free methods have a greater sensitivity for linkage detection than do model-based methods.

Clearly, there is no one correct method for linkage detection. The studies reviewed in this article (see the "Linkage Studies" subsection, above) used a variety of methods, including nuclear families with sib pairs, extended pedigrees, and model-free and model-based analysis. Given the acknowledged complexities, the use of complementary methods might be advisable, provided the advantages and disadvantages of the various approaches are recognized.

Statistical significance.—As mentioned, simulation studies suggest guidelines for genomewide significance of linkage results in studies of complex traits (Lander and Kruglyak 1995). In parametric analysis, the categories of significant and suggestive linkage correspond to LOD scores of 3.3 and 1.9, respectively; the corresponding pointwise *P* values in sib-pair analysis are .000022 (LOD score of 3.6) and .00074 (LOD score of 2.2). Once significant linkage is observed, a *P* value of .01 in an independent study is required for replication. However, although these guidelines are widely used (see the "Linkage Studies" subsection, above), debate continues about what constitutes appropriate thresholds for significance. What appears to be significant linkage can be a false-positive result, even in the presence of presumed replication. Conversely, linkage findings that fall short may be worth pursuing, especially if contiguous markers in the candidate region show positive results.

Linkage versus association.—As mentioned, there are numerous association studies of candidate genes. Although linkage studies continue to play a pivotal role, association mapping is becoming a competing strategy. The advantages and disadvantages of linkage and association mapping have been widely debated (Crowe 1993; Kidd 1993; Risch and Merikangas 1996; Owen et al. 1997; Terwilliger and Weiss 1998; Risch 2000; Weiss and Terwilliger 2000; Ott and Hoh 2000; Baron 1997 and in press). The advantages of association studies can be summarized as follows: (1) Most of the genetic variance in complex disease is due to genes of modest effect. Such genes are probably detectable by association analysis but may not be amenable to the linkage approach, which is best suited for genes of larger effect. (2) The sample-size requirements for linkage detection are much higher (possibly beyond reach) than those for association mapping. (3) The slow progress in linkage mapping of complex disease attests to the constraints of this approach. (4) The emergent maps of high-density single-nucleotide polymorphisms (SNPs) should enable genomewide association studies with tens of thousands of candidate-SNPs. This may allow systematic assessment of all candidate genes for complex traits such as psychiatric disease.

There are, however, caveats. First, although linkage analysis is, indeed, geared toward genes of moderate-to-large effect, a few examples of common disease alleles of modest effect have been detected by linkage analysis. Two examples are apolipoprotein E (ApoE), which predisposes to both a common form of Alzheimer dementia and to cardiovascular disease, and HLA, which predisposes to type I diabetes. Some simulations show that modest-effect genes (genotypic relative risk = 2) are detectable by linkage analysis with realistic sample sizes (~400 sib pairs) (Hauser et al. 1996). Second, enrichment of the sample for disease-allele carriers, by using clinical subtypes or biological endophenotypes, can augment the power to detect linkage. Examples of the success of this approach include early-onset familial breast and prostate cancer and, possibly, the aforementioned linkages to catatonic schizophrenia (15q13-15) and to the putative schizophrenia endophenotypes P50 (15q13-15) and the P50-antisaccade composite (22q11-13). Third, as mentioned (see the "Candidate genes" subsection, above), the pattern of conflicting results in association studies is at least as pronounced as that in linkage studies. Also, seemingly significant disease-marker associations are more likely than not to be spurious, because of the infinitesimally small odds of selecting a likely candidate gene from among the multitude of genes expressed in human brain. To curtail false-positive results, the requirements for statistical significance

would have to be much more stringent, even in samples substantially larger than those that are deemed feasible. A further complication arises from spurious results caused by sample stratification (in case-control designs), although this can be rectified by using family-based controls. Second, although systematic genome searches with SNPs can circumvent limitations in current designs that focus on a few favored candidate genes, there are potential drawbacks. For example, given the vast number of test results, there are questions concerning the statistical thresholds required to curb false-positive results. Also, in the presence of substantial allelic heterogeneity, there may never be enough power for the confident detection of modest gene effects, even with huge population samples. There are also questions about the efficiency of SNP mapping. For example, the number of required markers may have to be severalfold larger (hundreds of thousands, including noncoding SNPs), compounding the effects of multiple testing and augmenting an already substantial and costly genotyping effort. Also, a linkage disequilibrium map is needed for the entire genome, given the high variability across the genome. Further statistical, computational, and technological advances are needed to render this approach fully applicable.

Joint linkage and association.—It may be argued that a two-stage procedure would be more feasible and cost-effective than the aforementioned genomewide association strategy, namely, initial genome scan using linkage analysis followed by high-density association (linkage disequilibrium) mapping with candidate SNPs, only in target regions identified by the preceding linkage analysis (Baron in press). For example, pursuant to the initial accounts of linkage between schizophrenia and chromosome 6p21 (see the "Linkage Studies" subsection, above), Wei and Hemmings (2000) conducted a linkage disequilibrium test with densely spaced DNA markers (including SNPs) in the major histocompatibility complex region, which is mapped to 6p21. They showed that two haplotypes for the gene NOTCH4, which may be involved in neurogenesis, are strongly associated with schizophrenia ($P = .0000078$ and $P = .000011$, respectively). Of course, a potential drawback is that genes of minor effect may elude detection in the initial linkage stage.

The presence of allelic association can, in turn, augment the power of linkage analysis to uncover gene effects that might otherwise remain ambiguous. For example, a joint linkage and association test has revealed evidence for two complex disease genes: a major locus for psoriasis, on chromosome 6p21 (Trembath et al. 1997), and the type 1 angiotensin II receptor gene related to essential hypertension (Kainulainen et al. 1999).

Meta-analyses.—Sample-size requirements for linkage detection in complex traits depend on the underlying gene effects. For example, a locus with a genotypic relative risk of 2 may require 400 sib pairs for adequate power (Hauser et al. 1996), whereas a smaller relative risk may necessitate much larger samples (Risch and Merikangas 1996). The samples required for replication may be larger yet (Suarez et al. 1994). Large samples may augment weak linkage signals found in small data sets (if linkage is present) and are less susceptible to random statistical fluctuations that may lead to false-positive results in smaller samples. Because samples of this magnitude are generally not available in single studies, meta-analyses of multiple independent data sets have been proposed as an alternative. Several analyses have been reported that focus on chromosomal regions with prior evidence of possible linkage.

Gill et al. (1996), following up on a previous, smaller meta-analysis of chromosome 22q11-13 (Pulver et al. 1994*b*), analyzed a combined sample of 620 sib pairs in 574 pedigrees collected by 11 independent research groups. They focused on marker D22S278 because it showed the strongest evidence for linkage in three previous studies. When a narrow disease definition was used, the combined sib-pair analysis showed modest support for excess allele sharing at D22S278 ($P = .001$ or $P = .006$, depending on the availability of parental genotypes).

Subsequently, 14 research groups studied 14 markers on chromosomes 3p, 6p, and 8p in 567 pedigrees, including 687 independent sib pairs (Schizophrenia Linkage Collaborative Group for Chromosomes 3p, 6p, and 8p 1996). There was no evidence for linkage to chromosome 3p. When a narrow diagnostic model was used, suggestive support for linkage was observed for chromosomes 6p22-24 (sib-pair analysis, $P = .0004$ for the combined sample, $P = .001$ after removing the sample in which the first linkage finding was reported) and 8p21-22 (heterogeneity LOD score of 3.06, $P = .00018$ for the combined sample, LOD score of 2.22, $P = .0014$ with the original sample removed).

Recently, Levinson et al. (2000) analyzed candidate regions on chromosomes 5q, 6q, 10p, and 13q in 734 pedigrees, including 824 independent sib pairs, collected by eight research groups. They found modest support for linkage to chromosome 6q21-22 (a LOD score of 3.10, $P = .0036$, sib-pair analysis; nonparametric LOD score of 2.47, $P = .0046$; recessive LOD score of 2.47), with or without the sample in which linkage evidence was first reported. Weak support for linkage was observed on chromosome 10p11-15, with no evidence for linkage to chromosomes 5q or 13q.

At face value, these multicenter studies support previously reported linkage to some chromosomal regions (6p, 6q, 8p, and 22q), although the evidence is far from conclusive in spite of the sizable sample. The evidence in other implicated regions (10p and 13q) is substantially

weaker than that in the original reports. However, there are drawbacks that limit the interpretation of results (Rice et al. 1997). These include differences among samples—in ascertainment, diagnostic and laboratory methods, marker density and informativeness, or other factors—and possible selection bias resulting from (1) the inclusion of the original positive data sets or (2) the proclivity of researchers to study more intensively chromosomal regions in which they already have evidence of linkage or to select these regions prior to others, to the exclusion of a more systematic study of the genome. A potential bias of this type may have occurred in the 22q-multicenter study (Gill et al. 1996), which included the original samples with linkage evidence at marker D22S278.

Meta-analyses may be useful in guiding the search for disease genes. However, in most cases, a single sizable study involving a systematic genomewide search (or a set of studies with a common design) is preferable to a post hoc meta-analysis of multiple data sets collected under various conditions. Several such studies are under way.

Novel analytical models.—Most current models do not allow the simultaneous consideration of susceptibility loci from various chromosomal regions. Instead, they treat separate disease loci as if they were independent of each other. As a result, these models may not have sufficient power to detect the various genes involved in complex disease, in particular genes of small effect. Recently, new statistical methods have been developed to address this issue. For example, Cox et al. (1999) described an approach to assessing statistical interactions between different chromosomal regions whereby the evidence for linkage at one region is taken into account in assessing the evidence for linkage elsewhere in the genome. Using this approach, they showed an interaction between loci on chromosomes 2 and 15 that increases susceptibility to non–insulin-dependent diabetes (NIDD1). Interestingly, conventional linkage analysis failed to detect linkage to chromosome 15 in the initial genome scan. Because the genetic complexity of schizophrenia appears comparable to that of diabetes, this example is of potential interest. The use of other novel techniques that involve neural networks is proposed to examine the inheritance of all markers jointly over the entire genome (Lucek et al. 1998; Hoh and Ott 2000). This approach may uncover interactions among the multiple genes that underlie complex disorders such as schizophrenia. Power to detect genes of small effect can also be increased by methods that analyze multiple tightly linked markers, an approach that can extract more information on genetic linkage than is provided by existing statistical models (Zhao et al. 2000). It may also be possible to enhance the abilities of linkage and association analysis to detect genes of small effect by the combined use of path analysis, segregation analysis, and linkage/association analysis (Rao and Province 2000). This method may allow systematic examination of multiple risk factors, both genetic and nongenetic. Finally, the recent emergence of technologies based on microarrays (DNA chips) may enable an extensive evaluation of interactions among thousands of genes in the entire genome, a task that exceeds the capacity of current linkage and association mapping (Ott and Hoh 2000).

Summary and Outlook

Methodological issues notwisthanding, the available evidence supports multiple candidate regions as possible sites for schizophrenia-susceptibility genes—in particular, chromosomes 1q, 4q, 5p, 5q, 6p, 6q, 8p, 9q, 10p, 13q, 15q, 22q, and Xp. However, as with other complex diseases, not all studies agree. Most of the positive results are at the suggestive level; and the chromosomal regions implicated are large, thereby complicating the search for disease genes. It remains to be seen which, if any, of these hypothesis-generating findings will result in gene discovery. The definitive studies have yet to be done. In particular, (1) the collection of large-scale, well-characterized data sets (including detailed phenotypic information and cell lines from extended pedigrees, sib pairs, simplex families, and population-based case-control samples) using common, standardized research protocols; (2) marker-intensive genomewide searches for linkage and association, using the ever-improving genomic maps and gene catalogue; (3) application of novel technologies such as DNA pooling, DNA-chip methods, and high-speed SNP testing, as well as advanced statistical and biocomputing tools. These approaches are better suited than hitherto published efforts to the identification of genes for schizophrenia and to the improvement of cost-effectiveness. All the same, existing studies with promising results need not await the completion of the more definitive large-scale efforts such as phenotypic refinement, application of new statistical tools, and intensive molecular studies of candidate regions may bear fruit in some cases. It may well be that genes of moderate-to-large effect will be the first to be identified, if such genes exist. The search for multiple genes of minor effects will be more painstaking.

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