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GENETICS OF MANIC DEPRESSIVE ILLNESS

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KEY WORDS: bipolar disorder, linkage, nonmendelian inheritance, candidate genes, ethics

ABSTRACT

Manic depressive illness is a common and frequently debilitating familial psychiatric disorder. Efforts to understand the mechanisms of inheritance have been hindered by the complexity of the phenotype, which may range from benign mood swings to chronic psychosis, and by apparently nonmendelian modes of transmission. Early reports of linkage to chromosomal loci have fallen into doubt; however they have helped encourage the development of more sophisticated methods for analyzing complex phenotypes. Using such methods, linkage of manic depressive illness to loci on chromosome 18 has been reported and apparently replicated, and work is proceeding to identify genes associated with what is probably a genetically heterogeneous set of disorders. As molecular mechanisms of inheritance are elucidated, it will be important to consider the ethical implications of genetic testing in a clinically and genetically complex disorder such as manic depressive illness.

INTRODUCTION

A discussion of the mechanisms of inheritance of mood disorders is the story of the process of discovery, as there is not yet an established genetic mechanism for these disorders. The direct study of the genetic basis of manic depressive and other common disorders has been stimulated by dramatic developments in the molecular maps of the genome and has stimulated new developments in the statistical analysis of complex phenotypes. We are beginning to understand mood disorders (even classical manic depressive illness) as highly complex phenotypes.

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CLINICAL DESCRIPTION

Diagnosis and Phenotype Definition

Manic depressive illness (MDI) was defined by Kraepelin (1921), who made the first systematic observations on hospitalized patients:

> As a rule the disease runs its course in isolated attacks more or less sharply defined from each other or from health....Accordingly we distinguish first of all manic states with the essential morbid symptoms of flight of ideas, exalted mood, and pressure of activity, and melancholia or depressive states with sad or anxious moodiness and also sluggishness of thought and action. These two opposed phases of the clinical state have given the disease its name. But besides them we observe also clinical "mixed forms," in which the phenomena of mania and melancholia are combined with each other.

Kraepelin also discriminated MDI from schizophrenia, a nosologic distinction supported later by evidence from family studies (Loranger 1981; Gershon et al 1982, 1988; Rice et al 1987). Although the term MDI is not used clinically as a diagnostic category, for this discussion, MDI denotes a phenotype that includes the modern diagnosis "bipolar disorder type I" (BPI) and other disorders of mood instability (American Psychiatric Association 1994). We believe "manic depressive" better describes the phenotype than "bipolar." Whereas bipolar implies two separate and distinct mood states, MDI allows for the mixed states (including dysphoric manias and agitated depressions) also commonly seen in the bipolar disorders, but not adequately described by the term. The term is also sufficiently general to allow for uncertainty about the boundaries of the phenotype. Where more specific diagnostic definitions are required, we use the bipolar/unipolar terminology.

Boundaries of the MDI phenotype have been much disputed, and only in the past two decades has there been sufficient agreement about the diagnoses comprising the phenotype to allow useful comparison across studies. There is growing agreement that in addition to BPI, MDI encompasses several mood disorders related phenomenologically and genetically to BPI. These include bipolar disorder type II (BPII) (depression plus distinct but less severe manic symptoms, i.e. hypomania), some cases of major depressive disorder without manic symptoms [recurrent unipolar disorder (RUP), as defined by Research Diagnostic Criteria (Spitzer et al 1975)], and some cases of schizoaffective disorder (in which symptoms of psychosis persist in the apparent absence of the mood disorder). The MDI phenotype may include other, milder manic-depressive spectrum disorders such as minor depression, hypomania without major depression, dysthymia, and cyclothymia, but this is less certain.

Morbidity and Comorbidity

MDI produces severe social, interpersonal, and occupational impairment and is associated with an average suicide rate of 15–20% (Guze & Robins 1970,

Goodwin & Jamison 1990). Moreover, it is associated with other psychiatric disorders (comorbidity). Sixty percent of patients with MDI meet diagnostic thresholds for alcoholism and/or substance abuse (Regier et al 1990), and 20% have comorbid anxiety disorders, especially panic disorder (MacKinnon et al 1994, Chen & Dilsaver 1995), which further contribute to the disability and societal cost of MDI.

On the other hand, a large proportion of people who upon examination are found to have MDI fail to recognize it, ascribing depressive states to ill-fortune and enjoying hypomanias as a relief from gloom and lethargy. At least a few find mood fluctuations to be a source of creative energy and derive personal or religious meaning from transient states of exaltation and despair (Jamison 1993, 1995).

Pharmacotherapy

Although pharmacologic treatments for depression have been available for 40 years, effective pharmacotherapy for MDI has been widely available in the United States only since the 1970s, when lithium was approved for use by the Food and Drug Administration (FDA). Lithium remains the mainstay of preventive treatment for MDI (Gurscott & Taylor 1994), although anticonvulsants (e.g. carbamazepine and valproic acid) also can be effective at preventing or ameliorating episodes of both depression and mania. These empiric remedies, however, do not always work; likewise all have adverse effects and not infrequently are intolerable to patients. A greater understanding of disease mechanisms that could lead to rational therapies is highly desired and a major public health priority.

Pathophysiology

The biology of mood disorders was last discussed in this series in 1979 (Sachar & Baron 1979). Research since then has painted a more complex picture of hypothetical disease mechanisms, mainly involving neurotransmitter systems (Hyman & Nestler 1993). This work has contributed to the development of new antidepressant agents that operate on serotonergic, noradrenergic, and dopaminergic systems. There is as yet no direct evidence that outlines the molecular pathophysiology of MDI, and no fully developed explanation linking receptor systems to disease phenomenology.

EPIDEMIOLOGY

Population Rate

Recent large-scale community samples find BPI in 0.5–1.0% of the population (Robins et al 1984, Kessler et al 1994). This is almost surely an underestimate of the prevalence of MDI, as these figures include neither BPII nor cases of

RUP that might represent expressions of the MDI phenotype. Indeed, there is evidence from family studies that BPII is the most common expression of the MDI phenotype (Simpson et al 1993).

Twin, Family, and Adoption Studies

MDI is consistently found more often in relatives of probands with MDI than in relatives of probands with other or no psychiatric disorders. Risk increases with the proportion of shared genetic endowment (Figure 1). The concordance rate for MDI (applied loosely, including RUP) in monozygotic twins has been reported in the range of 50–70% (McGuffin & Katz 1989), and may be as high as 100% if suicide is considered a phenotypic form (Rifkin & Gurling 1991). Concordance rates in dizygotic twins, from the same studies, range from 13% for BPI alone to 30% for the broader phenotype (BPI, BPII, and RUP).

Family studies vary widely in ascertainment and diagnostic methodology; consequently, reported rates of MDI in relatives of probands with MDI vary

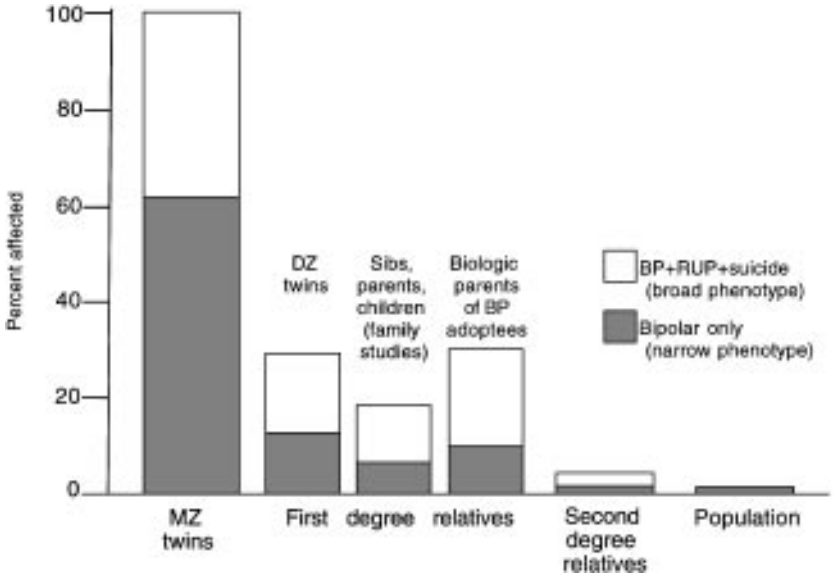

Figure 1 Risk of MDI in relatives of bipolar probands, by degree of relatedness. Family and twin data are the weighted averages of studies reviewed in Tsuang & Faraone (1990), with additional data from McGuffin & Katz (1989) and Rifkin & Gurling (1991). Adoption study data are from Mendlewicz & Ranier (1977). The population rate for the narrow phenotype is derived from Epidemiologic Catchment Area (Robins et al 1984) and National Comorbidity Survey (Kessler et al 1994) data; these studies do not discriminate single episode from recurrent major depression, so data for the broad phenotype are not included.

widely (Coryell et al 1981). Nevertheless, they consistently report an elevated risk for MDI in first-degree relatives of probands with BPI compared to the general population and normal controls, and higher rates of BPI and BPII in relatives of BPI and BPII probands compared to relatives of unipolar probands (Weissman et al 1984, Andreasen et al 1987). Data on the risk of MDI in second-degree relatives of probands with MDI reflect a rate intermediate to that of first-degree relatives and the population (Gershon et al 1982).

Relatively high mood disorder rates in the biological but not the adoptive parents of adoptees with MDI imply genetic versus environmental transmission of mood disorder. An adoption study from Belgium that examined the rate of MDI and other mental disorders in biological versus adoptive parents of adoptees with BPI, compared to parents of adoptees without mental illness, revealed significantly higher rates of mood disorders among biological versus adoptive parents (Mendlewicz & Rainer 1977). In this study, which is the only adoption study to date to focus on adoptees with BPI and to interview all parents, 18% of the biological parents and 7% of adoptive parents of adoptees with BPI could be diagnosed with a mood disorder (evaluators were blinded to the adoptive and diagnostic status of the offspring). As a control, 1% of biological and 4% of adoptive parents of unaffected adoptees could be given a mood disorder diagnosis.

Analysis of segregation of the phenotype in pedigrees has failed, however, to reveal a simple, mendelian mode of transmission, although there is evidence favoring single major locus models over multifactorial models (Rice et al 1987, Spence et al 1995).

EARLY APPROACHES TO LINKAGE

Positive Linkage Findings

Several researchers have reported a linkage of MDI to the color blindness and G6PD phenotypes on the X-chromosome (Reich et al 1969, Baron 1977, Baron et al 1987), to immunologic variability [e.g. in the human leukocyte antigen (HLA) system on chromosome 6] (Turner & King 1983, Stancer et al 1988), and to restriction fragment length polymorphisms (RFLPs) of the insulin gene and of the Harvey-*ras* oncogene on chromosome 11 in an extended Amish pedigree (Egeland et al 1987). These findings remain unreplicated, even in the same families from which they were originally claimed (Kelsoe et al 1989, Law et al 1992, Baron et al 1993).

Problems in Replication

Failure to replicate a positive finding after numerous attempts (and especially in the original families) suggests that the initial positive reports were chance

findings. Contrary to early expectations that linkage studies would be subject to many false negative (type II) errors, false positive (type I) errors in genome-wide screens are likely to be common at conventional standards of statistical significance (Lander & Kruglyak 1995). On the other hand, the amount of data required to replicate a linkage finding in a complex, nonmendelian disorder may be greater by an order of magnitude (requiring a thousand or more sib-pairs under some models) than the amount required to establish the initial finding (Suarez et al 1994). Therefore, most, if not all, replication studies to date may lack sufficient power to exclude linkage if the true mechanisms of inheritance are complex.

Another oft-cited explanation for inconsistent linkage results is genetic heterogeneity. Perhaps, the argument goes, the initial result was a true finding, but for only a subset of the population. Although heterogeneity is likely to be a factor in MDI (see below) and to complicate statistical analysis, its use as an explanation for linkage inconsistency remains weak until an a priori division of families into subtypes leads to replicable linkages (Risch 1990a).

An unanticipated but significant problem of early studies was the use of large, complex pedigrees. Linkage studies in these families assumed genetic homogeneity; often the analysis depended on unaffected family members and on a few crucial individuals. The Amish study revealed possible genetic heterogeneity within the family. A change in the diagnosis of two individuals (initially believed to be unaffected) later reduced the evidence favoring linkage by two orders of magnitude (Kelsoe et al 1989). The linkage analysis in the original study also depended on 19 affected and 62 unaffected family members. A further hazard of extended pedigree studies is that it is difficult to find other extended families in which to replicate the findings. Later MDI linkage studies have aimed to avoid these difficulties by amassing large numbers of nuclear families, in which nonparametric and affected-only analyses can be performed and replication is more straightforward. Homogeneity within these families is more readily assumed than in complex pedigrees, and it is unnecessary to assume genetic homogeneity of the phenotype. When large families and unaffected individuals are required in a linkage study, sensitivity analysis (Hodge & Greenberg 1992) can reveal which unaffected (hence, potentially affected) individuals in the pedigree make a large contribution to the statistical odds of linkage (i.e. the logarithm of the odds, or lod).

MODES OF COMPLEX (NONMENDELIAN) INHERITANCE

Until relatively recently, human genes could only be mapped when they were associated with clear phenotypes transmitted in one of the classical, single-gene

patterns. Most disorders mapped in this fashion are apparent at birth, severely impair reproductive capacity, and consequently, are rare.

In contrast, many common familial disorders demonstrate complex patterns of inheritance. Progress in identifying and mapping genes related to these disorders has required taking these complexities into account. Some or all of the following may be factors in the complex inheritance of MDI.

Heterogeneity

Two or more genes may cause similar phenotypes in different families, as seen in breast cancer (Narod et al 1995). If this is the case in MDI, it may be possible to test a hypothesis of clinical heterogeneity (e.g. families transmitting BPII but not BPI, or families with high rates of certain comorbid diagnoses) by looking for allele sharing in affected members of familial subgroups in a linkage sample.

Oligo- or Polygenic Inheritance

Two or more different genes may act together to produce a phenotype, as seems to be the case for diabetes mellitus (Davies et al 1994). This might account for the observation of subclinical mood disorders in families with MDI. For example, inheriting one of the predisposing genes might lead to mood cycling, but without the other gene, psychosis is unlikely to occur.

Incomplete Penetrance

The presence of a given genotype does not necessarily lead to expression of the phenotype, perhaps because the gene produces disease only in the presence of environmental cofactors, as is the case for asthma (Postma et al 1995), or in the absence of protective factors. In MDI it is occasionally observed that an index episode of mania is triggered by the use of a psychostimulant or antidepressant; without this environmental influence, expression of the phenotype is not readily observed.

Anticipation

Anticipation is a tendency for the disease phenotype to worsen (e.g. to be expressed at an earlier age and to run a more severe course) in consecutive generations. In Huntington Disease (HD), anticipation correlates with expansion of trinucleotide repeat sequences in the gene (Ranen et al 1995). In MDI, anticipation has been observed in a large family study (McInnis et al 1993) and might account for differences in illness severity within families.

Imprinting

Variation in phenotype, given the same genetic defect, may depend on the sex of the parent transmitting the disease-related allele. This is seen most distinctly in Angelman and Prader-Willi syndromes (Dittrich et al 1992). The phenomenon

of imprinting might explain some of the observations of gender imbalance in the transmission of MDI (McMahon et al 1995).

NEW APPROACHES TO LINKAGE ANALYSIS

Technological Developments

Three technological developments in the past decade have made it possible to overcome the limitations of the early linkage analyses. The first is the proliferation of fast, sophisticated computers and the development of increasingly efficient algorithms to reduce computation time, allowing for multi-locus comparisons. A second is the increasing availability and informativeness of DNA markers [RFLPs to short sequence repeat polymorphisms (SSRPs)] across the entire genome, allowing for the construction of dense haplotypes. The third is the polymerase chain reaction (PCR), which has dramatically reduced the time required to produce genotypes.

Statistical Developments

The statistical methods developed to analyze simple mendelian disorders are neither sensitive nor specific enough to detect linkage in the context of high genetic complexity (Risch 1990b, Lander & Schork 1994), so more sophisticated analytic methodologies have been developed to take into account heterogeneity, incomplete penetrance, and polygenic transmission. At the same time, nonparametric methods of analysis are being refined. Thanks to the development of highly polymorphic markers, it is possible to examine allele-sharing by siblings and other relatives genetically identical by descent (IBD) at a given locus–i.e. possessing not simply the same allele, but the same allele from a given parent (Kruglyak & Lander 1995a). Using these methods, one may derive the maximal information from genetic data without sacrificing the statistical power to detect linkage. Such a loss of power may occur in parametric analysis as a result of erroneous assumptions in genetic models, which must be specified in the absence of established genetic mechanisms.

RECENT DEVELOPMENTS AND NEW DIRECTIONS IN MDI GENETICS

Several MDI linkage studies are under way that span or will span the genome by using highly polymorphic SSRP markers and nonparametric statistical methods as well as the conventional lod score methods. Many loci have been studied, and one positive result on chromosome 18 has been identified and now replicated.

Chromosome 18 Linkage and Replication

In 1994, Berrettini's group, using nonparametric methods of analysis, reported linkage of MDI to loci on the short arm of chromosome 18 (18p) in 22 families (Berrettini et al 1994). Upon learning of this result, our group (the Charles A. Dana Foundation Consortium on the Genetic Basis of Manic Depressive Illness) attempted to replicate this finding in 28 families. We were successful in identifying a large region of linkage of MDI on chromosome 18 (Stine et al 1995). For one marker in the region, D18S37, 29 of 46 sib-pairs (64%) in our families with either bipolar disorder or RUP shared the same allele at that locus ($p = 0.0003$), and 56% of Berrettini's sib-pairs, using the same phenotype definition, shared an allele at that locus ($p = 0.0083$). The presence of other closely linked markers with higher than expected sib-pair sharing in both studies strengthens the claim for linkage of MDI to a region of the short arm of chromosome 18.

However, there were two other notable observations in our study. Several markers on the long arm of chromosome 18 (18q) produced positive lod scores and higher-than-expected rates of allele sharing by affected sib-pairs. Though they exceeded conventional standards of statistical significance, our results did not at first appear sufficiently robust to establish linkage confidently. We also observed a parent-of-origin effect on the linkage result (Figure 2). We had previously reported a higher than expected proportion of mothers (versus fathers) who transmit MDI to their children in our families (McMahon et al 1995). When this parent-of-origin effect was applied in the linkage analysis, the evidence for linkage was confined to those pedigrees in which the father transmitted MDI to offspring. This result was particularly striking for markers on 18q–where the rate of allele sharing at D18S41 by siblings with bipolar or RUP disorders rose from 55% ($p = 0.04$), when all pedigrees were considered, to 81% ($p = 0.00002$), when only the paternally transmitted alleles in paternal pedigrees were considered. Reevaluation of the families in Berrettini's study (Gershon et al 1996) confirmed a preponderance of pedigrees in which only mothers transmitted MDI and revealed no evidence of linkage in these families, but did reveal evidence for linkage in the remaining families (which included the families with paternal transmission). Thus, these data support a parent-of-origin effect. Exploratory analyses of the published data suggest that there are (at least) two loci for MDI on chromosome 18 (J Xu, personal communication).

The observation of a parent-of-origin effect and its successful use as a tool for stratifying families in linkage analysis open up several new possibilities for investigating mechanisms of inheritance of MDI, including genetic imprinting and mitochondrial transmission. Thus, although the identification of a gene or genes from the chromosome 18 linkage findings may be far from

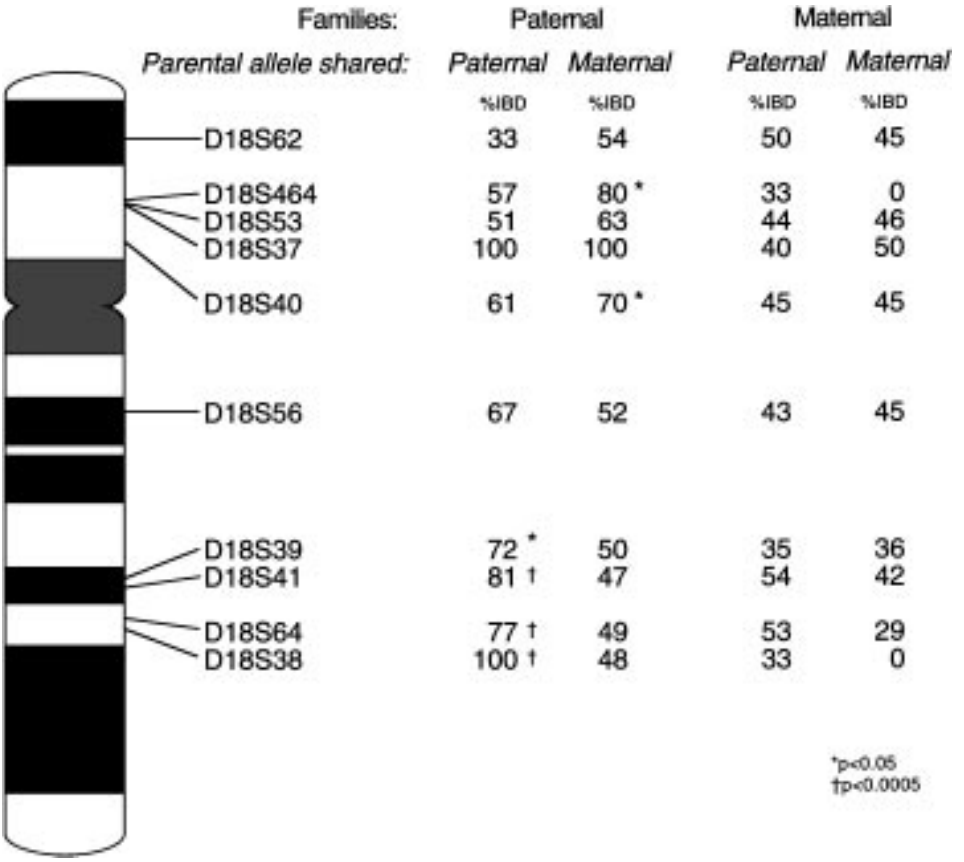

Figure 2 Affected sib-pair results [percent of shared alleles, identical-by-descent (IBD)] for selected chromosome 18 loci in 28 families with BPI probands. Nominal *p*-values <0.1 are reported. The following loci show statistically significant allele sharing in paternal pedigrees for either paternal or maternal alleles: D18S464, D18S37, D18S40, D18S41, D18S64, and D18S38. Although D18S37 showed 100% sharing, the number of informative sib-pairs for paternal or maternal alleles considered separately was too small to achieve statistical significance. (Derived from Stine et al 1995.)

straightforward, these findings have already contributed to a reinvention of the genetics of MDI (Gelernter 1995).

Mitochondrial Inheritance

The observation that mothers, but not fathers, transmit MDI in some families suggests that mothers in these families may transmit disease-related mutations in nonnuclear, i.e. mitochondrial, DNA. Although no molecular evidence supports this hypothesis, several features of MDI fit with what is known of the

life cycle of mitochondria and the disease patterns of other mitochondrial disorders.

Anticipation and Trinucleotide Repeat Expansion

The size of the trinucleotide repeat (TNR) expansion correlates with illness variability in HD, Spinocerebellar Ataxia I (SA) (Jodice et al 1994), and Fragile X Syndrome. Anticipation has been detected in our families (McInnis et al 1993) and may be associated with expansion of TNR sequences as a source of genetic variability in MDI. Moreover, TNR expansion has been shown in HD and SA to be subject to a parent-of-origin effect. These TNR sequences may be of further value as a means of identifying genes of interest in advance of finely mapped linkages.

Clinical and Genetic Heterogeneity

Just as linkage findings on chromosome 18 were supported using a priori distinctions based on mode of inheritance, other clinically observable distinctions (e.g. clinical comorbidity) may be useful in defining heterogeneous subtypes and thus increasing the capability of genome-screening studies to detect linkage. For example, there is evidence that panic disorder segregates with MDI in a subset of our families and that individuals with MDI in these same families are at lower-than-average risk of comorbid substance abuse disorders; hence, comorbid panic disorder in a family may predict genetic heterogeneity (MacKinnon et al 1996). Post-linkage analyses of our published data suggest that the locus identified on 18q is closely associated with the BPII phenotype (F McMahon, personal communication). Other variables that may be useful as markers of heterogeneity include clinical features of MDI (e.g. sequence of manic versus depressive episodes; presence of diurnal mood variation or psychosis), biochemical measures (e.g. dexamethasone suppression test), age of onset, and pharmacologic response.

ANTICIPATED DEVELOPMENTS IN MDI GENETICS

The region of chromosome 18 delimited by the markers studied in Berrettini's and our pedigrees encompasses 80 centimorgans and is likely to contain many genes with plausible connections to MDI. Several strategies may be useful in the next few years to move from linkage to anonymous DNA sequences on a wide swath of chromosome to identification of genes of pathophysiologic importance. The following approaches may be of help.

More Linkage Studies

We expect additional groups to explore chromosome 18; should more linkages be reported, the larger sample size from pooled analyses could be used to map regions of interest more finely (Kruglyak & Lander 1995b).

Allelic Association Studies

Genetic markers are now sufficiently polymorphic and densely mapped that it is often common to find heterozygous alleles of multiple closely linked markers in both parents. When these highly informative haplotypes are compared in offspring, a case-control type of analysis can be performed that uses the untransmitted alleles as a control. Thus, in the absence of information about linkage of disease to an allele, a geneticist may still be able to calculate the offspring's relative risk of developing the phenotype for any given allele, i.e. the haplotype-relative risk (Knapp et al 1993).

These exact alleles can be compared across families, as well, to see if a specific allele associates with the phenotype under investigation (Spielman et al 1993, Jorde 1995). Such an analysis is based on the assumption of linkage disequilibrium, i.e. the alleles clustered around a gene at the time it is transformed (by mutation, deletion, TNR expansion, etc) are more likely to be transmitted unchanged through successive generations the closer they are to the gene in question. Studies of linkage disequilibrium in MDI are currently under way in genetically isolated populations in Sardinia and Costa Rica (Freimer et al 1996), where the plausible assumption that a single, historically remote, genetic transformation is the source of all local cases of MDI (a founder effect) may increase the chances of finding an allelic association with MDI.

If one or a few mutations account for a large proportion of cases, however, an association study of unrelated patients versus normal controls may be used as a test of the contribution of a candidate gene to disease vulnerability. Two genes, each with activity consistent with putative psychiatric pathophysiology and each located near purported regions of MDI linkage, have yielded positive results when studied with this method. A weak association of one allele of monoamine oxidase A (MAOA; X chromosome) and MDI was reported in 1994 (Lim et al 1994) and awaits replication. Certain alleles of tyrosine hydroxylase (TH; chromosome 11) have also been found more frequently in patients with MDI than in normal control subjects in some studies (Cauli et al 1995, Meloni et al 1995), but not in others (Korner et al 1994).

Candidate Genes

In addition to MAOA and TH, a number of functional candidate genes have been evaluated in linkage and association studies. Thus far, markers closely linked to genes for receptors for dopamine, gamma-aminobutyric acid, epinephrine, glucocorticoid hormones, and serotonin have not yielded positive findings; nor have markers linked to a G-protein subtype, to pro-opiomelanocortin, and to several other enzymes of importance in neurotransmitter metabolism.

In contrast, the use of structural candidate genes (i.e. genes with known sequence or location but unknown function) is likely to enhance the search for

genes of pathophysiologic importance once linkage to a chromosomal locus is established. For example, if anticipation in MDI implies expanded TNR sequences in the relevant genes, then techniques used to isolate, amplify, and map SSRPs can be used to identify regions containing expanded TNR sequences; these regions can then be the focus of more detailed investigations for the presence of genes of interest. Another method for identifying structural candidates is to make use of maps (currently being developed) of expressed sequences. These maps are derived from mRNA that has been isolated from tissue, labeled, and mapped back to the complementary sequences in genomic DNA. Thus, within a few years, any given locus will be linked to a number of expressed sequences, which may then be examined directly for genetic variation.

Animal Models

Knowledge of genes of possible pathophysiologic importance is being expanded by the use of animal models and quantitative trait locus (QTL) mapping (Plomin et al 1994). Strains of mice are inbred, or selectively bred for a trait of interest, eventually yielding a strain from which a specific gene or set of genes connected to the trait can be identified and mapped. The problem is to identify a homologous phenotype for MDI in mice; strains of mice exhibiting abnormal circadian rhythms and response to stress are under development (Nurnberger et al 1995).

As molecular genetic knowledge of MDI begins to take shape, it is worthwhile to begin to consider what can be done with this knowledge.

ETHICAL PROBLEMS OF GENETIC TESTING IN MDI

If MDI-related alleles are discovered using the technology currently available, then genetic testing may come into clinical use shortly thereafter as the technologies for discovery and testing are similar and easily disseminated. Genetic testing may be of diagnostic utility in MDI; indeed, it may become the only reliable diagnostic test for MDI. However, such a test can only support, not make, a diagnosis. The possession of alleles related to disease is not the same as having a disease. Unlike other genetic disorders, MDI is not usually fatal, has an intermittent course, has symptoms that can be treated (and even prevented), may benefit some individuals who express the phenotype, and may benefit society as well. Therefore, some of the specific ethical difficulties of genetic testing for MDI are worth examining.

A majority of individuals with MDI wait years between the onset of mood symptoms and the correct diagnosis and treatment (Lish et al 1994). A genetic test for MDI would be a useful means of confirming a clinical suspicion of MDI and allowing for early prophylactic treatment. Depending on the predictive

power of such tests, it might be helpful to know, for example, that a teenager presenting to a therapist with "adjustment" problems is at genetic risk for early-onset MDI. In this case, prophylactic treatment with lithium or another mood stabilizer might prevent a severe manic or depressive episode at a critical stage of development. It is widely believed that early intervention improves outcome in MDI; hence, the earlier the diagnosis and prophylactic therapy, the greater the improvement in outcome.

Whether information about alleles can predict not only the risk of MDI in an individual but also the severity and course of illness remains to be seen. Wide variation in course and severity seems to occur even within nuclear families, whose affected members have presumably inherited many of the same alleles. Intrafamilial variation may be related to nongenetic factors, for example, marital status, health and stability of other family members, birth order, and the availability of substances of abuse. If, in fact, these nongenetic factors play a major role in determining course and severity in MDI, then genetic testing may be a poor predictor of outcome and thus an inadequate reason to initiate prophylactic treatment for MDI (which may be costly and hard to tolerate) at the first signs of adolescent angst. Investigating the relative importance of genetic versus nongenetic factors in MDI will be a crucial area of research once genetic factors are isolated.

We hope that knowledge of the genetic mechanisms of MDI will lead to rational therapies, but even with present-day empiric therapies, therapeutic benefit may be derived from genetic testing. If MDI is a genetically heterogeneous disorder, as is suspected, then different familial MDI subtypes might respond preferentially to different agents or combinations of agents. For example, information from a genetic test that a patient has such-and-such MDI alleles, and therefore is unlikely to develop antidepressant-induced mania, would allow a clinician greater latitude in treating that patient's depression.

Assuming for a moment that molecular diagnosis of MDI proves to be a poor predictor of course and severity, and leads to no tangible therapeutic improvements, it might yet be valuable for a young person to know of the genetic risk for MDI anyway, so as to make prudent life decisions. A person at risk might, for example, choose a profession or trade that does not require sleep deprivation, which can trigger episodes of mania. There would be greater incentive to avoid heavy drinking or experimentation with drugs of abuse. A woman forewarned about her high MDI risk might choose to bear children early in life, prior to illness onset and the necessity of beginning lithium prophylaxis (which may cause a higher rate of birth defects). On the other hand, knowledge of risk for MDI may trigger shame in individuals who would feel stigmatized as a result of having a mental illness. As is the case for other genetic disorders, genetic testing in MDI, when it becomes available, should be done in the context

of genetic counseling and informed consent about the risks as well as benefits of knowing one's genetic vulnerabilities (Sorenson 1992).

The greater harm of a genetic test for MDI would arise from the extra-clinical use of genetic information by insurance companies, employers, or the government. If genetic information becomes public, there is great potential for social and economic injustice. It may seem reasonable to expect that genetic information would and should be as freely available as many other medical data—i.e. HIV tests, blood pressure readings, urine toxicology screens, and even psychotherapy records, which are often demanded as a condition of insurance, employment, or security clearance. But there is a critical difference between these data and information about genetic susceptibility. Whereas all of the aforementioned tests measure stages of a disease process, a genetic test measures only the potential for a disease.

If a genetic panel for MDI were available today, and if the results were made public, many individuals carrying MDI-related alleles might be denied certain insurance benefits and employment opportunities. However, because MDI is likely to be incompletely penetrant, individuals who carry the disease-related alleles but do not have mood disorder symptoms, or at least do not seek treatment or suffer impairment as a result of them, would be unfairly assessed higher insurance costs or denied employment opportunities due to a mental illness they would never have. Although the social or economic arguments for and against limiting insurance coverage or employment opportunity for individuals who are impaired by and seek treatment for the syndrome of MDI are worthy of serious public debate, there is no reasonable justification for doing so on the basis of a genetic predisposition. After all, every human being carries a number of genetic abnormalities, including several fatal recessive genes; in the long run, there may be little economic incentive to single out a group at high genetic risk for MDI.

The most ominous ethical difficulty of genetic testing in MDI may be its potential for use in a program of eugenics, i.e. prenatal screening to restrict the transmission of alleles related to MDI. There is ample recent historical precedent to arouse suspicion that genetic testing may support, somewhere in the world, a program to eliminate mental illness from the gene pool (Garver & Garver 1991). In the United States early this century, in Germany prior to and during World War II, and in present-day China, the mentally ill were and are coercively sterilized for eugenic purposes. Identification of genetic risk at the molecular level is not required for such a program of eugenics but might easily play a supporting role.

In a society where coercive sterilization is abjured, phenotypes like MDI might be priced out of existence. There soon may be a variety of commercially available genetic tests parents can use to screen themselves and/or an early

fetus for genetic diseases, or even nondisease traits (sex, height, body habitus, skin coloring, intelligence, excitement-seeking behavior, etc). If parents knew their fetus carried a genetic risk for MDI, and if that knowledge were available also to, say, a medical insurance company in the practice of denying coverage to individuals carrying MDI-related alleles, then there would be a financial incentive to abort the pregnancy (in addition to the probably misguided desire by the parents-to-be to select a genetically "ideal" baby).

An effort to eliminate a disorder like MDI from the gene pool (if such a thing is even possible) by free parental choice with or without financial coercion is morally repugnant to many and might also change society in unpredictable, and possibly detrimental, ways. MDI is one of the rare phenotypes that, like the sickle cell trait, confers advantages on some, at some times, but otherwise may be of sufficient severity to cause impairment and morbidity. Artists and scientists, as well as business, religious, and social leaders, may describe their success in life as occurring not only despite suffering from manias and depressions, but in part because of these temperamental states in their milder forms. More than a dozen studies have found a greatly increased rate of MDI and its related temperaments in renowned writers, artists, and composers (Jamison 1993). Individuals with MDI may not only survive with their illness, but prosper and move society because they express the phenotype. Thus, an untoward effect of the use of this technology might be selection against not only the disease of MDI, but also some of the socially constructive traits associated with MDI, including creativity, high energy states, intense emotionality, and risk-taking.

Serious ethical issues about the privacy, beneficence, and justice of genetic testing for MDI are unlikely to be resolved by pronouncements from the scientific community about the use and abuse of genetic research findings; however, persistent scientific attention to these issues as the technology develops will be essential for good policy (Annas & Elias 1992). We hope that these issues will be kept in awareness by policymakers as the search for genes leads (perhaps inevitably) to the production of commercially available genetic tests and beyond, to the rockier ethical terrain of gene therapy. As the genetic mechanisms of inheritance in MDI are worked out, further discussion about the implications of genetic research in general and about the genetics of MDI specifically should help to plan an initial course of action. At the very least, such discussions will result in a clarification of the most important ethical and societal concerns.

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