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Genetic Models of Affective Disorder: Application to Twin Data

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Twin data on bipolar and unipolar affective disorders are analyzed by multiple threshold models of inheritance. The two illness types are represented in the models on a continuum of genetic–environmental liability in which bipolar illness has a higher liability threshold than unipolar disorder. Autosomal single major locus model provides an acceptable fit to observed concordance rates in monozygotic twins. The multifactorial-polygenic model is rejected.

Key words: Affective disorder, Genetic models, Twin concordance

INTRODUCTION

Strong evidence for genetic factors in affective disorders is provided by twin, family, and adoption studies [7, 10, 15]. However, Mendelian ratios cannot account for observed morbidity risks, and two alternate genetic models, a single dominant autosomal gene with modified penetrance, and polygenic inheritance, give an equally acceptable fit to the data [7]. X-linkage inheritance has been implicated in a subset of pedigrees, but is unlikely to be generalized to affective illness at large [7]. The problems posed for genetic analysis are further confounded by the possibility of genetic heterogeneity, ie, different hereditary modes accounting for the transmission of affective illness, and by the finding of multiple forms of affective illness within families. These include bipolar (manic-depressive) and unipolar (recurrent depression) disorders.

Genetic models for traits transmitted without clear Mendelian ratios in which affected individuals may have multiple phenotypic manifestations have recently been advanced [8, 12–14]. The models postulate independent liability thresholds on a genetic–environmental continuum whereby affected individuals are subdivided into "severe" and "mild" categories. The severe illness form has a higher liability threshold and is more deviant from

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the general population mean than the other. Compared to families of probands with the mild form of the disorder, the severe case has a higher morbid risk for all illness forms combined and for the severe illness type as opposed to relatives of probands with the mild form. The multiple threshold model has been successfully applied to family data on pyloric stenosis [9], stuttering [8], and Tourette syndrome [2] using sex effect as a threshold determinant.

Recent reviews of family data on major affective illness indicate that bipolar and unipolar disorders are consistent with the severe and mild illness forms, respectively [1, 7]. When tested for congruence with multifactorial-polygenic and single major locus models of disease transmission, the same underlying genetic disposition could be manifest clinically as either bipolar or unipolar illness in first-degree relatives of affected individuals.

In a recent review of six studies of monozygotic (MZ) twins [11, 17], 43 out of 50 twin pairs unequivocally concordant for affective illness (86%) were also concordant for the type of affective disorder, ie, bipolar and unipolar, but 14% had one bipolar and one unipolar twin. Similarly, Bertelsen et al [3] reported 78% concordance and 22% discordance in the type of affective illness. The data imply that bipolar and unipolar disorders may be related to the same genetic diathesis. The purpose of the current analysis is to test the fit of the multiple threshold hypothesis to these data. This type of genetic analysis has not as yet been attempted in twin studies of affective disorder.

MATERIALS AND METHODS

The sample consists of the pooled data on affective illness in MZ twin pairs in the six studies reviewed by Perris [11], and in the study of Bertelsen et al [3]. In the whole, 138 pairs were available for analysis. Although diagnostic criteria were not applied uniformly across studies, clinical subtypes of affective disorder were generally consistent with Feighner [5] and Winokur [16]. According to these criteria bipolar illness is characterized by alternating episodes of mania (a symptom cluster including elevated mood, hyperactivity, irritability, pressured speech, and insomnia) and depression (a symptom cluster including depressed mood, psychomotor retardation, poor concentration and memory, tearfulness, and insomnia). Unipolar disorder consists of recurrent depressive episodes. Of the 138 pairs, 35 were concordant for bipolar illness and 33 were concordant for unipolar disorder; in 14 pairs one twin was bipolar and and the other unipolar; 23 other pairs in which the concordance and the type of polarity, ie, bipolar or unipolar, could not be determined unequivocally, were omitted from the sample in order to permit a conservative estimate of the data; finally, 33 pairs were discordant. The overall concordance rate for affective illness regardless of polarity was 63%.

The multiple threshold single major locus (SML) and multifactorial-polygenic (MFP) models have been described in detail elsewhere [1, 6, 8, 9, 12–14]. The SML model is based on five parameters: the frequency of the "ill" allele, the low threshold (for unipolar illness), the higher threshold (for bipolar disorder), the heterozygote's mean, and the independent variance. The SML parameters are used to predict the probability for each of the three genotypes of manifesting the disorder. This probability is the area of the genotype's normal curve above the threshold (the penetrance). The prevalence of the disorder among relatives is a function of the penetrance, the conditional probability for predicting the genotype of a relative given the genotype of a proband, and the conditional probabilities that an individual has each genotype given that he/she is ill. The MFP model has four parameters: the population prevalence of bipolar illness, the population prevalence of all affective disorders, and the correlation between siblings and between parents and offspring. These parameters are used to compute expected morbid risks for bipolar and unipolar disorders in relatives of probands. The prevalence is represented by the area of a normal distribution of liability above the appropriate threshold. The analysis of either model is based on varying parameter values until a "best-fit" solution is found, ie, parameter-set which minimizes the chi-square value of the difference between observed and expected numbers of ill relatives.

Using the "best-fit" parameter-set shown by Baron et al [1] to provide the best approximation of

predicted to observed morbidity risks among first-degree relatives of affected probands, expected concordance rates for bipolar and unipolar disorder in MZ twins were computed as described elsewhere [9]. The SML parameters were gene frequency of 0.3%, a bipolar threshold of 0.92, a unipolar threshold of 0.55, a heterozygote's mean of 0.96, and an independent variance of 0.14. The MFP parameters were a bipolar prevalence of 0.4%, an overall prevalence of 2.4%, and a correlation of 0.59 for both siblings and parent-offspring. These parameter-sets were preferred to other analyses of affective disorder data [6, 7], since they were based on the largest available data-set that was found applicable to multiple threshold analysis and that allowed for discrimination between the SML and MFP models of transmission [1].

The expected concordance rates were then compared to the observed data using the actual numbers of relatives. To reject predictions made in either model, significance level of less than 0.05 was required.

A schematic representation of the SML model is presented in the Figure.

RESULTS

The best-fit solution in the SML and MFP models is diplayed in Table 1. The observed and predicted concordance rates in MZ twins are presented in Table 2. The expected rates for bipolar and unipolar disorders in the SML model are 58.4% and 47.9%, respectively. If one twin is bipolar and the other unipolar, or vice versa, the rates are 7.8% and 3.9%. The total chi-square on the pooled data of first degree relatives [1] and twins does not show significant difference between predicted and observed concordance rates for the two illness types in the SML solution ($\chi^2 = 11.32$, df = 7; $P > 0.10$; Table 2). Thus, the SML model provides an acceptable fit to the data. On the other hand, a significant difference between predicted and observed rates was observed in the MFP solution ($\chi^2 = 39.75$, df = 9; $P < 0.001$; Table 2). The SML model parameters predict that 45% of bipolars and 66% of unipolars do not carry the allele for the disorder, ie, are nongenetic phenocopies.

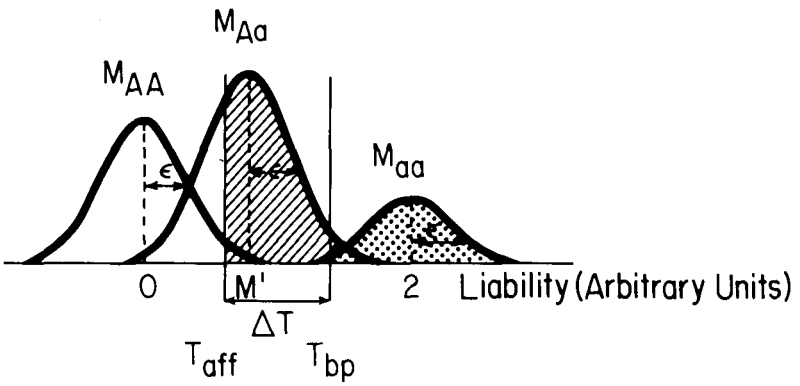

Figure. Parameters of the two threshold single major gene model. Horizontal axis is a scale of liability to a disorder, which is a function of genetic and independent (random or environmental) components. Thresholds shown are for the wide illness form, ie, T_{aff} = threshold for all affective disorders, and T_{bp} = threshold for bipolar illness, ie, the narrow illness form. M_{AA}, M_{Aa}, and M_{aa} are the mean liability values for each genotype. ϵ is the square root of the independent variance (random or environmental) of liability, which in the model shown has the same value for each genotype. M' is the liability value for the heterozygote. The liability values for the homozygotes are set at arbitrary values of 0 and 2. For each genotype, the hatched and dotted areas represent the proportion of persons with that genotype who will have unipolar or bipolar affective disorder. This figure was adapted from Baron et al [1].

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TABLE 1. The Best-fit Solutions in the Single Major Locus (SML) and Multifactorial-Polygenic (MFP) Models

Parameter description[a]		
SML Solution		
q	Gene frequency	0.003
M_1	Heterozygote's mean	0.96
T_{BP}	Threshold for bipolar disorder	0.92
T_{UP}	Threshold for unipolar disorder	0.55
ϵ^2	Independent variance	0.14
MFP Solution		
K_{BP}	Population prevalence of bipolar disorder	0.004
K_{Aff}	Population prevalence of all affective disorders	0.024
R	Correlation between probands and relatives	0.59

[a]Values taken from Baron et al [1].

TABLE 2. Concordance Rates for Major Affective Disorders According to the Single Major Locus (SML) and Multifactorial-Polygenic (MFP) Models

Twin 1	Twin 2	Observed concordance rate	Predicted concordance	
			SML	MFP
Bipolar	Bipolar	0.454	0.584	0.724
	Unipolar	0.104	0.078	0.145
Unipolar	Bipolar	0.103	0.039	0.082
	Unipolar	0.568	0.479	0.670
χ^2			11.32	39.75
P			> 0.10	< 0.001

Chi-square values refer to the pooled data on twins and first-degree relatives. Data on first-degree relatives were published separately [1]. The SML solution has 7 degrees of freedom (the difference between the number of independent observations, ie, 12 for 3 classes of relatives; sibs, parents-offspring, and twins, and the number of parameters, ie, 5). Similarly, the MFP solution has 9 degrees of freedom.

DISCUSSION

The current analysis is consistent with the multiple threshold concept of major affective illness. Bipolar affective disorder appears more deviant genetically than unipolar disorder and is represented in the model at a higher liability threshold on a genetic continuum. The fit of observed to predicted concordance rates in MZ twins indicates that the multiple threshold approach previously applied to data on nuclear families [1, 6] is also applicable to twin data. It is also worth noting that the same genetic mode, ie, single major locus, can explain both twin and family data [1, this study].

Although the multiple threshold model augments the discriminatory power of alternate genetic hypotheses and seems especially appropriate for application to spectrum disorders such as affective illness, several caveats are in order. First, the twin data analyzed in the present study are not based on a coherent and well-defined population sample, but represent seven different studies. They provide, however, a sizeable body of twin data based on

similar diagnostic distinctions. Furthermore, the concordance rates are generally consistent across the larger samples reported [3]. Particularly noteworthy is the observation that the overall concordance rate for effective illiness in the data of Bertelsen et al [3] (58%) which are based on a systematic survey of the Danish Twin Register, is not strikingly different from Perris' [11] review data on twin concordance in affective disorder (67%). Nevertheless, the small sample size and the variability in concordance rates in some of the twin studies, as well as possible errors with regard to ascertainment, zygosity and diagnostic determinations, should indicate caution in interpreting the present results. Second, the model parameters used in the current analysis were not derived from the same population base. However, these parameters represent the largest available set of family study data on affective disorder and are the first to successfully discriminate between single major locus and multifactorial-polygenic threshold models of affective illness [1]. Furthermore, as discussed elsewhere [1, 7], three different data sets drawn from a cross-cultural population pool have been found to fit the multiple threshold model despite inconsistencies in model parameters. This may indicate that multiple threshold inheritance may be relevant to the genetics of affective disorder in different populations. Third, many of the occurrences of affective disorder are due to nongenetic phenocopies, ie, affected individuals who lack the ill allele. Consequently, the model does not provide a satisfactory explanation for all cases of affective disorder. Fourth, the possibility of genetic heterogeneity, ie, subsets of affective illness transmitted according to different genetic models including autosomal single major locus, X-linkage, and more than one allele, requires further exploration. Finally, other genetic models using complex segregation analysis and maximum liklihood methods [4, 14] may be of interest in future analyses.

In conclusion, the multiple threshold SML model provides an acceptable fit to observed data on concordance rates for bipolar and unipolar affective illness in MZ twins. The MFP model cannot account for the data. The current analysis should be considered preliminary, however. Further study based on larger samples of twin pairs free of possible errors in ascertainment, zygosity, and psychiatric diagnosis is warranted.

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