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Genetic Segregation Analysis of Early-Onset Recurrent Unipolar Depression

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Summary

Major depression is a relatively common psychiatric disorder that can be quite debilitating. Family, twin, and adoption studies indicate that unipolar depression has both genetic and environmental components. Early age at onset and recurrent episodes in the proband each increase the familiality of the illness. To investigate the potential genetic underpinnings of the disease, we have performed a complex segregation analysis on 832 individuals from 50 multigenerational families ascertained through a proband with early-onset recurrent unipolar major depression. The analysis was conducted by use of regressive models, to test a variety of hypotheses to explain the familial aggregation of recurrent unipolar depression. Analyses were conducted under two alternative definitions of affection status for the relatives of probands: (1) "narrow," in which relatives were assumed to be affected only if they were diagnosed with recurrent unipolar depression; and (2) "broad," in which relatives were assumed to be affected if diagnosed with any major affective illness. Under the narrow-definition assumption, the model that best explains these family data is a transmitted (although non-Mendelian) recessive major effect with significant residual parental effects on affection status. Under the broad-definition assumption, the best-fitting model is a Mendelian codominant major locus with significant residual parental and spousal effects.

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Introduction

The fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, or DSM-IV (American Psychiatric Association 1994, pp. 317–391), includes a wide variety of mood disorders. The severity of these conditions ranges widely, from normal affective responses to stressful life events that are typically transient (e.g., bereavement) to chronic or recurrent mood disorders whose natural histories are associated with lifelong disability and increased mortality from both natural causes and suicide. The challenge of disentangling these manifold mood disorders so that etiologically distinct pictures can be drawn is formidable, requiring the efforts of many different scientific disciplines, including human genetics.

An important clinical distinction has been made between bipolar I disorder (BPI) and unipolar major depression (UPD). The essential feature of BPI is the occurrence of manic episodes, whereas only major depressive episodes occur in UPD. Several lines of evidence suggest that these two affective disorders have different etiologic underpinnings as well. Lifetime prevalence rates for BPI are 0.3%–1.3%, whereas for UPD the lifetime prevalence rates are higher, at 5%–17% (Boyd and Weissman 1981; Weissman et al. 1991; Kessler et al. 1994). Rates of BPI are equal in males and females, whereas females are more than twice as likely as males to become affected with UPD (Boyd and Weissman 1981; Weissman et al. 1991; Kessler et al. 1994). In addition, the average age at onset is earlier in BPI than in UPD.

Family studies have demonstrated a significant familial disposition to UPD. For example, first-degree relatives of UPD probands have a 15%–25% lifetime risk of becoming affected (Gershon et al. 1982; Weissman et al. 1984*a;* Bland et al. 1986; Kupfer et al. 1989). Importantly, early age at onset and recurrent major depressive episodes in probands each increase the morbid risk of major depression in first-degree relatives (Weissman et al. 1984*b,* 1986; Bland et al. 1986; Price et al. 1987; Kupfer et al. 1989). Twin and adoption studies suggest

both genetic and environmental contributions to the development of UPD (Cadoret 1978; Torgersen 1986; Wender et al. 1986; Englund and Klein 1990).

To investigate the mode of transmission of the major affective disorders, genetic segregation analyses have been performed for families ascertained through UPD probands and for families ascertained through BPI probands (Crowe et al. 1981; Goldin et al. 1983; Price et al. 1985; Tsuang et al. 1985; Rice et al. 1987; Cox et al. 1989; Sham et al. 1991; Pauls et al. 1995; Spence et al. 1995). These studies have generally yielded inconclusive results, and the mode of inheritance, both for UPD and for BPI, is still unclear. For example, although the segregation analysis performed by Price et al. (1987) demonstrated that UPD is familial, it was not possible to discriminate between single-major-locus models and multifactorial models of inheritance. In an analysis of BPI, evidence was found for a single major effect, but the transmission probabilities were non-Mendelian (Rice et al. 1987). However, reanalysis of the same BPI data by use of liability classes that were more appropriate showed that the single major effect did not fit the data better than a polygenic model (Sham et al. 1991). The results of Cox et al. (1989) suggested single-major-locus inheritance both for UPD and for BPI, but only over a narrow range of population prevalences and only for a restricted definition of affection status. Pauls et al. (1995) presented evidence for a single major effect in a series of Old Order Amish BPI families, but the results were dependent on the diagnostic categories used and on the subset of families analyzed. Spence et al. (1995) also reported some evidence for a single major locus in families ascertained through probands with BPI.

We have performed a complex segregation analysis of multigenerational families ascertained through probands with early-onset recurrent UPD. This severe form of unipolar depression in the probands was chosen to increase familial aggregation, potentially increasing the genetic loading for severe depression in these families as well. The analysis was performed by use of regressive models, as programmed in Statistical Analysis for Genetic Epidemiology (SAGE 1994), to estimate parameters and to calculate the likelihoods of a variety of hypotheses to explain the familiality of recurrent unipolar depression.

Subjects and Methods

Family Acquisition

Fifty multigenerational families (832 family members) were each ascertained through one proband with early-onset (age at onset $\leqslant 25$ years) recurrent (two or more episodes) nonpsychotic UPD. Furthermore, each proband's family was included in this study, regardless of whether there were additional affected relatives. Therefore, the data were collected under single incomplete ascertainment.

Families were ascertained through two sources at the Western Psychiatric Institute and Clinic, Pittsburgh: 32 families were collected as part of the Molecular Genetics of Affective Disorders Project (B.B.K., principal investigator), and 18 families were recruited from the Sleep and Family Evaluation Study (D.E.G., principal investigator). The sleep study recruited probands with UPD, first episode or recurrent, with onset at age <40 years. However, only those sleep-study probands meeting the same inclusion and exclusion criteria as those in the affective-disorders study (i.e., nonpsychotic recurrent UPD and age at first onset <25 years) were included in this analysis.

The major difference between the two studies was that families with a first-degree relative with BPI were excluded from the sleep study but not from the affective-disorders study. In practice, very few early-onset recurrent-UPD probands were excluded from the sleep study for this reason, whereas only 2 (6%) of the 32 affective-disorders families had a first-degree relative with BPI. In addition, probands in the sleep study were required to have four available first-degree relatives, whereas probands in the affective-disorders study were only required to have three. Because these differences in selection criteria were minor, families from the two studies were combined to create a data set with power to address the research question.

Probands meeting the inclusion criteria were recruited into both studies by a screening of consecutive admissions to the adult-mood-disorder services at the Western Psychiatric Institute and Clinic. Probands from four of the sleep-study families were also recruited from outpatient clinics of the Affective Disorders Unit at the University of Texas Southwestern Medical Center, Dallas.

Diagnostic Methods

Available probands and first-degree relatives were interviewed by experienced clinicians using the Schedule for Affective Disorders and Schizophrenia (SADS-L) semistructured interview (Spitzer and Endicott 1975). The SADS-LB, a version of the SADS-L modified to ascertain "soft signs" of bipolarity, was used for seven recently collected families. Children ages 6–17 years were interviewed by use of the K-SADS-E (Puig-Antich et al. 1980). In addition, family-history diagnostic information was collected on all first- and second-degree relatives, from multiple informants. The family-history interview was modified to identify recurrent major depressive episodes, as well as to differentiate between BPI and bipolar II disorders (BPII), although these distinctions were not possible in all cases. Personal-inter-

Table 1

Numbers of Individuals, by Affection Status, in 50 Families Ascertained through Probands with Recurrent Unipolar Depression

Affection Status and Gender	No. of Individuals	
	Narrow Definition	Broad Definition
Affected:		
Probands:		
Male	15	15
Female	35	35
Relatives:		
Male	25	77
Female	45	109
Unaffected:		
Male	301	264
Female	271	220
Unknown:		
Male	75	60
Female	65	52
Total	832	832

view data were available for 74% of the probands and first-degree relatives, whereas second-degree relatives and spouses were diagnosed primarily on the basis of family-history interviews (86% by family history only). Consensus Research Diagnostic Criteria (RDC; Spitzer et al. 1978) diagnoses were generated from a best estimate derived from the personal interviews, family histories, and available medical records. Family-history RDC diagnoses (Endicott et al. 1975) were assigned to those individuals who did not receive a personal interview. The best-estimate diagnoses were established separately by the clinical-assessment teams of each study.

The diagnostic methods differed between first- and second- degree relatives. Thus, differences in reliability between family-history and personal-interview data could perhaps have biased the results of this analysis. To evaluate the significance of this potential problem, a reliability study was conducted on four large families ascertained through the affective-disorders study. RDC diagnoses were established for 54 family members by use of SADS-L interviews conducted by experienced clinicians. Family-history RDC diagnoses were generated for the same individuals by clinicians who were blind to the RDC diagnoses.

Eight of the 54 individuals had RDC diagnoses of minor affective or nonaffective illnesses. These individuals were excluded, leaving a total of 46 family members for the reliability study. By use of the SADS-L interview, 21 individuals were diagnosed with the following RDC diagnoses: major depressive disorder (single-episode or recurrent UPD), BPI, or BPII disorder. The family-history method diagnosed 16 of these people as having RDC diagnoses of either UPD (single episode or recurrent, when known) or bipolar disorder. When these diagnoses were combined into the general category of major affective illness (the "broad" definition given below), the sensitivity of the family-history method was 76%, relative to the SADS-L interview; sensitivity was lower (59%) when the diagnoses of minor affective illnesses were compared. With regard to specificity, 25 of the 46 individuals were determined, by SADS-L interview, not to have any RDC diagnosis; 24 of these 25 were also found to have no family-history RDC diagnosis. Thus, the specificity of the family-history method was 96%, relative to the SADS-L interview. The segregation analyses were conducted only on major affective illnesses, since the reliability of family-history data was not adequate for minor affective illnesses.

Affection Status

Two separate analyses were performed with different definitions of affection status for the relatives of the early-onset recurrent-UPD probands. In the first analysis, relatives were considered affected only if they had been diagnosed with recurrent unipolar depression. For this "narrow" phenotype, the only difference between the affection-status definition for the proband and that for the family members was that probands had to have an age at onset of $\leqslant 25$ years, whereas the age at onset for family members was not restricted. In the second analysis, family members with BPI or BPII, as well as family members with recurrent or single-episode UPD were all considered affected. The second analysis therefore employed a "broad" definition of affection status, hypothesizing the presence of genes that predispose to a range of severe mood disorders. Individuals diagnosed with minor affective illness or other nonaffective psychiatric disturbances were considered unaffected in these analyses. The status of individuals whose diagnoses could not be established with certainty was considered unknown. Table 1 presents the numbers of unaffected, affected, and unknown individuals in the 50 families, under the narrow and broad definitions of affection status.

Population Prevalence Rates

In order to adjust for age and gender differences in the prevalence of early-onset recurrent UPD, population prevalence estimates were incorporated into the analysis (for details, see below). Prevalence rates were estimated separately for men and women in two age categories (0–44 years and $\geqslant 45$ years) and were derived from the affective-disorders rates determined by the Epidemiological Catchment Area Study (table 2; Weissman et al. 1991). To our knowledge, the population prevalence rates for *recurrent* UPD have not been reported. Therefore, the prevalence rates for recurrent major depression (narrow definition) were estimated by multiplying the reported rates for UPD by 2/3. This estimate was based

Table 2

Population Prevalences for Narrow and Broad Definitions of Affection Status

Age	Prevalence of Affection (%)	
	Narrow Definition	Broad Definition
0–44 Years:		
Male	2.4	5.4
Female	6.6	12.2
⩾45 Years:		
Male	1.1	2.0
Female	2.8	4.6

on our clinical experience of the percentage of early-onset single-episode unipolar-depression patients in which a second major depressive episode occurs. The rates for major affective disorders (broad definition) were determined by summing the reported rates for BP disorder and UPD.

Statistical-Analysis Methods

Major-locus segregation analysis of the narrow- and broad-definition phenotypes was accomplished by fitting the class A regressive model of Bonney (1986) by use of the REGD routine (Sorant et al. 1994) in the software package SAGE (1994). REGD is a program for segregation analysis of dichotomous traits under regressive models and can incorporate residual non-Mendelian familial effects and covariates into the analysis model (Sorant et al. 1994). The analysis tested whether the pattern of depression in the data could be explained by the segregation of alleles at a single Mendelian locus, by a single transmitted factor that does not follow Mendelian segregation, or by a nontransmitted factor, with and without additional non-Mendelian familial effects.

In regressive models as proposed by Bonney (1984), the statistical dependency among family members is modeled as a Markovian process, in which each individual's trait is influenced by his or her own covariates, as well as by the observed traits of preceding family members (Bonney 1984; also see Demenais 1991). In REGD, there are assumed to be three possible "types" (AA, AB, and BB). Two individuals have the same type if and only if the expected phenotypic distributions of their offspring by a mate of a given type are identical (e.g., see Cannings et al. 1978; Go et al. 1978). Genotypes are the special case of types (or ousiotypes, to follow Cannings et al. 1978) that transmit to offspring in a Mendelian fashion. When there is no transmission from one generation to the next, the model allows for only a single type. The parameters of the model are (1) the baseline regression coefficients for the three possible genotypes under a two-allele (N = unaffected allele; and D = depression allele), Mendelian single-major-locus model; (2) the frequency of the D ("affected") allele (q_D) and corresponding genotypic frequencies; (3) transmission probabilities (τ's) for the three types; (4) the regression coefficients for any covariates included in the model; and (5) residual familial effects that are not transmitted in a Mendelian fashion.

Because population prevalence figures cannot be automatically incorporated into the current version of REGD, parameter estimation may be biased, especially in small sample sizes. Following Lustbader et al. (1992), we therefore constructed a covariate for the regression analysis, consisting of the natural logarithm of $[r_k/(1 - r_k)]$, where r_k is the prevalence of the kth combination of age category and gender. Table 2 summarizes the prevalences for the narrow and broad definitions of affection status. The final regression equation was therefore $y_i = \beta_{g_i} + \delta Z + \log[r_k/(1 - r_k)] + \beta\ (\mathrm{co}\boldsymbol{v}\mathrm{ariates}_i)$, where y_i is the log of the odds of being affected for individual i with type g_i, β_{g_i} is the baseline regression coefficient for type g_i, δ is the vector of residual family effects, Z is the vector of dummy variables depending on the family effects in a particular model, $\log[r_k/(1 - r_k)]$ is the covariate to adjust for population prevalence for the kth age and sex category, and β is vector of regression coefficients for any covariates, and $\mathrm{covariates}_i$ are the covariate values for individual i.

Ascertainment was through probands and was a single incomplete ascertainment scheme. An ascertainment correction was applied by conditioning the likelihood on the probands.

For hypothesis tests, parameter estimates and likelihoods were obtained by use of REGD for each model of interest corresponding to various restrictions on the parameters. Hypothesis tests were based on the likelihood-ratio criterion comparing each restricted model to the general, unrestricted model. In addition, the Akaike (1974) information criterion (AIC) was used to select the most parsimonious model among equally likely models for the data. The AIC for any model is $[-2(\ln\mathrm{Likelihood}) + 2$ (number of estimated parameters. The model with the smallest AIC is the most parsimonious.

Results

All analyses were done twice in the entire data set of 50 families—once with the narrow definition of affection status and once with the broad definition. Results are presented separately for each definition.

Narrow Definition: Recurrent Unipolar Depression

Table 3 presents the results of analysis of the 50 families under the narrow definition of affection status for probands' relatives. Hypothesis tests were performed

Table 3

Narrow-Definition Phenotype: Segregation-Analysis Results for 50 Families

	No Transmission		Mendelian Transmission			Non-Mendelian Transmission		
							τ_{ND} Arbitrary	
	No Parental Effects (Model I)	Parental Effects (Model II)	Codominant (Model III)	Dominant (Model IV)	Recessive (Model V)	$\tau = q$ (Model VI)	Recessive (Model VII)	Codominant (Model VIII)
q_D	[1.0]	[1.0]	.22	.07	.24	.45	.12	.22
β_{NN}	1.96	1.02	−.29	.02	−.003	−.35	.40	.43
β_{ND}	$=\beta_{NN}$	$=\beta_{NN}$	.46	$=\beta_{DD}$	$=\beta_{NN}$	$=\beta_{NN}$	$=\beta_{NN}$	.34
β_{DD}	$=\beta_{NN}$	$=\beta_{NN}$	4.24	2.66	4.07	2.56	4.58	4.56
τ_{NN}	…	…	[1.0]	[1.0]	[1.0]	$=q$	[1.0]	[1.0]
τ_{ND}	…	…	[.5]	[.5]	[.5]	$=q$	.20	.19
τ_{DD}	…	…	[.0]	[.0]	[.0]	$=q$	[.0]	[.0]
$\delta_{\text{unaffected parent}}$	[.0]	.60	1.03	.93	1.00	.88	.78	.78
$\delta_{\text{affected parent}}$	[.0]	.90	1.13	.84	1.27	1.37	1.18	1.19
No.[a]	1	3	6	5	5	5	6	7
−2lnL	579.42	557.40	549.42	550.28	549.75	555.32	542.77	542.77
AIC	581.42	563.40	561.42	560.28	559.75	565.32	554.77	556.77
χ^2 (df)	36.65 (6)	14.63 (4)	6.65 (1)	7.51 (2)	6.98 (2)	12.55 (2)	.0 (1)	…
P	$\ll$.0001	.006	.01	.02	.03	.002	1.0	…

NOTE.—Square brackets denote that parameter was fixed to the value shown.

[a] No. of independent parameters estimated: (no. of parameters in model) − (no. of fixed parameters) − (no. of dependent parameters) − (no. of parameters that converged to a boundary).

versus model VIII, the most general model. Models I and II in table 3 are models of a single type—that is, there is no transmission of a major effect. In addition, model I has no familial effects, whereas model II incorporates nontransmissible parental effects (i.e., δ). Both "no-transmission" models could be rejected ($P < .01$). Models III–V represent codominant, dominant, and recessive Mendelian transmission of a major effect plus residual parental effects. These models have approximately equal likelihoods. Model V (recessive) has the smallest AIC and is therefore the best-fitting of the Mendelian hypotheses. To test type-specific transmission, model VI set all transmission probabilities equal to the gene frequency. Model VI could be rejected ($P = .002$), indicating that there was type-specific transmission. To test the Mendelian transmission of the major effect, model VIII estimated τ_{ND} and significantly improved the fit to the data. That is, models III–V could be rejected ($P < .05$), implying that the major effect does not fully conform to Mendelian transmission.

A large number of potential hypotheses were tested, but only one subset of the results is presented here, because certain combinations did not improve the fit to these data—for example, age and sex covariates, major-locus parameters estimated separately by gender, residual spouse effects, and separate parental effects for mothers and fathers. In testing Mendelian transmission of the major effect, only τ_{ND} was successfully estimated in these data, as reported above. τ_{NN} and τ_{DD} converged to their respective boundary values of 1.0 and .0 (consistent with the Mendelian expectations) when estimated separately; the data set was not sufficient to estimate all three τ's jointly.

Broad Definition: Any Major Affective Illness

Table 4 presents the results of analysis of the 50 families under the broad definition of affection status for the probands' relatives. As in the narrow definition, hypothesis tests were performed versus model VIII, the most general model. Again both no-transmission models (models I and II) could be rejected ($P < .0001$). Model I includes no familial effects, whereas model II incorporates nontransmissible parental and spousal effects. As in the case of the results under the narrow definition, models III–V had approximately equal likelihoods. Model III (codominant) had the smallest AIC and is therefore the best-fitting of the Mendelian hypotheses. To test type-specific transmission, model VI set all transmission probabilities equal to gene frequency. Model VI could be rejected ($P = .003$), indicating that there was type-specific transmission. To test the Mendelian transmission of the major effect, model VIII estimated τ_{ND}. Models III—V could not be rejected versus model VIII ($P > .05$). Therefore, there was no significant departure from Mendelian transmission for the broad definition of affection status. Because model VII was the best-fitting model for the narrow definition of affected status, Mendelian transmission under a recessive model was also tested for the broad definition (model VII), and again there was no significant departure from Mendelian transmission.

Table 4

Broad-Definition Phenotype: Segregation-Analysis Results for 50 Families

	No Transmission		Mendelian Transmission			Non-Mendelian Transmission		
							τ_{ND} Arbitrary	
	No Parental Effects (Model I)	Parental Effects (Model II)	Codominant (Model III)	Dominant (Model IV)	Recessive (Model V)	$\tau = q$ (Model VI)	Recessive (Model VII)	Codominant (Model VIII)
q_D	[1.0]	[1.0]	.44	.16	.49	.36	.45	.45
β_{NN}	2.24	1.69	.14	.0	−.11	−45.35	.05	.07
β_{ND}	$=\beta_{NN}$	$=\beta_{NN}$	−3.10	$=\beta_{DD}$	$=\beta_{NN}$	.72	$=\beta_{NN}$	−3.22
β_{DD}	$=\beta_{NN}$	$=\beta_{NN}$	4.36	3.29	3.67	20.96	3.74	4.29
τ_{NN}	…	…	[1.0]	[1.0]	[1.0]	$=q$	[1.0]	[1.0]
τ_{ND}	…	…	[.5]	[.5]	[.5]	$=q$	.40	.51
τ_{DD}	…	…	[.0]	[.0]	[.0]	$=q$	[.0]	[.0]
$\delta_{\text{unaffected spouse}}$	[.0]	.58	1.97	.82	1.05	1.75	1.11	1.99
$\delta_{\text{affected spouse}}$	[.0]	.89	2.51	1.56	1.86	2.56	1.87	2.53
$\delta_{\text{unaffected parent}}$	[.0]	.13	1.08	.63	.66	.74	.48	1.12
$\delta_{\text{affected parent}}$	[.0]	.69	2.36	.62	.84	2.52	.64	2.43
No.	1	5	8	7	7	8	8	9
−2lnL	879.61	858.22	824.93	830.06	829.67	833.67	828.07	824.93
AIC	881.61	868.22	840.93	844.06	843.67	849.67	844.07	842.93
χ^2 (df)	54.68 (8)	33.29 (4)	.0 (1)	5.13 (2)	4.74 (2)	8.74 (1)	3.14 (1)	…
P	$\ll$.0001	$\ll$.0001	1.0	.08	.09	.003	.08	…

NOTE.—See footnotes to table 3.

In testing Mendelian transmission of the major effect, only τ_{ND} was successfully estimated in these data, as reported above. τ_{NN} could not be estimated, and τ_{DD} converged to its boundary value .0 when evaluated separately; the data set was not sufficient to estimate all three τ's jointly. Furthermore, none of the following improved the fit to the data: age and sex covariates, major-locus parameters estimated separately by gender, and separate parental effects for mothers and fathers.

Table 5

Predicted Risks of Recurrent Unipolar Depression Calculated from the Best-Fitting Narrow-Definition Model (Model VII in Table 3), by Age, Gender, Genotype at Major Locus, and Affection Status of Parents

	Predicted Risk of Recurrent Unipolar Depression (%)	
Age and Genotype	Neither Parent Affected	One Parent Affected
0–44 Years:		
Male:		
NN, ND	14.80	20.49
DD	91.96	94.43
Female:		
NN, ND	33.40	42.65
DD	97.06	98.00
⩾45 Years:		
Male:		
NN, ND	7.31	10.47
DD	83.84	88.50
Female:		
NN, ND	16.94	23.22
DD	93.06	95.21

Risk Estimates and Conclusions

Tables 5 and 6 show the predicted risk of affection, by genotype, age, gender, and parental and spousal affection status. As can be seen from these tables, an individual's genotype makes the largest contribution to his or her risk of becoming affected, for each affection-status definition. Then, for recurrent unipolar depression (narrow definition), if a parent is affected, the risk of becoming affected increases by 1%–9%, depending on the age/gender/genotype category. The risk of affection for any major affective disorder (broad definition) increases by 1%–19%, depending on category, if a parent is affected, and by an additional amount ($\leqslant$5%) if a spouse is affected.

In summary, under the narrow-definition phenotype of recurrent unipolar depression, the model that best fits these family data is a transmitted major effect with two types, as in a recessive mode of inheritance (table 3; model VII). However, the transmitted effect is non-Mendelian in that the maximum-likelihood estimate of τ_{ND} is .20—significantly less than the expected value of .50. Moreover, there are significant residual parental effects on risk of affection. Under the broad-definition phenotype of any major affective illness, the codominant model is the best-fitting model (table 4; model III), and Mendelian transmission cannot be rejected. Mendelian transmission can also not be rejected for a recessive

Table 6

Predicted Risks of Any Major Affective Disorder, Calculated from the Best-Fitting Broad-Definition Model (Model V in Table 4), by Age, Gender, Genotype at Major Locus, Affection Status of Parents, and Affection Status of Spouse

	Predicted Risk of Major Affective Disorder (%)			
	Neither Parent Affected		One Parent Affected	
Age and Genotype	Spouse Unaffected	Spouse Affected	Spouse Unaffected	Spouse Affected
0–44 Years:				
Male:				
NN, ND	35.40	54.98	39.71	59.47
DD	96.01	98.17	96.66	98.47
Female:				
NN, ND	57.17	74.83	61.59	78.13
DD	98.32	99.24	98.60	99.37
⩾45 Years:				
Male:				
NN, ND	16.36	30.36	19.04	34.38
DD	89.58	95.04	91.18	95.84
Female:				
NN, ND	31.62	50.74	35.72	55.32
DD	95.31	97.84	96.07	98.20

model (table 4; model V) under the broad definition (note that the recessive is the best-fitting model under the narrow definition). Furthermore, there are significant residual parental and spousal effects on risk of affection.

Discussion

We have detected evidence of transmission of a major effect in unipolar depression, using families ascertained through probands with early-onset recurrent unipolar depression. Our data set (50 families, with 832 individuals) was adequate for detection of substantial effects, since the REGD module converged and generated parameter estimates for both the narrow- and the broad-definition phenotypes, under a range of hypothesis tests. Limiting probands to those with early-onset recurrent UPD may have contributed to our ability to detect transmission of a major effect, because of the high recurrence risk of affective illness in relatives of probands with early-onset and/or recurrent UPD (Weissman et al. 1984*b*, 1986; Bland et al. 1986; Price et al. 1987; Kupfer et al. 1989). Except for the BPI exclusion criteria used in the sleep study, which in practice had only a minor effect on the ascertainment of families, we did not recruit families on the basis of the phenotypes of the family members. This simplified the determination of the ascertainment correction and may also have increased our ability to detect the presence of a major transmissible effect in a relatively small sample size.

The narrow- and broad-definition analyses each fit the data better when nontransmissible parental and/or spousal effects were incorporated into the analysis along with the major transmissible effect. For both phenotype definitions, the effect of an individual's genotype was most important in the determination of the risk of illness. Then, the presence of an affected parent raised one's risk of developing depression, presumably through a change in the parent/offspring environment. For any major affective illness (broad definition), additional nontransmissible effects—that is, the presence of an affected spouse—further increased risk, beyond that ascribed to the affected parent alone. Sample-size limitations prevented us from dissecting these effects further by gender or age.

The only phenotypic definitions employed in this analysis involved diagnoses of severe affective illnesses, in which the sensitivity of the family-history RDC, when compared with the SADS-L, was judged to be adequate. Even with this restriction, it is likely that diagnosis of major affective illness was a conservative estimate with regard to the 62 first-degree relatives not available for personal interview. Furthermore, second-degree relatives may have been underdiagnosed, by $\leqslant 20\%$, for the major affective illnesses, compared with first-degree relatives. For the narrow definition of affection status, a second source of phenotypic underestimation probably occurred among those individuals with a single episode of major depression. These individuals were considered unaffected under the narrow definition, even though some of them will, in all likelihood, develop recurrent major depression in the future.

These underestimates could have obscured the role of a major locus, perhaps causing the τ's to shift away from Mendelian values. It may be one reason that Mendelian transmission of the narrow-definition phenotype was rejected, with the best estimate of τ_{ND} being .20. Even with this potential bias, we were able to find evidence for the segregation of a major effect under both the narrow-definition phenotype and the broad-definition phenotype and could not reject Mendelian codominant transmission for the broad-definition phenotype of any major affective illness.

Evidence for the segregation of a major locus or major effect has also been reported for bipolar disorder (Pauls et al. 1995; Spence et al. 1995). Pauls et al. (1995) found evidence of familial transmission in 42 large Old Order Amish families ascertained through BPI probands. With the computer program POINTER, single-locus autosomal-dominant inheritance could not be rejected in a subset of 19 closely related families. When the entire data set was analyzed, Mendelian inheritance could be rejected for some diagnostic categories of affected relatives (e.g., BPI only) but not for others (e.g., BPI, BPII, and schizoaffective, manic). Thus the results were not robust

to either the diagnostic scheme or the subset of families tested. In a sample of 186 families ascertained through BPI and BPII probands, Spence et al. (1995) reported that, when bipolar disorder was used as the affected phenotype in relatives, the best-fitting genetic model was a dominant, Mendelian, single-major locus. However, oligogenic and polygenic models that are more complex were not tested. Thus, it is possible that major disease-susceptibility loci are segregating both in families of both bipolar-disorder probands and in families of UPD probands.

UPD is a complex, common illness, which is likely to arise from multiple etiologies. Efforts to determine the biological underpinnings of UPD by use of physiological measures that themselves show familial aggregation—measures such as serotonergic markers (Sheline et al. 1995) or REM latency abnormalities (Giles et al. 1988, 1989)—can reduce etiologic heterogeneity, simplify phenotypes, and improve detection of inheritance patterns. Although studies of biological markers often detect differences between patients and controls, no marker has yet been found with discriminatory power sufficient to be useful for diagnosis. Thus, there is no obvious biochemical evidence to suggest that the actions of a single major locus, even if it has pleiotropic effects, are responsible for the majority of UPD cases. It is perhaps surprising, then, that we observed evidence for a single major transmissible effect in this relatively small data set. When a broad definition is used for assigning affection status to probands' relatives, the transmissible effect is consistent with Mendelian genetic transmission—that is, transmission, at a major locus, of a gene for susceptibility to a range of severe affective disorders.

Our results suggest that, within families, a major locus or other transmissible effect may be operating. It is important to note that our results do not determine whether the same major effect or genetic locus is segregating across families in our data set. Therefore, we cannot address the issue of how many major loci/effects are segregating for severe UPD—that is, we cannot determine the degree to which genetic heterogeneity is present. Nevertheless, these results provide support for linkage efforts, in that they suggest that major genes for UPD may be segregating within families ascertained through severely affected UPD probands.

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References

Akaike H (1974) A new look at the statistical model identification. IEEE Trans Automatic Control AC-19:616–623

American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, 4th ed. American Psychiatric Association, Washington, DC

Bland RC, Newman SC, Orn H (1986) Recurrent and nonrecurrent depression: a family study. Arch Gen Psychiatry 43:1085–1089

Bonney GE (1984) On the statistical determination of major gene mechanisms in continuous human traits: regressive models. Am J Med Genet 18:731–749

——— Bonney GE (1986) Regressive logistic models for familial disease and other binary traits. Biometrics 42: 348–353

Boyd JH, Weissman MM (1981) Epidemiology of affective disorders: a reexamination and future directions. Arch Gen Psychiatry 38:1039–1046

Cadoret R (1978) Evidence for genetic inheritance of primary affective disorder in adoptees. Am J Psychiatry 33:463–466

Cannings C, Thompson EA, Skolnick MH (1978) Probability functions on complex pedigrees. Adv Appl Prob 10:26–61

Cox N, Reich T, Rice J, Elston R, Schober, Keats B (1989) Segregation and linkage analysis of bipolar and major depressive illness in multigenerational pedigrees. J Psychiatr Res 23:109–123

Crowe RR, Namboodiri KK, Ashby HB, Elston RC (1981) Segregation analysis and linkage analysis of a large kindred of unipolar depression. Neuropsychobiology 7:20–25

Demenais FM (1991) Regressive logistic models for familial diseases: a formulation assuming an underlying liability model. Am J Hum Genet 49:773–785

Endicott J, Andreasen N, Spitzer RL (1975) Family history—research diagnostic criteria. Biometrics Research Department, New York State Psychiatric Institute, New York

Englund SA, Klein DN (1990) The genetics of neurotic-reactive depression: a reanalysis of Shapiro's (1970) twin study using diagnostic criteria. J Affect Dis 18:247–252

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

Giles DE, Biggs MM, Rush AJ, Roffwarg HP (1988) Risk factors in families of unipolar depression. I. Psychiatric illness and reduced REM latency. J Affect Dis 14:51–59

Giles DE, Kupfer DJ, Roffwarg HP, Rush AJ, Biggs MM, Etzel BA (1989) Polysomnographic parameters in first-degree relatives of unipolar probands. Psychiatr Res 27:127–136

Go RC, Elston RC, Kaplan EB (1978) Efficiency and robustness of pedigree segregation analysis. Am J Hum Genet 30: 28–37

Goldin LR, Gershon ES, Targum SD, Sparkes RS, McGinniss M (1983) Segregation and linkage analyses in families of patients with bipolar, unipolar, and schizoaffective mood disorders. Am J Hum Genet 35:274–287

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, et al (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 51:8–19

Kupfer DJ, Frank E, Carpenter LL, Neiswanger K (1989) Family history in recurrent depression. J Affect Dis 17:113–119

Lustbader ED, Williams WR, Bondy ML, Strom S, Strong LC (1992) Segregation analysis of cancer in families of childhood soft-tissue-sarcoma patients. Am J Hum Genet 51: 344–356

Pauls DL, Bailey JN, Carter AS, Allen CR, Egeland JA (1995) Complex segregation analysis of Old Order Amish families ascertained through bipolar I individuals. Am J Med Genet 60:290–297

Price RA, Kidd KK, Pauls DL, Gershon ES, Prusoff BA, Weissman MM, Goldin LR (1985) Multiple threshold models for the affective disorders: the Yale-NIMH collaborative family study. J Psychiatr Res 19:533–546

Price RA, Kidd KK, Weissman MM (1987) Early onset and panic disorder as markers for etiologic homogeneity in major depression. Arch Gen Psychiatry 44:434–440

Puig-Antich J, Orvaschel H, Tabrizi MA, Chambers W (1980) The schedule for affective disorders and schizophrenia for school children—epidemiological version (Kiddie-SADS-E), 3d ed. New York State Psychiatric Institute and Yale University School of Medicine, New York

Rice J, Reich T, Andreasen NC, Endicott J, Van Eerdewegh M, Fishman R, Hirschfeld RMA, et al (1987) The familial transmission of bipolar illness. Arch Gen Psychiatry 44: 441–447

SAGE (1994) Statistical analysis for genetic epidemiology, release 2.2. Computer program package available from Department of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland

Sham PC, Morton NE, Rice JP (1991) Segregation analysis of the NIMH collaborative study: family data on bipolar disorder. Psychiatr Genet 2:175–184

Sheline YI, Bardgett ME, Jackson JL, Newcomer JW, Csernansky JG (1995) Platelet serotonin markers and depressive symptomatology. Biol Psychiatry 37:442–447

Sorant AJM, Bonney GE, Elston RE (1994) Segregation analysis of a discrete trait under approximations to class A regressive models (REGD version 5.0). In: Statistical analysis for genetic epidemiology, release 2.2. Computer program package available from Department of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland

Spence MA, Flodman PL, Sadovnick AD, Bailey-Wilson JE, Ameli H, Remick RA (1995) Bipolar disorder: evidence for a major locus. Am J Med Genet 60:370–376

Spitzer RL, Endicott J (1975) Schedule for affective disorders and schizophrenia—lifetime version. Biometrics Research Department, New York State Psychiatric Institute, New York

Spitzer RL, Endicott J, Robins E (1978) Research diagnostic criteria: rationale and reliability. Arch Gen Psychiatry 35: 773–782

Torgersen S (1986) Genetic factors in moderately severe and mild affective disorders. Arch Gen Psychiatry 43:222–226

Tsuang MT, Bucher KD, Fleming JA, Faraone SV (1985) Transmission of affective disorders: an application of segregation analysis to blind family study data. J Psychiatr Res 19:23–29

Weissman MM, Bruce ML, Leaf PJ, Florio LP, Holzer C III (1991) Affective disorders. In: Robins LN, Regier DA (eds) Psychiatric disorders in America: The Epidemiological Catchment Area Study. Free Press, New York, pp 53–80

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

Weissman MM, Merikangas KR, Wickramaratne P, Kidd KK, Prusoff BA, Leckman JF, Pauls DL (1986) Understanding the clinical heterogeneity of major depression using family data. Arch Gen Psychiatry 43:430–434

Weissman MM, Wickramaratne P, Merikangas KR, Leckman JF, Prusoff BA, Caruse KA, Kidd KK, et al (1984*b*) Onset of major depression in early adulthood. Arch Gen Psychiatry 41:1136–1143

Wender PH, Kety SS, Rosenthal D, Schulsinger F, Ortmann J, Lunde I (1986) Psychiatric disorders in the biological and adoptive families of adopted individuals with affective disorders. Arch Gen Psychiatry 43:923–929