Early Onset (Under Age 30 Years) and Panic Disorder as Markers for Etiologic Homogeneity in Major Depression

R. Arlen Price, PhD; Kenneth K. Kidd, PhD; Myrna M. Weissman, PhD

- Early onset of major depression (age, <30 years) in probands confers high risk to relatives, whereas late-onset depression (age, >40 years) involves no elevation of risk over population rates. Analyses of data from families of probands with early onset from the Yale Family Study (47 three generation and 17 two generation) favored a major gene effect over polygenic inheritance. However, no genetic model was supported unambiguously. The increase in prevalence of depression over the past several decades complicates the genetic interpretation of results. Restriction of analyses to older (age, >18 years) age cohorts appeared to simplify the pattern of transmission, but a consequent reduction of sample size provided only limited power for tests of competing genetic hypotheses. In a subgroup of 28 families in which the proband had both depression and panic disorder, a major gene mode of inheritance was not supported.

(Arch Gen Psychiatry 1987;44:434-440)

Affective disorders are strongly familial, with rates in parents, siblings, and children of depressed individuals being at least double those of individuals selected at random from the population. Familial aggregation suggests the possibility of genetic involvement, although nongenetic factors may be involved as well. Twin studies support a genetic interpretation of the familial pattern, but the limited data available from adoption studies are conflicting. Analyses of pooled family data with threshold models have mainly focused on the fact that a wide range of symptoms from depression to mania tend to co-occur in individuals and to aggregate in families. These analyses have confirmed that a wide range of genetic models is consistent with the observed familial aggregation but have not identified the specific mode or modes of inheritance for the affective disorders. A few studies have utilized segregation analysis, which does not require that data be pooled across families, to study the pattern of transmission of major depression. Neither autosomal nor sex-linked single-gene models were supported by these analyses.

A demonstration of linkage to a known genetic marker would establish genetic involvement unequivocally as well as confirm the specific mode of genetic transmission. Until quite recently only a few genetic markers were known in humans. Still, a number of reports of genetic linkage of affective disorders have been published, and those reports have generated considerable controversy, because they have presented conflicting results. Linkage is indicated to markers on the X chromosome in some families, and on chromosome 6 in other families, and on chromosome 11 in at least one family. The apparent contradictory nature of some of these results may be due to the presence of distinct forms of affective illness with unique genetic etiologies.

HETEROGENEITY OF RISK FOR MAJOR DEPRESSION

The lack of consistency across studies and families is not surprising. The affective disorders are highly heterogeneous in symptom patterns, age at onset, recurrence, and comorbidity of other disorders. This diversity may be a reflection of etiologic heterogeneity. Recent studies provide an approach to identifying subgroups of depression that are etiologically homogeneous. Weissman and associates found in the Yale Family Study that the clinical features of the probands independently associated with familial risk were early-onset major depression (age, <30 years), anxiety, and alcoholism. Rates of major depression are highest in families of probands with onset before age 20 years. Rates were also higher in groups in which the probands had onset during their 20s or 30s. However, rates in relatives of probands with onset at age 40 years or older did not differ from rates in normal controls. These differences were not due to confounding of onset age with age cohort, with
Leckman et al.41 have reported that anxiety in depressed probands greatly increases the risk for both anxiety disorders and major depression in adult relatives. Panic disorder in probands accounted for the greatest increase in risk. Weissman et al.44 have replicated these findings in a sample of children under age 18 years.

**INCREASE IN PREVALENCE OF MAJOR DEPRESSION**

There is good evidence for an increase in the rates of major depression over the last few decades,42-43 and this change complicates the analysis of genetic transmission. The largest increase in rates is found in the cohort that was born after 1935 and came to maturity after World War II.42 This increase is not restricted to the United States.43 The increase may be an artifact of reporting, selection, and other factors, a large increase in rates can distort familial patterns between generations and obscure genetic transmission. Failure to make allowances for the cohort effect can affect whether genetic models are accepted or rejected.45 These trends must be taken into account to obtain a realistic view of transmission.

This article attempts to identify genetically homogeneous subsets of major depression by fitting genetic models to subsets of families defined by early onset and by panic disorder also occurring in the depressed probands. These overlapping subgroups have a high familial risk, and there is some evidence that there is some shared etiology. All models allow for sex and age cohort differences in rates of major depression.

**SUBJECTS AND METHODS**

**Subjects**

The data analyzed in this study were obtained from the Yale Family Study3 of depressive disorders. The original study included diagnostic estimates on offspring aged 18 years or older. Additional family history data were available on children aged 6 to 18 years.4 The family history data have been supplemented by direct interviews from a follow-up study of children at high and low risk for depression.46 The data reported herein combined information from all these sources. Children aged 12 years or older were included.

Lifetime major depression was defined by modified Research Diagnostic Criteria4 in all first-degree relatives of probands. Criteria were modified to require major social role impairment, a minimum four-week episode, and the presence of at least four symptoms. Diagnoses were based on a best-estimate procedure using all available information.46 Variability in information available on relatives led to differences in diagnostic certainty. For these analyses, relatives with a probable or definite diagnosis of major depression were considered affected. Though a primary diagnosis of schizophrenia or alcoholism in a proband was a reason for exclusion, no exclusionary criteria were used for other diagnoses, eg, panic disorder or secondary alcoholism.47 Though the primary symptoms of all probands were affective, panic disorder was not clearly secondary to depression in every case. However, in all but four cases the earliest episode of panic disorder in the proband was later than or concomitant with the earliest depressive episode, and in two of these the diagnosis of panic was probable rather than definite.

Children of probands who were included in the high-risk study met DSM-III criteria for major depression and had at least one four-week depressive episode.48 Diagnoses in children in the high-risk study were based on independent structured interviews of both the mother and child using the Children's Schedule for Affective Disorders and Schizophrenia, Lifetime version. Offspring of probands consistently reported much higher rates of depression than indicated in the mother's interview on the child.

This was particularly true for the children under age 18 years included in the high-risk study. According to the best-estimate procedure used for this analysis, a child was considered as having major depression if either informant reported it. The fact that each diagnosis of a child from the high-risk study was based on two direct interviews contributed to the higher rate of depression found in children compared with the rate in the proband and parental generations. Whether the large number of DSM-III diagnoses in children truly represents clinical depression is not known and is currently being investigated. For further details see Weissman et al.44

Genetic analyses in the present study focused on three overlapping subgroups. Two subgroups were defined by early onset and panic disorder, respectively, in the probands. These subgroups of families were chosen because they have high risk to relatives. A breakdown of rates of major depression by subgroup, sex, and generation is given in Table 1. The first group included 105 nuclear families identified through 64 probands with an early onset (age, <30 years) of major depression. (See the description of methods of genetic analysis given below for an explanation of what constituted a nuclear family in this study.) Overall, 28% of first-degree relatives had major depression. The second group of families studied were those in which the proband had secondary panic disorder. This group included both families with an early onset and families with a child onset (n = 7) of major depression in the proband. There were 50 nuclear families of 28 probands. The overall percentage of depression among relatives of these probands was 24%. A third subgroup was made up of those families that were included in the overlap of groups 1 and 2, ie, the group of families with both early onset and secondary panic in the proband. There were 58 families of 21 probands in this group, and the proportion of affected relatives was 29%.

**Genetic Models**

The method of genetic analysis used was complex segregation analysis using the computer program POINTER.47 This method of analysis tests components of a genetic model (a threshold model) that includes an autosomal major gene that exists in two forms. One form of the gene causes an increased risk for becoming depressed. Penetrance (the probability that an individual with a particular genetic makeup will become ill) depends on the major genotype, an inherited polygenic background, and random factors. In the real world, polygenic transmission in families is confounded with cultural transmission. Our analysis was based on a model of pure polygenic inheritance with no cultural transmission. The version of the computer program POINTER that we used incorporates the estimation of transmission probabilities into the mixed model in which allows us to test the pattern of transmission conforms to Mendelian expectations.

The method of genetic analysis utilized is applied only to nuclear families (parents and children). All families were identified through one affected family member, the proband. All probands were adult offspring in one nuclear family. When probands had children aged 12 years or older, the proband was included in a second nuclear family along with his or her spouse and children. Thus, the total number of nuclear families exceeds the number of probands. For example, there were 105 nuclear families of 64 early-onset probands, because 41 of the probands had children aged 12 years or older. Since all families were identified through one affected family member, the proband, the probability of identifying families with the number of affected children in the second nuclear family and children was independent of the number of probands per family. The probability of ascertaining a proband as an adult offspring was assumed to be a small value (.01). For the second set of nuclear families in which the proband was also a parent, ascertainment of affected children of the proband was assumed to be complete (P = 1.0).

The specific details of the model and methods of analysis follow. The major locus parameters are gene frequency (q) for the abnormal allele (a); the displacement between means of homozygotes at the major locus (t) scaled to have a global mean of 0.0 and variance of 1.0; the relative displacement of the heterozygote mean (d) ranging from 0.0 (recessive) to 1.0 (dominant); and probabilities of transmitting the normal allele (A) for the three genotypes
Table 1.—Frequency of Major Depression in Families
Arranged by Proband Classification*

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Early Onset</th>
<th>Major Depression</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fathers</td>
<td>55</td>
<td>9</td>
<td>64</td>
</tr>
<tr>
<td>Mothers</td>
<td>49</td>
<td>15</td>
<td>64</td>
</tr>
<tr>
<td>Brothers</td>
<td>77</td>
<td>18</td>
<td>95</td>
</tr>
<tr>
<td>Sisters</td>
<td>81</td>
<td>24</td>
<td>105</td>
</tr>
<tr>
<td>Sons</td>
<td>36</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>Daughters</td>
<td>36</td>
<td>21</td>
<td>57</td>
</tr>
<tr>
<td><strong>Total first-degree relatives (%)</strong></td>
<td>334 (77)</td>
<td>99 (23)</td>
<td>433 (100)</td>
</tr>
<tr>
<td>Husbands</td>
<td>23</td>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td>Wives</td>
<td>8</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td><strong>Secondary Panic</strong></td>
<td>25</td>
<td>3</td>
<td>28</td>
</tr>
<tr>
<td>Fathers</td>
<td>18</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>Mothers</td>
<td>16</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>Brothers</td>
<td>33</td>
<td>7</td>
<td>40</td>
</tr>
<tr>
<td>Sisters</td>
<td>20</td>
<td>11</td>
<td>31</td>
</tr>
<tr>
<td>Sons</td>
<td>19</td>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td>Daughters</td>
<td>15</td>
<td>11</td>
<td>26</td>
</tr>
<tr>
<td><strong>Total first-degree relatives (%)</strong></td>
<td>121 (74)</td>
<td>42 (26)</td>
<td>163 (100)</td>
</tr>
<tr>
<td>Husbands</td>
<td>10</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Wives</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

*Early onset is defined as onset before the age of 30 years; this group had 105 nuclear families of 64 probands. The secondary panic group had 50 families of 28 probands; the overlapping group that had both early onset and secondary panic had 38 families of 21 probands.

(tAAA, tAaA, taaA), which are assumed to be 1.0, 0.5, and 0.0, respectively, under the Mendelian hypothesis. For example, tAAA is the probability that a heterozygous parent, Aa, will transmit the normal allele, A. Penetrances, probabilities of becoming depressed given genotypes, are functions of the estimated parameters.

Specific single-gene models were tested against an unrestricted model in which the transmission probabilities were free to assume any values. An attempt was made to estimate transmission probabilities in the mixed model in POINTER, but parameters did not converge to a solution when all parameters were free. Obtaining convergence required fixing some parameters at bounds, notably polygenic heritability (h), which approached 0. In cases in which convergence was achieved, parameter estimates were large, particularly for h. We tested the Mendelian major locus and polygenic models against the Mendelian mixed model. The statistic for a test of competing models was the difference in the log-likelihood for \([-2 \ln(L) + k]\), where L is the likelihood and k is a constant, for a specific hypothesized model and an unrestricted one in which it was nested. This difference in log-likelihoods is asymptotically distributed as a \(\chi^2\) with degrees of freedom equal to the difference in the numbers of free parameters between the two models. The best-fitting model arbitrarily has been assigned a value of \([-2 \ln(L) + k]\) equal to 0.0. For all other models, \([-2 ln(L) + k]\) values are expressed as positive deviations from the best model to make them interpretable as \(\chi^2\) values.

Table 2.—Population Prevalence Estimates Defining Liability Classes by Age Cohort and Sex

<table>
<thead>
<tr>
<th>Cohort, y</th>
<th>M</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>0.0263</td>
<td>0.0577</td>
</tr>
<tr>
<td>20-29</td>
<td>0.0546</td>
<td>0.1147</td>
</tr>
<tr>
<td>30-39</td>
<td>0.0430</td>
<td>0.1553</td>
</tr>
<tr>
<td>&gt;40</td>
<td>0.0174</td>
<td>0.0382</td>
</tr>
</tbody>
</table>

Sex and Age Cohort—Specific Penetrances

A major methodologic concern in these analyses was the dependence of risk for major depression on sex, age, and age cohort. This variability was controlled by estimating genotype penetrances that varied according to sex, age, and age cohort of the individual. Population prevalences must be specified for all classes of individuals for whom penetrances are expected to vary systematically. The prevalences are used to define threshold positions on an underlying liability continuum from which penetrances are estimated. We included eight separate sex-by-cohort prevalences. No attempt was made to correct for age effects within sex and birth cohort because of a computer program limitation to the specification of ten prevalences. However, the variation in risk within cohort due to age should be small relative to differences between the sex-by-age cohorts. The cohorts were defined as under 20, 20 to 29, 30 to 39, and over 40 years within each sex. All deceased relatives fell into the older cohort. Two who died before age 40 years were assigned a population prevalence reflecting the cumulative risk through age 30 to 39 years for the older cohort (>40 years). Population prevalences for each cohort were taken to be the midpoint values for each corresponding age and sex cohort estimated from the Epidemiological Catchment Area (ECA) New Haven (Conn) sample. For comparability with the sample of the present study, we calculated prevalences on a subset of the ECA sample that excluded nonwhites. The ECA diagnoses were based on DSM-III. The observed prevalences have a curvilinear relationship with age cohort, with risk increasing and then decreasing for older cohorts. The cohorts, with corresponding prevalences, are given in Table 2.

RESULTS

For the three subsets of families examined there was a large improvement in likelihood for any model allowing for transmission between generations. Thus, a model of no familial transmission was rejected in all three subgroups.

For the early-onset group, the full results are presented in Table 3. The best-fitting Mendelian mixed model, the model with the lowest value of \([-2 \ln(L) + k]\), was at a boundary at which polygenic heritability (h) approached 0. It is a model of a major gene with the dominantly expressed predisposing allele (d = 1) having a frequency (q) of about 4%. The model allows for incomplete penetrance of the major gene and 40% phenocopies, i.e., 40% of cases of depression in individuals without the predisposing gene. There was no support for a significant contribution from h. The mixed model with h approaching 0 appears to be the maximum likelihood solution since it was reached from several different starting points on the likelihood surface, i.e., with different initial parameter estimates. The likelihood of this model is equivalent to that for the major gene model.

When the major gene is excluded from the model, there is a moderately high h (0.68), consistent with the high rates of depression found in the relatives of the early-onset probands. The fit of the mixed model solution including a major gene and polygenic background (estimated at 0) is significantly better than the simple polygenic model (\(\chi^2(3) = 12.10, P < .01\)). Thus, a major locus model explains the observed data significantly better than a polygenic model.

An additional conservative test of the major locus hypothesis is to estimate the probabilities that the three genotypes transmit one form of the putative gene. These probabilities differed significantly from their expected Mendelian values (1.0, 0.5, 0.0), primarily due
Table 3.—Segregation Analysis of Major Depression in Families of Probands With Early Onset*

<table>
<thead>
<tr>
<th>Model</th>
<th>Major Locus</th>
<th>d</th>
<th>t</th>
<th>q</th>
<th>tAAA</th>
<th>tAa</th>
<th>taaA</th>
<th>Polygenic (h)</th>
<th>-2 ln(L) + k†</th>
<th>No. of Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>No transmission (major locus or polygenic)</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mendelian</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>36.28</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Recessive (d = 0)</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2.01±0.154</td>
<td>0.252±0.030</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
<td>3.62±0.096</td>
</tr>
<tr>
<td>Additive (d = 0.5)</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
<td>3.62±0.264</td>
<td>0.037±0.010</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Dominant (d = 1)</td>
<td></td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1.91±0.097</td>
<td>0.037±0.008</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Mendelian</td>
<td></td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1.91±0.097</td>
<td>0.037±0.008</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>General (tAAA, tAaA, taaA)</td>
<td></td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2.68±0.710</td>
<td>0.0004±0.0004</td>
<td>0.88±0.031</td>
<td>0.10±0.38</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Test of tAaA</td>
<td></td>
<td>0.56±0.096</td>
<td>1.77±0.134</td>
<td>0.125±0.079</td>
<td>1</td>
<td>0.00‡</td>
<td>0</td>
<td>20.15</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Test of tAAA</td>
<td></td>
<td>0.97±1.59</td>
<td>2.98±4.56</td>
<td>0.001±0.001</td>
<td>0.89±0.024</td>
<td>0.5</td>
<td>0</td>
<td>0.52</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Polygenic</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.63±0.05</td>
<td>34.93</td>
<td>1</td>
</tr>
<tr>
<td>Mendelian mixed model†</td>
<td></td>
<td>1.0</td>
<td>1.90</td>
<td>0.037</td>
<td>1</td>
<td>0.5</td>
<td>0.01</td>
<td>22.82</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

| No transmission (major locus or polygenic) |             |  0 |  0 |  0 |      |      |      |               |                |                  |
| Mendelian                     |             | 0  | 0  | 0  | 2.47±0.206 | 0.251±0.022 | 1    | 0.5           | 0              | 9.93            |
| Recessive (d = 0)             |             | 0  | 0  | 0  | 2.47±0.206 | 0.251±0.022 | 1    | 0.5           | 0              | 9.93            |
| Additive (d = 0.5)            |             | 0  | 0  | 0  | 0.5  | 3.86±0.313 | 0.056±0.012 | 1    | 0.5           | 0              | 1.45            |
| Dominant (d = 1)              |             | 1  | 0  | 0  | 2.09±0.144 | 0.046±0.007 | 1    | 0.5           | 0              | 2.45            |
| Mendelian                     |             | 0.63±0.16 | 3.17±0.70 | 0.054±0.011 | 1 | 0.5 | 0       | 1.20          | 3                |
| General (tAAA, tAaA, taaA)   |             | 0.71±0.19 | 3.36±0.746 | 0.048±0.008 | 1.0 | 0.61±0.06 | 0.00       | 0.00          | 6                |
| Test of tAaA                  |             | 0.71±0.19 | 3.36±0.746 | 0.048±0.008 | 1 | 0.61±0.06 | 0.00       | 0.00          | 4                |
| Test of tAAA                  |             | 0.63±0.16 | 3.17±0.705 | 0.054±0.011 | 1 | 0.5 | 0       | 1.20          | 4                |
| Polygenic                     |             | 0  | 0  | 0  | 0    | 0    | 0    | 0.86±0.07     | 6.06           | 1                |
| Mendelian mixed model         |             | 0.75±0.30 | 2.54±1.09 | 0.061±0.020 | 1 | 0.5 | 0.15±0.20  | 0.87          | 4                |

*The first analysis included 105 nuclear families, including families in which probands were parents as well as those in which they were siblings; the second analysis excluded consideration of nuclear families in which probands were parents, and included 64 families. Early onset was defined as onset before the age of 30 years; d indicates relative displacement of the heterozygote mean; t displacement between means of homozygotes at the major locus; q, gene frequency; A, normal allele; a, abnormal allele; h, polygenic heritability; L, likelihood; and k, a constant. Transmission parameter values are expressed as mean±SE.
†Expressed as a deviation from the maximum likelihood.
‡Converged to boundary.
§No convergence.

The model of no familial transmission (all major locus and polygenic model parameters set to 0) was rejected. The best-fitting mixed model is for a major gene (q = 0.06, t = 2.5, d = 0.75) with low background h (h = 0.15), which does not differ from 0. In this restricted sample, the major locus model conforms to Mendelian expectations (x^2[1] = 1.2). However, the mixed model including a major locus and polygenic inheritance improved the likelihood over that of a purely polygenic model, but not significantly so (x^2[3] = 5.19). The polygenic model was not supported when compared with the mixed model (x^2[1] = 0.33).

Transmission probabilities were estimated in the mixed model for the 64 early-onset nuclear families with adult offspring. The tAAA and tAaA had to be fixed (at 0.0 and 0.5, respectively) to obtain convergence when h was greater than 0.0. When free, tAAA went to the boundary of 1.0 and the likelihood was identical to the solution for the Mendelian mixed model. The large SE for h (0.20) in the mixed model and the very small difference in likelihood (0.87) of this solution from the Mendelian major locus model indicate that the most parsimonious model is the Mendelian single-gene model with no polygenic background (h = 0.0).

In the subgroup with early-onset major depression and panic disorder in the proband (families of 21 probands), the best-fitting Mendelian mixed model was for a major gene with liability to illness nearly as high in the heterozygote as in the "abnormal" homozygotic individuals (q = 0.03, t = 2.75, d = 0.79) and with no effect of polygenic background (h = 0.003). However, neither the major locus nor polygenic subhypotheses were clearly supported, and the major locus transmission probabilities were non-Mendelian.

In the panic subgroup (families of 28 probands with both early-

to a deviation in the estimated transmission probability for individuals homozygous for the predisposing allele (0.88 vs an expected value of 1.0) (x^2[3] = 22.83). Thus, for this sample either there was an error in the specification of ascertainment probabilities, sex- and cohort-specific prevalences are inaccurate, or the major gene model is wrong.

Transmission probabilities were also estimated in the mixed model. Even imposing the restriction that taaA = 0.0 never resulted in a convergent solution that had as high a likelihood as those obtained when h was fixed at 0. The pattern of results indicates that the "true" value of the parameter h is 0.0, and that mixed model solutions with h greater than 0.0 behaved as if the models were overparameterized. Either SEs were large, eg (h = 0.38, SE = 0.93), or there was a failure to estimate SEs because of singularity of the information matrix.

One way to examine which possibility might be true is to use only the 64 nuclear families ascertained through adult offspring, ie, to exclude from the analysis families including probands as parents, along with their spouses and children. We separately examined the 64 nuclear families in which the proband with early onset was an adult offspring. This restricted sample removes from the analysis the spouses and children of probands, including many in the high-morbidity 12- to 18-year age range, for whom clinical depression may be questionnable in spite of the fact that all of these children met diagnostic criteria. The elimination of nuclear families in which the proband is a parent also allows the computation of joint likelihoods of children's and parents' affection status, which provides more information for the estimation of model parameters. The results from these analyses are given in Table 3.
and late-onset depression), the best-fitting Mendelian mixed model was for a major locus with dominantly expressed liability to illness ($g = 0.03, t = 1.93, d = 1.00$) and with moderate heritability of the polygenic background ($h = 0.25$). Again, neither major locus nor polygenic inheritance models were clearly supported, and transmission probabilities were non-Mendelian.

**COMMENT**

Single-gene models for complex multiply determined traits are open to criticism for being overly simplistic. Due to the apparent complexity of the affective disorder phenotypes, polygenic models have some appeal. However, polygenic models are abstractions that are remote from gene action. If clearly identified, a single-gene model has the advantage that it can be validated by genetic linkage studies. A specific single-gene model is likely to be appropriate only for a limited number of families of probands with major depression. Other factors, including other major gene effects, will probably be responsible for transmission in other families.

There have been few attempts to apply complex segregation analysis to the familial transmission of major depression. Gewein and al. did not find support for a single-gene mode of transmission using a single pedigree with unipolar depression. Goldin et al. analyzed 18 families with unipolar depression and were able to reject both autosomal and X-linked hypotheses. Goldin et al. were not able to reject a model of no familial transmission. Though Goldin et al. examined subsets of bipolar disorder, the limited number of unipolar families ($n = 18$) precluded subsetting of the unipolar depression sample. Tsuang et al. rejected both dominant and recessive Mendelian models and could not reject a model of no familial transmission.

**Early Onset as a Marker for Etiologic Homogeneity**

Our approach of subsetting the sample by markers for high familial risk allows for genetic heterogeneity in major depression. There is no expectation that all major depressive disorder is uniform either in clinical course or in etiology. It would be naive to expect to find one gene that accounts for all cases of major depression. On the other hand, it is quite possible that eventually we will be able to identify a major gene effect that accounts for transmission in a subset of cases. A clear understanding of the cause of even a small subset of major depression will provide a major advance in the understanding of the causes of affective disorders. The recognition of subtypes has contributed to the study of other heterogeneous disorders, eg, diabetes mellitus and hypercholesterolemia. In affective disorders, early onset may be one marker for a genetic form of unipolar depression.

The high familial risk conveyed by early onset has been observed by other investigators, usually defining age 40 years as the dividing point between early and late onset. Winokur et al. defined depressive spectrum disease as having early onset (age, <40 years), with depression typically being more prevalent in women and alcoholism more prevalent in men. Depression and alcoholism often co-occur and, along with secondary anxiety and early onset of depression in the proband, this occurrence contributes to an elevated risk for depression in relatives. However, depression and alcoholism do not seem to be manifestations of the same disorder, since depressed probands without alcoholism do not transmit alcoholism to their relatives.

Mendlewicz and Baron found an elevated risk for unipolar depression in relatives of unipolar probands with onset before age 40 years. Smeraldi et al. reported an earlier age at onset in affectively ill (unipolar and bipolar) patients with at least one affected parent. Their analysis was at least partially confounded by the earlier age at onset and higher familial risk associated with bipolar illness. Still, considering only their unipolar probands, rates of affective illness in relatives of probands with onset at age 30 years or younger was 20% but was only 13% for those with onset after age 30 years, a difference that does not reach statistical significance in their sample.

**Depression and Panic Disorder**

We examined the subset of probands with panic disorder because panic in probands causes an elevation of risk for depression that is independent of early onset even though this subgroup of probands accounted for about one third (21/64) of our early-onset group. A number of studies have noted an association between depression and panic disorder. Leckman et al. found that panic disorder in probands increased the risk to adult relatives for both anxiety disorder and major depression over the risk for relatives with depression alone. Weissman et al. extended this finding to children under age 18 years. Leckman et al. suggested that depression and panic disorder share, at least partially, an underlying diathesis.

As reported by Leckman et al., rates of depression in first-degree relatives were higher in the subgroup of families defined by panic disorder in the proband, and we found strong evidence for some family transmission when we applied genetic models. However, neither in the full group of probands with major depression with panic (n = 28) nor in the subset with early onset of primary major depression (n = 21) was support provided for either a major locus or a polygenic mode of inheritance.

The major-locus model was the most strongly supported model in both panic subsamples, but the single-gene model did not receive statistically significant support ($\chi^2(3) = 5.46$ and 6.77, respectively) when the mixed model was compared with a nested model with only polygenic inheritance. It is possible that a larger sample of families or an extension of these analyses to include second-degree relatives would provide support for major locus inheritance in these subsamples.

**Differences in Risk by Age Cohort**

Recently, Klerman et al. reported data from the National Institute of Mental Health Collaborative Study on the Psychobiology of Major Depression that show a marked cohort effect in major depression. There has been an increase in lifetime rates of major depression in every ten-year birth cohort from 1910 to 1950. The report by Hagnell et al. of a similar trend in the Swedish population between 1947 and 1972 suggests that this may be an extensive phenomenon in industrialized countries.

Age effects are commonly incorporated into genetic models. For multiple-threshold models that require data that is pooled over families, rates of depression in relatives may be adjusted for the proportion of risk passed by each individual. Methods for making this adjustment have included that of Strömgren, modifications of the Strömgren method, eg, that of Gershon et al., and life-table methods. When information in pedigrees is not reduced to rates in relatives, age effects may be controlled by an age-dependent penetrance function.

Though it has been common to control for age effects in analyses of affective disorders, there have been few attempts to control for differences in age cohort. Rice et al. did control for age cohort in their analysis. Using survival analysis, these authors found elevated rates of major depression in siblings when parents were affected. Rates were
higher in siblings if a mother was affected, if individuals were from a relatively younger age cohort, and if the individuals were female.

From a genetic perspective, two-generation families span age cohorts, but an increase across generations does not fit any simple genetic model. Recently, Price et al. have shown that if the pooled rates used in multiple-threshold models are separated by generation, the cohort differences that are not included in the genetic model lead to rejection of genetic hypotheses, even though the familial pattern is strong.

Possible Mis specification of Genetic Models

The departure from Mendelian expectation that we found in the full early-onset sample could mean that genetic factors do not play a role in mediating the secular increase in depression or that we have misspecified the nature of the interaction between genotype and time. The differences in rates of depression by age cohorts, as well as those in men and women, were modeled as differences in thresholds. The role of genetic factors in such a model is to establish an underlying predisposition to depression. Environmental factors, including those correlated with time, modify the placement of the threshold on an underlying continuum of vulnerability. Under such a genotype-time interaction model, one would expect the largest increase over generations to occur in families with increased genetic vulnerability. Families with the highest rates of depression should therefore have a higher genetic loading. To the extent that the increase in depression in successive age cohorts is independent of genetic predisposition, the observed data will diverge from the pattern expected under the genetic threshold model used in the present study.

The rates of depression reported in children included from the high-risk study are about double the lifetime rates reported in adults. This difference may be due to overreporting in children or to reporting of true depression that occurs at high rates in adolescence and is then either forgotten in adulthood or attributed to emotional growing pains of adolescence. The high rate in children suggests that the phenotype may not be clinically comparable across generations. Specification of age-specific risks may not be sufficient to compensate for this lack of continuity in reporting and/or clinical expression across generations.

Another possible model misspecification that we examined is that some models we examined assumed random mating. In Table 1, the rates of depression given for spouses of probands indicate assortative mating for depression, i.e., a spouse concordance rate that exceeds chance expectations. In the full early-onset sample (Table 3), assortative mating should not affect results since the likelihood of the observed pattern of illness in offspring was calculated conditional on parental phenotypes. Conditional likelihoods should be insensitive to an excess of concordant spouses. Nonrandom mating should affect the estimation of transmission probabilities only if the genotype distribution of unaffected spouses is distorted because some spouses have incompletely expressed subclinical forms of depression that are genetically determined. In the sample in which children of probands were excluded (Table 3), spouses of probands were not included in the analysis. In the Yale sample there was no assortative mating among parents of probands. Thus, it seems unlikely that assortative mating could have had a substantial effect on the outcome of any of the analyses.

This research was supported in part by Biomedical Research Support grant RR-07068 and Alcohol, Drug Abuse, and Mental Health Administration grants MH-28274 and MH-36197 from the Center for Studies of Affective Disorders, Yale Mental Health Clinical Research Center; by grant MH-30529 and Research Training Grant in Psychosocial Epidemiology MH-00035 from the National Institute of Mental Health; and by grants from the John D. and Catherine T. McArthur Foundation to the Network on Health Promoting and Health Damaging Behaviors and to the Network on Risk and Protective Factors in the Major Mental Disorders.

We gratefully acknowledge the comments, suggestions, and support contributed by James F. Leckman, MD; David L. Pauls, PhD; Kathleen R. Merikangas, PhD; and Brigittte A. Prusoff, PhD.

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