

Different Familial Transmission Patterns in Bipolar I Disorder With Onset Before and After Age 25

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Gene identification in common disorders such as Alzheimer disease and breast cancer has greatly profited from the use of age of onset as criterion to delineate subgroups of disease characterized by different inheritance patterns. In bipolar affective disorder, where the majority of linkage studies have produced conflicting results, studies reporting clinical characteristics and familial occurrence of disease have suggested that age of onset might serve as an indicator for identifying more homogeneous subgroups of disease. Our study was the first to examine this hypothesis by the means of segregation analysis. We investigated a sample of 177 bipolar I probands recruited from consecutive admissions and their first- and second-degree relatives (2,407 subjects). Probands were subdivided into an early-onset ($n = 107$) and a late-onset group ($n = 70$) using an age of onset of 25 as a cut-off point. This age was chosen because the observed age of onset distribution was bimodal with a cut-off of 25 years. Morbid risks for affective disorder were found significantly higher ($P = 0.01$) in relatives of probands with an early onset than in probands with late onset of disease. The segregation analysis showed that the disease is transmitted differently in early- and late-onset groups. In the early-onset group, a non-Mendelian major gene with a polygenic component was favored while the data in the late-onset group were compatible with a multifactorial model.

This result may have important implications for future molecular studies aiming at the identification of disease-associated genes. © 2001 Wiley-Liss, Inc.

KEY WORDS: manic depression; bipolar affective disorder; segregation analysis; inheritance models; age of onset

INTRODUCTION

Bipolar affective disorder (BP), also known as manic depressive illness, is characterized by severe aberrant mood swings in alternating periods of mania and depression. The disorder is common with a lifetime prevalence of about 1% in all human populations and results in high costs in terms of morbidity as well as mortality. Although the etiology and pathophysiology is widely unknown, family, twin, and adoption studies argue for a strong genetic determination of the disease [Nurnberger and Gershon, 1992]. Recent linkage studies have suggested chromosomal localization of several susceptibility genes, but none of the linkage findings has been consistently replicated [Leboyer et al., 1998b; Berrettini, 2000].

The high rate of nonreplication in linkage studies of BP, in spite of standardized interviews and diagnostic criteria for defining the phenotype, has stimulated interest in identifying clinical variables that define more homogeneous subgroups of disease. Based on studies reporting clinical characteristics and familial occurrence of disease, it has been suggested that age of onset might serve as such a variable [Leboyer et al., 1998a; Bellivier et al., 1999].

Although several segregation analyses have been undertaken in BP [Gershon et al., 1976; Goldin et al., 1983; Tsuang et al., 1985; Rice et al., 1987; Sham et al., 1991; Pauls et al., 1995; Spence et al., 1995], to our knowledge, no analysis so far was concerned with comparing transmission patterns in early- versus late-onset BP. Todd et al. [1993] have previously performed a segregation analysis in families of BP probands with

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childhood and adolescent onset, but they had no late-onset group for comparison.

The objective of our work was to examine whether transmission patterns are different in families of probands with an early age of onset versus late age of onset. The POINTER method was applied to a data set comprising 177 BPI probands and their first- and second-degree relatives ($n = 2,407$).

MATERIALS AND METHODS

Recruitment

The proband sample consisted of 177 BPI patients (93 females [52.6%] and 84 males [47.4%]) recruited from consecutive admissions in the Obregia Hospital, a state and university psychiatric hospital in Bucharest with a large catchment area. The mean age of onset was 24.1 ± 8.7 years (median = 22), mean age at investigation was 37.3 ± 12.9 years (median = 40).

The criteria for inclusion of patients in our study were history of at least two hospitalized illness episodes (one manic and one depressive episode, or two manic episodes) to confirm the diagnosis of BPI, acceptance that family members could be contacted, and giving informed consent to participate in the study. Hospital records were used for all probands to verify the presence of the symptoms reported by the patient and his or her relatives retrospectively for previous episodes. Presence of familial psychopathology was not a recruitment condition for the probands. BPI probands with known bilineal affective psychopathology in their families were not included.

There were no reported drug abusers in the sample because drugs were not available in Romania as of 1994. There were also no drug abusers among probands recruited thereafter. The sex composition of the total family sample including the probands, their first- and second-degree relatives, and the probands' spouses was as follows: 1,357 males (50.4%) and 1,338 females (49.6%). Leaving the spouses apart, there were 1,215 males (50.5%) and 1,192 (49.5%) females among first- and second-degree relatives of the probands.

Diagnostic Assessment of Probands

All BPI probands were administered the Diagnostic Interview for Genetic Studies (DIGS) [National Institute of Mental Health, Molecular Genetics Initiative, 1995] and the Family Interview for Genetic Studies (FIGS) [National Institute of Mental Health, Molecular Genetics Initiative, 1992] at the end of their hospitalization. The DSM-IV diagnostic criteria [American Psychiatric Association, 1994] underlay the diagnostic instruments. Each instrument was administered by a different member of the research team. The information provided by the patient with respect to his or her illness episodes was compared with medical records and the information provided by close relatives both with respect to illness episodes and symptom-free intervals. The final diagnostic procedure was consensual and involved the interviewers, a blind rater, and the treating psychiatrist. When divergent diagnostic

opinions were expressed, the opinion of the blind rater was given priority.

Diagnostic Assessment of Relatives

A total of 80.9% (702/867) of the first-degree relatives, 24.7% (380/1540) of the second-degree relatives, and 73.6% (81/110) of the spouses were directly interviewed; a few individuals were interviewed by phone. The percent of directly interviewed first-degree relatives by onset group reached 89.7% (407/454) in the early-onset group and 71.4% (295/413) in the late-onset group. The percent of second-degree relatives directly interviewed was 31.2% (303/971) in the early-onset group and 13.5% (77/569) in the late-onset group. Directly interviewed spouses were 79.2% (38/48) in the early-onset group and 69.4% (43/62) in the late-onset group.

The interviewers of the relatives were kept blind to the diagnosis of the probands. The DIGS was used to interview all relatives available for direct investigation. Additionally, the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II) [First et al., 1994] was administered to all interviewed relatives in whom the DIGS did not evidence any disorder.

The psychopathological information about the first- and second-degree relatives who were not available for direct investigation was collected by the family history method using the FIGS administered to the probands and to one or two relatives. The mean number of FIGS informants was 2.3 in the early-onset group and 2.1 in the late-onset group.

The medical records of the relatives who were hospitalized in the Obregia Hospital or treated as outpatients in the psychiatric services of the outpatient clinics of Bucharest could also be studied. Additionally, the information provided by the proband about his or her relatives and the information provided by the spouse of the patient about the patient's family was considered.

The final diagnosis of the relatives was consensual, involving two blind raters and the direct interviewers, and it was based on all available information about every relative. Contradictory information was resolved by the acceptance of those statements that confirmed a certain diagnosis in order to compensate for the shortcomings of the family history method used for the relatives who were not available for interview.

Relevant diagnoses in relatives included BP; schizoaffective disorder, bipolar type (SA-BP); schizoaffective disorder, manic type (SA-M); unipolar major depression; cyclothymia; hypomania; and dysthymia. For BP disorder in relatives, we did not distinguish between BPI and BPII since it was difficult to differentiate between the two diagnoses in family members investigated through family history method and for whom no medical records were available. Moreover, the FIGS interview has no symptom checklist for hypomania.

Definition of Early Age of Onset

Age of onset was defined as the age at which the probands first experienced symptoms qualifying for a manic or a major depressive episode according to

DSM-IV criteria. The information was derived from interviews and medical records. Since there are no validated age of onset thresholds for the clinical and genetic study of BPI, we inspected the distribution of the age of onset of BPI in probands (Fig. 1) before choosing the cut-off point between early and late onset. The distribution had two distinct central values (two modes), one at age 18 and one at age 28, determining a curve with two humps separated by the cut-off age 25. A curve fit analysis (Fig. 2) showed that the segment of the observed distribution (filled square line) below age 25 deviated from the normal distribution (straight line; Kolmogorov-Smirnov test = 0.10; $P = 0.01$), while the segment above age 25 closely clustered around the normal distribution line.

We compared the histogram of the age of onset in our BPI probands with published histograms of the age of onset in other BPI proband samples recruited from consecutive hospital admissions without previous consideration of familial psychopathology. The age of onset curve derived by Loranger and Levine [1978] from a sample of 200 BP patients showed a clear cut-off point at age 25. The examination of the histogram of the age of onset in 211 BPI probands used by Bellivier et al. [2001] for an admixture analysis suggested that the first of the three revealed onset classes should have the upper limit at age 25 (41.4% of all onsets in the respective sample). Recently, Schürhoff et al. [2000] presented a bimodal distribution of the age of onset in a sample of 210 BPI patients. Although for their own studies, early onset was defined as occurring by age 18, their distribution curve indicated a later age (29–30 years) as a cut-off point. Histograms of the age of onset in BPI probands recruited for linkage studies under the condition of having affected relatives also showed bimodal distributions with a cut-off point at age around 25–26 years [McMahon et al., 1994; Leboyer et al., 1998a]. In conclusion, we chose the age of 25 as the atural cut-off point for distinguishing early- and

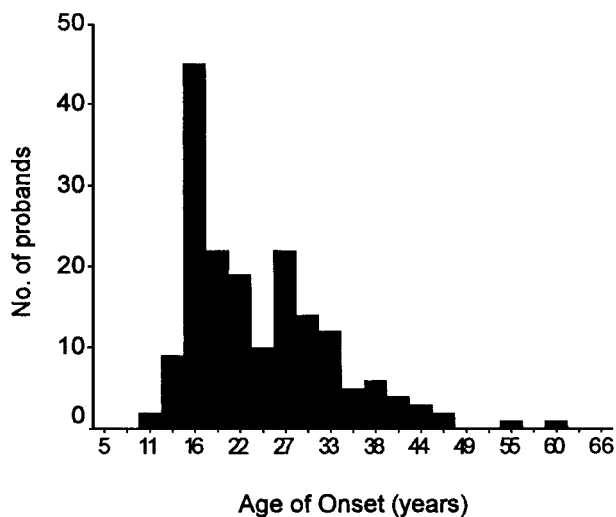


Fig. 1. Histogram of the age of onset of BPI disorder in probands.

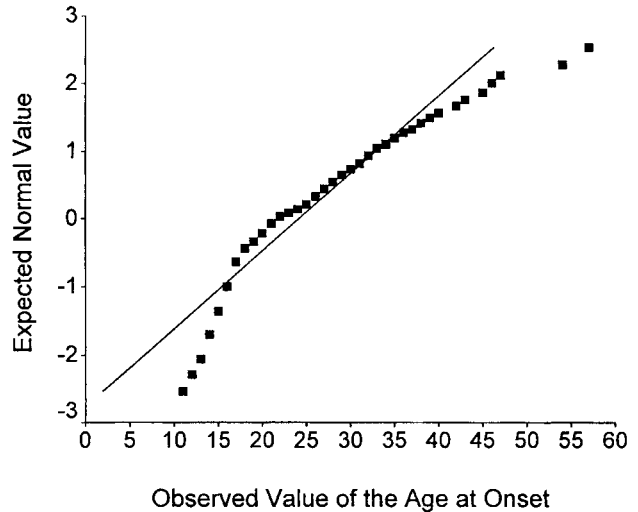


Fig. 2. Curve fit analysis of the observed age of onset of BPI disorder in probands. Filled square line = observed age of onset; straight line = normal distribution.

late-onset BPI based on the analysis of our own and published age of onset distributions.

In the early-onset group, there were 49 male BPI probands (45.8%) and 58 female BPI probands (54.2%). They had 454 first-degree relatives (221 males [48.7%] and 233 females [51.3%]) and 1,425 first- plus second-degree relatives (725 males [50.2%] and 700 females [49.8%]). In the late-onset group, there were 35 male BPI probands (50%) and 35 female BPI probands (50%). They had 413 first-degree relatives (206 males [49.9%] and 207 females [50.1%]) and 982 first- plus second-degree relatives (490 males [49.9%] and 492 females [50.1%]). Sex distribution of BPI probands was not significantly different in the two onset groups (chi-square = 0.30, $df = 1$, $P = 0.58$).

Definition of Affected Phenotype in Relatives for Segregation Analysis

The affected phenotype in relatives was restrictively defined. Only BP and SA-BP/SA-M were included in the affected phenotype. The fact that we did not distinguish between BPI and BPII should not introduce a major bias since it was shown by several studies [Coryell et al., 1985; Endicott et al., 1985; McMahon et al., 1994; Benazzi, 1999] that there is no significant difference in age of onset between the two forms of BP.

Broadening the spectrum of the affected phenotype to include unipolar major depression that has a significantly later onset than BP [Endicott et al., 1985; McMahon et al., 1994] or other affective disorders would have introduced age-of-onset heterogeneity in the relatives' phenotype compared to the probands' phenotype.

Statistical methods

Computation of lifetime morbid risks. Kaplan-Meier estimates of the morbid risk for BP disorder (BPI,

BPII), BP disorder plus schizoaffective disorder (BPI, BPII, SA-BP, SA-M), and any affective disorder (BPI, BPII, SA-BP, SA-M, unipolar major depression, cyclothymia, hypomania, dysthymia) in relatives of the early- and late-onset probands were computed with SPSS software (version 9.0). The Wilcoxon-Gehan (WG) test was used for between-group comparisons of the morbid risks.

Segregation analysis. Segregation analysis was conducted under the unified model [Lalouel et al., 1983], which incorporates the three transmission probabilities defined by Elston and Stewart [1971] into the mixed model [Morton and MacLean, 1974]. The model allows for both major locus and additive polygenic components to transmission of the trait. In this model, an autosomal diallelic locus with alleles A and a is assumed to be in Hardy-Weinberg equilibrium. The parameters of the model include q , the frequency of the susceptibility allele A; t , the distance in standard deviation units on the liability scale between the two homozygous means; d , the relative displacement of the heterozygous mean; h , the proportion of the total phenotypic variance attributable to the polygenic component; τ_{AAA} , the probability that an individual with AA genotype transmits the A-allele; τ_{AaA} , the probability that an individual with Aa genotype transmits the A-allele; τ_{aaa} , the probability that an individual with aa genotype transmits the A-allele.

Analyses were performed incorporating age-specific liability classes. Four liability classes were considered: liability classes 1, 2, and 3 correspond to individuals aged between 13 and 19, between 20 and 29, and between 30 and 39, respectively. Individuals of age 40 and over were assigned to liability class 4. Individuals under the age of 12 with a negligible morbid risk were removed from the sample since none was affected. Since the affected phenotype in proband relatives was narrowly defined, females and males were assumed to have the same morbid risk. Values for each liability class were derived from population prevalences [Predescu et al., 1987] so that the lifetime prevalence was equal to 0.4%. For each proband, the probability of ascertainment was set to 0.001, approximating single selection.

The bipolar pedigrees were analyzed using the POINTER strategy as developed by Lalouel and Morton [1981]. These pedigrees were thus broken into 355 nuclear families in the early-onset group and 260 nuclear families in the late-onset group, introducing pointers. Each pedigree was partitioned into three components: nuclear families with the proband as a child (PCF) (incomplete selection); nuclear families with the proband as a parent (PPF) (complete selection); nuclear families including the proband's father or the proband's mother as a child (PFF, including the pointer). Parameters of the model were estimated by maximizing the likelihood of the offspring's phenotypes conditional either on the parents' phenotypes for PCF and PPF families or on the parents' and pointer's phenotypes for PFF families. Subhypotheses of the full model were tested using the likelihood ratio criterion. Evidence for a major gene effect under the mixed model

was obtained via a likelihood ratio test comparing the mixed model to the multifactorial model. Segregation of a major gene was then asserted by testing the null hypothesis of Mendelian transmission of this major gene against the general transmission probability model.

Homogeneity tests were based on an a priori subdivision of the sample. The pedigrees were separated into those showing an age of onset lower or equal to 25 in the BPI proband ($n = 107$) and those showing an age of onset greater than 25 in the BPI proband ($n = 70$). Homogeneity tests between early- and late-onset subsets were done by calculating the difference between the maximum likelihood of the overall data set (early onset + late onset) and the summed maximum likelihoods over the two subsets; twice this difference can be compared to a chi-square with degrees of freedom equal to the number of estimated parameters in the subsets. All computations were done with the computer program POINTER [Lalouel and Yee, 1980].

RESULTS

Morbid Risks for Affective Disorders in Relatives of Early- and Late-Onset BPI Probands

First-degree relatives of early-onset probands were significantly more often affected with BP ($P = 0.01$), with BP plus SA-BP/SA-M ($P = 0.01$), and with any affective disorder ($P = 0.01$) compared to first-degree relatives of late-onset probands (Table I). This effect was mainly due to a smaller number of affected male relatives with BP disorder ($P = 0.003$), with BP plus SA-BP/SA-M ($P < 0.001$), and with any affective disorder ($P = 0.003$) among first-degree relatives of late-onset probands compared to first-degree relatives of early-onset probands (Table I). Within the early-onset group, male and female first-degree relatives were equally affected with BP and BP plus SA-BP/SA-M; for any affective disorder, there was a nonsignificant trend ($P = 0.10$) to more frequently affected females. Within the late-onset group, female first-degree relatives were significantly more frequently affected than male first-degree relatives with BP ($P = 0.01$), BP plus SA-BP/SA-M ($P = 0.01$), and any affective disorder ($P = 0.01$; Table I).

Table II shows the morbid risks for BP disorder, for BP plus SA-BP/SA-M and for any affective disorder in first-degree relatives of early- and late-onset probands by relative type. Fathers of early-onset probands were significantly more frequently affected than fathers of late-onset probands with BP ($P = 0.004$), BP plus SA-BP/SA-M ($P < 0.002$), and any affective disorder ($P = 0.006$). The affection rate of mothers did not differ significantly between early- and late-onset probands. The early-onset probands had significantly more offspring with BP ($P < 0.05$) and both more offspring ($P < 0.05$) and more siblings ($P < 0.03$) with BP plus SA-BP/SA-M than late-onset probands.

Within the early-onset group, probands' daughters were significantly more frequently affected than

TABLE I. Morbid Risk for Affective Disorders in First-Degree Relatives by Early- vs. Late-Onset in BPI Probands

	BP disorder, relatives of		BP + SA-BP/SA-M, relatives of		Any affective disorder, relatives of	
	Early-onset probands	Late-onset probands	Early-onset probands	Late-onset probands	Early-onset probands	Late-onset probands
Males	10.2% ^a (16/221)	2.0% ^{a,b} (3/206)	12.6% ^d (20/221)	2.7% ^{d,e} (4/206)	20.0% ^g (32/221)	8.9% ^{g,h} (13/206)
Females	8.6% (15/233)	9.3% ^b (12/207)	10.7% (19/233)	11.8% ^e (16/207)	25.0% (45/233)	18.1% ^h (46/207)
Total	9.4% ^c (31/454)	5.5% ^c (15/413)	11.7% ⁱ (39/454)	7.1% ^f (20/413)	22.5% ⁱ (77/454)	18.7% ⁱ (59/413)

^aWG = 8.6, *P* = 0.003.
^bWG = 5.2, *P* = 0.01.
^cWG = 5.8, *P* = 0.01.
^dWG = 10.7, *P* < 0.001.
^eWG = 5.3, *P* < 0.01.
^fWG = 6.3, *P* < 0.01.
^gWG = 8.4, *P* = 0.003.
^hWG = 5.8, *P* = 0.01.
ⁱWG = 5.9, *P* < 0.01.

probands' sons with any affective disorder (*P* = 0.0005); a nonsignificant trend to more affected daughters than sons was also observed for BP (*P* = 0.06) and BP plus SA-BP/SA-M (*P* = 0.06) in this group. No other sex difference was evident in first-degree relatives of early-onset probands.

Within the late-onset group, mothers of probands were significantly more frequently affected than fathers with BP (*P* = 0.05), BP plus SA-BP/SA-M (*P* = 0.01), and any affective disorder (*P* = 0.01). Probands' sisters were significantly more frequently

affected than brothers (*P* < 0.05) and daughters were more frequently affected than sons (*P* < 0.0003) with any affective disorder. The morbid risks in first- plus second-degree relatives paralleled the results reported for first-degree relatives (data not shown).

Segregation Analysis

Table III shows parameter estimates and $-2(\ln)L$ values generated by the segregation analysis and Table IV displays the significance of the tested models.

TABLE II. Morbid Risk for Affective Disorder by Relative Type in First-Degree Relatives of Early- vs. Late-Onset BPI Probands

	BP disorder, relatives of		BP + SA-BP/SA-M, relatives of		Any affective disorder, relatives of	
	Early-onset probands	Late-onset probands	Early-onset probands	Late-onset probands	Early-onset probands	Late-onset probands
Mothers	4.9% (5/107)	11.3% ^b (7/70)	4.9% (5/107)	14.2% ^d (9/70)	19.0% (19/107)	26.1% ^h (18/70)
Fathers	11.2% ^a (11/107)	0% ^{a,b} (0/70)	12.9% ^e (13/107)	0% ^{d,e} (0/70)	21% ⁱ (22/107)	5.7% ^{h,i} (4/70)
Sisters	7.9% (7/90)	4.9% (4/84)	17.9% (11/90)	7.7% (6/84)	17.8% (16/90)	16.7% ^j (14/84)
Brothers	6.9% (5/77)	4.0% (3/84)	11.5% (6/77)	5.5% (4/84)	11.7% (9/77)	9.5% ^j (8/84)
Siblings	7.2% (12/167)	4.2% (7/168)	15.0% ^f (17/167)	6.6% ^f (10/168)	15.0% (25/167)	13.1% (22/168)
Offspring	12.7% ^c (4/72)	1.1% ^c (1/105)	12.7% ^g (4/72)	1.1% ^g (1/105)	25.8% (11/72)	19.7% (15/105)
Sons	10.5% (1/37)	0% (0/52)	10.5% (1/37)	0% (0/52)	10.4% ^k (1/37)	2.2% ^l (1/52)
Daughters	16.7% (3/35)	2.4% (1/53)	16.7% (3/35)	2.4% (1/53)	41.6% ^k (10/35)	38.2% ^l (14/53)

^aWG = 7.9, *P* = 0.004.
^bWG = 3.8, *P* < 0.05.
^cWG = 3.8, *P* < 0.05.
^dWG = 5.9, *P* < 0.01.
^eWG = 9.3, *P* < 0.002.
^fWG = 4.6, *P* < 0.03.
^gWG = 3.8, *P* < 0.05.
^hWG = 5.8, *P* < 0.01.
ⁱWG = 7.3, *P* < 0.006.
^jWG = 3.7, *P* < 0.05.
^kWG = 12.0, *P* < 0.0005.
^lWG = 12.9, *P* < 0.0003.

TABLE III. Segregation Analysis in Families of BPI Probands by Age of Onset in Probands

Model	Parameters							$-2 \ln(L)$
	d	t	q	H	τ_1	τ_2	τ_3	
Early-onset sample (355 nuclear families)								
Sporadic	(0) ^a	(0)	(0)	(0)	(1)	(0.5)	(0)	-789.655
Multifactorial	(0)	(0)	(0)	0.956	(1)	(0.5)	(0)	-942.168
Major gene	0.74	5.62	0.024	(0)	(1)	(0.5)	(0)	-942.669
Recessive	(0)	3.39	0.11	(0)	(1)	(0.5)	(0)	-933.614
Additive	(0.5)	5.39	0.02	(0)	(1)	(0.5)	(0)	-942.666
Dominant	(1)	2.15	0.01	(0)	(1)	(0.5)	(0)	-939.993
Mixed	0	2.46	0.42	0.077	(1)	(0.5)	(0)	-955.281
General	0	8.20	0.06	(0)	0.90	0.39	0	-950.066
No parent-offspring transmission (τ_2)	0	1.59	0.04	0.84	(1)	0	(0)	-946.801
No parent-offspring transmission (τ_1)	0.99	4.50	0.0001	0.92	1	1 = (τ_1)	1 = (τ_1)	-942.666
Unified	0.99	4.09	0.031	0.0024	1	0.39	1	-1000.892
Late-onset sample (260 nuclear families)								
Sporadic	(0)	(0)	(0)	(0)	(1)	(0.5)	(0)	-510.673
Multifactorial	(0)	(0)	(0)	0.977	(1)	(0.5)	(0)	-598.378
Major gene	0.83	2.55	0.006	(0)	(1)	(0.5)	(0)	-596.512
Recessive	(0)	3.53	0.149	(0)	(1)	(0.5)	(0)	-589.347
Additive	(0.5)	4.24	0.006	(0)	(1)	(0.5)	(0)	-596.469
Dominant	(1)	2.13	0.006	(0)	(1)	(0.5)	(0)	-596.510
Mixed	0	1.90	0.73	0.096	(1)	(0.5)	(0)	-600.759
Unified	0.47	3.44	0.22	0.002	0.46	0.81	0	-624.311
Total sample (615 nuclear families)								
Sporadic	(0)	(0)	(0)	(0)	(1)	(0.5)	(0)	-1300.328
Multifactorial	(0)	(0)	(0)	0.964	(1)	(0.5)	(0)	-1540.303
Major gene	0.34	5.9	0.01	(0)	(1)	(0.5)	(0)	-1536.618
Recessive	(0)	3.2	0.13	(0)	(1)	(0.5)	(0)	-1521.022
Additive	(0.5)	4.1	0.009	(0)	(1)	(0.5)	(0)	-1536.014
Dominant	(1)	2.1	0.008	(0)	(1)	(0.5)	(0)	-1535.475
Mixed	0.80	2.4	0.44	0.07	(1)	(0.5)	(0)	-1553.850
No parent-offspring transmission (τ_2)	0	1.6	0.75	0.38	(1)	0.91	(0)	-1569.553
No parent-offspring transmission (τ_1)	0.84	5.3	0.0001	0.88	1	1	1	-1540.636
Unified	0.03	3.3	0.32	0.002	0	1	0	-1631.618

^aParentheses indicate that the parameter was fixed at the shown value.

Families of early-onset BPI probands. In the 107 families of the early-onset probands (split into 355 nuclear families), there was a high familial correlation in the transmission of BP ($P < 0.00001$ for the sporadic versus the multifactorial model). The absence of the polygenic component was strongly rejected ($P < 0.001$ for Mendelian monogenic gene/mixed model). The absence of major gene effects was equally rejected ($P < 0.01$ for multifactorial/mixed model). The Mendelian transmission probabilities of major gene effects were rejected ($P < 0.0001$ for mixed/unified model). The “no parent-offspring” transmission model was rejected ($P < 0.00001$ for no parent-offspring transmission τ_1 with iterated H versus the unified model; $P < 0.0001$ for no parent-offspring transmission τ_2 with iterated H versus unified model). The best model for the families of early-onset probands was the unified model that includes non-Mendelian major gene effects and a polygenic component.

Families of late-onset BPI probands. The 70 families of the late-onset probands were split into 260 nuclear families. In these families, the absence of the familial transmission was strongly rejected

($P < 0.00001$ for sporadic/multifactorial model). The absence of polygenic component was marginally rejected ($P < 0.05$ for Mendelian monogenic/mixed model). The absence of major gene effects was not rejected (nonsignificant chi-square for multifactorial/mixed model) and Mendelian major gene effects were also rejected ($P < 0.0001$ for mixed/unified model). The best model fitting the data was the multifactorial model.

Total sample. All 177 families were split into 615 nuclear families. The familiarity of BP was high ($P < 0.00001$ for sporadic/multifactorial model). The absence of the polygenic component was rejected ($P < 0.0001$ for Mendelian monogenic/mixed model). The absence of major gene effects was rejected ($P < 0.01$ for multifactorial/mixed model). Mendelian transmission probabilities of major gene effects were rejected ($P < 0.0001$ for mixed/unified model). The absence of parent-offspring transmission was also rejected ($P < 0.00001$ for no parent-offspring transmission τ_1 with iterated H/unified model; $P < 0.00001$ for no parent-offspring transmission τ_2 with iterated H/unified model). The best model in the total group was the

TABLE IV. Significance of Models Tested in Segregation Analysis

Model	Chi-square	df	P
Early-onset sample			
Sporadic vs. multifactorial	152.513	1	< 0.00001
Mendelian monogenic vs. mixed	12.612	1	< 0.001
Multifactorial vs. mixed	13.113	3	< 0.01
Mixed vs. unified	45.611	3	< 0.0001
No parent-offspring τ_1 vs. unified	58.226	2	< 0.00001
No parent-offspring τ_2 vs. unified	54.091	2	< 0.0001
Late-onset sample			
Sporadic vs. multifactorial	87.705	1	< 0.00001
Mendelian monogenic vs. mixed	4.247	1	< 0.05
Multifactorial vs. mixed	2.381	3	NS
Mixed vs. unified	23.552	3	< 0.0001
Total sample			
Sporadic vs. multifactorial	239.975	1	< 0.00001
Mendelian monogenic vs. mixed	17.232	1	< 0.0001
Multifactorial vs. mixed	13.547	3	< 0.01
Mixed vs. unified	77.786	3	< 0.0001
No parent-offspring τ_1 vs. unified	90.982	2	< 0.00001
No parent-offspring τ_2 vs. unified	66.066	2	< 0.00001

unified model (non-Mendelian major gene effects with a polygenic component).

Heterogeneity Tests

Heterogeneity tests were not significant for all but two models of parent-offspring transmission (τ_1 and τ_2).

DISCUSSION

The major finding of our study was that age of onset in probands with BPI had a significant impact on the transmission of the disease in families. While the early-onset form of BPI was associated with a non-Mendelian major gene transmission with polygenic background, the late-onset form of the disorder was characterized by a multifactorial transmission model. Although several segregation studies have been previously performed in bipolar disorder [Gershon et al., 1976; Goldin et al., 1983; Tsuang et al., 1985; Rice et al., 1987; Sham et al., 1991; Pauls et al., 1995; Spence et al., 1995], none of them has compared transmission patterns in early- versus late-onset probands. The study by Todd et al. [1993] has previously investigated segregation models in 22 families of BPI and BPII probands with childhood and adolescent onset; in accordance with our results in families of early-onset probands, their data were compatible with a non-Mendelian major gene transmission.

The results from our study may have implications for molecular genetic attempts aiming at the identification of disease-associated genes at the molecular level. Specifically, our results suggest that concentrating on families from early-onset BPI probands might increase the chance to detect genes of major effect.

The increased morbid risk for affective disorder in relatives of early-onset in comparison to late-onset probands is similar to findings from previous studies [Gershon et al., 1976; Taylor and Abrams, 1981; Rice et al., 1987] and supports the notion that differences

exist between early- and late-onset groups. The sex ratio of affected relatives reported for childhood and adolescent onset BP (with more male than female BP relatives) [Todd et al., 1993; Carlson et al., 2000] was not replicated in our study within the early-onset group, where the sex ratios were nearly equal for BP and SA-BP/SA-M disorders. Since in our sample the female:male ratio approached 1:1 both in probands and their relatives, the results can not be due to gender selection bias. Our results are in accordance with the results of Strober et al. [1988], who found no significant sex differences for BP disorder in first-degree relatives of BPI probands with onset in childhood and adolescence.

In a previous study [Grigoriu-Serbanescu et al., 1998], we found that the non-Mendelian major gene model with polygenic component was mainly associated with a paternal transmission of BPI disorder. In the present study, the same genetic model appeared to be associated with the early-onset form of BPI disorder. Probably, paternal transmission has a more penetrant genetic effect than maternal transmission, resulting in an earlier age of onset in the proband and increasing the risk for BP or SA-BP/SA-M in first-degree relatives, especially in offspring. An independent support for our findings was provided by the study by Kornberg et al. [2000], who found a higher morbid risk for BPI illness in offspring of BPI probands with paternal inheritance than in offspring of BPI probands with maternal inheritance of the disease. Similarly, previous studies observed a younger age of onset in BP probands who had an affected father with BP or unipolar major depression than in BP probands who had an affected mother [Grigoriu-Serbanescu et al., 1995, 1997; Kato et al., 1996]. A biological explanation of these phenotype-derived findings could eventually be suggested by recent studies on linkage to chromosome 18. On this chromosome, vulnerability loci for BP disorder were detected mainly in families with paternal transmission [Stine et al., 1995; Gershon et al., 1996; McMahon et al.,

1996; Nöthen et al., 1999; Turecki et al., 1999]. The characterization of the responsible gene(s) may provide a biological basis for the observed findings.

Unfortunately, there is no universally accepted cut-off between early- and late-onset disease [Gershon et al., 1976; Carlson et al., 2000; Schürhoff et al., 2000; Bellivier et al., 2001]. In our study, we have not tried to test different cut-off points to distinguish between early- and late-onset BP probands. Our cut-off was based on the observed age of onset distribution in our sample and we therefore felt it most reasonable to use the age 25 as a natural cut-off. We are aware of the possibility, however, that the choice of another cut-off may have led to different conclusions. Moreover, the fact that the observed age of onset distribution in the early-onset probands deviated from the normal regression line might hide a mixture of distributions. The application of more sophisticated statistical methods [Celeux and Diebolt, 1990] may help to clarify this point.

A further limitation of our study could reside in the fact that the BPI probands were all hospitalized for at least two illness episodes and this indicates a certain illness severity. This requirement was motivated by the findings of Rice et al. [1987], who showed that diagnostic (phenotypic) stability was enhanced by increasing number of illness episodes and by hospitalization. However, we are aware that our inclusion criterion might have selected against less severe cases characterized for example by good lithium response. Therefore, it may be a matter of future studies to investigate whether similar results can be obtained in families of less strictly defined BPI patients.

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