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Understanding the Genetic Basis of Mood Disorders: Where Do We Stand?

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Introduction

In this issue of the *Journal,* Sherman et al. (1997) describe the promise of genetic approaches for understanding human behavior and point out a number of obstacles to realization of this promise; these include the methodological challenge of identifying genes for complex traits and the societal challenge of appropriately using the information that will be gained if such genetic-mapping efforts are successful. Genetic-mapping studies in humans rest on the premise that traits of interest can be reduced to one or more discrete phenotypes and that these phenotypes result, at least in part, from particular alleles at susceptibility loci of reasonably large effect. As discussed in this review, abundant evidence suggests that severe bipolar mood disorder (BP) fulfills this premise better than other human behavioral traits (Tsuang and Faraone 1990; Escamilla et al. 1997). The diagnosis of BP is highly reliable, and its delineation as a distinct syndrome has proved to be clinically useful in predicting course and response to treatment (Goodwin and Jamison 1990). However, one must keep in mind that this diagnostic category, like all psychiatric classifications, is based on operational criteria (derived from a combination of epidemiological and clinical observations), rather than on any anatomical or physiological evidence. This fact differentiates psychiatric disorders from other etiologically complex categories of disease, such as hypertension or diabetes mellitus. In this review we discuss our current understanding of the genetic basis of BP and other mood disorders and indicate how our body of knowledge has been influenced by different approaches to the definition of disease phenotypes.

The term "mood disorders" encompasses a group of conditions in which a disturbance of mood is recognized as the predominant feature of the syndrome. In most current diagnostic systems, mood is viewed as carrying greater heuristic and practical value than other signs and symptoms that might also be present, such as anxiety, cognitive impairment, or alteration in vegetative functions (American Psychiatric Association 1994). Epidemiological studies have provided strong support for a genetic component in the etiology of these disorders (Tsuang and Faraone 1990), particularly in comparison with other classes of mental illness. However, as noted above, our current categorical classification of psychiatric disorders, although reliable, lacks demonstrated etiologic validity. It is thus by no means certain that disturbance of mood represents the best indicator of common genetic etiology for this class of conditions. For example, major depressive disorder (MDD), the most common mood disorder, is conceptualized as distinct from panic disorder (PD), a common anxiety syndrome, although two-thirds of patients with PD also will have a lifetime diagnosis of MDD (Breier et al. 1984), and comorbidity between the two syndromes is common (Kendler et al. 1987; Coryell et al. 1988). Psychiatric disorders are, of course, not unique in this regard, and similar issues regarding the etiologic validity of diagnostic constructs also complicate genetic mapping of many medical disorders.

The list of mood disorders most commonly includes MDD, dysthymic disorder (a more chronic but generally less severe depressive disorder), BP (in which episodes of major depression alternate with mania), cyclothymic disorder (characterized by many episodes of brief and/or less severe depressions alternating with symptoms of mild mania (hypomania)), and mood disorders due to a general medical condition or induced by substance abuse. BP is divided further into BP-I (MDD and severe mania) and BP-II (MDD and hypomania), and both of these categories also often are referred to as "manic-depressive illness." The degree to which these diagnoses are related genetically or are distinct entities is currently unknown (Tsuang and Faraone 1990; Pauls et al. 1995; Spence et al. 1995). This uncertainty has impeded efforts to construct realistic models for linkage analysis of BP. Furthermore, although most (but not all) genetic-mapping studies treat mood disorders and thought disorders

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(notably schizophrenia) as independent entities, a substantial number of individuals are afflicted with schizoaffective disorder, in which disturbances in thought processes are as prominent as the mood alteration (Escamilla et al. 1997).

Genetic Epidemiology of Mood Disorders

Uncertainty regarding the etiologic relationship between BP and other psychiatric disorders has not been resolved by a large number of family, twin, and adoption studies aimed at evaluating the degree of familial aggregation and heritability of various mood disorders. Nevertheless, although family studies of BP, conducted over a period of several decades, have utilized several different designs, including varying definitions of what constitutes BP, they consistently have demonstrated familial aggregation of both severe and mild mood disorders. One of the most striking findings of these studies has been that BP shows far greater familial aggregation than other mood disorders. For example, Weissman et al. (1984) observed a relative risk for BP of almost 25, compared with a relative risk of ~3.0 for MDD. Similarly, twin studies have indicated a higher heritability for BP, compared with that for other forms of mood disorder. For example, the classic twin study by Bertelson et al. (1977), utilizing the Danish Twin Registry, indicated a concordance rate, for narrowly defined BP, of .79 for MZ twins, versus .19 for DZ twins (as opposed to .54 and .24, respectively, for major depression). Although most epidemiological studies suggest that some cases of MDD probably are genetically related to BP, only inconclusive results have been obtained from efforts to identify particular MDD subtypes that are most likely to reflect a shared genetic etiology with BP (Goodwin and Jamison 1990).

It is instructive to compare the evidence showing the high degree of heritability of narrowly defined BP to that for either of the traits used for illustrative purposes by Sherman et al. in this issue of the *Journal*—namely, schizophrenia and emotional stability; for example, the MZ concordance rate of .79 for BP (Bertelsen et al. 1977) compares with an MZ concordance rate of .46 for schizophrenia (results from several studies, pooled by Sherman et al.). The calculated heritability of BP has been estimated at .59 (Tsuang and Faraone 1990), compared with .27–.61 for emotional stability (as compiled by Sherman et al.).

Sherman et al. point out that twin studies have a number of inherent limitations and that their results therefore should be interpreted cautiously. Such caution is particularly warranted for psychiatric disorders, because of the special complexities that we already have noted. Relatively little attention has been paid to the fact that the majority of twin studies of psychiatric syndromes were conducted ≥2 decades ago, using (*a*) phenotype-assignment methods that currently would not be widely accepted and (*b*) diagnostic categorizations that differ from those employed in almost all recent genetic-mapping studies. An example is the study by Bertelsen et al. (1977), discussed above, which has had a substantial influence on current views regarding the genetic basis of mood disorders. The determination of phenotype in that investigation derived from an unstructured psychiatric interview conducted by a single individual; in contrast, most current investigators would accept diagnostic-interview data only if these were collected by standardized interviews. Additionally, the findings of Bertelsen et al. (1977) were based on diagnostic criteria different than those currently in use—for example, combining individuals with hypomania and individuals with mania into the same category. Reexamination of epidemiological studies such as that by Bertelsen et al. (1977) further emphasizes the special difficulty of psychiatric genetics; there is inherent subjectivity in recording even individual behavioral features, let alone in determining categorical diagnoses that change over time. This fact makes the delineation of affected status in current studies as problematic as the proper interpretation of past data.

It is not likely that we will attain a more refined approach for diagnostic classification of mood disorders until we begin to identify the genes that underlie risk for these disorders. From that point we may learn to make distinctions finer than are now possible between different classes of mood disorders and also may discover that particular (and currently unexpected) phenotypic features are etiologically related to one another. Such use of genetics to redefine phenotypic categories has, of course, been one of the most tangible results of positional cloning of genes responsible for relatively simple disorders. Such diagnostic refinement, however, will not be possible for mood disorders unless the currently available classification schemes will permit us to first map the responsible genes. Genes for several phenotypically complex (nonpsychiatric) disorders have now been mapped. Success in mapping such traits usually has depended on the delineation of narrowly defined phenotypes that are most likely to share common genetic causation, as determined by examination of the findings of genetic-epidemiological studies (McInnes and Freimer 1995; Escamilla et al. 1997). These examples could be used to guide our approach to genetic-mapping investigations of mood disorders; although the epidemiological studies of these syndromes are imperfect, they clearly suggest that severe BP (i.e., BP-I) should be considered such a narrowly defined phenotype.

Genetic Mapping Studies of Mood Disorder

The effort to map genes for BP may have attracted more scrutiny from the scientific and general media than

has the search for genes responsible for any other human trait. Remarkably, several cycles of misplaced excitement and exaggeration of failure were widely reported before a single study had even attempted to screen the entire genome for linkage to BP. In fact, the initial series of studies suggesting localization of BP genes on chromosomes 11 (among the Old Order Amish) and X (among non-Ashkenazi Israeli Jews) were reported at a time when the available genetic markers permitted evaluation of linkage across only a tiny fraction of the entire genome (Baron et al. 1987; Egeland et al. 1987) and when linkage had only been demonstrated for a handful of diseases, all with clear-cut Mendelian transmission. These initial linkage studies were predicated on two broad assumptions: first, that relatively simple Mendelian models could account for the transmission of an enormous range of mood-disorder phenotypes and, second, that the power of linkage approaches was sufficiently great that BP genes could be identified even if the first assumption was incorrect. With the benefit of hindsight it is obvious that such preconceptions were naive, although it should be noted that the results of the studies, particularly that of the Amish study, were widely accepted until follow-up examination of the same pedigrees failed to support the original findings (McInnes and Freimer 1995). It became clear that investigators had failed to account for uncertainty in the assignment of phenotypes; for example, the fall in the evidence for linkage on chromosome 11 in the Amish was due largely to the development of mood disorder in two previously unaffected individuals whose marker genotypes in this chromosome region differed from those of the originally affected family members (Kelsoe et al. 1989). Additionally, the majority of the linkage information in both the Amish and Israeli studies derived from individuals with diagnoses other than classic BP—for example, unipolar MDD (Baron et al. 1987, 1993; Egeland et al. 1987; Kelsoe et al. 1989). As indicated above, it already had been known, from family studies, that the relative risk for BP was substantially greater than that for MDD (Weissman et al. 1984) and, from twin studies, that the heritability of BP was substantially greater than that for MDD (Bertelsen et al. 1977).

Subsequent to these initial "follow-up" linkage studies, additional efforts have been made to evaluate the degree to which the inheritance patterns of various forms of mood disorder are consistent with the models used in most linkage studies—that is, the assumption that the action of a single major locus (SML) is involved. Spence et al. (1995), in the largest such study, have shown in a British Columbian sample that, although there is good evidence for SML inheritance of BP (in particular, of BP-I), the evidence argues against SML inheritance for MDD and other psychiatric disorders. Even more strikingly, segregation analyses of the Old Order Amish community suggest possible SML inheritance only for BP-I, not for other mood disorders (Pauls et al. 1995). These studies should not be interpreted as supporting SML inheritance of BP (Craddock et al. 1997; Spence et al. 1997), but they clearly indicate that such a model is unlikely for broadly defined mood disorders. Despite these observations, many (but not all) subsequent linkage studies have continued to focus on data sets in which a high proportion of the genetic information derives from individuals with diagnoses other than BPI. Efforts continue to attempt to identify forms of mood disorder that reflect a common genetic etiology with BP; these remain unsuccessful (Blacker et al. 1996).

Beginning in the early 1990s, the availability of highly polymorphic microsatellite markers had a major impact on genetic-linkage studies for BP. Several groups reported single suggestive localizations for BP genes, loci based on testing multiple markers in several locations but not, however, on complete screening of the genome. These studies utilized mainly cosmopolitan collections of pedigrees from North America and Europe. Examples of these results include possible BP localizations on chromosomes 21q (Straub et al. 1994), in the pericentromeric region of 18 (Berrettini et al. 1994), on 16p (Ewald et al. 1995), and on 5p (Kelsoe et al. 1996). The results of Berrettini et al. (1994) have attracted particular attention, because they have been supported by an independent investigation using a different set of North American pedigrees (Stine et al. 1995). The results supporting BP linkage in the pericentromeric region of chromosome 18 are confined largely to families in which BP appears to be inherited through the paternal lineage. This intriguing observation has suggested the possibility of a parent-of-origin effect. It is unclear what mechanism would account for such a finding; however, it may be noteworthy that this region contains one of the most dramatic instances, in the genome, of suppression of male recombination relative to female recombination (Silverman et al. 1996).

Several recently reported linkage studies of BP differ from previous ones in three important respects: (1) Linkage analysis is focused primarily on individuals with severe mood disorder (BP-I only in Ginns et al. 1996; McInnes et al. 1996; and BP-I and BP-II in Blackwood et al. 1996) (2) The bulk of information for linkage is derived from affected, rather than from apparently unaffected, individuals (Blackwood et al. 1996; Ginns et al. 1996; McInnes et al. 1996). (3) Results can be interpreted in the light of complete screening of the genome in the relevant study populations (Blackwood et al. 1996; Ginns et al. 1996; McInnes et al. 1996).

What do these studies tell us? In the study by Blackwood et al. (1996), an argument could be advanced for statistically significant linkage to chromosome 4p. This result was limited to a single extended Scottish pedigree

and was not found in other pedigrees from the same population. Additionally, the evidence for linkage depended on the inclusion of BP-II individuals. Ginns et al. (1996), in a new analysis of the Old Order Amish, identified regions on chromosomes 6, 13, and 15 in which excessive allele sharing among affected individuals suggest the possible location of loci for BP-I susceptibility. None of these possible localizations, however, attain statistical significance. McInnes et al. (1996), in a study of two extended pedigrees from the genetically homogenous population of Costa Rica, identified possible localizations for BP-I in several chromosomal regions, notably 11p, 18p, and 18q. The 18q localization was supported by identification of extremely long haplotypes shared by most of the affected individuals in both families, including several alleles that are very rare in the general Costa Rican population (Freimer et al. 1996). In the Costa Rican study the linkage evidence also did not attain statistical significance. Each of these reports, however, identifies regions of the genome that require more intensive study. In two cases (Blackwood et al. 1996; Freimer et al. 1996), the suggested linkage findings are accompanied by extended marker haplotypes in the majority of affected individuals within the relevant pedigrees. These haplotypes indicate that the designated regions are identical by descent (IBD) among affected individuals; since each of these studies draws on subjects from genetically homogeneous populations, there is the possibility of testing whether these regions are shared IBD by other (apparently unrelated) patients from the same populations. This opportunity also offers the hope that the region of IBD sharing can be narrowly delineated on the basis of the expectation that more distantly related affected individuals will share small regions IBD, as a result of recombination over several generations that separate them from their common ancestor(s). Ultimately it may be possible, by use of such isolated populations, to define, for BP loci, candidate regions sufficiently narrow to permit positional cloning of causative genes.

It is unlikely that a single major susceptibility gene exists that is responsible for a high proportion of BP cases in all populations. How, then, should we interpret the fact that several genome-screening studies have highlighted multiple possible chromosomal regions that could contain BP-susceptibility genes? Genetic-mapping studies of complex traits may be viewed as a highly iterative process, in which initial genome-screening studies serve to propose hypotheses to be tested through additional investigation (McInnes et al. 1996). According to this view, one does not expect the explosive progress toward gene identification that has characterized the study of simple Mendelian traits (Jamison and McInnis 1996), and we can anticipate that many (if not most) of the currently suggested BP localizations will prove spurious. In this respect the results of genome-screening studies of BP are roughly comparable to those recently observed for other complex traits, such as insulin-dependent diabetes mellitus and multiple sclerosis (Davies et al. 1994; Hashimoto et al. 1994; Ebers et al. 1996; Haines et al. 1996; Kuokkanen et al. 1996; Sawcer et al. 1996). Some commentators have suggested that the difficulties and uneven rate of progress inherent in mapping genes for complex traits are somehow particular to BP, perhaps because of the glib references that can be made to the euphoria of apparent success and the dysphoria of apparent failure (Morell 1996; Risch and Botstein 1996). Such publicity may have the unfortunate result of generating undue pessimism, among the scientific community and the general public, regarding the possibility of ultimately elucidating the genetic basis of BP and other mood disorders.

Societal Implications

Even if, in the near future, one or more susceptibility genes for bipolar disorder are identified, it will be difficult, as Sherman et al. point out, to know how to utilize such information clinically. The societal stigma of bipolar disorder and other psychiatric conditions, as well as their variable course, make it likely that the problems already identified in the genetic testing of other common complex diseases, such as breast cancer and colon cancer, will be multiplied when genetic testing in psychiatric disorders becomes feasible. The opportunity exists, however, to identify the salient issues and to plan for the day when genetic risk of psychiatric illness can be assessed reliably. For example, our group has surveyed individuals with mood disorder, their friends and relatives, and health-care providers, to explore the implications of genetic testing in bipolar disorder (Smith et al. 1996). We have observed that reproductive decisions and attitudes toward presymptomatic testing in children differ markedly between consumer groups and health-care providers and that they depend greatly on presumed severity of illness and the availability of as yet undetermined preventive strategies that might ameliorate the severity or course of illness. Individuals who are likely to pursue genetic testing may find it difficult to accept the inherent uncertainty in the prediction of genetic risk and may misinterpret the information in such a way as to adversely affect their own and/or other family member's life experiences. In our study, psychiatric physicians were much more likely to endorse termination of a pregnancy than were either patients and support-group members or medical students, if informed of a probable fetal inheritance of bipolar disorder. This difference in interpretation of data was particularly evident in scenarios in which the likelihood of developing BP disorder was high and in which the course of illness was severe.

Surprisingly, patients and support-group members expressed greater interest in genetic testing than did psychiatrists, even when it was assumed that no prophylactic treatment existed. The need for further study of attitudes toward mood disorders is clear. It most likely will be at least a few years before genes for BP are identified. This provides us an opportunity to investigate systematically the societal implications of the ability to determine genetic risk for this disorder—before the reality is thrust upon us.

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