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LINKAGE ANALYSIS IN PSYCHIATRIC DISORDERS: The Emerging Picture

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■ **Abstract** Gene finding in genetically complex diseases has been difficult as a result of many factors that have diagnostic and methodologic considerations. For bipolar disorder and schizophrenia, numerous family, twin, and adoption studies have identified a strong genetic component to these behavioral psychiatric disorders. Despite difficulties that include diagnostic differences between sample populations and the lack of statistical significance in many individual studies, several promising patterns have emerged, suggesting that true susceptibility loci for schizophrenia and bipolar disorder may have been identified. In this review, the genetic epidemiology of these disorders is covered as well as linkage findings on chromosomes 4, 12, 13, 18, 21, and 22 in bipolar disorder and on chromosomes 1, 6, 8, 10, 13, 15, and 22 in schizophrenia. The sequencing of the human genome and identification of numerous single nucleotide polymorphisms (SNP) should substantially enhance the ability of investigators to identify disease-causing genes in these areas of the genome.

INTRODUCTION

Since 1950, genetic causes have been identified for many diseases for which the patterns of inheritance are clear. Linkage analysis in large pedigrees, followed by positional cloning, has become the method of choice for identifying the genes responsible for Mendelian disorders. Application of these techniques to disorders whose inheritance patterns and phenotypes are complex has pointed inconsistently to many regions of the genome where disease-susceptibility alleles may lie. However, these studies raise methodological, statistical, and phenotypic questions that have led to great skepticism about the veracity of the results.

For psychiatric disorders, the Freudian emphasis in the first half of the 1900s on early experience as a prominent cause of psychiatric symptoms led the public and clinicians to regard these disorders as induced and, therefore, nongenetic. Unfortunately, early, highly publicized positive-linkage findings in both bipolar disorder and schizophrenia turned out to be less persuasive than originally reported

and reinforced this mistaken impression. A wealth of family data confirms that these diseases have as strong a genetic component as many other complex disorders, including coronary artery disease, inflammatory bowel disease, asthma, and noninsulin-dependent diabetes mellitus. Over the past 10 years, substantial evidence has emerged that many of the modest-linkage regions reported for bipolar disorder and schizophrenia may in fact harbor disease-susceptibility alleles. Although in each individual case the alleles may be weak and insufficient on their own to produce disease, they may still be common and have a large population effect. This review details the strong evidence for many psychiatric disorders as being highly heritable and measurable traits and examines the emerging evidence that there are regions of the genome that are very likely to harbor disease alleles for the two most-extensively studied psychiatric diseases, schizophrenia and bipolar disorder.

INHERITANCE PATTERNS IN PSYCHIATRIC DISEASE

The following basic principles have been learned about diseases like cystic fibrosis and sickle cell anemia that follow simple Mendelian patterns of inheritance. For each disease, a single gene, or a small number of genes, may harbor any of a large number of rare mutations. Each mutation alone is both necessary and sufficient to produce a disease phenotype and, therefore, will be more easily detectable across family studies. In contrast to this, complex genetic disorders do not run in families in clearly identifiable Mendelian patterns. The following general observations apply to complex genetic disorders. First, they are common in the general population. Second, disease concordance is less than 100% in monozygotic twins. Third, the severity of the illness varies greatly among affected individuals. Fourth, the genetic contribution to the disease is often substantial but does not explain the full susceptibility to the disorder, implying that the environment makes a substantial contribution to risk. Fifth, the risk of disease is significantly less in second- and third-degree relatives than is observed for Mendelian diseases. Sixth, diseased individuals are often found in both the maternal and paternal lineage. The conclusions to be drawn from this are that (*a*) there may be multiple disease alleles that increase one's individual risk, but each allele only increases the risk a certain amount; and (*b*) genes do not explain the entire risk, but other environmental/nongenetic factors are also involved.

EPIDEMIOLOGY OF SCHIZOPHRENIA AND BIPOLAR DISORDER

Family and twin studies clearly demonstrate a strong genetic component for autism, bipolar disorder, and schizophrenia. Of the adult psychiatric disorders, bipolar disorder and schizophrenia have the strongest genetic basis. The distinctions between

these disorders were recognized as early as 1899 by Emil Kraepelin. He first described a syndrome called dementia preacox, what is now known as schizophrenia, and subsequently described a syndrome with prominent mood symptoms, manic-depressive insanity, that is now called bipolar disorder. In fact, he realized at that time that families appeared to express a hereditary component to their mood symptoms. The rise and popularity of Freudian ideas as well as those of other psychoanalysts like Menninger who questioned the diagnostic classifications of Kraepelin led psychiatrists and the public to dismiss the possibility of identifying underlying genetic distinctions. The advent of a number of treatments for bipolar disorder and schizophrenia, including mood-stabilizing lithium and early antipsychotic medication, as well as accumulating family and twin data led to a resurgence of interest in these diseases as distinct, identifiable entities that might have genetic causes.

Modern diagnostic criteria divide schizophrenia and bipolar disorder into separate disease entities, and these distinctions have clinical and genetic support. In fact, clinical psychiatric researchers have spent significant efforts in determining that these diagnostic distinctions can be made reliably. Structured interviews have been developed based on the diagnostic scheme codified in the Diagnostic and Statistical Manual of Mental Disorders (DSM). Although these diagnoses may not reflect the underlying genetics of the disorders, the screening tools have high interrater reliability for certain diagnoses and reflect genetic distinctions for some diagnoses (124) (see below). The majority of linkage studies rely on the diagnostic categories established in the third revised edition of the DSM (DSM-III-R) (4) or the more recent fourth edition (DSM-IV) (5).

Bipolar Disorder: Diagnosis and Inheritance

Using modern diagnostic criteria, bipolar disorder belongs in the mood disorder family of illnesses, which are typified by their prominent mood-altering symptoms. The most salient feature of bipolar disorder, often called bipolar I disorder (BP I), is the presence of manic episodes characterized by distinct periods where mood is elevated, with additional symptoms including inflated self-esteem, grandiosity, decreased sleep, rapid speech, agitation, and excessive involvement in pleasurable activities. In its most severe forms, mania often includes hallucinations and delusions. Several related forms of mood disorder are also recognized, including bipolar II disorder (BP II) and schizoaffective disorder (SA). BP II is the occurrence of repeated episodes of major depression with manic-like episodes that are not as severe as those described above. Patients with schizoaffective disorder appear to have both components of schizophrenia and components of bipolar disorder, that is, they have periods where they have prominent depressive or manic symptoms at the same time that they have the major symptoms of schizophrenia. In order to distinguish this syndrome from bipolar disorder with psychosis, patients must also have hallucinations and delusions in the absence of any mood symptoms. Two forms of schizoaffective disorder have been

distinguished: (*a*) schizoaffective disorder–bipolar type (SAM) in which a manic episode is part of the patient's presentation and (*b*) schizoaffective disorder–depressive type (SAD) in which only major depressive episodes are part of the presentation.

Strong evidence that bipolar disorder has a substantial genetic component can be easily appreciated from over 30 years of family and twin studies. There are at least 20 studies in which the risk of having bipolar disorder in relatives of bipolar probands has been evaluated using modern diagnostic criteria for BP I. Eight of these studies have included control subjects and show an approximately sevenfold increased risk to first-degree relatives of BP I probands (70, 71, 81, 97, 113, 131, 177, 180). Furthermore, unipolar major depression and BP II disorder are found with increased frequency in relatives of BP I probands, whereas schizophrenia is not (70, 81, 97, 113, 166). It is noteworthy that schizoaffective disorder–manic subtype (SAM, schizoaffective disorder with a current or previous episode of mania) is also found more frequently in the families of BP I probands (70). Several groups have remarked on a parent-of-origin effect on the relative risk and inheritance pattern of bipolar disorder, but the extent to which these factors influence risk is unclear. However, lifetime risk of affective disorder in the relatives of bipolar probands increases both with early age-of-onset (70) and with number of affected relatives (166).

Twin studies also support a substantial genetic contribution to bipolar disorder, with a number of studies using modern diagnostics that show an elevated risk in the monozygotic (MZ) co-twin of a bipolar proband relative to that seen in dizygotic (DZ) co-twins. The proband-wise concordance rates vary from 36%–79% for MZ co-twins to 0%–8% for DZ co-twins (2, 19, 26, 99, 169). Two of these studies found a low concordance rate between MZ twin pairs. However, each utilized either questionnaires or hospital-note-based diagnoses and may have underestimated the cases of bipolar disorder present in their samples (26, 99); thus, the MZ concordance rate is likely to be higher, in the range of 60%. Although twin studies indicate there is a substantial genetic component to bipolar disorder, they also make clear that nongenetic factors may contribute to the disease risk.

Most linkage studies of bipolar disorder analyze several diagnostic groups. In general, there is a narrowly defined group that includes BP I, BP II, and SAM. As described above, the genetic justification for including these diagnoses is strong. Using the DSM-III-R, the interrater reliability is high for BP I ($\kappa = 0.83$), although slightly lower for BP II and SAM ($\kappa = 0.62$ and $\kappa = 0.49$, respectively) (59, 147). A broader diagnostic classification often includes recurrent unipolar depression (RUP), characterized by recurrent episodes of depression but without any history of mania. RUP has a high lifetime prevalence in the general population (4.4%) (178) but does not have a high recurrence risk for first-degree relatives of RUP probands, indicating that a substantial portion of the risk may be derived from noninherited causes. The rationale for including this diagnosis in a broader classification is that RUP is clearly an affective disorder and may be a less penetrant expression of a

bipolar gene segregating within a family. In more-recent linkage studies, the effect of broadening the diagnoses of the linkage findings is often evaluated, which is helpful in interpreting the results.

Schizophrenia: Diagnosis and Inheritance

Schizophrenia (SCZ) is a psychotic disorder characterized by the presence of hallucinations, delusions, disorganized speech or behavior, and the so-called negative symptoms that include flat or inexpressive affect, decreased interest in goal-directed behavior, and prominent disturbance in functioning at work or in the ability to care for oneself. Schizophrenia spectrum disorders are often included in genetic studies of schizophrenia. These SCZ-related disorders include schizophreniform disorder (SCZ without the disturbance in functioning) and other nonaffective forms of psychosis including: (*a*) brief psychotic disorder, a sudden but brief episode of psychosis with no long-term effect on functioning; (*b*) schizotypal personality disorder, behavior patterns that may include problems in interpersonal relatedness and odd speech, ideas, beliefs, or perceptual experiences; and (*c*) paranoid personality disorder, behavior patterns that include interpreting the actions of other as deliberately demeaning or threatening.

As with bipolar disorder, substantial evidence from family and twin studies indicates a strong heritable component for SCZ. Data have been pooled from a large number of European family and twin studies that were completed from 1920 to 1987 (76), and together these studies indicate that the lifetime risk of SCZ in the general population is approximately 1%. The pooled family data show that the risk to first-degree relatives is approximately 12-fold higher than in the general population, and the twin data show concordance rates of 48% for MZ twins and 16% for DZ twin pairs (61, 100, 129, 135, 168). A study in the United States that relied on twins who were inducted into the army demonstrated a slightly lower overall concordance rate than the European data but also showed that the MZ concordance rate was approximately three times the DZ concordance rate (135).

Many linkage studies have relied on a narrow diagnosis of schizophrenia that includes only SCZ and SA. Justification for this is provided by the studies of interrater reliability for these diagnoses (62) as well as other family studies. A number of linkage studies also include spectrum disorders, but the genetic relatedness to SCZ is more tenuous. Defining certain diagnoses as part of a spectrum of schizophrenic disease is based on the notion that there is a continuum of liability to schizophrenia, with the spectrum disorders possessing less liability (137). As with bipolar disorder, the rationale for including these diagnoses is to increase power by including family members with less-penetrant forms of the disease. Of course, power will only be increased if the additional family members share the same underlying susceptibility allele. If not, then the power is likely to decrease as locus heterogeneity and phenocopies are introduced into the analysis.

INTERPRETATION OF LINKAGE FINDINGS IN SCHIZOPHRENIA AND BIPOLAR DISORDER

Defining the Phenotype

The difficulties in finding disease genes for complex disorders are not unique to schizophrenia and bipolar disorder. There are only a handful of complex disorders for which chromosomal regions and/or genes have been convincingly identified by a linkage-based approach. These include apolipoprotein E in Alzheimer's disease with a region of chromosome 19 (134) and, more recently, *NOD2* in Crohn's disease (85, 128). Many factors may contribute to the apparent lack of success in identifying chromosomal intervals containing susceptibility alleles for schizophrenia and bipolar disorder. The lack of a quantifiable biological marker, as well as the feeling that behavioral disorders are intuitively less amenable to quantification, has led to considerable attention to understanding the nature of the phenotype and to establishing guidelines whereby these diagnoses can be made reliably between investigators and across studies. Good interrater reliability has been obtained for some diagnoses, as discussed in detail above. However, no clear consensus exists regarding the heritability of many of the spectrum diagnoses for either bipolar disorder or schizophrenia, and thus, there is no common format for deciding who is affected.

Two methods for addressing these diagnostic problems are being explored. The first and most obvious is to limit diagnoses to those in which a demonstrated strong genetic heritability and high interrater reliability is present. The disadvantage to this approach is the potential loss of power if affected family members are expressing a variable or less-penetrant version of the same underlying allele. A second method is to attempt to focus on phenotypes that may be simpler, more penetrant, or have a quantifiable phenotype. Such phenotypes have been called endophenotypes and have been identified from neurophysiological studies of affected patients and their family members. Two endophenotypes in schizophrenia have been extensively studied. The first is a sensory-gating deficit (35, 91, 105) measured by recording the P50 wave of the auditory evoked response. Sensory gating is a heritable neurophysiological trait, as evidenced in a twin study in which a significant portion of the variance in this trait was shown to be due to heritable factors (182). Sensory-gating deficits are hypothesized to represent underlying abnormalities in cognitive processing of the frontal cortex, and although abnormal gating is also found in some normal individuals, this deficit may be found in as many as 50% of patients with schizophrenia (64). A second well-studied neurophysiological endophenotype is an abnormality in smooth-pursuit eye movement (the inability to follow a slowly moving target) (37, 83, 150). Smooth-pursuit eye movement abnormalities have been hypothesized to be manifestations of the underlying information-processing deficits often seen in patients. Family and twin studies have demonstrated impaired tracking in unaffected first-degree relatives, and twin studies have also demonstrated increased heritibility (94).

Methods of Analysis

The availability of markers spaced across the genome has led to the use of linkage analysis as the sine qua non of family-based genetic studies. In the typical genome scan, markers [originally, restriction length polymorphisms (RFLPs); more recently, microsatellites; and in the future, single nucleotide polymorphisms (SNPs)] are used to follow the inheritance of chromosomal segments through a family, looking to identify genetic regions that are coinherited by family members with the phenotype or disease. Although traditional linkage analysis makes no assumptions in terms of disease etiology or pathogenesis, it does rest on several statistical assumptions including a known, or specifiable, mode of inheritance as well as sample sizes and numbers of genetic markers that are sufficiently large. Calculation of the overall likelihood that the disease in question in a particular family (or pedigree) is linked to a particular marker is represented by the lod score, i.e., the logarithm of the odds of linkage, between the marker and the disease (122).

There have been ongoing discussions in the literature about the most appropriate methods and family configurations to use in complex disorders where specification of the mode of inheritance is difficult (75, 77, 82, 102, 167, 173). Nonparametric methods, or allele-sharing methods, may be the most appropriate formats for studies of complex disease because they make no assumptions about the mode of inheritance, allele frequency, or penetrance, which are usually not known with any precision. However, these methods are generally not as powerful as parametric methods, when an appropriate genetic model is used.

Statistical Significance

Genetic mapping of disease loci relies on statistical parameters established to minimize the false-positive and -negative rates. For traditional parametric analyses, the thresholds of a lod score of 1.9 for suggestive linkage and a lod score of 3.0 for a significant linkage have been well established both on theoretical grounds and by numerous practical examples of linkage in the literature. For genome-wide studies, Lander & Kruglyak recommend the following thresholds to account for the large number of markers tested: 3.3 for lod score analysis and 3.6 for allele-sharing methods (104). The interpretation of significance for multifactorial genetic traits is complicated by the testing of multiple models—both genetic and diagnostic—and although testing of several models may be necessary to extract the maximum information from a particular group of pedigrees, it does require some adjustment in the significance level. For the purposes of this review, the standard criteria for assessing linkage is used (104), and no adjustments others than those provided by individual investigators are added. As an aid to interpretation of the many findings, information is provided about the consistency and number of models tested. Although the guidelines for interpretation of linkage data are addressed in all published linkage studies, linkage evidence in genomic regions that do not meet stringent criteria for significance in at least one study, but may

have multiple studies with modest or suggestive findings, is interpreted in a highly variable manner. As noted by Lander & Kruglyak, however, "without channels by which investigators can report such tentative hints of linkage, the discovery of disease genes may be delayed in an overzealous attempt to avoid all error" (104).

CURRENT STATUS OF LINKAGE DATA IN BIPOLAR DISORDER

Overview

Genetic studies in bipolar disorder have moved forward in sync with the field of human genetics. With the small number of markers available initially, investigators attempted to interpret the resulting linkage data using parametric linkage analyses that required specification of a genetic model, allele frequencies, and penetrance—none of which are known for bipolar disorder. Such criteria led to several high-profile reports of linkage to chromosome 11p15 [in the Amish population (52)] and chromosome Xq28 that could not be replicated. Since then, numerous individual studies, either partial or genome wide, have been performed using more informative sets of markers (microsatellites rather than RFLPs) and nonparametric methods of data analysis. Many of these studies have identified interesting regions of the genome that have then been followed up in a focused manner by other investigators. To date, genome scans have been published on seven independent multiplex family samples with genotyping of 258 pedigrees (Table 1).

TABLE 1 Characteristics of genome-wide scans of bipolar disorder undertaken in more than five pedigrees[a]

Study (first author, year)	Reference	Population	Pedigrees (n)	Affecteds (n)	Number of markers (n)
Coon 1993	(32)	Utah	8	51	328
Straub 1994	(163)	U.S./Israeli	47	NA	5–153/family
NIMH GI 1997		U.S.: Indiana,	97	320	318
Detera-Wadleigh (ch. 4, 7, 9, 18, 19, 20, 21)	(47)	Hopkins, Washington University, NIMH			127
Edenberg (ch. 3, 5, 15, 16, 17, 22)	(51)				74
Rice (ch. 1, 6, 8, 10, 12)	(146)				65
Stine (ch. 2, 11, 13, 14, X)	(160)				53
Detera-Wadleigh 1999	(45)	U.S.: NIMH/Amish	22	276	607
Friddle 2000	(67)	U.S.: Hopkins	50	236	267
Kelsoe 2000	(96)	U.S./Canada	20	43	443
Maziade 2001	(115)	Eastern Quebec	14	72	220

[a]Studies of fewer than five pedigrees, or those that present data from a single chromosome, are not listed.

ch., chromosome; NA, not available.

Collection of the largest single group of families was sponsored by the National Institute of Mental Health (NIMH). The NIMH Genetics Initiative was formed in 1988 to establish an archival resource for genetic studies (125). Four sites were chosen for the collection of bipolar disorder pedigrees, Indiana University [J. Nurnberger, principal investigator (P.I.)], Johns Hopkins University (J. Raymond DePaulo, P.I.), the NIMH Intramural Research Program (E. Gershon, P.I.), and Washington University of St. Louis (T. Reich, P.I.). A genome-wide scan of 97 families collected by this collaborative group investigated 319 markers at an average spacing of 10 cM and was presented in a series of papers in 1997 (47, 51, 146, 160). These samples have been made available to researchers and are frequently used as the basis for a replication sample of preliminary findings. Although not listed in Table 1, genome scans have been published in single, large, and/or isolated families (discussed below) (20, 65). Several additional scans have been reported at meetings [The Wellcome Trust U.K.–Irish Bipolar Sib-pair Study (12) and a study from the University of Bonn, Germany (29)], and findings presented at the World Congresses of Psychiatric Genetics can also be found in the literature (43, 44). A selection of the most promising and reproducible findings in bipolar disorder are presented, whereas preliminary data presented at meetings are not discussed. Review of the published literature indicates that the most persuasive linkages are found on chromosomes 13q32, 21q22, and 22q11-12. Because virtually all of chromosome 18 has been implicated in bipolar disorder, the status of evidence for linkage on this chromosome is reviewed. Finally, several interesting regions that have been identified in single or small groups of families on chromosomes 4p and 12q are addressed.

Chromosome 13q32

In genome scans of multiplex pedigrees, a potential susceptibility allele for bipolar disorder on chromosome 13q32 has been identified. Table 2 demonstrates the relative positions of the markers, the linkage results, and the models tested in these scans. Previous studies have also suggested a potential locus for schizophrenia on this chromosome, and positive linkage results for schizophrenia (discussed below) are shown for comparison.

The strongest evidence for linkage to bipolar disorder was observed in a study by Detera-Wadleigh et al. as part of a large genome-wide screen of 22 families (45). Multipoint linkage results showed excess allele sharing in the region of D13S1271–D13S779 for both narrow and broad diagnostic groups (lod 3.4, $P = 0.000039$, and lod 3.3, $P = 0.000051$, respectively). The report from the NIMH Genetics Initiative (160) also noted excess allele sharing for chromosome 13 at marker D13S800 ($P = 0.04$) and marker D13S793 ($P = 0.02$), which are approximately 2 Mb proximal to D13S1271. Additional support for these findings comes from the study by Kelsoe et al. (96) that found a two-point lod score of 2.4 at D13S154, approximately 4 Mb proximal to D13S1271, under a recessive genetic model and broad diagnostic scheme (BP I, BP II, SAM, and RUP). Suggestive lod scores were also found for

TABLE 2 Summary of genome-wide-scan results on chromosome 13q32

Marker	Position (Mb)[a]	Disorder	Linkage evidence lod or NPL (p value)	Reference	Analysis type[b]	Phenotype[c]
D13S800	74.8	BP	0.50 (0.04)	(160)	N	BP I, SAM
D13S170	82.7	SCZ	1.83 (<0.03)	(155)	N	SCZ, SA
D13S154	98.6	BP	2.40	(96)	R	BP I, BP II, SAM, RUP
D13S793	100.6	BP	1.12 (0.02)	(160)	N	BP I, SAM
D12S128	101.6	SCZ	~2	(110)	D	SCZ
D13S1271	102.6	BP	3.30 (0.000051)	(45)	N	BP I, BP II, SAM, (+/−)RUP
D13S779	104.2	BP	3.40 (0.000039)	(45)	N	BP I, BP II, SAM, (+/−)RUP
D13S779	104.2	BP	~1	(115)	NA	BP I
D13S779	104.2	SCZ	~1	(115)	NA	SCZ
D13S779	104.2	SCZ-BP	~1.5	(115)	NA	BP I, SCZ, SAD
D13S779	104.2	SCZ	4.42	(23)	R	SCZ, SA, SPD, PPD, NAPD
D13S225	104.3	BP	2.22	(96)	R	BP I, BP II, SAM
D13S174	105.8	SCZ	4.18 (0.00002)	(21)	N	SCZ, SA
D13S796	111.6	BP	2.34	(96)	D	BP I, BP II, SAM, RUP

[a]Position on the Human Genome Browser, August 2001 freeze, http://genome.ucsc.edu/.

[b]R, parametric, recessive; D, parametric, dominant; N, nonparametric; NA, not available.

[c]SCZ, schizophrenia; SA, schizoaffective disorder; BP I, bipolar I; BP II, bipolar II; SAM, schizoaffective manic; RUP, recurrent unipolar depression; SAD, schizoaffective depressed; SPD, schizotypal personality disorder; PPD, paranoid personality disorder; NAPD, nonaffective psychotic disorder.

two other markers, D13S225 and D13S796. In the genome-wide scan by Friddle et al., the maximum heterogeneity lod (hlod) in this region was approximately 0.4 (67), and in the genome-wide scan by Maziade et al., the lod was 1.0 (115).

The evidence for a susceptibility allele is encouraging because the majority of genome-wide scans (three of the five total in multiplex pedigrees) have signals in this region. A strong result was found in the study by Detera-Wadleigh et al. (45), suggestive results in the study by Kelsoe et al. (96), and moderate findings in the NIMH genetics initiative study. Moreover, two additional genome-wide scans are not completely negative in this region. However, most genome scans in small or isolated populations have not reported this locus. Thus, on balance, there probably is a susceptibility allele in this region. The observation of linkage signals in the majority of studies attempted suggests that should a susceptibility allele be found it may have a substantial population impact.

As shown in Table 2, strong signals for these markers have also been found in schizophrenia. There are several possible explanations: First, schizophrenia

and bipolar disorder share a common genetic basis because they are a single disorder with alternative phenotypic expression. As described earlier, family and twin studies, however, do not support this interpretation. Second, each disorder is multigenic, and each shares one or more underlying sub- or endophenotypic traits. Clinical overlap between the disorders is well described and includes many of the manifestations of psychosis. A simple explanation for this is that the findings of linkage in both disorders represent a susceptibility allele for such a phenotype that is common to both. A recent study by Maziade et al. (115) begins to address this issue by simultaneously scanning patients with bipolar disorder and schizophrenia. At marker D13S779, they observe a lod score of 1.5 for a combined phenotype that includes SCZ, BP I, and SAD.

Chromosome 21q22

Linkage to chromosome 21 was first reported by Straub et al. in 1994 (163) as part of an ongoing genome-wide scan. In a study of 47 families, they identified a single family with 18 affected members, which produced a lod score of 3.41 at the marker PFKL locus under a dominant model with a broad phenotype that included BP I, BP II, and RUP. In the analysis of all 47 families, the lod score at this marker was negative, although a multipoint lod score of 2.80 was reported 30 cM away. Analysis of 95 sib-pairs using nonparametric methods including affected pedigree method (APM) and affected sib-pair (ASP) analyses gave mixed results. The APM produced a *P* value of 0.0003, whereas the ASP method did not show excess allele sharing.

These results were followed up by Gurling et al. who tested three chromosome 21q22.3 markers in 6 Icelandic and 17 English pedigrees (79). Using a dominant model that included only BP I and BP II as affecteds, they obtained a two-point lod of 1.28 at D21S171, whereas no positive lod scores were obtained for the other two markers. Using a broader model that included unipolar depression, the ASP analysis showed excess allele sharing at D21S171 ($P = 0.001$) (79). The complete sequence of chromosome 21 is available, thus the precise physical location of markers can be determined. PFKL is located very close to marker D21S171, separated by only 0.5 Mb. Detera-Wadleigh et al. provided additional evidence for a locus on chromosome 21q22.3 (46). Using 18 markers located on 21q in a sample of 22 multiplex bipolar pedigrees, several individual markers under both dominant and recessive models yielded lod scores between 1.0 and 2.0. Maximum allele sharing was detected $\sim$35 cM proximal to the PFKL locus, under a diagnostic model including BP I, BP II, and SAM ($P = 0.0008$). Modest excess allele sharing was also observed for several markers closer to PFKL. In an overlapping three-marker multilocus ASP analysis, excess allele sharing was detected among HMG14, D21S266, and S21S212 in the more distal region of chromosome 21 and closer to PFKL for both the restricted and broader diagnostic grouping ($P = 0.0002$ and 0.0001, respectively). In a three-marker analysis including the two markers that previously were reported as positive, PFKL and D21S171 revealed modest allele sharing ($P = 0.0095$ and 0.0086, respectively).

The strongest evidence for linkage was provided by Aita et al. (1) in a extension of the original Straub dataset (163). An additional 31 markers were genotyped on 21q with an average marker spacing of <2 cM (1). The maximum two-point lod score under heterogeneity was found at D21S1260, approximately 2.9 Mb from PFKL (lod = 3.35, $P = 0.000156$), under a dominant model with a broad phenotype similar to the original study including BP I, BP II, SAM, and RUP. Although the study by Aita et al. did include the original family that provided the most significant evidence for linkage in the original Straub report, its removal from analysis had little effect on the results, suggesting that the signal in this study was the result of multiple families. Further, this study has an advantage in that it took an affecteds-only approach, avoiding the problems associated with unaffected pedigree members having the disease genotype. Recently, Kelsoe et al. reported a two-point lod score of 2.04 under a broad phenotype (BP I, BP II, SAM, and RUP) with dominant inheritance (96). Unfortunately, surrounding markers were not positive, and no multipoint analysis was presented. Similarly, Maziade et al. (115) found a lod of 2.03 in their genome-wide scan.

Negative or mixed results on chromosome 21 have been obtained in several smaller studies. Byerley et al. reported genotyping of seven chromosome 21 markers in six bipolar pedigrees (24). Two-point lod-score results were negative for the markers tested, and no excess allele sharing was detected. Similar results were obtained in a study of three markers in two large Danish pedigrees in which no two-point lod scores >1 were found (58).

Several large genome-wide scans do not support the earlier data on chromosome 21. In the 97 families collected by the NIMH Genetics Initiative, ASP analysis using 20 markers on chromosome 21 revealed little excess allele sharing (47). Because the diagnostic models were somewhat different from those reported previously, the analysis was repeated using the earlier diagnostic scheme without significantly changing the results. However, in a four-locus model, they obtained an impressive P value ($P = 0.0009$; D21S1254, D21S265, D21S1252, D21S1440) with a broad model that included RUP. These markers span 12.2 Mb and are 6.6 Mb proximal to PFKL. Using multipoint analysis, the study by Friddle et al. obtained an hlod of 1.0 for distal 21q markers (67).

In summary, the only report to achieve statistical significance is the expanded dataset of Aita et al. (1), with the caveat that no adjustment was made for the multiple models tested. However, two additional reports by Kelsoe et al. (96) and Detera-Wadleigh (46) meet the criteria for suggestive linkage. Furthermore, two small studies without sufficient power to rule out a chromosome 21 locus did not observe linkage (24, 58). However, the study by Friddle et al., which had sufficient power to detect a locus should it account for bipolar disorder in greater than 50% of the families, did not find evidence for linkage to 21q22 (67). On balance, over half of the genome scans reported display suggestive results in this region, and thus a susceptibility gene identified here could have a substantial population impact. Fortunately, the sequence of chromosome 21 is available in the databases (80), with a finite fraction of the genes mapping to the 21q22 region. Access to extensive

SNP maps in this region should rapidly allow for the identification of a causative allele, should one exist (48).

Chromosome 22q11-12

An increase in the frequency of both schizophrenia and bipolar disorder has been noted in patients with velo-cardio-facial syndrome (VCFS), which maps to chromosome 22q11, and positive linkage results have been obtained with both diseases. For comparison, the location and results of markers on chromosome 22 in both bipolar disorder and schizophrenia are presented in Table 3. Evidence of linkage was first presented by Lachman et al. (103) in 17 families using a dominant model and BP I, BP II, SA, and RUP on 22q. In a subset of these families, a maximum lod score of 2.51 was found at D22S303 (103). Using an expanded group of families, a genome-wide scan performed by Kelsoe et al. continued to find support for chromosome 22 (96). A maximum two-point lod score of 3.84 was obtained at D22S278, located approximately 12 Mb distal to D22S303, and six other nearby markers produced lod scores >1.0. These results were obtained under a dominant model that included only BP I, BP II, and SAM. Eight informative families were then used for multipoint analysis, resulting in a maximum lod score of 3.1 at D22S278. In an attempt at replication, 57 additional families were obtained from the NIMH Genetics Initiative and genotyped for these same markers (96). A maximum two-point lod score of 1.58 was obtained for marker D22S278; however, this was obtained under a relaxed diagnostic model that included RUP in addition to the above diagnoses. Additional positive lod scores were obtained for

TABLE 3 Summary of genome-wide-scan results on chromosome 22q11-12

Marker	Position (Mb)[a]	Disorder	Linkage evidence lod or NPL (p value)	Reference	Analysis type[b]	Phenotype[c]
D22S446	18.7	SCZ	2.16 (<0.01)	(155)	N	SCZ, SA
D22S303	~20.9	BP	2.51	(103)	D	BP I, BP II, SAM, RUP
D22S533	22.4	BP	2.46	(51)	P	BP I, BP II, SAM, RUP
D22S419	22.5	BP	2.72	(96)	R	BP I, BP II, SAM
D22S689	25.5	BP	2.10 (0.00094)	(45)	N	BP I, BP II, SAM, RUP
D22S685	31.2	BP	2.10 (0.00094)	(45)	N	BP I, BP II, SAM, RUP
D22S278	33	BP	3.84	(96)	D	BP I, BP II, SAM
D22S283	33.3	SCZ	1.64 (<0.02)	(155)	N	SCZ
IL2RB	34.1	SCZ	2.82	(140)	D	SCZ, SA
D22S55	~49	SCZ	1.17	(33)	R	SCZ, SA

[a]Position on the Human Genome Browser, August 2001 freeze, http://genome.ucsc.edu/.

[b]R, parametric, recessive; D, parametric, dominant; N, nonparametric; P, parametric, not specified.

[c]SCZ, schizophrenia; SA, schizoaffective disorder; BP I, bipolar I; BP II, bipolar II; SAM, schizoaffective manic; RUP, recurrent unipolar depression.

a second locus (D22S419), although a recessive genetic model was used. Previous genotyping in the entire NIMH Genetic Initiative sample of 97 families revealed a multipoint lod of 2.5, slightly proximal to D22S533 (51).

These data have been supported by Detera-Wadleigh et al. in 22 multiplex pedigrees from the NIMH Intramural Program. Multipoint linkage data showed excess allele sharing between D22S689 and D22S685 under a broad diagnostic model (BP I, BP II, SAM, and RUP) with $P = 0.00094$ (45). This region, however, is somewhat proximal to that observed by Kelsoe et al. (96). Multipoint analysis of chromosome 22 in the study by Friddle et al. produced hlod scores of <1.0 (67). Maziade et al. saw no evidence for linkage on chromosome 22 (98).

Thus, the majority of genome-wide scans (three out of five total in multiplex pedigrees) have signals in this region. Strong results were found in the Kelsoe study (96) and suggestive results found in both the NIMH (51) and the Detera-Wadleigh (45) studies. Confidence in this region is tempered by the testing of several genetic models in the Kelsoe study as well as the slightly different phenotype definition that included the RUP phenotype. As with chromosome 21, the relatively small size of the chromosome, coupled with the availability of sequence and high-density SNP maps of the region, should allow for rapid identification of disease genes if they exist (39, 123). Evidence for the involvement of this region in schizophrenia is presented below.

Chromosome 18

18p11.2 (MAFD1, MIM125480) Chromosome 18 has the distinction of being the most thoroughly investigated, as well as the most confusing, chromosome in bipolar disorder. Many published linkage scans, including several reanalyses of data, specifically address putative positive regions. Increasingly, the location of microsatellites on the physical map of the genome is available. Because much of chromosome 18 has been implicated in bipolar disoder, Table 4 is presented to identify the current relative position of the markers.

In 1994, Berrettini et al. first reported linkage to markers in the pericentromeric region of chromosome 18 as part of a genome-wide search for bipolar vulnerability genes (16). Two diagnostic models were tested in 22 multiplex pedigrees consisting of 368 individuals. Positive results were obtained under a broad diagnostic model (BP I, BP II, SAM, and RUP). Using an ASP analysis, they obtained a maximal P value at marker D18S21 ($P = 0.0004$). This was followed by a report of 28 families by Stine et al. (161). With ASP analysis, evidence for excess allele sharing was found for pericentromeric markers using a similar diagnostic model in families with paternal inheritance ($P = 0.004$), although a later multipoint analysis did not show evidence of linkage (112). In this study, the most positive results obtained were for more distal markers on 18q (discussed below). Reanalysis of the original Berrettini data also demonstrated a paternal effect (69). Although both groups tested several diagnostic and statistical models, no corrections for multiple testing were made in the reported linkage data.

TABLE 4 Position of markers on chromosome 18

Marker	Position (Mb)[a]
D18S21	9.2
D18S32	NA
D18S53	12.3
D18S453	14.4
D18S36	33.0
D18S1145	48.3
D18S41	64.0
D18S51	71.0
D18S61	78.0
D18S541	81.2
D18S554	86.7
D18S70	90.0

[a]Position on the Human Genome Browser, August 2001 freeze, http://genome.ucsc.edu/.

In 1997, Berrettini et al. reported a further analysis of the same pedigrees including a small number of additional individuals (15). Using ASP analysis, the best result was obtained at marker D18S32 ($P < 0.00001$), less than 5 cM from D18S21, with a multipoint analysis of four markers in the region showing positive results ($P = 0.00008$). As presented, the data unadjusted for the multiple hypotheses tested constitute a suggestive linkage finding. Using these same pedigrees with additional markers, investigators again obtained suggestive findings (45).

Because of the importance of these data, the Tenth Genetic Analysis Workshop made available to investigators five datasets for analysis of chromosome 18, the results of which were published in a single volume of *Genetic Epidemiology* in 1997. Analyzing the data from over 1000 affected individuals in 185 families, Lin & Bale found significant excess allele sharing in their sib-pair analysis ($P = 2.8 \times 10^{-8}$) without confirming a paternal inheritance pattern (109). Interpretation of this study is hindered by the use of a single marker with no multipoint data presented, as well as inclusion of the original datasets from Berrettini et al. and Stine et al. Using a variety of analytic methods, others who have studied the total data set have found no evidence for linkage (38, 49, 50, 108), although several noted suggestive linkage in the original data set.

Although Berrettini and others (14, 68) consider that the linkage results on chromosome 18p11 constitute a confirmed linkage, several subsequent large genome scans do not completely support these results. A genome-wide scan of the 97 families collected in the NIMH Genetics Initiative did not produce positive results (47). Furthermore, a reanalysis of the same NIMH families utilizing the model-free

pedigree analysis approach was also negative (63). Using markers confined to the relevant region of chromosome 18, Knowles & collaborators at Columbia University, using a diagnostic model similar to the original model (a broad classification including BP I, BP II, and unipolar depression), were also unable to confirm the earlier results (15, 16) despite the excellent power in their sample of more than 300 sib-pairs (101). Using a diagnostic classification restricted to BP I patients, excess allele sharing was detected at D18S53 ($P = 0.0005$). Again, using a broad diagnostic scheme, Nothen et al. in Bonn, Germany, found minimal indication of allele sharing in paternal or maternal pedigrees (paternal, D18S453, $P = 0.054$; maternal D18S36, $P = 0.0064$) (126). ASP analysis for all families combined was not presented. A full-genome scan performed on the 22 pedigrees originally reported by Berrettini et al. (16) using their earlier diagnostic classification with additional markers showed a multipoint sib-pair analysis of only $P = 0.0011$, whereas a more restrictive diagnostic classification did achieve a suggestive P value ($P = 0.00054$) (45). Friddle et al., in an expansion and full-genome scan of the sample reported in Stine et al. (161), found no evidence for linkage on 18p (hlod <0.5) (67).

In summary, interpretation of the studies in the 18p11 region of chromosome 18 remains difficult. Clearly, no single study meets the criteria for significant linkage, although suggestive evidence for markers within 5 Mb of each other were found in the full-genome scan by the groups of Berrettini (16) and Knowles (101). The literature is relatively silent on how to interpret several positive findings in the face of an equal or larger number of negative findings for the same markers. Furthermore, if impressive P values are obtained for different diagnostic models, these cannot be considered as simple replications. A single replication study meeting the $P = 0.01$ criterion in the face of multiple negative studies must therefore be interpreted with caution, unless it can be clearly demonstrated that the negative studies were underpowered and thus unable to detect the effect. The absence of findings in the overwhelming majority of genome scans suggests that the initial observation may have been a false positive. Of course, it is impossible to rule out a gene that confers a very low risk of bipolar disorder. Continued discussion about the significance of these findings can be found elsewhere (9, 10, 13).

18q21-23 Linkage has also been reported on the other arm of chromosome 18 in the region of 18q21-23. In addition to the signal on 18p, Stine noted excess allele sharing at D18S41 ($P = 0.0004$), approximately 40 cM from the region on 18p implicated in the original report by Berrettini et al. (161). In a genome scan of two large Costa Rican families, two-point linkage analyses were performed under a nearly dominant model using a conservative diagnostic scheme that included only BP I and SAM (65, 116). Several markers that mapped to 18q22-23 yielded lod scores that were marginally positive (from 0.96–2.26) in each family individually as well as in the combined data set. Because these pedigrees were from the Central Valley of Costa Rica and were descended from a small number of founders several centuries ago, members of the family who were affected may have inherited a

chromosomal segment identical by descent (IBD) in the disease region from a common ancestor. For this reason, marker haplotypes were reconstructed, and a large region of approximately 40 cM displaying excess allele sharing was noted. The evidence for linkage and association was evaluated jointly in a test estimating the recombination frequency and proportion of disease chromosomes sharing a common allele to derive a linkage/asssociation-based lod score of 3.7 and 4.06 for the best markers (D18S554 and D18S70, respectively) (65).

Following these initially encouraging reports, several other groups investigated families for chromosome 18 markers. A Jewish Ashkenazi family and a Belgian family were genotyped for 14 markers, using a broad diagnostic classification (BP I, BP II, SAM, SAD, RUP, and single episode unipolar depression). Although no data in this study reached significance, in one of the families, several markers in the region of 18q21.33-q23 showed excess allele sharing (D18S51, $P = 0.0007$; D18S61, $P = 0.02$) as well as a multipoint lod score of 1.34 for these markers (41). In a follow-up of a patient sample reported some years earlier, Coon et al. genotyped 21 additional informative markers on chromosome 18, finding minimal, if any, evidence for linkage (31). As mentioned above, additional pedigrees with markers on chromosome 18 were analyzed at Johns Hopkins by Stine et al. (117). In contrast to their earlier study (161), the peak IBD score occurred at D18S541 ($P = 0.015$), approximately 25 cM from the earlier signal. It is interesting to note that a small parent-of-origin effect was again detected, but it was not consistently paternal. Finally, in addition to finding evidence for linkage on 18p, Nothen et al. reported nonparametric lod (NPL) scores of $\sim$2.0 in the region of 18q22-23 (126). Recently, a genome-wide scan from multigenerational pedigrees for Eastern Quebec identified a strong linkage result on 18q12 at marker D18S1145, located between the two other linkage signals on 18p and 18q (115). Of note, these data meet criteria for significant linkage following some adjustments for the number of hypotheses tested. At this time, it is difficult to conclusively determine if all the data on 18q results from a single locus or multiple bipolar loci.

Several recent genome-wide analyses do not support evidence for a major locus on 18q; however, a reanalysis of the NIMH Genetics Initiative data using nonparametric linkage analyses reported no positive lod scores from chromosome 18 (63). An enlarged set of 50 pedigrees, including the original families reported in Stine et al. (161), found no lod score greater than 1.0 on chromosome 18 (67). Finally, a recently published genome-wide scan of patients from San Diego and Vancouver found no lod score greater than 1.5 on chromosome 18 (96). These genome-wide scans represent data from over 1000 genotyped individuals with 544 affecteds. Additional linkage analyses may not resolve the question of whether a gene for bipolar disorder resides on chromosome 18. Therefore, on the assumption that there is a gene, albeit one with potentially modest effects, several groups have begun isolating cDNAs from chromosome 18 in order to isolate and test microsatellite and SNP markers within and near genes present there (18, 28, 149, 157, 174, 181).

Chromosome 12q23-24.1

In 1994, Craddock et al. reported familial aggregation of affective disorder and Darier's disease (keratosis follicularis) on 12q23-q24.1 (36). Subsequently, the gene for Darier's disease was identified as a sarcoplasmic/endoplasmic reticulum calcium-pumping ATPase, *ATP2A2* (150). Mutational analysis of this gene identified 17 novel mutations that showed some minimal evidence for clustering in the 3′ end of the gene in Darier's disease patients with neuropsychiatric phenotypes (88).

Further evidence for linkage to 12q has been obtained in two large families from the Saguenay Lac St-Jean region of Quebec, a settlement derived from the migration of a small number of founding families into this region in the 1830s (121). Parametric analysis of a single large pedigree under both dominant and recessive models identified several positive markers (lod = 1–1.61), and similar findings were obtained in nonparametric analyses. Unfortunately, reconstruction of haplotypes from these data did not identify a common haplotype, making it difficult to define the risk region further.

Two large Danish families with multiple affected members in several generations were genotyped for 16 markers in the aforementioned region of chromosome 12 (56). Under a dominant mode of inheritance, an affecteds-only analysis found a two-point lod score of 3.37 ($P = 0.00002$) at D12S1639, approximately 14 cM from D12S86. Although simulations determined this lod score to be significant, they only appear to have been attempted under one of the models tested. Haplotypes were constructed in each family, and a minimal overlapping region of 3.8 cM was observed in all but one bipolar patient.

In addition to the data obtained in Darier's disease and the large Canadian and Danish families, several genome-wide scans have detectable signals in this region. For markers at D12S1343-2070 (in the region of both ATP2A2 and the Quebec result), lod scores of 1.24 (45) and 0.75 (67) were reported. The NIMH Genetics Initiative (146) and Kelsoe et al. (96) found minimal evidence for linkage in the region of 12q23, as did Maziade et al. (115).

Suggestive lod scores have been detected in a small number of large multigenerational families, corresponding linkage signals have not been found in the large genome-wide studies of nuclear families. A susceptibility gene that accounts for the risk of disease in the large multigenerational families may be found in this region, although it is unlikely to be a general susceptibility allele for bipolar disorder.

Association analysis has been performed with several genes in this region. A case-control sample of 54 bipolar patients found an association between bipolar disorder and the 122-bp allele of a single tandem repeat polymorphism (STRP) in the first intron in phospholipase A1 (*PLA2*) (odds ratio = 0.42) (40). However, evidence for association was not obtained in independent studies using the STRP or other SNPs in the coding sequence of *PLA2A* (86, 87). Another gene in this region, *DUSP6* (dual specificity MAP kinase phosphatase 6), revealed no association in a case-control study of Japanese bipolar patients with a missense SNP in the gene

(170). Analysis of further SNPs within these genes and additional genes in the region will likely be required to identify the susceptibility alelle.

Chromosome 4p15-16

As part of a genome-wide search for bipolar genes in a large Scottish pedigree, Blackwood et al. found that a number of markers on chromosome 4 gave positive lod scores in a two-point analysis. Using a diagnostic model that included only BP I and BP II, and a dominant mode of inheritance, a lod score of 4.09 was detected at D4S394 (20). Adding 11 smaller families to the data reduced the lod score to 2.9 at this marker. However, testing for genetic heterogeneity supported linkage, with only 35% of families linked. Additional support for this locus comes from a study of two Danish families by Ewald et al. (57). In a study of 16 markers from chromosome 4p using a broader diagnostic model with dominant inheritance, no lod scores greater than 1 were detected. However, using a recessive model, a two-point lod score of 2.0 was obtained at D4S4394, with an empirical *P* value of 0.0006. Because the mode of inheritance was different than that of Blackwood et al., caution needs to be exercised in interpreting the Ewald study (57) as a clear replication.

In support of the original finding, Detera-Wadleigh et al. note that in one of their earlier studies they detected one family with a parametric lod score of 3.24 under a dominant model, using a narrow diagnostic model (BP I, BP II, SAM). However, multipoint analyses in their total set of 22 multiplex pedigrees were only positive for the broad diagnostic model, which includes RUP (D4S2408-2632, $P = 0.0022$) (45). Unfortunately, other genome-wide scans have shown only marginally positive results on chromosome 4p (67, 96, 116).

In summary, a susceptibility allele may exist in the large Scottish family, but it is unlikely to be found in a large number of bipolar families. Two genes, the Wolfram syndrome gene (*WFS1*) and the dopamine receptor 5 gene (*DRD5*), that lie in the region implicated by genome scans have been investigated using association analysis. Six SNPs within the coding region of *WFS1* were identified in DNA from bipolar patients; however, none segregated with the disease in families. Also, no association was found between a microsatellite marker near DRD5 and bipolar in a case-control study ($n = 120$) (6). More recently, Evans et al. have reported the building of a 6.9-Mb high-resolution BAC/PAC contig of this region and the identification of 57 expressed sequence tags (ESTs) and nine known genes. Resequencing of candidate genes and construction of a high-density SNP map of the region will facilitate linkage disequilibrium (LD) mapping across the putative risk region (55).

Summary of Findings in Bipolar Disorder

This review of the linkage literature has identified several chromosomal regions as likely candidate susceptibility loci. Table 5 summarizes the most significant

TABLE 5 Summary of most significant linkage findings in bipolar disorder

Chromosome	Reference	Families (n)	Most significant evidence for linkage[a] lod or NPL value	Multiple models genetic + phenotypic > 2	Replicated[b]	Encouraging data in same region[c] less than two studies within 10 Mb
4p15-16	(20)	12	4.10	Yes	Yes	Yes
12q23	(56)	2	3.37	Yes	No	No
13q32	(45)	22	3.40 (0.000039)	Yes	No	Yes
18p11.2	(45)	22	2.32 (0.00054)	Yes	No	Yes
18q12	(115)	21	4.03	Yes[d]	No	No
18q22	(65)	2	4.06 (0.0005)[e]	No	No	Yes
21q22	(1)	57	3.35	Yes	Yes	Yes
22q11-q12	(96)	20	3.84	Yes	Yes	Yes

[a]In cases where the same family sample was utilized in multiple reports, the linkage results for the study with the largest sample size are presented.

[b]Significant linkage in one study and replicated ($p < 0.01$) in independent sample.

[c]Original study and at least one additional study in an independent sample with suggestive evidence for linkage.

[d] Authors adjusted their significance level for number of hypotheses tested.

[e]Linkage/association-based lod score.

findings obtained in each region. As highlighted throughout the preceeding sections, most studies utilized multiple diagnostic and phenotypic models and require some caution in interpretation. Findings in several of these regions are nominally significant in a single study and have been obtained in an independent replication sample (4p15, 21q22, 22q22). The findings on 21q22 and 22q22 were detected in three or more studies of multiplex families and, if they represent true susceptibility alleles, may account for a more substantial portion of the risk than those seen for 4p15. Suggestive evidence for linkage for 12q23, 13q32, 18p, and 18q22 was found in more than one study. Although the evidence for a susceptibility allele on either end of chromosome 18 is not compeling.

CURRENT STATUS OF LINKAGE DATA IN SCHIZOPHRENIA

Overview

In contrast to bipolar disorder, there are several chromosomal regions that meet the more-stringent criteria for significant, suggestive, or confirmed linkage for schizophrenia. Historically, as with bipolar disorder, an initial strong positive report of linkage to chromosome 5q (156) was followed by a large number of studies that were unable to replicate the result (33, 60, 95, 107, 120, 165). Again, lack of replication led to scepticism in the genetics community and a feeling that there might be something inherently different and difficult about assessing behavioral phenotypes as opposed to other complex-disease phenotypes. Recently, reanalysis

TABLE 6 Characteristics of genome-wide scans of schizophrenia undertaken in more than five pedigrees[a]

Study (first author, year)	Reference	Population	Pedigrees (n)	Affecteds (n)	Type[b]	Number of markers (n)
Coon 1994	(33)	U.S.: Utah	9	35	FAM	329
Moises 1995	(120)	Iceland	5	37	FAM	413
Blouin 1998	(21)	U.S.: Maryland	54	276	FAM	452
Faraone 1998	(60)	NIMH GI–European American	43	96	FAM	459
Kaufman 1998	(95)	NIMH GI–African American	30	79	FAM	459
Levinson 1998	(107)	Australia/Philadelphia/ Iowa/New York	43	126	FAM	310
Shaw 1998	(155)	European/Caucasian	70	182	FAM + ASP	338
Straub 1997	(165)	Irish	265	961	FAM	>131
Rees 1990	(144)	England/Wales/Japan	13	75	FAM	298
Williams 1999	(179)	Britain	154	327	FAM + ASP	229[c]
Bailer 2000	(7)	Austria	5	17	FAM	388
Brzustowicz 2000	(22)	Canadian (Celtic/ German)	22	123	FAM	381
Ekelund 2000	(53)	Finland	134	308	FAM + ASP	370[c]
Schwab 2000	(153)	German/Israeli	7	196	FAM + ASP	463[c]
Stober 2000	(162)	German	12	57	FAM	356
Gurling 2001	(78)	British/Icelandic	13	68	FAM	365
Maziade 2001	(115)	Eastern Quebec	21	81	FAM	220

[a]Studies of fewer than five pedigrees, or those that present data from a single chromosome, are not listed.

[b]FAM, includes both extended pedigrees and nuclear families; ASP, affected sibling pairs.

[c]First tested as part of a staged approach in a smaller number of ASP.

of the original chromosome-5q families revealed that several pivotal markers were incorrectly mapped, thus resulting in erroneous lod score results (92). Table 6 details the large number of genome-wide scans of schizophrenia that have been published, many within the past three years (7, 21, 22, 33, 34, 53, 60, 78, 84, 120, 153, 165, 179). Successes have generally been achieved through careful diagnoses under a limited diagnostic scheme that does not include spectrum disorders whose genetic connection to schizophrenia is not fully understood. In general, fewer genetic models were tested per study, and there was somewhat more uniformity in the analytic methods. A selection of the most promising and reproducible findings in schizophrenia is noted, whereas preliminary data presented at meetings is not discussed. Review of the published literature indicates that the most persuasive linkages are found on chromosomes 1q21-22, 8p21, and 13q32. In each case, there is a significant study and a positive replication sample. Finally, the evidence for

a locus on chromosome 22 as well as recent linkage to a neurophysiological endophenotype obtained on chromosome 15 are discussed. As with bipolar disorder, an overview of other findings, including those presented in preliminary form at the World Congress on Psychiatric Genetics Chromosome Workshops, can be found in other reviews (8, 43, 44, 138, 171).

Chromosome 8p21 (SCZD6, MIM603013)

As part of an ongoing genome scan, Pulver et al. initially reported positive results that observed excess allele sharing at D8S258, using a narrow diagnostic group (SCZ and SA) in 57 primarily European families (141). Reanalysis of these families was performed using nonparametric methods after removal of uninformative families and inclusion of other informative families (21). The maximum NPL score was 3.64 ($P = 0.0001$, near D8S1771) and coincided with a parametric lod score of 4.54, under a dominant model assuming heterogeneity. In an attempt at replication, Pulver et al. then genotyped an additional 51 families for chromosome-8 markers, thereby obtaining a peak NPL score of 1.95 ($P = 0.023$) at D8S1752, approximately 3 Mb distal to D8S1771.

In a fascinating study investigating the role of phenotypic heterogeneity in these results, Pulver et al. reanalyzed earlier data with an eye to extracting the contributions on the linkage results from psychotic affective disorder and schizophrenia spectrum personality disorder diagnoses (142). First-degree relatives of affected family members were assessed for the presence of these other phenotypes. The most significant allele sharing was detected on chromosome 8p21 at D8S1771 (NPL $= 5.04$, $P = 2 \times 10^{-6}$), following inclusion of the diagnoses schizoid, schizotypal, and paranoid personality disorders, with the largest increases in allele sharing resulting from the inclusion of paranoid personality disorder in the diagnostic group.

The 8p21 findings of Pulver et al. (141) are also supported by the 1996 Irish Study of High-Density Schizophrenia Families (98). Fifteen chromosome-8 markers were genotyped in 265 families and analyzed under four diagnostic and four genetic models. Although the diagnostic grouping does not match a simple narrow versus broad framework, a maximum heterogeneity lod score of 2.34 was found at D8S258 (the same marker Pulver et al. noted), under a dominant model and broad phenotype (SCZ and SA plus other psychosis and related personality disorders).

A collaborative effort formed by reseachers at 14 institutions to investigate putative positive results on chromosomes 3, 6, and 8 (151) collected a large sample of new pedigrees and genotyped five markers on chromosome 8. The maximum heterogeneity lod score was obtained for marker D8S261 (hlod $= 2.22$, $P = 0.0014$), slightly proximal to previously reported markers. When the families previously reported by Pulver et al. were included in the analysis, an increased hlod of 3.06 ($P = 0.00018$) was found, providing continued support for an 8p21 locus.

Further support of these data has been obtained from a large number of other studies. In 1998, using a recessive model and a narrow diagnostic group that

only included SCZ, Shaw et al. found an NPL score of 2.25 at D8S439, ∼3 Mb distal to D8S1771 (155). Similar results were obtained from the NIMH Genetics Initiative for a subsample of 30 nuclear African-American families, with an NPL score of 2.27 and $P = 0.013$ at D8S1791, ∼15 Mb distal to D8S1771 (95). In 2000, strong support for this region was produced in the study by Brzustowicz et al. (22). In their 22 Canadian families, a maximum three-point hlod of 2.80 was obtained for D8S136, under a dominant model with a broad phenotype that included nonaffective psychotic disorder, schizotypal personality disorder, and paranoid personality disorder. In 2001, a study of 13 Icelandic and British families found a maximum hlod of 3.2 ($P = 0.0005$) at D8S1771, under a recessive model that included the diagnoses SCZ, SA, and functional psychosis (78). Evidence for linkage was not obtained in several studies (7, 34, 53, 84, 107, 115, 179), although most utilized small and/or isolated populations (7, 34, 53, 84).

In summary, the balance of evidence supports a schizophrenia susceptibility locus on chromosome 8. There are six reports of suggestive evidence of linkage, although several studies used differing diagnostic models, including a report that achieves significance under an expanded diagnostic model. Only three reports from large general population samples do not detect linkage to chromosome 8p21.

Chromosome 1q21-22 (SCZD9, MIM604906)

The single most significant finding in schizophrenia has been obtained by Brzustowicz et al. in set of 22 Canadian families as part of a genome-wide scan (22). Multipoint analysis found a maximum heterogeneity lod score of 6.50 ($P = 0.0002$) between markers D1S1653 and D1S1677 (12 cM), with a narrow diagnostic model and recessive inheritance. Although several models were tested, adjustments for the multiple hypotheses, even if conservative, would not have significantly altered the finding.

Although most prior studies have not detected chromosome 1 findings, several studies have reported positive findings. In a report on 70 families of European descent, Shaw et al. found a maximum heterogeneity lod of 2.40, using a narrow recessive diagnostic model (155). Recently, in the analysis of 13 Icelandic and British families, a five-point peak hlod of 3.2 ($P = 0.0003$) was detected using a narrow phenotype and recessive model (78). Furthermore, Schwab et al. found a multipoint lod of 1.04 at D1S2675, located ∼4 Mb from the finding of Brzustowicz (153). Interestingly, linkage to this region has been reported in bipolar disorder by Detera-Wadleigh et al. (45). Thus, it appears likely that there is a susceptibility allele in this region because of the strength of the findings. One extremely strong study [Brzustowicz et al. (22)] and two studies with strong replication of these results under similar diagnostic and genetic models (78, 155) also exist. However, linkage with these markers was not seen in the majority of studies and may indicate that this allele will not account for schizophrenia in a majority of families.

KCNN3, a calcium-activated potassium channel, was initially mapped to chromosome 22q11, where linkage to schizophrenia was found, but more recently it

has been remapped to the chromosome 1q21 region. This gene is an attractive candidate for schizophrenia because it belongs to a family of ion channels important to neuronal function. Furthermore, *KCNN3* contains two trinucleotide repeats, one of which is polymorphic. Although controversial, there is some evidence for inheritance of schizophrenia consistent with anticipation that has been associated at the molecular level with unstable and expanding trinucleotide repeats. Chandy et al. initially reported overrepresentation of the long alleles ($\geq$20 repeats) in a case-control study of schizophrenia (27). Support from two other case-control studies was obtained. However, a large number of family-based studies have not shown association with longer repeat alleles nor a tendency for instability between generations in a family [for review, see (127)]. Thus, the data indicate that large alleles at the *KCNN3* locus do not account for a substantial risk of schizophrenia, but additional data and meta-analysis will be needed to establish whether this locus is a risk allele of modest impact.

Other evidence for a locus on chromosome 1 comes from a rare t(1:11)(q42.1:q14.3) translocation that segregates with mental illness found in a single large Scottish family (159). However, this region is significantly distal to the linkage results obtained by others on chromosome 1. Nonetheless, cytogenetic abnormalities tend to implicate smaller regions than linkage studies do and can be extremely useful in locating disease genes. Blackwood & colleagues have cloned the chromosome 1 breakpoint and have identified two novel RNAs that they have named *DISC1* and *DISC2* (Disrupted-In-Schizophrenia 1 and 2) (119). *DISC1* has an open reading frame of 854 amino acids, and the predicted protein has structural homology to coiled-coil-containing proteins. Interestingly, many proteins with these domains are involved in axon guidance, intracellular transport, and synaptic functioning. An open reading frame has not been detected for *DISC2*. It is tempting to speculate that the *DISC1* gene may be involved in structural development of the nervous system, and hence, its alteration or absence could be detrimental to brain function. Further biological data about the function of this gene in normal and disease states will be required to determine this.

Chromosome 13q32 (SCZD7, MIM603176)

Linkage to chromosome 13q32 was first reported by Lin & colleagues (110, 111). In a study of 18 markers in 13 families from Europe and Japan, they found multipoint hlod scores of 2 at D13S128, using a narrow diagnostic model including only schizophrenia. Unfortunately, analysis using either parametric or nonparametric methods of a new sample of pedigrees for the same 18 markers did not lead to replication of these results. The authors note that, in a subanalysis of Caucasian patients under a narrow diagnostic model, some support for linkage was obtained.

These results were followed by a strikingly positive study by Blouin et al. (21). A genome scan was performed on 54 families using a restricted diagnosis that included only SCZ and SA. Using nonparametric analyses, they found significant allele sharing near D13S174 (NPL $= 4.18$, $P = 0.00002$). They confirmed the presence of this schizophrenia susceptibility locus in an additional 51 families

(a subset of families from the NIMH Genetics Initiative), obtaining a maximum NPL score of 2.36 ($P = 0.007$) ~1.5 Mb from their original marker. Worthy of note is the fact that these investigators did not use multiple diagnostic models. Thus, these findings constituted a confirmed linkage in schizophrenia. In general, the chromosome 13 finding is not uniformly observed in other genome-wide scans, although this is to be expected given the likely heterogeneity of schizophrenia. In fact, Blouin et al. estimated that only 48% of the original families show linkage to chromosome 13 (21). Shaw & colleagues concluded that their genome-wide scan examining 70 Caucasian families did not provide support for the earlier chromosome 13 findings. Although under a similar diagnostic model (SCZ and SA), they found an NPL score of 1.83 ($P = 0.03$ for D13S170) ~24 Mb from D13S174 (155). Strong support was also obtained for chromosome 13 in a study focused on chromosomes 8 and 13 in 21 extended Canadian families (23). A maximum hlod of 4.42 was obtained in the interval D13S793 and D13S779 (~1–5 Mb proximal to D13S174); however, this was with a broader diagnostic model that included schizotypal personality disorder and paranoid personality disorder. Assuming homogeneity, the narrow diagnostic model (SCZ and SA) yielded a maximum lod score of 3.08. These results were supported by a genome-wide scan in the same families (22).

A large multicenter study of four chromosomal regions in schizophrenia was recently published (106). This consortium, called the Schizophrenia Linkage Collaborative Group III, was formed comprising eight clinical centers to follow up promising linkage results. Their resulting sample contained over 800 pedigrees affected with schizophrenia, and genotypes were obtained for 1937 affected individuals (1003 ASPs). Diagnoses were limited to the narrow definition of schizophrenia (SCZ and SA). Eight markers were genotyped from 13q in all of the samples, including those reported by Blouin et al. (21). Analyses included multipoint ASP analysis as well as multipoint NPL analysis and did not find excess allele sharing. Interpretation of these findings presents problems in view of the strength of initial reports but the lack of replication. At this time, it is impossible to know if subtle biases in ascertainment or diagnosis could account for these divergent results. Furthermore, several groups with positive signals in this region did not participate in the collaborative group. Other studies have not detected signals on chromosome 13 (7, 33, 53, 78, 153).

In summary, there are two scans with significant results for chromosome 13q32 and two scans that provide modest support for this region. However, the majority of scans did not detect linkage signals. Despite the negative studies, the strong signal observed in two independent samples as well as the replication imply the presence of a susceptibility allele, with heterogeneity both within and between samples being the most likely cause of the lack of findings in this region in many studies.

Chromosome 6p22-24 (SCZD3, MIM600511)

Linkage to chromosome 6p was first reported by Wang et al. in a study of 186 multiplex Irish pedigrees (175). In a genome scan of 12 chromosomal regions, evidence

was obtained for linkage to 6p using a very broad definition of schizophrenia with a maximum two-point lod score of 3.2 at D6S260 ($P = 0.0006$). Multipoint analyses found an hlod score of 3.9 in this region, with additional support for these findings from ASP and APM analysis. In an expanded set of 265 Irish families including the 186 families previously reported, Straub et al. obtained further evidence for linkage to 6p24-22 (164). Testing 16 markers spanning 38.4 cM of chromosome 6 under multiple diagnostic and genetic models, evidence for linkage was obtained with a maximum two-point hlod score of 3.51 ($P = 0.0002$) at D6S296 ($\sim$8 MB from D6S260) under a penetrance model with a broad phenotype definition.

Supportive evidence has been obtained in several other studies. In a sib-pair study of 43 German families and 11 Sephardic Jewish families using 25 markers on 6p, Schwab et al. detected excess allele sharing at D6S274/D6S285 (located close to D6S260) using a narrow affected phenotype (SCZ and SA) with a maximum multipoint lod score of 2.2 (152). Their data also provided support for a large region of approximately 40 cM. However, lod scores were negative at D6S296, previously positive in Straub et al. (164). The authors discuss the substantial differences in diagnostic groupings between the two studies that may account for this discrepancy and also note that the original Straub et al. data detected modest findings at markers D6S274/D6S285. In an international genome-wide scan, five large Icelandic families were genotyped with 413 markers, with several markers from 6p yielding nominally positive P values ($P < 0.05$) (120). This result was followed up in a larger group of families from Sweden, Utah, Italy, Germany, Scotland, and Canada. Using NPL analysis, investigators obtained the maximum evidence for linkage at D6S274 ($P = 0.005$). Thirteen additional markers on 6p were then genotyped in a group of schizophrenic patients from China, and multipoint analysis was positive for an adjacent marker D6S285 ($P = 0.05$). This result was then combined with the earlier data by Wang et al. (175), and significant evidence for linkage was obtained ($P = 0.00004$). However, the significant differences in the diagnostic assumptions were not commented on, making conclusive interpretation of the data difficult.

Schwab et al. have completed a genome-wide scan with 463 markers in an expansion of families reported earlier (153). Forty-two markers from chromosome 6 were genotyped, and the maximum NPL score in their genome scan was obtained at HLA-DQB1 (NPL = 3.3, $P = 0.001$), approximately 14 Mb proximal to their earlier positive marker, D6S274. A number of other 6p markers, including D6S260, had NPL scores >2.5. In 1996, the Schizophrenia Linkage Collaborative Group investigated five markers on chromosome 6p (151) in a total of 567 pedigrees using a narrow model (SCZ and SA). The data were divided into (*a*) a new sample that represented all data with the exception of the original positive report and (*b*) a combined sample of the entire data set. Multipoint ASP analysis found a lod score of 2.19 ($P = 0.001$) for the new sample and 2.68 ($P = 0.004$) for the combined sample at D6S470 ($\sim$6.5 Mb from D6S260). Other individual studies have found no evidence for linkage on chromosome 6p, however (22, 25, 60, 78, 148, 179).

Overall, three studies that have found suggestive evidence of linkage, and a combined analysis of many of these pedigrees again detected suggestive evidence for

linkage, with the study of Straub et al. nominally meeting criteria for significance without adjusting for the number of phenotypic and genetic models examined. As has been the case for most of the other regions discussed, however, several genome-wide scans have not detected linkage. These divergent results likely have many of the same explanations as covered previously. On balance, the strength of the three positive studies suggests that there is likely a susceptibility allele on 6p21. Because of the evidence for linkage to 6p21, an association study was undertaken at the NOTCH4 locus located in this region (176). NOTCH4 is a member of a family of genes that plays a role in cell-fate determination. Using the transmission disequilibrium test, Wei & Hemmings (176) found a strong association between two polymorphisms and schizophrenia in a family-based sample of 80 parent-proband trios. A two-locus haplotype analysis with the two polymorphisms was strikingly positive, with a P value of 8×10^{-6}. Unfortunately, several studies including a large collaborative study using the same markers in a sixfold larger sample did not support an association between schizophrenia and NOTCH4 and ruled out this locus as a general-risk allele for schizophrenia (158).

Chromosome 6q21-22 (SCZD5, MIM603175)

In a two-stage linkage scan, Cao et al. investigated 53 families (81 ASPs), using 41 microsatellite markers on chromosome 6 (25). Using a diagnostic scheme that included only SCZ and SA, they obtained no positive results on 6p; however, a large cluster of results spanning 60 cM was obtained on 6q, with the strongest evidence for linkage at D6S416 ($P = 0.00024$). In an attempt to replicate these results, a second sample was obtained from the NIMH Genetics Initiative, and 109 sib-pairs were tested. Excess allele sharing was observed over a 24-cM region that overlaps the one previously detected, with the maximum sharing detected at D6S424 ($P = 0.0004$, ~19 cM proximal to D6S416).

In an attempt to replicate these results, an additional independent sample of 66 ASPs from 40 pedigrees from the United States and Australia were genotyped for 12 markers on 6q (114). Multipoint analysis resulted in a peak lod of 1.07 ($P = 0.013$) at marker D6S424. Combined analysis of their two replication datasets yielded a lod score of 3.82 ($P = 0.000014$) between D6S424 and D6S301. Although analysis of both datasets provides evidence for significant linkage, such was obtained for an interval 19 Mb proximal to the original findings; and thus, the location of a susceptibility gene remains unclear. Additional modest evidence of linkage was also found in a study of five multiplex Austrian families in which Bailer et al. obtained a NPL score of 2.24 ($P = 0.02$) at D6S1570, ~4.3 Mb from D6S424 (7). The Schizophrenia Linkage Collaborative Group III also tested eight markers across a 39-cM region of chromosome 6q (106). ASP analysis found a maximum lod score of 3.10 for the entire dataset ($P = 0.0036$, near D6S242) as well as a maximum lod score of 2.47 ($P = 0.01$), when the original data of Cao et al. was omitted. Of note, overall the most significant NPL scores in the large collaborative study were obtained on 6q, with an NPL

score of 2.47 ($P = 0.0046$) in the total dataset and 2.51 in the replication samples only.

In summary, all the data combined provide some evidence for a susceptibility locus on chromosome 6q. No individual study meets the criteria for significant linkage. However, suggestive findings were obtained in a large collaborative study.

Chromosome 10p11-15

In the multicenter collaborative study of the NIMH, a genome scan of 50 European-American sib-pairs, using nonparametric multipoint analysis, found evidence for linkage to chromosome 10p (D10S1423, NPL = 3.36, $P = 0.0004$) (60). These results were obtained under a narrow diagnostic model containing only SCZ and SAD. Additional evidence was reported in this region by several other groups. Schwab et al. genotyped 72 families (59 German and 13 Israeli) for 20 markers on chromosome 10 (154). ASP analysis demonstrated excess allele sharing for the same marker noted in the earlier study, D10S1423, whereas the maximum NPL score of 3.2 ($P = 0.0007$) was obtained for D10S1714 (154). In the study by Straub et al., 12 markers from the region of chromosome 10p were tested in 265 multiplex families with schizophrenia under four genetic models and four diagnostic models. The strongest supporting evidence was found at marker D10S2443, assuming an intermediate phenotype and a recessive genetic model (hlod 1.95, $P = 0.005$), although this marker is somewhat proximal to those in the earlier studies.

This region of chromosome 10 was also investigated by the Schizophrenia Linkage Collaborative Group III (106). The group analyzed a narrow definition of schizophrenia that included SCZ and SA. ASP analysis was not positive, and the total NPL score was 1.01, with $P = 0.14$. However, logistic-regression analysis found intersample heterogenity, and modest evidence for linkage was obtained when allowing for this heterogenity (empirical $P = 0.04$). Using a much broader phenotype, Maziade et al. recently reported an hlod of 2.41 at D10S245 under a dominant model (115). In the reanalysis of the NIMH Bipolar Genetics Initiative pedigree reported by Foroud et al., linkage to bipolar disorder was detected in this region (D10S1423, lod = 2.5) (63). Several additional groups have not detected linkage to this region either in small studies or on isolated populations (7, 22, 53, 84).

In summary, three large genome scans find suggestive evidence of linkage. The absence of a strong signal in the majority of genome scans makes it seem less likely that a susceptibility allele will be detected here. Furthermore, a large collaborative study found evidence for significant differences between samples, which may explain the difficulty in obtaining strong and reproducible signals. Until the variables that accont for this are understood, it may be impossible to convincingly find linkage support for this region.

Chromosome 22q11-13 (SCZD4, MIM600850)

Linkage has been detected to chromosome 22q11-13 in schizophrenia and bipolar disorder. Table 3 summarizes the positions for markers in this region for both

diseases. Linkage was first reported on chromosome 22 in schizophrenia by Pulver et al. as part of an ongoing genome scan (140). Using an autosomal dominant model including only the diagnoses of SCZ and SA in a study of 39 families, a maximized lod score of 2.8 was obtained at the *IL2RB* (interleukin 2 receptor, beta chain) locus. To extend these results, a collaborative group comprising four centers was formed (139) to genotype the *IL2RB* locus in an additional sample of 217 American, British, Irish, and French families. Again, SCZ and SA were used as the affected phenotype under a dominant model; support for the original observation was not obtained.

Contemporaneously, other investigators obtained evidence for linkage to chromosome 22q. Coon et al., in a study of nine families, detected maximum lod scores >1 for two markers on 22q (D22S84 and D22S55) under an autosomal recessive inheritance model (33). In 1998, Shaw et al. reported parametric lod scores of >1.5 for two markers (D22S446 and D22S283), with a maximum NPL score of 2.16 ($P = 0.01$) at D22S446 using a phentoypic definition including SCZ and SA $\sim$13 Mb from *IL2RB* (155). No evidence of linkage was found in a large number of recent genome scans (22, 60, 78, 107, 136, 153, 179).

It is difficult to assess the overall data from chromosome 22. Multiple results meet the criteria for suggestive linkage, although there are a number of large genome-wide scans that are negative in this region. Collaborative analyses on this region have not been finished, and thus, it is not yet known whether intersample heterogeneity that has been observed will be detected with this locus. Interestingly, suggestive findings have been observed with markers in the same regions in bipolar disorder and might represent a shared susceptibility locus.

Despite the paucity of strong linkage findings, this region deserves special consideration because chromosomal abnormalities have been identified in isolated patients with schizophrenia (11). Karayiorgou et al. reported a microdeletion on 22q11 that is found more frequently among patients with schizophrenia than controls (93). This locus overlaps the proximal portion of the region of chromosome 22 implicated in velo-cardio-facial/DiGeorge (VCFS/DGS) syndromes. VCFS/DGS patients have a combination of congential heart disease, cleft palate, facial dysmorphologies, and learning disabilities. In addition, Pulver et al. demonstrated that 4 out of 14 children with VCFS and 22q11 deletions develop SCZ or SA (143). Recently, several genes have been identified that that may play major roles in the etiology of VCFS/DGS. In mice that are hemizygous for the region deleted in VCFS/DGS, insertion of *TBX1*, a transcription factor of the T-box family, rescues many of the defects (118). Furthermore, *TBX1*-null mutant mice displayed many of the features of VCFS/DGS, including cardiac malformations, low-set ears, first and second pharyngeal abnormalities, and thymic and parathyroid hypoplasia (89).

Several genes in the VCFS/DGS region may be candidates for psychiatric phenotypes. Catechol-O-methyl transferase (COMT) is involved in the degradation of the catecholamine dopamine, norepinephrine, and epinephrine in the brain. COMT-null mutant mice have increased levels of dopamine in the frontal cortex, increased anxiety-like behaviors, and increased aggression in males (73). However, there was no effect on sensorimotor gating, as tested by prepulse inhibition,

which is abnormal in patients with schizophrenia. COMT activity in humans is regulated by a common coding G to A transition at codon 158 leading to a valine to methionine replacement; valine encodes the high-activity form and methionine the low-activity form of the enzyme. Numerous association studies between this SNP and schizophrenia, bipolar disorder, and obsessive-compulsive disorder have been reported, and the results are mixed, although there is a preponderance of negative studies. Resolution of the role of this SNP in these disorders will require further large studies or a meta-analysis of the existing literature.

A second gene from the VCFS/DGS region is relevant to psychiatric phenotype (74). *PRODH*, proline dehydrogenase, is involved in proline degradation, and dysfunction will produce high proline levels. A mutation in this gene accounts for a hyperprolinaemic mouse strain, and it is interesting to note that these mice display abnormal sensorimotor gating. Further investigations will be necessary to determine the extent to which abnormalities in these genes account for or model aspects of psychiatric phenotypes.

Chromosome 15q14 (SCZD10, MIM605419)

Elevation of the P50 auditory-evoked potential has previously been shown to correlate with decreased performance in tasks of sustained attention and word recognition that occurs in patients with schizophrenia. A genome-wide scan of 542 markers in nine families was performed using the neurophysiologic elevation of the P50 ratio as a phenotype. A maximum lod score of 5.3 ($P = 0.001$) was obtained for a marker located within 300 kb of the alpha-7 nicotinic receptor. Nonparametric analyses were also positive for this marker (NPL $= 3.95$, $P = 0.0002$). Several suggestive lines of evidence, including the observations that nicotine transiently normalized the P50 inhibition in humans and that schizophrenia patients are often heavy tobacco smokers, make this an attractive candidate gene.

In a study of periodic catatonia, Stober et al. conducted a genome-wide scan in 12 multiplex German pedigrees (162). Periodic catatonia is a subtype of schizophrenia that usually has an acute psychotic episode but also involves psychomotor disturbances of facial expression and gestures, with a lifetime prevalence estimated to be 0.1% in the population. Excess allele sharing was observed at 15q15 (NPL $= 4.05$, $P = 0.000026$) at D15S1012. To date, these authors have not been able to evaluate the P50 amplitude in their patients. Support for this region has not been obtained in most other studies (22, 78, 153, 179). However, the linkage findings in each of the studies above are both strong and for distinct phenotypes, suggesting that a susceptibility allele is likely, but not necessarily for DSM-defined schizophrenia.

Summary of Findings in Schizophrenia

This review of the linkage literature has identified several chromosomal regions as likely candidate susceptibility loci. Table 7 summarizes the most significant findings obtained in each region. Findings in several of these regions are nominally significant in a single study and found in an independent replication sample

TABLE 7 Summary of most significant linkage findings in schizophrenia

Chromosome	Reference	Families (n)	Most significant evidence for linkage[a] lod or NPL value	Multiple models genetic + phenotypic > 2	Replicated[b]	Encouraging data in same region[c] less than two studies within 10 Mb
1q21-22	(22)	22	6.5	Yes	Yes	Yes
6p22-24	(164)	265	3.51	Yes	Yes	Yes
6q21-22	(106)	734	3.10 (0.0036)	No	No	Yes
8p21	(21)	54	4.54	Yes	Yes	Yes
10p11-15	(60)	43	3.36 (0.0004)	No	No	Yes
13q32	(21)	54	4.18 (0.00002)	Yes	Yes	Yes
22q11-13	(155)	70	2.16	Yes	No	No

[a]In cases where the same family sample was utilized in multiple reports, the linkage results for the study with the largest sample size is presented.

[b]Significant linkage in one study and replicated ($p < 0.01$) in independent sample.

[c]Original study and at least one additional study in an independent sample with suggestive evidence for linkage.

(1p, 6p, 8p, 13q). Strong findings were obtained on 1p, 8p, and 13q, with replication in independent samples. Suggestive findings were detected for multiple studies on 6p, 6q, and 10p; and if they represent true susceptibility alleles, they may account for a more substantial portion of the risk. The evidence for linkage to chromosome 22 in schizophrenia is limited, but it remains interesting because of the *PRODH* observations and may represent a minor-risk allele that is specific for a subset of schizophrenia with sensory motor gating deficits.

FUTURE DIRECTIONS AND GENOMIC APPROACHES

The primary conclusion that can be drawn from this review of the literature is that there are chromosomal regions that are particularly likely to harbor susceptibility alleles for schizophrenia and bipolar disorder. Of course, given the large number of genome scans completed, it is expected that one or more of the results might have achieved statistical significance by chance. For areas of the genome in which there are confirmed linkages or linkages that have met the criteria for significance in at least one study, the presence of one or several negative studies with markers in the same region need not indicate that these are false positives. Differences in diagnoses, sample size, and locus heterogeneity are all likely to account for some variability between studies. The cases where no studies have reached statistical significance, but the preponderance of large genome-wide studies show suggestive findings, are also likely to contain susceptibility alleles. For regions in which there are only a small number of studies that have suggestive results, or where there are several suggestive studies but a preponderance of negative studies, the case remains unclear.

General observations can be made about the difficulties in identifying disease genes for schizophrenia and bipolar disorder. It appears that studies of schizophrenia have produced more convincing evidence for linkage than those for bipolar

disorder for several reasons including the use of larger sample sizes, a narrow phenotype, and more conservative and uniform data analyses. Further difficulties arise from the need to adjust for multiple diagnostic and phenotypic models that are not fully independent yet are not identical as well as from combining previously analyzed families with additional new families. A significant advance has been the development of several large collaborative efforts as a way to obtain sufficient data and power. Development of a uniform diagnostic and analytic standard would facilitate study comparisons.

Several additional mechanisms are being used to address the remaining uncertainies: (*a*) collection of very large sib-pair samples for linkage analysis (presupposes rare alleles of strong effect), (*b*) collection of isolated populations, and (*c*) direct LD mapping in areas implicated across the genome. Additional areas of investigation that are likely to yield interesting results are (*a*) the continued investigations of endophenotypes for schizophrenia, (*b*) the identification of endophenotypes in bipolar disorder, (*c*) the transgenic technologies used to identify the genes for behaviors in mice, and (*d*) the use of cytogenetic abnormalities in patients to indicate more narrow regions of the genome for investigation.

The Case for Isolated Populations

Genetically isolated populations have been useful in the mapping and identification of disease genes for Mendelian diseases (42, 54, 90, 130, 132, 133). The lower allelic complement should prove useful and make identifying genes for schizophrenia and bipolar disorder more tractable. Unfortunately, there is little empirical evidence that isolated populations can profitably be used in this way.

It has been hypothesized that several types of complementary isolated populations may be required for mapping complex diseases. In the initial localization of a disease gene, an isolated population that retained the largest block of LD would be most useful; this would occur in populations that were younger, i.e., in which fewer recombinations had occurred. Fine-scale mapping would then be most productively pursued in populations that had undergone a larger number of recombinations and had smaller overall blocks of LD.

In order to explore the hypothesis that isolated populations will allow the mapping of genes for schizophrenia and bipolar disorder, many investigators are collecting samples in preparation for genome-wide scanning. As noted above, isolated populations have been described for bipolar disorder from among the Amish (72), from the Central Valley of Costa Rica (66), and from the Saguenay Lac St-Jean region of Quebec (121). Searches of the NIH Crisp database to identify currently funded collections of patients also show that isolated populations are being collected from the Azores and the Ashkenazi Jewish population. For schizophrenia, data from isolated populations have been reported from Finland (7) and are being collected from Palau, Micronesia; from Daghestan, a genetic isolate in the Northern Caucasus in Russia; and the Afrikaner population of South Africa. Each of these populations will vary in number of founders, date of founding, type of expansion, and bottlenecks experienced, which will likely result in differences in allele spectrum and extent of LD.

Genomic Approaches to Linkage Data

The Human Genome Project (30) and Celera Genomics (172) have completed sequencing of the human genome. The sequence of the three billion DNA bases is now largely available in the public databases, allowing us to search for disease genes using a complementary approach, i.e., use known genes or use sequence similarity to known genes to predict the function of novel genes, then select candidates for use in association studies and LD.

Several recent advances have placed large numbers of SNPs in public repositories. In collaboration with the National Human Genome Research Institute, The National Center for Biotechnology Information has established the dbSNP database (http://www.ncbi.nih.gov/SNP/) to serve as a central repository for single-base nucleotide substitutions discovered primarily, although not exclusively, from in silico overlapping of DNA sequences. The dbSNP database includes SNPs discovered by the SNP Consortium Ltd. (TSC), a nonprofit foundation organized for the purpose of providing public genomic data. They have developed methods for identifying SNPs randomly dispersed throughout the genome (http://snp.cshl.org) (3).

In order to make use of these SNPs, their positions within the genome as well as location within genes must be mapped. The human genome browser provides a searchable view of the draft of the human genome (http://genome.ucsc.edu/) and a variety of information about individual genomic regions, including sequence, mRNAs, ESTs, and SNPs. Data are freely available to the scientific community and are being integrated with other genomic databases. With the completion of the human genome project and the existence of dbSNP, the SNP consortium, and the Human Genome Browser, it is now possible to take a combined positional and functional approach to association analysis. As suggested above, the successful use of the wealth of new genomic information will be governed by the quality of phenotype assessment and the number of samples available for study.

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