Are Schizophrenic and Bipolar Disorders *Related*? A Review of Family and Molecular Studies

Wade H. Berrettini

Schizophrenic and bipolar disorders are similar in several epidemiologic respects, including age at onset, lifetime risk, course of illness, worldwide distribution, risk for suicide, gender influence (men and women at equal risk for both groups of disorders), and genetic susceptibility. Despite these similarities, schizophrenia and bipolar disorders are typically considered to be separate entities, with distinguishing clinical characteristics, non-overlapping etiologies, and distinct treatment regimens. Over the past three decades, multiple family studies are consistent with greater nosologic overlap than previously acknowledged. Molecular linkage studies (conducted during the 1990s) reveal that some susceptibility loci may be common to both nosologic classes. This indicates that our nosology will require substantial revision during the next decade, to reflect this shared genetic susceptibility, as specific genes are identified. Biol Psychiatry 2000;48:531–538

Key Words: Genetic linkage, schizophrenia, bipolar disorder, family studies

Introduction

The hypothesis that schizophrenic (SZ) and bipolar (BP) syndromes share some genetic risk factors is the subject of this article. To consider this question, epidemiologic, family, and molecular linkage studies are reviewed. If there is shared genetic risk for these syndromes, then we might reasonably expect some similarities in epidemiology. Epidemiologic characteristics common to both BP and SZ disorders are reviewed. Further, if there is shared genetic risk for these syndromes, then family studies should reveal some overlap in familial aggregation. Schizophrenic and BP family studies reveal partial overlap in risk for illness. Finally, if there is shared genetic risk, some susceptibility loci (identified through linkage studies) should be common to both disorders. A review of BP and SZ molecular linkage studies reveals several genomic regions potentially relevant to both nosological classes. It is concluded that SZ and BP disorders share some genetic risk factors. It is not the thesis of this article that the two nosologic categories represent a single entity or a continuum, but that the two groups of disorders are more closely related than previously considered.

From the Department of Psychiatry and the Center for Neurobiology and Behavior, University of Pennsylvania, Philadelphia.

Address reprint requests to Wade H. Berrettini, M.D., Ph.D., Director, Center for Neurobiology and Behavior, University of Pennsylvania School of Medicine, Room 111, Clinical Research Building, 415 Curie Blvd, Philadelphia PA 19104.

Received January 12, 2000; revised March 18, 2000; accepted March 20, 2000.

Epidemiologic Similarities

Bipolar and SZ disorders are common, chronic groups of illnesses that share many epidemiologic features (for review see Nurnberger and Berrettini 1998). They each affect ~1% of the world's populations, occurring at approximately the same rate across all continents. Although they are common in young adulthood (onset of illness typically occurs prior to age 25 years), these disorders are unusual in prepubertal children. Thus, BP and SZ diagnostic categories have similar ages at onset. These two nosologic classes describe psychotic disorders that often assume episodic courses of illness (with partial to complete remissions and clear exacerbations), although relatively chronic, unremitting SZ disorders are frequently encountered. With rare exceptions, BP and SZ disorders are lifelong conditions. In general, once DSM-4 criteria for BP or SZ diagnoses are met, the disorder persists through life. Spontaneous and lifelong (permanent) remissions of either BP or SZ disorders are very unusual. Increased risk for suicide is another characteristic that these two groups of disorders share. Both syndromes affect men and women equally. Familial aggregation has been demonstrated repeatedly for SZ and for BP. Twin and adoption studies of BP and SZ disorders are consistent with substantial heritability. From twin studies, estimates of heritability for these disorders are quite similar: ~50% for SZ disorders and ~65% for BP disorders.

There are, however, clear clinical distinctions between these two nosologic categories, such that their classic presentations are not often mistaken for one another. The majority of BP individuals benefit from lithium therapy, whereas few persons with SZ are helped substantially. Bipolar disorder manifests as a disturbance of mood, whereas SZ is a primary disorder of cognition. There are

0006-3223/00/$20.00
PII S0006-3223(00)00883-0

several electrophysiologic (Adler et al 1999; Freedman et al 1997; Ford 1999) abnormalities in SZ that do not characterize BP disorder. In the context of these shared epidemiologic characteristics, is there any evidence that these two syndromal classifications share genetic risk factors? If this hypothesis is true, then we would expect to find increased risk for SZ syndromes among the first-degree relatives of BP probands, and, conversely, increased risk for BP syndromes among the first-degree relatives of SZ probands.

Review of Family Studies

A review of BP family studies reveals the following: First-degree relatives of BP probands are at increased risk for several nosologically related disorders: BPI, BPII (hypomanic and recurrent unipolar [RUP] episodes in the same person), schizoaffective (SA) and RUP (Angst et al 1980; Baron et al 1983; Gershon et al 1982; Helzer and Winokur 1974; James and Chapman 1975; Johnson and Leeman 1977; Maier et al 1993; Weissman et al 1984; Winokur et al 1982, 1995). Despite numerous careful investigations, no study of the first-degree relatives of BP probands reveals increased risk for SZ.

Similarly, a review of SZ family studies reveals that the first-degree relatives of SZ probands are at increased risk for SZ, SA, and RUP disorders (Gershon et al 1988; Maier et al 1993). Kendler et al (1993) describe increased risk for psychotic affective illness among relatives of SZ probands. Despite numerous carefully conducted investigations, no family study of SZ reports increased risk for BP disorders among first-degree relatives of SZ probands; however, the first-degree relatives of SZ probands *and* the first-degree relatives of BP probands are at increased risk for SA and RUP disorders. The overlap in elevated risk for SA and RUP diagnoses is evident. Therefore, these family studies are consistent with *partial* overlap in familial susceptibility for BP and SZ disorders; however, these family studies are limited in size and power. A small increase in risk for SZ among the first-degree relatives of BP probands might have been undetected. There is a need for large, systematic family studies of SA probands.

It is argued here that the epidemiologic and family study similarities suggest that these two *groups* of disorders are more closely related than previously considered. Because BP and SZ nosologic classes each represent multiple disease entities (with some clinical similarities), it is hypothesized here that some of these disease entities might produce syndromes that may be assigned to either nosologic group (BP or SZ), depending on the genetic background on which they arise. This hypothesis implies that the partial overlap in epidemiologic and family studies may originate in genetic susceptibility.

Given the evidence for *partial* overlap in familial susceptibility for BP and SZ disorders, one may ask whether the overlap may have genetic origins. If this partial overlap is genetic, then molecular linkage studies of BP and SZ disorders should have detected some loci in common. The next section will review BP and SZ molecular linkage studies.

Review of BP and SZ Molecular Linkage Studies

In genetic linkage analysis of common complex disorders, failure of subsequent studies to confirm previously nominated susceptibility loci has become commonplace. This is as true for diabetes mellitus (Concannon et al 1998; Hanis et al 1996) as it is for SZ and BP disorders. This failure to confirm has multiple origins. The most important origin is power to detect a susceptibility locus of limited effect size in the presence of genetic heterogeneity. Common, complex disorders (e.g., asthma, epilepsy, diabetes mellitus, and SZ disorders) are most probably the manifestations of multiple susceptibility loci, within an affected individual, which interact with each other and the environment to produce these well-known syndromes. For these disorders, no single susceptibility locus has a major effect on risk for illness in a majority of the ill population. Loci that increase risk by factors greater than 2 are unusual for common, complex disorders. Despite Herculean efforts in numerous disorders, only two loci that increase risk by a factor of >2 in a large fraction of ill people have been detected: one is HLA for insulin-dependent diabetes mellitus (increased risk = $\sim$3 [Davies et al 1994]; the other is apolipoprotein E in late onset Alzheimer's disease (Corder et al 1993; Mayeux et al 1993; Tsai et al 1994). Substantial sample sizes are required to detect such loci which increase risk by factors of $\leq$2. As Hauser et al (1996) have shown, $\sim$400 affected sibling pairs are needed to have $>$90% power to detect ($p < .0001$ or log of the odds ratio [LOD] > 3) loci that increase risk by a factor of 2. No single linkage study of BP or SZ disorders published in the 1990s has exceeded this sample size, although meta-analyses of multiple independent data sets have larger sample sizes.

A second major reason for lack of confirmation is a failure to appreciate the limited ability of linkage methods to localize susceptibility genes to small ($\sim$5 million base pairs of DNA or $\sim$5 cM) genomic regions. Linkage analyses of complex traits are not able to localize disease genes to narrow ($<$5 cM) genomic regions with currently available ($<$2000 affected sibling pairs) sample sizes (Kruglyak and Lander 1995). For example, the BRCA1 gene was cloned (Futreal et al 1994) $\sim$15 cM from the peak of the original LOD score (Hall et al 1990). Roberts

et al (1999) simulated linkage studies for a complex, genetically heterogeneous disorder. They found that the 95% confidence interval for location estimates (from simulated linkage studies of 200 affected sibling pairs) is ~30 cM.

A third major reason for lack of confirmation in linkage studies of common complex disorders has been delineated by Suarez et al (1994), who conducted simulation studies to evaluate the power to replicate linkage. They simulated linkage data for a complex disease caused in part by six equally frequent independent (unlinked) disease loci. They found that a larger sample size was required to confirm linkage of a previously detected locus, because independent pedigree samples might (through sampling variation) contain an over-representation of different susceptibility loci, rather than the locus initially detected. Given that investigators often draw their pedigrees from different ethnic backgrounds (in which prevalence of a particular susceptibility locus might vary), sampling variation is an important origin of confirmation failure. Thus, expectations of universal agreement (even when sample size is adequate) regarding susceptibility loci for common complex traits are unrealistic.

Although validity (through confirmation) of previously reported linkages is difficult for common, complex disorders, some guidelines for validity have been proposed (Lander and Kruglyak 1995; Lander and Schork 1994). These guidelines include a threshold for an initial report of "significant" linkage (LOD score = ~3.6 or nominal p = ~.00002) and for confirmation (LOD score = 1.2 or p = ~.01). These guidelines should limit false positives to less than 5%. These thresholds for statistical significance assume analysis of one affection status model (phenotypic definition of caseness), for example BPI, SA, and BPII disorders. If several (overlapping) affection status models are used in multiple linkage analyses (dominant, recessive, and nonparametric approaches) then some "Bonferroni" correction for multiple hypothesis testing may be necessary.

The Lander and Kruglyak (1995) guidelines for statistical significance in linkage studies (LOD score = ~3.6 or nominal p = ~.00002 and one confirmation LOD score = 1.2 or p = ~.01) were determined through simulation to represent a false positive rate less than 5% (one in 20 genome scans). It seems logical that three or more independent studies, each with $p \leq .001$, should provide a similar level of statistical confidence, although this has not been tested through simulation.

If analysis is limited to "confirmed" BP and SZ linkage susceptibility loci, then the risk for false positive conclusions should be minimized. Our approach will have two facets. First, confirmed BP susceptibility loci will be examined, asking the question: Is there at least one report, in this same region, of linkage to SZ with a p value $\leq$ .001? Second, we will examine all confirmed SZ susceptibility loci, asking the question: Is there at least one report, in this same region, of linkage to BP disorder with a p value $\leq$ .001?

Evidence for Linkage of BP and SZ Disorders to 18p11

Berrettini et al (1994, 1997) reported evidence for a BP susceptibility locus on 18p11 using affected sibling pair (ASP) and affected pedigree member (APM) methods ($p = 10^{-4} - 10^{-6}$). Independent evidence of confirmation of this finding was reported by Stine et al (1995), Nothen et al (1999), and Turecki et al (1999). Evidence for linkage was found most often among those families with paternally transmitted illness (Gershon et al 1996; Nothen et al 1999; Stine et al 1995). As part of Genetic Analysis Workshop #10, independent BP chromosome 18 linkage data sets, including ~1200 samples, were assembled for meta-analyses (Goldin et al 1997). An affected sibling pair (n = 382 sibling pairs) meta-analysis yielded $p = 2.8 \times 10^{-8}$ at marker D18S37 (Lin and Bale 1997).

Schwab et al (1998) employed ~20 chromosome 18 markers in a linkage study of 59 multiplex German and Israeli SZ pedigrees, in which there were 24 affective disorder cases (two were BP). When these data were analyzed in two-point parametric methods, the maximum LOD score was 3.1 at D18S53. A multipoint nonparametric analysis revealed p = .002, at D18S53.

One may be concerned that Schwab et al (1998) studied kindreds whose probands were misdiagnosed or unusual in some undetected characteristics; however, the SZ kindreds studied for 18p11 linkage by Schwab et al (1998) are not nosologically or genetically distinct from other multiplex SZ kindreds. If the SZ kindreds of Schwab et al (1998, 1995, 1999) were nosologically unique (perhaps misclassified affective disorder kindreds), then one would not expect to find confirmations of other SZ loci in those kindreds. These kindreds show linkage to chromosome 6p (Schwab et al 1995), as reported in other series of multiplex SZ kindreds (Straub et al 1995; Maziade et al 1997; Moises et al 1995). Similarly, Faraone et al (1998) and Straub et al (1998) report SZ linkage to 10p14, as did Schwab et al (1999). Nosological misclassification does not explain the chromosome 18p11.2 linkage to SZ detected by Schwab et al (1998). Thus, one region of potential overlap in susceptibility for BP and SZ syndromes is 18p11.2.

Evidence for Linkage of SZ and BP Disorders to 13q32

Lin et al (1997) observed a LOD score of 2.58 ($p = \sim 0.001$) at 13q32 markers (D13S122 and D13S128) in a linkage study of SZ. Blouin et al (1998), studying independent SZ kindreds, report a p value of .00002 (LOD = 3.6) at the 13q32 marker, D13S174, in 54 SZ kindreds. Subsequently, Brzustowicz et al (1999) confirmed these reports in 21 Canadian SZ families, with a maximal LOD score of 3.92 at the 13q marker D13S793. Thus, there are at least three independent reports, with substantial statistical significance, consistent with a 13q32 SZ susceptibility locus.

Detera-Wadleigh et al (1999) described linkage ($p = .00003$) to 13q32 markers (D13S1271 and D13S779) in 22 BP kindreds of European ancestry. One may be concerned that the kindreds studied by Detera-Wadleigh et al (1999) were misclassified; however, these kindreds reveal evidence for linkage to 21q21 (Detera-Wadleigh et al 1996), a BP susceptibility locus (see below). Kelsoe et al (1998) reported linkage of BP disorder to 13q32 markers, with LOD = 2.4 at D13S154. Thus, the 13q32 region has a confirmed SZ susceptibility locus, and there are statistically impressive reports of linkage at this locus in BP disorder.

Evidence for Linkage of SZ and BP Disorders to 10p14

In a recent series of articles, Faraone et al (1998), Straub et al (1998) and Schwab et al (1998) reported evidence for linkage of SZ to 10p14 markers. Faraone et al (1998) reported $p = .0004$ for marker D10S1423 and $p = .0006$ for D10S582, in a study of 43 American SZ kindreds of European ancestry. Straub et al (1998), in a study of Irish SZ kindreds, reported $p = .006$ for this region in a multipoint analysis. For marker D10S582, Schwab et al (1998) reported $p = .0058$ for German SZ kindreds. These three groups of investigators studied independent sets of kindreds that were of general European ancestry. Although no single report was consistent with significant linkage ($p = .00002$), these three reports probably constitute a true positive linkage, nonetheless.

Foroud et al (2000) studied BP kindreds from the National Institute of Mental Health Genetics Initiative. They found LOD = 2.5 ($p = .001$) for marker D10S1423. Thus, the 10p14 region may represent a third region of the genome at which there is shared susceptibility for BP and SZ disorders.

Evidence for Linkage of SZ and BP Disorders to 22q11-13

Lachman et al (1996), Edenberg et al (1997), Kelsoe et al (1998), and Detera-Wadleigh et al (1997) described evidence for a BP susceptibility locus on chromosome 22q11-13, near the velo- cardiofacial syndrome (VCFS) locus. Kelsoe et al (1999) report an LOD score of 3.8 at D22S278. Detera-Wadleigh et al (1999) report $p = .008$ for markers in this region. This VCFS has been associated with microdeletions of the 22q region. These individuals have a psychosis in ~30% of cases. The syndromal form of the psychosis has been termed schizophrenia-like (Pulver et al 1994b), whereas others have described it in terms of bipolar disorder (Carlson et al 1997; Papolos et al 1996). This region of 22q has been implicated in risk for schizophrenia (Gill et al 1996; Pulver et al 1994a). This region represents a fourth area of overlap for BP and SZ susceptibility loci.

Confirmed Susceptibility Loci Unique to BP Disorders

Although there are four regions of the genome (18p11.2, 13q32, 22q11-13, and 10p14) where BP and SZ susceptibility loci may overlap, the reader should not be left with the impression that this is true for all confirmed BP susceptibility loci. In fact, there are multiple other confirmed BP susceptibility loci at which no report is consistent with a SZ susceptibility locus. The "uniquely BP" susceptibility loci are summarized as follows.

Morissette et al (1999) reported evidence for a chromosome 12q24 BP susceptibility locus, detected through study of a population isolate (French ancestry) from the Saguenay River region of Quebec province. The LOD score exceeds 8 in a recent abstract (Barden et al 1998), clearly exceeding guidelines for significant linkage. Independent confirmation of this BP susceptibility locus has been observed by Ewald et al (1998a) in a study of Danish BP kindreds, with LOD = 3.3. Detera-Wadleigh et al (1999) observed modest support for this locus in a study of 22 American kindreds of European origin. There have been no reports of SZ linkage to this region. Thus, the 12q24 region represents a confirmed BP susceptibility locus.

Straub et al (1994) initially described linkage of BP disorder to 21q21 markers, in a study of American and Israeli BP kindreds. One BP pedigree with a LOD score of 3.41 was reported from a series of 57 BP kindreds; further, nonparametric analysis provided evidence for linkage ($p < .0003$ for the phosphofructokinase locus). An emendation of this original work has been published by Aita et al (1999). A confirmation has been described in a two-locus analysis of genotypic data from 21q21 and 11p15.5 (Smyth et al 1996). This 21q21 BP susceptibility locus has been confirmed by Detera-Wadleigh et al (1996), who employed multipoint nonparametric analyses ($p < .001$). Kwok et al (1999) described confirmatory evidence for linkage to this region in nonparametric analyses. Kelsoe et al (1999) reports an LOD of >2 in this region. Morisette

et al (1999) also report a confirmation for this locus in a population isolate of French ancestry. There are no reports of SZ susceptibility to this region, suggesting that the 21q21 region harbors a locus that increases risk for BP disorder.

An extended Scottish kindred showed linkage (LOD 4.1 at D4S394) to 4p16 DNA markers (Blackwood et al 1996). Confirmation of the 4p locus has been reported in a paper by Nothen et al (1997), in which increased allele sharing was noted at D4S394 ($p = .0009$). Another confirmation was described by Ewald et al (1998b), who noted a LOD of 2.0 at D4S394. Ginns et al (1998) reported linkage to this region for a *mental health locus,* meaning absence of any psychiatric disorder. This requires additional investigation. Thus, the 4p16 region has a confirmed BP susceptibility locus. No reports of SZ linkage are known.

A fourth region of the genome that harbors a BP susceptibility locus is 18q22. Stine et al (1995) initially reported linkage to this region in 28 American BP kindreds (LOD is 3.51 for D18S41) and the ASP method (0.00002 at D18S41). In an extension of this work, McMahon et al (1997) provided additional evidence for linkage to 18q21-2 in 30 new BP kindreds. This locus may have been detected by Freimer et al (1996) and McInnes et al (1996) who studied Costa Rican BP kindreds. McInnes et al (1996) described evidence for increased allele sharing at some of the same markers identified by McMahon et al (1997). For example, at D18S55, McMahon et al (1997) reported a nonparametric LOD score of 2.2, whereas McInnes et al (1996) at this same marker report a maximum likelihood estimate of the LOD score as 1.67. Although the genetic map position of greatest significance for these two studies are not identical (see Roberts et al 1999), there is sufficient map location overlap to conclude tentatively that the two studies detect the same locus.

In summary, there are four regions of the genome that appear to harbor unique BP susceptibility loci, including 21q21, 18q22, 12q24, and 4p16. For each of these four regions there are several consistent reports of linkage, indicating that these loci are probably true positives.

Confirmed Susceptibility Loci Unique to SZ Disorders

In parallel to the BP disorders linkage literature, there are SZ susceptibility loci that appear to be unique to that nosologic classification, in that there are no reports of BP disorders linkage to these genomic regions. Straub et al (1995) initially identified SZ linkage in Irish multiplex families to 6p22-24. Confirmations were published by Schwab et al (1995), who studied German SZ kindreds, and by Moises et al (1995). Levinson et al (1996), in a collaborative venture, noted support for this locus in a large data set. Maziade et al (1997) also confirmed this locus. Although no single report among these studies provides significant linkage (Lander and Kruglyak 1995), there is sufficient evidence in the original report and the several confirmations, that this is likely to be a true positive SZ locus on 6p22-24. There are no molecular reports of BP disorders linkage to this region.

A second "unique" SZ susceptibility locus is found on 8p. Blouin et al (1998) reported evidence for a SZ locus at 8p22, in 54 multiplex kindreds. The LOD score, assuming heterogeneity, was 4.5. Nonparametric analysis yielded $p = .0001$. Brzustowicz et al (1999) studied 21 extended Canadian SZ pedigrees with 8p markers. The maximum multipoint LOD score was 2.1 at D8S136, providing an additional confirmation of an 8p22 SZ locus. Levinson et al (1996), in a multicenter collaborative effort, reported independent results (that did not include the pedigrees of Blouin et al 1998), yielding $p = .00018$ in this same region of 8p22. Gurling et al (1999), in a study of 13 extended European SZ kindreds, reported an LOD of 3.6 for 8p22 markers. Thus, these reports constitute a confirmed SZ linkage, and there is no report of BP disorders linkage to this region.

A third unique SZ susceptibility locus may be found on 6q21 (Cao et al 1997; Martinez et al 1999). There is no statistically robust ($p \geq .001$) report of BP linkage at this locus.

Summary

A review of epidemiology and family studies suggests some similarities between SZ and BP disorders. Family studies, in particular, suggest partial overlap in risk for SA diagnoses and some affective disorders (Gershon et al 1988; Kendler et al 1993; Maier et al 1993). This overlap is consistent with shared genetic risk.

A review of molecular linkage studies reveals evidence for shared genetic loci at 18p11.2, 22q11-13, 13q32, and 10p14. This is consistent with the family studies. There remain independent BP susceptibility loci at 18q22, 21q21, 4p16, and 12q24, where there are no prominent reports of SZ susceptibility. Similarly, there are confirmed SZ susceptibility loci at 6p22, 6q21, and 8p22, where there are no reports of BP susceptibility. Thus, the molecular reports are consistent with the family studies, in suggesting partial shared genetic risk. The confirmed BP *and/or* SZ susceptibility loci, identified through linkage studies, are summarized in Figure 1.

If there were only a single genomic region of overlap, this might occur randomly; however, there are four genomic regions of overlap for BP and SZ susceptibility loci, observations that are consistent with the family study data. It is possible, however, that these regions of overlap are secondary to sources of error that are *common* to the several BP and

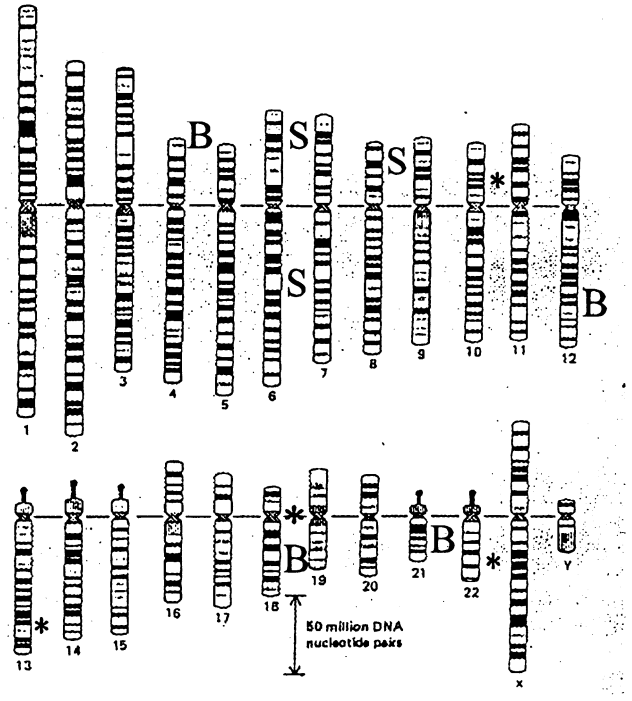

Figure 1. Ideograms of human chromosomes are marked *to the right* with *B* to indicate the location of susceptibility loci unique to bipolar disorder, with *S* to indicate schizophrenic loci, and with * for both bipolar disorder and schizophrenia.

SZ linkage studies. Although this seems improbable, it should be considered carefully in future studies.

It is expected that novel genes, corresponding to these loci, will be identified in the next several years. Direct study of these susceptibility alleles will allow for correlation between genotype and phenotype. Nosology for these disorders must be redefined accordingly, and this will require that we relinquish long-held (mis)conceptions about these disorders. In the bright light of new genetic knowledge concerning the origins of these disorders, we will be able to ask refined questions concerning environmental risk factors. Because environment drives gene expression, knowledge of the environmental risk factors will certainly enhance comprehension at the molecular level. This complex evolution of our understanding of SZ and BP disorder will require several decades at least. As a result of this effort, we can anticipate marked improvements in the outcomes for these disorders, which now shatter the lives of so many.

This article was prepared with the support of NIH Grant MH59553 and a NARSAD Distinguished Investigator Award.

Aspects of this work were presented at the conference, "Bipolar Disorder: From Preclinical to Clinical, Facing the New Millennium," January 19–21, 2000, Scottsdale, Arizona. The conference was sponsored by the Society of Biological Psychiatry through an unrestricted educational grant provided by Eli Lilly and Company.

References

Adler LE, Freedman R, Ross RG, Olincy A, Waldo MC (1999): Elementary phenotypes in the neurobiological and genetic study of schizophrenia. *Biol Psychiatry* 46:8–18.

Aita VM, Liu J, Knowles JA, Terwilliger JD, Baltazar R, Grunn A, et al (1999): A comprehensive linkage analysis of chromosome 21q22 supports prior evidence for a putative bipolar affective disorder locus. *Am J Hum Genet* 64:210–217.

Angst J, Frey R, Lohmeyer R, Zerben-Rubin E (1980): Bipolar manic depressive psychoses: Results of a genetic investigation. *Hum Genet* 55:237–254.

Barden N, Morisette J, Shink E, et al (1998): Confirmation of bipolar affective disorder susceptibility locus on chromosome 12 in the region of the Darier disease gene. *Am J Med Genet* 81:475.

Baron M, Gruen R, Anis L, Kane J (1983): Schizoaffective illness, schizophrenia and affective disorders: Morbidity risk and genetic transmission. *Acta Psychiatr Scand* 65:253–262.

Berrettini W, Ferraro T, Choi H, Goldin L, Detera-Wadleigh SD, Muniec D, et al (1997): Linkage studies of bipolar illness. *Arch Gen Psychiatry* 54:32–39.

Berrettini W, Ferraro T, Goldin L, Weeks D, Detera-Wadleigh SD, Nurnberger JI Jr, Gershon E (1994): Chromosome 18 DNA markers and manic depressive illness: Evidence for a susceptibility gene. *Proc Natl Acad Sci U S A* 91:5918–5921.

Blackwood DHR, He L, Morris SW, McLean A, Whitton C, Thomson M, et al (1996): A locus for bipolar affective disorder on chromosome 4p. *Nat Genet* 12:427–430.

Blouin J-L, Dombroski B, Nath SK, Lasseter VK, Wolyniec PS, Nestadt G, et al: Schizophrenia susceptibility loci on chromosomes 13q32 and 8p21. *Nat Genet* 20:70.

Brzustowicz LM, Honer WG, Chow EWC, Little D, Hogan J, Hodgkinson K, et al (1999): Linkage of famlial schizophrenia to chromosome 13q32. *Am J Hum Genet* 65:1096–1103.

Cao Q, Martinez M, Zhang J, Sanders AR, Badner JA, Cravchik A,et al (1997): Suggestive evidence for a schizophrenia susceptibility locus on chromosome 6q and a confirmation in an independent series of pedigrees. *Genomics* 43:1–8.

Carlson C, Papolos D, Pandita RK, Faedda GL, Veit S, Goldberg R, et al (1997): Molecular analysis of VCFS patients with psychiatric disorders. *Am J Med Genet* 60:851–859.

Concannon P, Gogolin-Ewens KJ, Hinds DA, Wapelhorst B, Morrison VA, Stirling B, et al (1998): A second-generation screen of the human genome for susceptibility to insulin-dependent diabetes mellitus. *Nat Genet* 19:292–296.

Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al (1993): Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 261:921–923.

Davies JL, Kawaguchi Y, Bennett ST, Copeman JB, Cordell HJ, Pritchard LE, et al (1994): A genome-wide search for human type 1 diabetes susceptibility genes. *Nature* 371:130–136.

Detera-Wadleigh SD, Badner JA, Berrettini WH, Yoshikawa T, Goldin LR, Turner G, et al (1999): Evidence for a bipolar susceptibility locus on 13q32 and other potential loci on 1q32 and 18p11.2. *Proc Natl Acad Sci U S A* 96:5604–5609.

Detera-Wadleigh SD, Badner JA, Goldin LR, Berrettini WH, Sanders AR, Rollins DY, et al (1996): Affected sib-pair

analyses reveal support of prior evidence for a susceptibility locus for bipolar disorder on 21q. *Am J Hum Genet* 58:1279–1285.

Detera-Wadleigh SD, Hsieh W-T, Berrettini WH, Goldin LR, Rollins DY, Muniec D, et al (1997): Genetic linkage mapping for a susceptibility locus to bipolar illness: Chromosomes 2, 3, 4, 7, 9, 10p, 11p, 22, and Xpter. *Neuropsychiatr Genet* 74:206–218.

Edenberg H, Foroud T, Conneally M, Sorbel J, Carr K, Crose C, et al (1997): Initial genomic scan of the NIMH genetics initiative bipolar pedigrees: chromosomes 3,5,15,16,17, and 22. *Neuropsychiatr Genet* 74:238– 246.

Ewald H, Degn B, Mors B, Kruse TA (1998a): Significant linkage between bipolar affective disorder and chromosome 12q24. *Psychiatr Genet* 8:131–140.

Ewald H, Degn B, Mors B, Kruse TA (1998b): Support for the possible locus on chromosome 4p15 for bipolar affective disorder. *Mol Psychiatry* 3:442–448.

Faraone SV, Matise T, Svrakic D, Pepple J, Malaspina D, Suarez B, et al (1998): Genome scan of European-American schizophrenia kindreds: Results of the NIMH Genetics Initiative and Millenium consortium. *Am J Med Genet* 81:290–295.

Ford J (1999): Schizophrenia: The broken P300 and beyond. *Psychophysiology* 36:667–682.

Foroud T, Castelluccio PF, Keller DL, Edenberg HJ, Mill M, Bowman E, et al (2000): Suggestive evidence of a locus on chromosome 10p using the NIMH Genetics Initiative bipolar affective disorder pedigrees. *Am J Med Genet* 96:18–23.

Freedman R, Coon H, Myles-Worsley M, Orr-Urtreger A, Olincy A, Davis A, et al (1997): Linkage of neurophysiological deficit in schizophrenia to a chromosome 15 locus. *Proc Natl Acad Sci U S A* 94:587–592.

Freimer NB, Reus VI, Escamilla MA, McInnes LA, Spesny M, Leon P, et al (1996): Genetic maping using haplotype, association and linkage methods suggests a locus for severe bipolar disorder (BPI) at 18q22–q23. *Nat Genet* 12:436–441.

Futreal PA, Liu Q, Shattuck-Eidens D, Cochran C, Harshman K, Tavtigian S, et al (1994): BRCA1 mutations in primary breast and ovarian carcinomas. *Science* 266:120–122.

Gershon ES, Badner JA, Ferraro TN, Detera-Wadleigh S, Berrettini WH (1996): Maternal inheritance and chromosome 18 allele sharing in unilineal bipolar illness pedigrees. *Neuropsychiatr Genet* 67:1–8.

Gershon ES, DeLisi LE, Hamovit J, Nurnberger JI Jr, Maxwell ME, Schreiber J, et al (1988): A controlled family study of chronic psychoses. *Arch Gen Psychiatry* 45:328–336.

Gershon ES, Hamovit J, Guroff JJ, Dibble E, Leckman JF, Sceery W, et al (1982): A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. *Arch Gen Psychiatry* 39:1157–1167.

Gill M, Vallada H, Collier D, Sham P, Holmans P, Murray R, et al (1996): A combined analysis of D22S278 marker alleles in affected sib-pairs: Support for a susceptibility locus for schizophrenia at chromosome 22q12. *Am J Med Genet* 67:40–45.

Ginns EI, St Jean P, Philibert RA, Galdzicka M, Damschroder-Williams P, Thiel B, et al (1998): A genome search for chromosomal loci linked to mental health wellness in relatives at high risk for bipolar affective disorder among the Old Order Amish. *Proc Natl Acad Sci U S A* 95:15531–15536.

Goldin LR, Gershon ES, Berrettini WH, Stine OC, DePaulo R, McMahon F, et al (1997): Description of the Genetic Analysis Workshop 10 bipolar disorder linkage data sets. *Genet Epidemiol* 14:563–568.

Gurling HMD, Kalsi G, Blaveri E, McQuillin A, Read I, Murphy P, et al (1999): Initial genome wide parametric genetic linkage analysis of schizophrenia and schizophrenia spectrum disorders finds LOD scores above 3.00 on four chromosomes at 1q22–23, 5q22–35, 8p21–23 and 11q14–24. *Mol Psychiatry* 4(suppl):S4.

Hall JM, Lee MK, Newman B, Morrow JE, Anderson LE, Nuey B, et al (1990): Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* 250:1684–1690.

Hanis CL, Boerwinkle E, Chakraborty R, Ellsworth DL, Concannon P, Stirling B, et al (1996): A genome-wide search for human non-insulin-dependent (type 2) diabetes genes reveals a major susceptibility locus on chromosome 2. *Nat Genet* 13:161–166.

Hauser ER, Boehnke M, Guo S-W, Risch N (1996): Affected sib pair interval mapping and exclusion for complex genetic traits. *Genet Epidemiol* 13:117–137.

Helzer JE, Winokur G (1974): A family interview study of male manic-depressives. *Arch Gen Psychiatry* 31:73–77.

James NM, Chapman CJ (1975). A genetic study of bipolar affective disorder. *Br J Psychiatry* 126:449–456.

Johnson GFS, Leeman MM (1977): Analysis of familial factors in bipolar affective illness. *Arch Gen Psychiatry* 34:1074–1083.

Kelsoe JR, Loetscher E, Spence MA, Foguet M, Sadovnick AD, Remick RA, et al (1998): A susceptibility locus for bipolar disorder on chromosome 22: Results of a genome survey. *Am J Hum Genet* 63(suppl):A295.

Kelsoe JR, Spence MA, Loetscher E, Sadovnick AD, Remick RA, Keck PE, et al (1999): A genome survey indicates a susceptibility locus for bipolar disorder on chromosome 22. *Mol Psychiatry* 4(suppl 1):S74.

Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D (1993): The Roscommon family study. *Arch Gen Psychiatry* 50:527–540.

Kruglyak L, Lander ES (1995): High-resolution genetic mapping of complex traits. *Am J Hum Genet* 57:1212–1223.

Kwok JB, Adams LJ, Salmon JA, Donald JA, Mitchell PB, Schofield PR (1999): Non-parametric simulaton-based statistical analyses for bipolar affective disorder locus on chromosome 21q22.3. *Am J Med Genet* 88:99–102.

Lachman HM, Kelsoe JR, Remick RA, Sadovnick AD, Rapaport MH, Lin M, et al (1996): Linkage studies support a possible locus for bipolar disorder in the velocardiofacial syndrome region on chromosome 22. *Am J Med Genet* 74:121–128.

Lander E, Kruglyak L (1995): Genetic dissection of complex traits: Guidelines for interpreting and reporting linkage results. *Nat Genet* 11:241–247.

Lander E, Schork N (1994): Genetic dissection of complex traits. *Science* 265:2037–2048.

Levinson DF, Schizophrenia Linkage Collaborative Group (1996): Additional support for schizophrenia linkage for chromosomes 6 and 8. *Am J Med Genet* 67:580–594.

Lin JP, Bale SJ (1997): Parental transmission and D18S37 allele sharing in bipolar affective disorder. *Genet Epidemiol* 14: 665–668.

Maier W, Lichtermann D, Minges J, Hallmayer J, Heun R, Benkert O, et al (1993): Continuity and discontinuity of affective disorders and schizophrenia. Results of a controlled family study. *Arch Gen Psychiatry* 50:871–883.

Martinez M, Goldin LR, Cao Q, Zhang J, Sanders AR, Nancarrow DJ, et al (1999): Follow-up study on a susceptibility locus for schizophrenia on chromosome 6q. *Am J Med Genet* 88:337–343.

Mayeux R, Stern Y, Ottman R, Tatemichi TK, Tang MX, Maestre G, et al (1993): The apolipoprotein E4 allele in patients with Alzheimer's disease. *Ann Neurol* 34:752–754.

Maziade M, Bissonnette L, Rouillard E, Martinez M, Turgeon M, Charron L, et al (1997): 6p24–22 region and major psychoses in the eastern Quebec population. *Am J Med Genet* 74:311–318.

McInnes LA, Escamilla MA, Service SK, Reus VI, Leon P, Silva S, et al (1996): A complete genome screen for genes predisposing to severe bipolar disorder in two Costa Rican pedigrees. *Proc Natl Acad Sci U S A* 93:13060–13065.

McMahon FJ, Hopkins PJ, Xu J, McInnis MG, Shaw S, Cardon L, et al (1997): Linkage of bipolar affective disorder to chromosome 18 markers in a new pedigree series. *Am J Hum Genet* 61:1397–1404.

Moises HW, Yang L, Kristbjarnarson H, Wiese C, Byerley W, Macciardi F, et al (1995): An international two-stage genome-wide search for schizophrenia susceptibility genes. *Nat Genet* 11:321–324.

Morissette J, Villeneuve A, Bordeleau L, Rochette D, Laberge C, Gagne B, et al (1999): Genome-wide search for linkage of bipolar affective disorders in a very large pedigree derived from a homogeneous population in Quebec points to a locus of major effect on chromosome 12q23–q24. *Am J Med Genet* 88:567–587.

Nothen MM, Cichon S, Franzek E, Albus M, Bormann M, Rietschel R, et al (1997): Systematic search for susceptibility genes in bipolar affective disorder—evidence for disease loci at 18p and 4 p. *Am J Hum Genet* 61S:A288.

Nothen MM, Cichon S, Rohleder H, Hemmer S, Franzek E, Fritze J, et al (1999): Evaluation of linkage of bipolar affective disorder to chromosome 18 in a sample of 57 German families. *Mol Psychiatry* 4:76.

Nurnberger JI Jr, Berrettini WH (1998): *Psychiatric Genetics.* London: Chapman and Hall.

Papolos DF, Faedda GL, Veit S, Goldberg R, Morrow B, Kucherlapati R, et al (1996): Bipolar spectrum disorders in patients diagnoses with VCFS: Does a hemizygous deletion of chromosome 22q11 result in bipolar affective disorder? *Am J Psychiatry* 153:1541–1547.

Pulver AE, Karayiorgou M, Wolyniec PS, Lasseter VK, Kasch L, Nestadt G, et al (1994a): Sequential strategy to identify a susceptibility gene for schizophrenia: report of potential linkage on chromosome 22q12–q13.1: Part 1. *Am J Med Genet* 54:36–43.

Pulver AE, Nestadt G, Goldberg R, Shprintzen RJ, Lamacz M, Wolyniec PS, et al (1994b): Psychotic illness in patients diagnosed with velo-cardio-facial syndrome and their relatives. *J Nerv Ment Dis* 182:476–478.

Roberts SB, MacLean CJ, Neale MC, Eaves LJ, Kendler KS (1999): Replication of linkage studies of complex traits: An examination of variation in location estimates. *Am J Hum Genet* 65:876–884.

Schwab SG, Albus M, Hallmayer J, Honig S, Borrmann, Lichtermann D, et al (1995): Evaluation of a susceptibility gene for schizophrenia on chromosome 6p by multipoint affected sib-pair linkage analysis. *Nat Genet* 11:325–327.

Schwab SG, Hallmayer J, Albus M, Lerer B, Hanses C, Kanyas K, et al (1999): Further evidence for a susceptibility locus on chromosome 10p14–p11 in 72 families with schizophrenia by non-parametric linkage analysis. *Am J Med Genet* 81:302–307.

Schwab SG, Hallmayer J, Lerer B, Albus M, Borrmann M, Honig S, et al (1998): Support for a chromosome 18p locus conferring susceptibility to functional psychoses in families with schizophrenia, by association and linkage analysis. *Am J Hum Genet* 63:1139.

Smyth C, Kalsi G, Brynjolfsson J, O'Neill J, Curtis D, Rifkin L, et al (1996): Further tests for linkage of bipolar affective disorder to the tyrosine hydroxylase gene locus on chromosome 11p15 in a new series of multiplex British affective disorder pedigrees. *Am J Psychiatry* 153:271–274.

Stine OC, Xu J, Koskela R, McMahon FJ, Geschwend M, Friddle C, et al (1995): Evidence for linkage of bipolar disorder to chromosome 18 with a parent-of-origin effect. *Am J Hum Genet* 57:1384–1394.

Straub RE, Lehner T, Luo Y, Loth JE, Shao W, Sharpe L, et al (1994): A possible vulnerability locus for bipolar affective disorder on chromosome 21q22.3. *Nat Genet* 8:291–296.

Straub RE, MacLean CJ, Martin RB, Ma Y, Myakishev MV, Harris-Kerr C, et al (1998): A schizophrenia locus may be located in region 10p15–p11. *Am J Med Genet* 81:296–301.

Straub RE, MacLean CJ, O'Neill FA, Burke J, Murphy B, Duke F, et al (1995): A potential vulnerability locus for schzophrenia on chromosome 6p22–24: Evidence for genetic heterogeneity. *Nat Genet* 11:287–293.

Suarez B, Harpe CL, Van Eerdewegh P (1994): Problems of replicating linkage claims in psychiatry. In: Gershon ES, Cloninger CR, editors. *Genetic Approaches to Mental Disorders. Proceedings of the 82nd Annual Meeting of the American Psychopathological Association.* Washington, DC: American Psychiatric Press, 23–46.

Tsai M-S, Tangalos EG, Petersen RC, Smith GE, Schaid DJ, Kokmen E, et al (1994): Apolipoprotein E: Risk factor for Alzheimer disease. *Am J Hum Genet* 54:643–649.

Turecki G, Grof P, Cavazzoni P, Duffy A, Grof E, Martin R, et al (1999): Lithium responsive bipolar disorder, unilineality and chromosome 18: A linkage study. *Am J Med Genet* 88:411–415.

Weissman MM, Gershon ES, Kidd KK, Prusoff BA, Leckman JF, Dibble E, et al (1984): Psychiatric disorders in the relatives of probands with affective disorder. *Arch Gen Psychiatry* 41:13–21.

Winokur G, Coryell W, Keller M, Endicott J, Leon A (1995): A family study of manic-depressive (bipolar I) disease. Is it a distinct illness separable from primary unipolar depression? *Arch Gen Psychiatry* 52:367–373.

Winokur G, Tsuang MT, Crowe RR (1982): The Iowa 500: Affective disorder in relatives of manic and depressed patients. *Am J Psychiatry* 139:209–212.