

# Patterns of Parental Transmission and Familial Aggregation Models in Bipolar Affective Disorder

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Two recent studies [McMahon et al., 1995: *Am J Hum Genet* 56:1277–1286; Gershon et al., 1996: *Am J Med Genet (Neuropsychiatr Genet)* 67:202–207] reported an excess of maternal transmission in bipolar affective disorder in multiply affected families. In a sample of 130 families ascertained through a bipolar proband without regard to psychiatric family history we analysed the frequency of maternal (MAT) and paternal (PAT) transmissions, the morbid risk (MR) in relatives of transmitting mothers and fathers and the inheritance patterns in families with MAT vs. PAT transmission of the disease. In the total sample of 130 families we identified 39 families where the disease was transmitted from the paternal side (PAT families) and 35 families where the disease was transmitted from the maternal side (MAT families). Counting PAT and MAT transmissions in these unilineal families we found nearly equal numbers for both transmission types under a narrow (BP: bipolar disorder, schizoaffective-bipolar type disorder) and a broad definition (AFF: BP, recurrent unipolar depression) of the phenotype. The MRs for narrow and broad phenotypes were not significantly different in any type of PAT relative in PAT families vs. MAT relatives in MAT families. However, in PAT families there were two times more affected females than males with both disease models, while in MAT families there was no MR difference by relatives' sex. The transmission of BP was compatible with the Mendelian major gene model in PAT families and with the multifactorial model in MAT fami-

lies. Extension of the relatives' phenotype led to borderline non-Mendelian major effects in PAT families and reproduced the multifactorial model in MAT families. *Am. J. Med. Genet. (Neuropsychiatr. Genet.)* 81: 397–404, 1998. © 1998 Wiley-Liss, Inc.

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## INTRODUCTION

Recent research reported an excess of maternal transmission of bipolar affective disorder in families with a high loading of the disease. Investigating a sample of 31 multiply affected unilineal families ascertained through bipolar probands having at least two affected sibs, or one affected parent and one affected sib, McMahon et al. [1995] reported a significantly higher than expected frequency of affected mothers, a 2.3- to 2.8-fold increased risk for bipolar illness and other major affective disorders in maternal relatives and a significantly higher risk for bipolar illness in offspring of affected mothers than in offspring of affected fathers. Moreover, in seven pedigrees no instances of apparent paternal transmission were discovered.

Gershon et al. [1996] also found an excess of maternal transmission in their series of unilineal bipolar pedigrees selected under the condition of the existence of at least six affected persons in the family [Berrettini et al., 1991]. The effect was observed in pairs transmitting a more restricted phenotype including only bipolar disorder and schizoaffective disorder-manic type as well as in pairs transmitting a more broad phenotype which included, besides the restricted phenotype, recurrent unipolar depression.

Results from epidemiologic studies, however, do not lend strong support to the observation of a significant excess of maternal transmission in bipolar illness. For example, Gershon et al. [1982] found that the morbid

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risk in relatives (parents and offspring) of male bipolar probands compared with relatives of female bipolar probands was about the same for bipolar I and II disorder, schizoaffective disorder, and unipolar depression. Rice et al. [1987] found in a sample of 187 randomly selected families with a bipolar proband 6.5% of the fathers and 6.4% of the mothers similarly affected. In the study by Arlen-Price et al. [1985] a nonsignificant trend towards an overrepresentation of affected mothers was observed; among relatives of bipolar I probands 2.24% (2/89) of the fathers and 6.59% (6/91) of the mothers were affected with BP illness.

Beside the studies of McMahon et al. [1995] and Gershon et al. [1996], the issue of a parental transmission difference in bipolar disorder has not been specifically addressed yet. In contrast to these previous studies we have investigated a sample of families that has not been preselected for the presence of multiple affected cases within a family. We have collected a sample of 130 families ascertained through a bipolar I proband from consecutive admissions in a state psychiatric hospital. The sample was ethnically homogeneous consisting of Romanian families. This sample was analysed with the following purposes: 1) counting the frequency of maternal and paternal transmission of bipolar illness and 2) searching for an eventual genetic heterogeneity in bipolar families by comparing morbid risks (MR) and segregation models in families with paternal vs. maternal transmission of the illness.

### METHOD Samples

The proband sample consisted of 130 hospitalized bipolar I patients (76 females and 54 males) contacted during one of their hospitalizations in the "Marinescu" Hospital, a large state psychiatric hospital (the only one in Bucharest) with a very large catchment area. All patients were informed of the study objectives and procedures. The only criteria for inclusion of patients in our sample were: giving informed consent to participate in the study, acceptance that family members be contacted and history including hospitalization for at least two manic and two depressive episodes (to confirm the diagnosis of bipolarity). Hospital records were used to verify the presence of the symptoms reported by the patient and his/her relatives retrospectively for previous episodes. Presence of familial psychopathology was not a recruitment condition for probands.

There were no reported drug abusers in the sample because drugs were not available in Romania as of 1994.

Sex composition of the total family sample was 50.3% males (1,024) and 49.7% females (1,018).

### Diagnosis of Bipolar Probands

All bipolar probands were administered the Diagnostic Interview for Genetic Studies (DIGS) [National Institute of Mental Health (NIMH)-Molecular Genetics Initiative, 1992], the Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II) [Spitzer et al., 1987] and the Family Interview for Genetic Studies

(FIGS) [NIMH-Molecular Genetics Initiative, 1991] at the end of their hospitalization. The diagnostic criteria underlying the diagnostic instruments are DSM-III-R [APA, 1987]. Each instrument was administered by a different member of the research team. The information provided by the patient with respect to his/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 it 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.

### Diagnosis of the Relatives of Bipolar Probands

The 519 (75.76%) of 685 first degree relatives and the 373 (29.3%) of 1,237 second degree relatives were directly interviewed, mainly by being visited at their homes (a few cases were interviewed by phone). 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. 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 two other relatives. The medical records of the relatives who were hospitalized in the "Marinescu" 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/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 was based on all the available information about every relative. Contradictory information was resolved by the acceptance of those statements, which 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.

### Counting Maternal and Paternal Transmissions in Families

When counting the transmissions of bipolar disorder and of any major affective disorder within unilineal families all affected relatives in three generations had to be considered; therefore any affected relative could play the interchangeable role of a parent or an offspring. Transmission was considered as bipolar to bipolar (BP-BP) if the transmitting parent or any of the parent's parents or sibs had bipolar disorder or schizoaffective disorder, bipolar type (narrow disease model, BP). Transmission was of the type "any major affective disorder to any major affective disorder" (AFF-AFF) if the transmitting parent or any of the parent's parents or sibs had bipolar disorder, schizoaffective-bipolar type disorder, or recurrent unipolar depression (broad disease model, AFF, "any major affective disorder to any major affective disorder").

tive disorder"). Schizoaffective disorder, unipolar, and manic type were not found in the sample.

We counted maternal (MAT) and paternal (PAT) transmissions of BP and any major affective disorder considering each transmitting parent only once regardless of the number of affected offspring.

### Selection and Definition of Paternal and Maternal Families

The total sample of 130 families, either unilineally affected or with sporadic cases, was examined for individuals with affective or schizoaffective disorder among the probands' relatives. Families were retained for the present analysis only if the proband's father or mother was himself/herself affected or had an affected sib or parent. Three families with affected individuals in both parental lines were excluded from the sample of 130 families discussed here. We identified 39 independent families with unilineal PAT transmission of BP and 35 independent families with unilineal MAT transmission. A PAT or MAT family was defined according to the parent who transmitted the disorder to the bipolar proband but in former generations of the pedigree MAT transmission was allowed within a PAT family and vice versa (see Fig. 1). The BP probands were sporadic cases in the remainder 56 independent families since no affective or schizoaffective disorder was reported by relatives on either parental side.

### Statistical Methods

**Computation of lifetime morbid risks.** We computed the lifetime MR for BP and for any major affective disorder in PAT relatives of the probands in PAT families and in MAT relatives of the probands in MAT families, respectively, using the SURVIVAL procedure of the SPSS software.

**Segregation analysis method.** We have examined the homogeneity/heterogeneity in the familial transmission of the disease according to the gender of the proband's transmitting parent, by performing segregation analysis of the unilineal bipolar families, under narrow (N = 51 pedigrees) and broad definition (N = 74 pedigrees) of the affected phenotype in relatives

of the bipolar probands. The definition of the affected phenotypes was as described above.

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 of 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; tAAA, the probability that an individual with AA genotype transmits the A allele; tAa the probability that an individual with Aa genotype transmits the A allele; taa 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 corresponded 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. For the narrow diagnostic scheme females and males were assumed to have the same morbid risk (N=51 pedigrees; 27 PAT and 24 MAT pedigrees). For the broad diagnostic scheme (N=74 pedigrees; 39 PAT and 35 MAT pedigrees), analyses were conducted assuming different morbid risks for males and females: four age-intervals, defined as above, were considered for each gender, leading to the specification of eight liability classes. Values for each liability class were derived for each diagnostic scheme from population prevalences [Botezat et al., 1994], so that the lifetime prevalence was equal to 0.8% under the narrow diagnostic scheme, and under the broad diagnostic scheme it was equal to 3% and 5% for males and females, respectively. For each proband, the probability of ascertainment, pi, was set to 0.001, approximating single selection.

The unilineal bipolar pedigrees were analysed using the POINTER strategy, as developed by Lalouel and Morton [1981]. These pedigrees were thus broken into 195 (broad diagnostic) or 133 (narrow diagnostic) nuclear families, introducing pointers. Each pedigree was partitioned into three components: nuclear families with the proband as a child (PCF) (incomplete selection, pi = 0.001); nuclear families with the proband as a parent (PPF) (complete selection); and nuclear families including the proband's father or the proband's mother as a child (PPF). Thus, when the affected individual was found in the proband's father's (or mother's) sibship, the ascertainment scheme approximates a truncate selection, with a corresponding probability of ascertainment equal to 1 (+ pointer who is the proband). Otherwise the affected relative is a parent of the proband's father (or mother) and the selection is complete (plus pointer who is the proband).

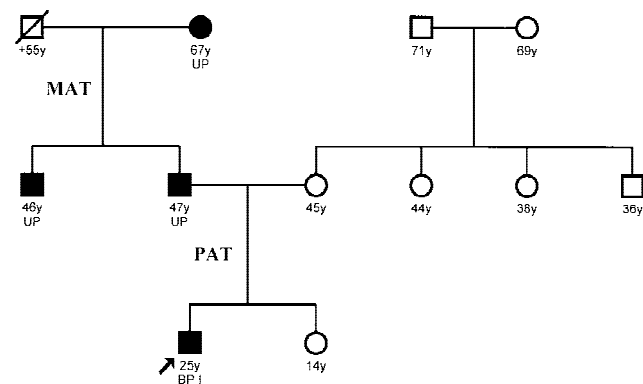


Fig. 1. Example of paternal (PAT) and maternal (MAT) transmission within a PAT family. BP I, bipolar I disorder; UP, recurrent unipolar depression.

TABLE I. Paternal and Maternal Transmissions in Paternal vs. Maternal Families

	BP-BP transmission			AFF-AFF transmission		
	Paternal families	Maternal families	Total	Paternal families	Maternal families	Total
Paternal transmissions	27	1	28	39	1	40
Maternal transmissions	5	24	29	5	37	42

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 is obtained via a likelihood ratio test comparing the mixed model to the multifactorial model. Segregation of a major gene is 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 a paternal transmission of illness (PAT pedigrees) and those showing a maternal transmission of illness (MAT pedigrees). Homogeneity tests between PAT and MAT subsets are done by calculating the difference between the maximum likelihood of the overall data (PAT+MAT) 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

### Paternal and Maternal Transmissions

Selecting families for unilineal inheritance resulted in a similar number of families with PAT and MAT transmission (39 PAT and 35 MAT). The number of affected mothers vs. affected fathers was 8 (6.2%) vs. 9 (6.2%) for BP and 19 (14.6%) vs. 17 (13.0%) for any major affective disorder, respectively.

Counting the presence of PAT and MAT transmissions in the sample of 74 unilineal families revealed 28 PAT and 29 MAT transmissions of the type BP-BP and 40 PAT and 42 MAT transmissions of the type AFF-AFF (Table I).

### Morbid Risk to Relatives

The MR for BP in first plus second degree paternal relatives of BP probands in PAT families was not different from the MR in first plus second degree maternal relatives in MAT families, although a slight tendency to more affected females was observed in PAT families and more affected males in MAT families (Table II). Since the computation of the MR in offspring depends on the parents' phenotype, probands' mothers in MAT families and probands' fathers in PAT families were excluded from computations. We also excluded proband's wife/husband, all maternal relatives in PAT

families and all paternal relatives in MAT families; proband's children were excluded because some of them were below the risk age, and young probands had no children; thus a potential bias source was removed.

The MR for any major affective disorder (Table III) computed in the same way as for BP did not differentiate the total group of paternal relatives in PAT families from the total group of maternal relatives in MAT families, but for paternal female relatives in PAT families the MR was two times higher than for male relatives ( $P = .02$  for the Lee-Desu statistic,  $DF = 1$ ), while in MAT families there was no difference by relative's sex.

We also compared the MRs in PAT and MAT families taking the probands' parents as probands (Table IV). This time the MRs for BP and for any affective disorder were computed only in first degree relatives of probands' parents since psychopathological information about their second degree relatives was not available.

The MR for BP and for any affective disorder in relatives of probands' fathers in PAT families was not different from the MR for BP and for any affective disorder in relatives of probands' mothers in MAT families. In PAT families, however, there was a two times higher MR in females than in males both for BP ( $P = .003$ ) and for any affective disorder ( $P = .0004$ ), while in MAT families male and female relatives were equally affected both with BP and any major affective disorder.

Because the first degree relatives of the bipolar probands' parents have passed through a longer period of risk than first degree relatives of bipolar probands, we also computed the MR for BP and for any major affective disorder in offspring of affected fathers and mothers. The risk was not significantly different in offspring of affected fathers vs. offspring of affected mothers neither for BP (48.4% vs. 37.2%;  $P = .87$ ), nor for any major affective disorder (54.0% vs. 43.3%) ( $P = .93$ ).

A next step was to look at the structure of the MR for BP in first degree relatives of all transmitting fathers and mothers. As shown in Table V, there is only one

TABLE II. Morbid Risk for BP Disorder in Paternal/Maternal First and Second Degree Relatives of BP Probands in Paternal vs. Maternal Families

	Paternal families	Maternal families
All first and second degree relatives	11.5% (21/212)	9.98% (18/212)
Male relatives	9.8% <sup>a</sup> (9/111)	11.72% <sup>a</sup> (11/103)
Female relatives	13.4% <sup>a</sup> (12/101)	8.16% <sup>a</sup> (7/109)

<sup>a</sup>No significant difference between male and female relatives either within paternal or maternal families.

TABLE III. Morbid Risk for any Major Affective Disorder in Paternal vs. Maternal First and Second Degree Relatives of BP Proband in Paternal vs. Maternal Families

	Paternal families	Maternal families
All first and second degree relatives	20.4% (39/212)	19.14% (37/212)
Male relatives	13.8% <sup>a,b</sup> (13/111)	18.71% <sup>b</sup> (18/103)
Female relatives	26.7% <sup>a,b</sup> (26/101)	19.74% <sup>b</sup> (19/109)

<sup>a</sup>Difference between male and female relatives within paternal families significant at  $P = .02$ .

<sup>b</sup>No significant difference between the same sex relatives in paternal vs. maternal families.

significant difference between transmitting fathers and mothers, i.e., transmitting fathers have more affected daughters than transmitting mothers ( $P = .04$ ). Moreover, the MR for BP is significantly higher in daughters than in sons and in mothers than in fathers of transmitting fathers. Transmitting mothers show only a trend to more affected brothers than sisters ( $P = .08$ ).

### Segregation Analysis

**Narrow definition of affected phenotype in relatives.** a) Results of the segregation analysis under the narrow definition are shown in Table VI. When the affected phenotype of probands' relatives is narrowly defined, there is a high familial correlation in the transmission of BP in PAT families ( $\chi^2$  for sporadic/multifactorial model = 13.26, DF = 1,  $P < .0001$ ). The heritability H was .44. Absence of parent-offspring transmission of the disease was rejected ( $\chi^2$  for parent-offspring transmission/general monogenic model was 6.35, df = 2,  $P < .05$ ). Absence of major gene effects was rejected ( $\chi^2$  for multifactorial/mixed model = 9.08, DF = 3,  $P < .03$ ) and absence of polygenic component was not rejected ( $\chi^2$  for major gene/mixed model = .006, DF

TABLE IV. Morbid Risks in First Degree Relatives of Transmitting Fathers and Mothers

	Transmitting father	Transmitting mother
A. Risk for BP disorder in first degree relatives		
All first degree relatives	23.90% (63/307)	24.33% (53/247)
Males	16.46% <sup>a,b</sup> (20/150)	25.56% <sup>b</sup> (28/120)
Females	30.48% <sup>a,b</sup> (43/157)	22.97% <sup>b</sup> (25/127)
B. Risk for any major affective disorder in first degree relatives		
All first degree relatives	32.80% (89/307)	31.85% (72/247)
Males	22.64% <sup>a,b</sup> (28/150)	31.43% <sup>b</sup> (35/120)
Females	41.50% <sup>a,b</sup> (61/157)	32.16% <sup>b</sup> (37/127)

<sup>a</sup>Difference between male and female relatives within paternal families significant at  $P < .003$ .

<sup>b</sup>No significant difference between the same sex relatives in paternal vs. maternal families.

TABLE V. Risk for BP Disorder in First Degree Relatives of BP I Proband's Parents by Type of Relative

	Transmitting father	Transmitting mother
All children	55.48% <sup>c</sup> (42/95)	46.68% <sup>c</sup> (38/105)
Sons	39.20% <sup>a,c</sup> (11/39)	48.52% <sup>c</sup> (18/48)
Daughters	65.93% <sup>a,b</sup> (31/56)	43.41% <sup>b</sup> (20/57)
Siblings	5.43% <sup>c</sup> (6/134)	10.44% <sup>c</sup> (7/72)
Brothers	7.20% <sup>c</sup> (4/72)	16.47% <sup>c,d</sup> (6/37)
Sisters	3.64% <sup>c</sup> (2/62)	3.12% <sup>c,d</sup> (1/35)
Fathers	13.85% <sup>a,c</sup> (5/39)	11.52% <sup>c</sup> (4/35)
Mothers	28.58% <sup>a,c</sup> (10/39)	12.24% <sup>c</sup> (4/35)

<sup>a</sup>Difference between male and female relatives within paternal families significant at  $P$  between .05 and .02.

<sup>b</sup>Significant difference at  $P < .05$  between the same sex relatives in paternal vs. maternal families.

<sup>c</sup>No significant difference between the same sex relatives in paternal vs. maternal families.

<sup>d</sup> $P = .08$  for the comparison between brothers and sisters in maternal families.

= 1). Mendelian transmission probabilities of major gene effects were not rejected ( $\chi^2$  for major gene/general, for major gene/general (t2) and for mixed/unified models was not significant). Thus, in PAT families the data were compatible with the Mendelian transmission of major gene effects. Among the three types of MG models the dominant model was rejected, while the additive and the recessive models were not rejected.

In MAT families there is also high familiarity in the transmission of BP ( $\chi^2$  for sporadic/multifactorial model = 27.69, DF = 1,  $P < .0001$ ). The heritability is H = .74, about two times higher than in PAT families. Both absence of polygenic component and of major gene effect are not rejected ( $\chi^2$  for multifactorial/mixed and for major gene/mixed model was not significant). In MAT families the best model fitting the data was the multifactorial model; major gene effects did not better explain the high familiarity than multifactorial effects.

In the pooled sample of PAT and MAT families there was also a high familiarity in the transmission of BP illness under the narrow definition of the affection status in relatives of BP probands ( $\chi^2$  for sporadic/multifactorial model = 39.36, DF = 1,  $P < .00001$ ). The heritability H was .57. Absence of parent-offspring transmission of BP disorder was rejected ( $\chi^2$  for parent-offspring transmission/general monogenic transmission was 8.52, DF = 2,  $P < .03$ ). The absence of major gene effects was rejected ( $\chi^2$  for multifactorial/mixed model = 13.64, DF = 3,  $P < .005$ ) and absence of polygenic component was not rejected ( $\chi^2$  for major gene/mixed model = .01, N.S.). Major gene effects were compatible with Mendelian transmission ( $\chi^2$  values for major gene/general model of MG and for major gene/general (t2) were not significant). The best model was the major gene model. The dominant model of MG ef-

TABLE VI. Segregation Analysis in Unilineal Pedigrees of BP I Probands Under the Narrow Definition of the Affected Phenotype in Probands' Relatives

Model	d	t	q	H	t1	t2	t3	-2ln (L)
Maternal sample (65 nuclear families)								
Sporadic	(0)	(0)	(0)	(0)	(1)	(.5)	(0)	-187.224
Multifactorial	(0)	(0)	(0)	.74	(1)	(.5)	(0)	-214.913
Major gene	.89	3.3	.06	(0)	(1)	(.5)	(0)	-218.128
recessive	(0)	2.6	.12	(0)	(1)	(.5)	(0)	-217.320
additive	(.5)	3.6	.06	(0)	(1)	(.5)	(0)	-218.275
dominant	(1)	2.0	.01	(0)	(1)	(.5)	(0)	-215.604
Mixed	.85	3.4	.06	.0001	(1)	(.5)	(0)	-218.146
General (t2)	.91	3.2	.06	(0)	(1)	0 <sup>a</sup>	(0)	-218.657
General	.38	6.4	.06	(0)	.95	.52	.22	-219.398
Paternal sample (68 nuclear families)								
Sporadic	(0)	(0)	(0)	(0)	(1)	(.5)	(0)	-226.929
Multifactorial	(0)	(0)	(0)	.44	(1)	(.5)	(0)	-240.187
Major gene	.08	10.6	.05	(0)	(1)	(.5)	(0)	-249.264
recessive	(0)	2.4	.10	(0)	(1)	(.5)	(0)	-249.008
additive	(.5)	5.5	.05	(0)	(1)	(.5)	(0)	-249.190
dominant	(1)	2.0	.03	(0)	(1)	(.5)	(0)	-244.872
Mixed	.00	2.4	.10	.0001	(1)	(.5)	(0)	-249.000
General (t2)	.09	7.9	.06	(0)	(1)	.62	(0)	-250.764
General	.00 <sup>a</sup>	8.2	.06	(0)	1	.56	.65	-254.863
Paternal and maternal sample (133 nuclear families)								
Sporadic	(0)	(0)	(0)	(0)	(1)	(.5)	(0)	-414.154
Multifactorial	(0)	(0)	(0)	.57	(1)	(.5)	(0)	-453.512
Major gene	.33	3.1	.07	(0)	(1)	(.5)	(0)	-467.134
recessive	(0)	2.4	.11	(0)	(1)	(.5)	(0)	-466.127
additive	(.5)	3.4	.08	(0)	(1)	(.5)	(0)	-467.026
dominant	(1)	2.0	.02	(0)	(1)	(.5)	(0)	-459.377
Mixed	.33	3.1	.07	.006	(1)	(.5)	(0)	-467.149
General (t2)	.44	2.0	.11	(0)	(1)	0	(0)	-468.339
General	.09	1.6	.16	(0)	0	0	1	-472.862

<sup>a</sup>Parameter estimate fixed at bound.

fects was rejected, but the additive and the recessive models were not rejected.

b) At the level of heterogeneity tests there was no significant difference between PAT and MAT families.

**Broad definition of affected phenotype in relatives.** a) The extension of the phenotype in probands' relatives to any major affective disorders resulted also in a high familial correlation with an H value of .36 in PAT families ( $\chi^2$  for sporadic/multifactorial model = 15.70, DF = 1,  $P < .0001$ ) (100 nuclear families). Major gene effects were borderline ( $\chi^2$  for multifactorial/mixed model was 7.57 and the required value for significance at  $P = .05$  with 3 df is 7.84). Absence of the polygenic component was not rejected. Mendelian transmission probabilities of major gene effects were rejected ( $\chi^2$  for major gene/general model of major gene was 8.71, df = 3,  $P < .05$ ;  $\chi^2$  for mixed/unified model was 9.71, df = 3,  $P < .05$ ). The best model fitting the data was the general monogenic transmission model in PAT families. No type of major gene model (recessive, additive, and dominant) was rejected, all of them fitting equally well the data.

In MAT families (95 nuclear families) heritability of the disorder was .64 under the broad definition ( $\chi^2$  for sporadic/multifactorial model = 31.28, DF = 1,  $P < .0001$ ), again two times higher than in PAT families. Both absence of the polygenic component and of the major gene effect was not rejected ( $\chi^2$  for multifactorial/mixed and for major gene/mixed model was not significant). The best model fitting the data was the multi-

factorial model; the familial resemblance could not be better explained by major gene effects than by multifactorial effects. In the mixed sample of PAT and MAT families (195 nuclear families) the familial correlation was .48 ( $\chi^2$  for sporadic/multifactorial model = 45.00, DF = 1,  $P < .00001$ ). The absence of major gene effect was rejected ( $\chi^2$  for multifactorial/mixed model was 10.06, df = 3,  $P < .02$ ) and absence of polygenic component is not rejected ( $\chi^2$  for major gene/mixed model = .001). But Mendelian transmission of major gene effects was rejected ( $\chi^2$  for major gene/general model of major gene was 11.25, df = 3,  $P < .04$ ;  $\chi^2$  for major gene/general (t2) was 10.29, df = 1,  $P < .001$ ). The best model was the general model of monogenic transmission. No type of major gene model (recessive, additive, dominant) was rejected, all of them fitting the data equally well.

Absence of parent-offspring transmission of the illness was borderline rejected ( $\chi^2$  for no parent-offspring transmission/general monogenic model was 5.34, df = 2 and the required value for  $P = .05$  is 5.99).

b) Heterogeneity tests were not significant. According to these tests the PAT and MAT families would not be different.

## DISCUSSION

By using a subset of our present sample we have previously found clinical evidence for the genetic mechanisms of imprinting and anticipation operating

in bipolar disorder [Serbanescu-Grigoriou et al., 1995, 1997]. We observed that PAT transmission was associated with a younger age at onset in probands when compared to MAT transmission. Additionally, in PAT families the affected offspring had a younger age at onset than their affected fathers. While our data suggested that age at onset is influenced by the transmitting parent, the MR seemed not to be influenced by the parental transmitting side. Two recent studies based on the analysis of bipolar families with a high loading of the disease suggested an excess of maternal transmission in bipolar disorder [McMahon et al., 1995; Gershon et al., 1996]. To specifically address this question we enlarged our previous set of systematically ascertained families. We selected for families with unilineal inheritance and performed different types of analyses. However, none of the comparisons indicate an excess of maternal transmission in our sample: the number of PAT and MAT transmissions were nearly identical, a similar number of fathers and mothers were affected, no excess of affecteds were detected among mothers' relatives, and affected mothers and fathers had similar rates of affected offspring. The results were not influenced by applying narrow or broad definitions of affected. We therefore conclude that the findings by McMahon et al. [1995] and Gershon et al. [1996] may not be generalizable to a family sample ascertained without regard to family history. As pointed out by Gershon et al. [1996] an excess of maternal transmission might not be expected in an illness such as bipolar disorder where little sex difference in the prevalence of the disease is observed. This argument is based on epidemiologic data and may hold true for a sample of systematically ascertained families, as was ours. However, it may not be applicable to families selected for genetic linkage studies where inclusion of the family requires additional affecteds in the family.

When we investigated MRs in PAT and MAT families we found a 2-fold higher MR for any major affective disorder in female than in male relatives of BP probands in PAT families but not in MAT families. When considering the transmitting fathers and mothers as probands, the same 2-fold increased MR was found in female relatives vs. male relatives in PAT families both for the narrow and the broad definition of affected but not in MAT families. This effect was accounted for by a significantly higher risk for BP in mothers compared to fathers and in daughters compared to sons of transmitting fathers. The differences in MRs between male and female relatives in PAT families but not in MAT families as indicated by the survival analysis, prompted us to examine the genetic heterogeneity of familial transmission models in these subgroups of families.

Both under the narrow and the broad definition of the affected phenotype in probands' relatives a high familial correlation was observed in PAT, MAT and the mixed PAT plus MAT samples, with an about two times higher heritability in MAT families than in PAT families. We could not find a plausible explanation for the nearly double heritability shown by MAT families. The different liability classes assigned to males and females were not responsible for this observation since for the narrow definition the liability classes were not

differentiated by sex. On the other hand, the higher heritability was not translated into higher MR in MAT families vs. PAT families. Because mothers and fathers were included in the segregation analysis but not in computations of the MR, we computed MR both for BP and for any major affective disorder including also the parents (data not shown). The differences between PAT and MAT families remained not significant.

Segregation analysis conclusions were consistent in PAT and MAT families across diagnostic schemes, but they were different by type of parental transmission.

Under the narrow definition absence of major gene effects was rejected and the Mendelian transmission probabilities were not rejected in PAT families, while in MAT families absence of major gene was not rejected. The data were compatible with the Mendelian transmission of a recessive or additive major gene in PAT families but not in MAT families. The mixed sample of PAT and MAT families replicated the results provided by the PAT sample; the absence of major gene effects was rejected and the best inheritance model was the major gene model, too. Evidence for major gene transmission in bipolar illness was previously reported by Rice et al. [1987], who used the same segregation method as us (Pointer method and program), and by Blangero and Elston [1989] and Spence et al. [1995], who used the S.A.G.E program. Both in our data and in the data set of Blangero and Elston [1989] the polygenic model did not fit well the data.

Under the broad definition, major gene effects were borderline and the inheritance pattern was not consistent with the simple Mendelian transmission of a single major gene in PAT families. The best inheritance model was the general major gene model. In MAT families there was no evidence for major gene effects and the best inheritance model was the multifactorial model. The combined sample of PAT + MAT families replicated exactly the segregation model of the PAT families. Thus, transmission patterns of BP illness were different in families with PAT vs. families with MAT transmission both under the narrow and the broad definition of the affected phenotype in relatives, but heterogeneity tests were not significant. Probably the reduced size of the PAT and MAT samples is one of the causes underlying the lack of significance of the heterogeneity tests. However, even if limited power may affect our results, this problem seems not to be the main cause of the difference in segregation models between PAT and MAT families since when reducing the dimension of the samples under the narrow definition tests of no major gene effects reached higher significance levels in PAT families.

In conclusion, we could not replicate the excess of maternal transmission for bipolar disorder reported for highly loaded families recruited for genetic linkage studies in our sample of systematically ascertained sample of bipolar I probands but we could evidence for differences in inheritance patterns of major affective disorders by parental transmitting side. It will be interesting to see whether replication studies can confirm or not the true existence of this difference.

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