

Family History Influences Age of Onset in Bipolar I Disorder in Females but not in Males

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Age of onset (AO) has been proposed as a promising criterion by which to select homogeneous subgroups for the genetic analysis of bipolar disorder. This is the first study to investigate the effect of the interaction between gender and family history (FH)-type on AO in bipolar disorder. In accordance with the literature, no difference in AO was observed between females and males in our sample of 264 Romanian bipolar I probands. Cox regression, however, showed a strong influence of FH-type on AO ($P = 0.006$). This was due to a significant variation in AO according to the type of FH in females ($P = 0.002$) but not in males ($P = 0.64$). Female bipolar disorder patients with a negative FH (FH⁻) had a later AO than females with either a FH of bipolar and/or schizoaffective disorder ($P = 0.001$) or a FH of recurrent unipolar major depression only ($P = 0.04$). Females with FH⁻ had a later AO than males with FH⁻ ($P = 0.03$). No sex difference was observed for AO in the group with a FH of recurrent unipolar depression. In the group with a FH of bipolar and/or schizoaffective disorder, females had an earlier AO than males ($P = 0.01$). A trend for support was observed in an independent sample

of 217 German bipolar I patients for an influence of FH-type on AO in females ($P = 0.09$) but not in males ($P = 0.15$). Female bipolar disorder patients with FH⁻ had a later AO than females with either a FH of bipolar and/or schizoaffective disorder ($P = 0.04$) or a FH of recurrent unipolar major depression only ($P = 0.05$). Females with FH⁻ had a later AO than males with FH⁻ ($P = 0.05$). Other comparisons were statistically not significant, which may be due to limited sample size. Our findings emphasize that the interaction between gender and FH-type is a source of heterogeneity for AO in bipolar disorder. © 2005 Wiley-Liss, Inc.

KEY WORDS: gender; psychosis; manic-depressive; family study; age of onset

INTRODUCTION

Epidemiologic and family studies of bipolar disorder have consistently reported equal age of onset (AO) in females and males [Loranger and Levine, 1978; Gershon et al., 1982; Smeraldi et al., 1983; Rice et al., 1987; Johnson et al., 2000]. As a consequence of this, scant attention subsequently has been paid in the literature to specific aspects of gender differences in AO in bipolar disorder [Leibenluft, 1996; Moorhead and Young, 2003].

McMahon et al. [1994] examined the relationship between AO and gender, using statistical methods appropriate for skewed distributions. They recruited a sample of 82 bipolar and unipolar depressive probands who had at least two relatives with a history of major affective disorder. In their analysis of AO according to gender, the authors grouped bipolar probands and their bipolar relatives together, and concluded that bipolar females have an earlier AO than bipolar males. No distinction was made between the types of familial loading, and no patients with negative family histories were included for comparison. This is true of other relevant studies published to date also.

Our study is the first to examine in detail the interaction between AO, family history (FH) type and gender in bipolar I patients recruited irrespective of family history status from consecutive admissions. We hypothesized that an interaction between FH-type and gender may exist, and serve to modify AO in bipolar disorder. For the purpose of our study, we grouped FH-type as follows: (i) no FH of major affective

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disorder, (ii) FH of recurrent unipolar major depression only, (iii) FH of bipolar and/or schizoaffective disorder.

MATERIALS AND METHODS

Sample

Two hundred seventy four bipolar I probands were recruited from consecutive admissions to the Obregia Psychiatric Hospital of Bucharest, a state university hospital with a large catchment area. Recruitment was made irrespective of family history status. Inclusion into the study depended on a history of at least two episodes of affective illness (manic, depressive, or mixed) that had required hospitalization. Only subjects who could give written informed consent were included. The mean number of hospitalized episodes per patient was 6.7 (SD = 4.4).

The requirement for patients to have had at least two hospitalized episodes was included to improve the validity of diagnosis. Winokur et al. [1985] and Rice et al. [1992] showed that diagnosis can change over time. Rice et al. [1992] reported that diagnostic stability is made more robust by an increasing number of illness episodes and by hospitalization.

Three cases were excluded on the grounds that they had relatives with schizophrenia. Patients were also excluded if they had characteristics, which might influence AO. McMahon et al. [1994] reported that bilineality may be associated with lower AO. Bilineality is defined as the presence of bipolar disorder, schizoaffective disorder, recurrent unipolar major depression, schizophrenia or any other psychosis in both parents or in a second-degree relative (grandparent, aunt, uncle) on both parental sides. Seven cases were excluded on these grounds. The final proband sample consisted of 264 bipolar I patients [140 females (53.1%) and 124 males (46.9%)].

The 264 probands had a total of 1,289 first-degree, and 2,204 second-degree relatives. Of these 3,493 relatives, 2,163 were still alive at the time of the probands' recruitment.

Assignment of Diagnoses

Patients were interviewed using 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]. All diagnoses were based on DSM-IV criteria [American Psychiatric Association, 1994]. Information from medical records and interviews with close relatives was used to corroborate proband and accounts of episodes of illness and symptom-free intervals. For each proband, the interviewers, a blind rater and the treating psychiatrist reached a consensual diagnosis using the best estimate procedure. The intraclass correlation coefficient for diagnostic agreement among the three raters was 0.95 ($P < 0.0001$).

Definition and Determination of the Age of Onset in Proband

AO was defined as the age at which DSM-IV criteria for a manic, mixed or major depressive episode was first met. Three sources were used to provide estimates of age of onset: the proband, a relative, and the medical records. The lowest of these estimates was used as the actual AO in the consensual diagnostic conference. Intraclass correlation coefficient for the agreement among the three raters regarding AO was 0.93 ($P < 0.0001$).

Diagnostic Assessment of Relatives

Sixty-three percent (1,363/2,163) of first and second degree relatives were interviewed using the DIGS and the FIGS. 71.4% (920/1,289) of the first-degree relatives and 20.1% (443/

2,204) of the second-degree relatives were interviewed. One hundred fifty two probands were married at the time of interview. One hundred thirty eight of the spouses provided information about the patient and their family. Information regarding familial psychopathology was collected using the family history method. The FIGS was administered to all directly interviewed probands and relatives. Medical records from relatives with a history of hospitalization for mental illness were traced when possible.

The final assigned DSM-IV diagnoses of relatives were consensual. They were established by a blind rater and the direct interviewers, and were based on all available information. All interviews were conducted by experienced psychiatrists and clinical psychologists. Intraclass correlation coefficient for the diagnostic agreement between the two raters was 0.89 ($P < 0.0001$). The intraclass correlation coefficient is a measure similar to kappa for inter-rater reliability. It was computed with the SPSS software (release 11) in an alpha model with two-way (subject by rater) random effects that tested the observed agreement against zero agreement among raters.

Diagnosis of Bipolar and Schizoaffective Disorder Subtypes in Relatives

We did not distinguish between bipolar I and bipolar II in the relatives of probands. This is because it is difficult to differentiate between the two diagnoses in family members assessed using the family history method, with no access to medical records.

The three types of schizoaffective disorder (manic, bipolar and depressive type) in relatives were grouped together. As these diagnoses were only made in 21 proband families, it was not possible to construct a separate and statistically meaningful FH group or further subdivide into types of schizoaffective disorder. Schizoaffective diagnoses coexisted with bipolar disorders in ten of these families.

Definition of Familial and Sporadic Cases

Cases were classified as familial when at least one first- or second-degree relative had been assigned a diagnosis of bipolar disorder, schizoaffective disorder, or recurrent unipolar major depression. A case of recurrent unipolar major depression in only one second-degree relative was deemed to express familiarity if the relative received treatment, was hospitalized or committed suicide because of the depressive illness. This criterion was used as second-degree relatives are often less available for direct interview and FH-data are less reliable. Relatives were not considered affected if they were diagnosed with a single depressive episode, treated or not. A proband was classified as FH⁻ (sporadic) if he/she had no first- or second-degree relative diagnosed with any of the above mentioned major affective disorders, or with schizophrenia or other psychosis. Relatives with other psychiatric disorders were not classified as being affected for the purpose of our study.

The probands were subdivided into three FH groups: (i) FH⁻, (ii) FH of recurrent unipolar major depression only, (iii) FH of bipolar and/or schizoaffective disorder. If two or three different major affective disorders were recorded in the relatives of a proband, the most severe disorder was used to determine the FH group assignment.

Independent Replication of the Romanian Sample Results

An independent sample of German bipolar I probands was used to replicate the results obtained in the Romanian sample. The Romanian study definitions of AO, bilineality, and FH were used. The German sample consisted of 224 bipolar I probands (105 males and 119 females) recruited from con-

secutive admissions to the Psychiatry Department of the University of Bonn, a state university hospital. Recruitment was made irrespective of family history status. All patients gave written informed consent. Three cases with relatives with schizophrenia and four bilineal cases were excluded from the German sample. The final German sample included 217 patients [104 males (47.9%) and 113 females (52.1%)].

Assignment of Diagnoses in the German Probands

German probands were interviewed using the Structured Clinical Interview for DSM-IV Axis-I disorders (SCID-I) [First et al., 1995] and the Family Informant Schedule and Criteria (FISC) [Mannuzza et al., 1985]. Diagnoses were made using a best estimate procedure and a consensus of several raters, with reference to information obtained from proband and relative interviews, and medical records. Interviews were conducted by experienced psychiatrists and clinical psychologists.

Assignment of Diagnoses in Relatives

In 35.7% (80/224) of probands, relatives were interviewed using the SCID-I. The family history of psychiatric illness was collected mainly using the family history method. The FISC was administered to all probands and to all available relatives and was also applied to the medical records. Diagnoses assigned to relatives were based on DSM-IV criteria.

Statistics

AO and age at interview (AI) are correlated and differences in AI distribution between sexes might produce results that are artefacts [Faraone et al., 1994]. The distributions of AI and AO were, therefore, tested with the Kolmogorov–Smirnov test (K–S) for one sample against the normal distribution. The K–S-test for two samples was used for comparisons between two groups. The AI mean values were compared with the *t*-test as this variable was normally distributed. Sex ratios were tested with the χ^2 -test.

As the AO distribution was skewed in the total sample and in the gender subsamples, univariate comparisons of the AO between groups were made using survival analysis techniques [the Wilcoxon–Gehan-test (WG) with one degree of freedom].

Cox regression models were used to determine the influence of gender, FH, and their interaction on AO. AO was treated as the dependent variable. The simultaneous influence of psychotic symptoms, degree of relatedness to the proband, and history of alcohol/drug abuse or dependence prior to the bipolar onset was also considered, and the AI was controlled for. All tests were two-tailed (SPSS software, release 11).

RESULTS

Characteristics of the Romanian Sample

The AI and the AO of the total Romanian sample and of the male and female subgroups are presented in Table I.

The AI distribution of the total sample was normal ($P = 0.67$ for the K–S-test). There was no difference in the mean AI between females and males (*t*-test = 0.41, $P = 0.66$). There was no difference in AI distribution between males and females (K–S = 0.70, $P = 0.68$).

The AO distribution of the total sample was skewed (K–S = 2.1, $P < 0.001$) with a median of 23 years, mean AO = 24.7 years, SD = 9.2, range 11–60. There was no AO difference between the female and male subgroups (WG = 2.02, $df = 1$, $P = 0.18$).

There was no significant male/female ratio difference in either the total sample or in the FH-type subgroups (data not shown).

Mood congruent and incongruent psychotic features (delusions and hallucinations) had been present in at least one episode of illness in 58.3% (154/264) of the probands. There was no significant sex difference for the presence of mood congruent or mood incongruent psychotic features (delusions and hallucinations) [65 of 124 males (52.4%) and 89 of 140 females (63.6%)] ($\chi^2 = 1.45$, $df = 1$, $P = 0.40$). There was no association between a history of psychotic symptoms in probands and the FH-type ($\chi^2 = 1.12$, $df = 2$, $P = 0.79$). Of the total sample, 35.7% (55/154) of psychotic cases were FH⁻, while 58.9% (63/107) of all cases with no psychosis had a positive FH.

Impact on Age of Onset of Gender, Family History Type, Psychotic Traits, and Comorbidity

The influence of FH-type and gender on AO, as calculated by the Cox regression models, is shown in Table II. FH-type had a strong effect on AO in the total sample ($P = 0.006$). Gender alone had no significant influence on AO. However, there was a significant gender effect when the type of FH was considered ($P = 0.01$). This effect was greatest for probands with a FH of both bipolar and/or schizoaffective disorder. Cases with no FH represented the reference category.

The presence of psychotic features showed a trend towards association with a lower AO in the total sample ($P = 0.07$). This trend did not become stronger in the male or female subsample. Comorbidity with alcohol/drug abuse or dependence showed no significant influence on AO ($P = 0.95$).

Cox regression analysis was repeated on the male and female subsamples (Table II). The influence on AO of FH-type was only significant in females ($P = 0.002$) and not in males ($P = 0.64$).

We conclude that, in our study, FH-type exerted an influence on AO in females with bipolar disorder but not in males with bipolar disorder.

Figure 1 shows the influence of FH-type and gender on AO in our sample. The statistical details are summarized in Table III.

Table III shows that for the group of females with bipolar disorder, those who are FH⁻ have the latest AO. This was significantly later than that for both patients with a FH of recurrent unipolar major depression only ($P = 0.04$), and for

TABLE I. Descriptive Data of the Romanian Bipolar I Proband Sample

Variable	Mean (SD)	Median	Range	Kolmogorov–Smirnov-test (K–S)
AI total sample (N = 264)	40.3 (13.2)	39.5	14–68	K–S = 0.72, $P = 0.67$
AI females (N = 140)	39.7 (13.6)	39	14–68	K–S = 0.70, $P = 0.68$ for the comparison between females and males
AI males (N = 124)	40.7 (13.3)	38.5	16–68	
AO total sample (N = 264)	24.7 (9.2)	23	11–60	K–S = 2.1, $P < 0.001$
AO females (N = 140)	24.5 (9.3)	22	11–57	K–S = 1.1, $P = 0.26$ for the comparison between females and males
AO males (N = 124)	25.5 (9.6)	23.5	13–60	

TABLE II. Impact of Family History Type, Gender, Psychotic Traits, and Alcohol/Drug Abuse on Age of Onset in Romanian Bipolar I Probands

Sample/variable	Beta	SE	Wald statistic	df	P	Model χ^2
Total sample (N = 264)						
Family history type ^a			10.19	2	0.006	$\chi^2 = 20.76, df = 9, P = 0.008$
Family history of R-UP ^b	0.19	0.21	0.81	1	0.37	
Family history of BP + SA ^c	0.67	0.14	10.02	1	0.002	
Gender	0.20	0.13	1.40	1	0.20	
Interaction FH by gender	0.37	0.11	5.39	1	0.01	
Psychotic symptoms	0.25	0.13	3.31	1	0.07	
Alcohol/drug abuse/dependence	-0.01	0.20	0.03	1	0.95	
Female subsample (N = 140)						
Family history type ^a			12.13	2	0.002	$\chi^2 = 24.74, df = 7, P < 0.001$
Family history of R-UP ^b	0.83	0.43	3.66	1	0.05	
Family history of BP + SA ^c	1.07	0.37	8.34	1	0.004	
Psychotic symptoms	0.19	0.19	0.91	1	0.34	
Alcohol/drug abuse/dependence	0.31	0.43	1.30	1	0.36	
Male subsample (N = 124)						
Family history type ^a			0.89	2	0.64	$\chi^2 = 3.42, df = 7, P = 0.75$
Family history of R-UP ^b	0.48	0.73	0.43	1	0.51	
Family history of BP + SA ^c	0.61	0.70	0.74	1	0.39	
Psychotic symptoms	0.33	0.20	2.73	1	0.10	
Alcohol/drug abuse/dependence	-0.20	0.23	0.73	1	0.40	

^aReference category = FH⁻ cases.
^bRecurrent unipolar major depression.
^cBipolar + schizoaffective disorder.

patients with a FH of bipolar and/or schizoaffective disorder ($P = 0.001$). Patients with a FH of recurrent unipolar depression only had a later AO than those patients with a FH of bipolar and/or schizoaffective disorder ($P = 0.02$). To summarize, in females, onset of the illness is earlier where there is a stronger family history of major affective disorder. In males no such gender effect was observed.

Overall comparison between males and females showed no difference in AO (Table III). However, comparison between males and females of the same FH-subtype revealed differences: females with a negative FH had a significantly later AO than males with a negative FH ($P = 0.03$). Females and males

with a FH of recurrent unipolar major depression only, showed no difference in AO ($P = 0.63$). Female cases with a FH of bipolar and/or schizoaffective disorder showed an earlier onset than men with this FH subtype ($P = 0.01$).

Replication of the Results in the German Sample

Several findings from the Romanian sample were replicated in the independent German sample. This was only possible in those subgroups with a sufficient size to allow meaningful statistical analysis. The German patients FH-type groups were: (i) FH⁻ = 126 cases (65 females, 61 males); (ii) FH

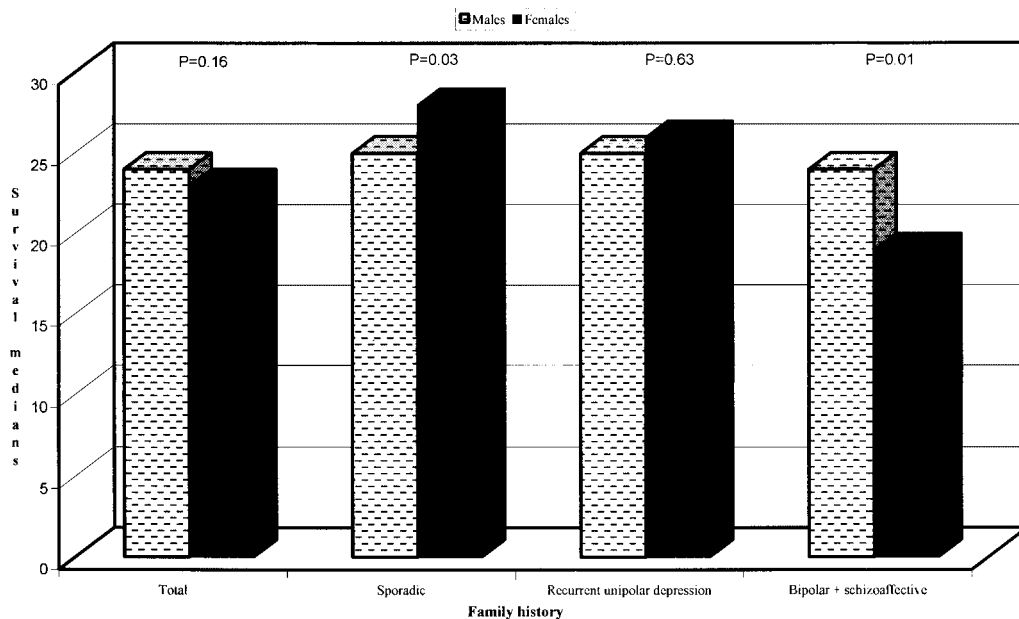


Fig. 1. Age of onset in Romanian bipolar I probands by gender and family history.

TABLE III. Age of Onset in Romanian Bipolar I Probands by Family History Type and Gender (Survival Medians)

Sex	Family history type				Comparison between FH-types within a sex group
	Total	FH ⁻	R-UP**	BP + SA***	
Females	22.9 (N = 140)	27.8 ^{a,b} (N = 49)	23.8 ^{a,c} (N = 23)	19.8 ^{b,c} (N = 68)	^a WG = 2.8; <i>P</i> = 0.04 ; ^b WG = 10.5; <i>P</i> = 0.001 ; ^c WG = 3.5; <i>P</i> = 0.02
Males	24.7 (N = 124)	24.5 ^{a,b} (N = 47)	25.8 ^{a,c} (N = 20)	24.7 ^{b,c} (N = 57)	^a WG = 0.2; <i>P</i> = 0.65; ^b WG = 0.3; <i>P</i> = 0.57; ^c WG = 0.03; <i>P</i> = 0.87
Comparison between sexes within a FH-type	WG* = 2.0; <i>P</i> = 0.18	WG* = 4.2; <i>P</i> = 0.03	WG* = 0.3; <i>P</i> = 0.63	WG* = 6.4; <i>P</i> = 0.01	

*Wilcoxon–Gehan test.

**Recurrent unipolar major depression.

***Bipolar + schizoaffective disorder.

of recurrent unipolar major depression only = 47 cases (27 females, 20 males); (iii) FH of bipolar and/or schizoaffective disorder = 44 cases (21 females; 23 males). The following findings in the German sample replicate findings from the Romanian sample.

- In males, there was no influence of FH-type on AO (N = 104) (WG = 3.84, *df* = 2, *P* = 0.15).
- For the total female group, the influence of FH-type on AO was observed as a trend that did not reach significance. (WG = 4.7, *df* = 2, *P* = 0.09). Female bipolar disorder patients with a negative FH (FH⁻) had a later AO than females with either a FH of bipolar and/or schizoaffective disorder (*P* = 0.04) or a FH of recurrent unipolar major depression only (*P* = 0.05). The survival medians were: 28.1 years for sporadic cases, 27.5 years for females with FH of recurrent major unipolar depression only, 22.5 years for females with FH of bipolar and/or schizoaffective disorder.
- There was a borderline significant difference in AO between males and females with a negative FH (survival median of 24.0 years for males and 28.1 years for females (WG = 3.63, *df* = 1, *P* = 0.05).
- There was no difference in AO between males and females with a FH of recurrent unipolar major depression only (WG = 0.27; *df* = 1, *P* = 0.60).
- There was no association between FH-type and the presence of psychotic features ($\chi^2 = 2.9$, *df* = 2, *P* = 0.23).

DISCUSSION

Although an abundance of literature regarding AO in bipolar disorder has been published, our study is the first to simultaneously examine familial loading type, proband gender and AO in unrelated bipolar I probands recruited irrespective of FH. We have replicated the previous finding that there is no overall difference in AO between females and males. However, we report two new findings: (1) the type of familial loading influences AO in females but not in males; (2) female bipolar patients with a negative FH have a significantly later AO than female patients with a FH of affective disorder.

This differential gender-effect of FH-type on AO in bipolar disorder requires replication in independent samples, a process that we have initiated in the German sample. The biological basis of this effect can only be speculated upon. Several factors such as the effect of genes with gender specific activity [Hawi et al., 1999; Zubenko et al., 2003] and interactions between hormones and neurotransmitter systems may be involved [Häfner et al., 1991; Halbreich and Lumley, 1993; Seeman, 1997].

Data from previous research on schizophrenia suggests a gender-specific influence of FH on AO. This influence has been observed in samples of unrelated probands recruited irrespective of the FH, females with schizophrenia showing a later AO than males [Loranger, 1984; Häfner et al., 1989; Faraone et al., 1994]. Reports suggest that this effect appears in cases with a negative FH, but that it is not detectable in patients with familial schizophrenia [DeLisi et al., 1994; Albus and Maier, 1995].

Finally, a comment upon our findings concerning the relationship between psychotic traits, FH-type, and AO. The occurrence of psychotic features (delusions and hallucinations) in probands was not associated with a positive FH of major affective disorder or with FH-type. This result is consistent with those of the study by Van Os et al. [1997] from a sample of probands with psychosis recruited irrespective of their FH-status. They showed that psychotic symptoms (delusions and hallucinations) were not related to familial loading, either in probands with affective disorders or in probands with schizophrenia or schizoaffective disorder.

Our study has limitations. The size of the group with FH of recurrent unipolar major depression only was small, and probably had insufficient power to demonstrate gender differences in AO in this group. The group was small as it only included probands who had relatives with recurrent unipolar major depression only, and no other coexisting major affective disorders.

A further limitation is the small number of probands with a FH of schizoaffective disorder. Twenty-one cases is too small a sample to allow either the construction of a statistically meaningful subgroup, or to be further subdivided by type of schizoaffective disorder and gender. If we consider the morbid risk of 1.5% for all schizoaffective disorders in first- and second-degree relatives of bipolar probands reported by Gershon et al. [1982], we would not expect a large number of probands to have relatives with schizoaffective disorder in a sample of 264 bipolar I patients.

A third limitation of the study is the retrospective collection of the AO data. This could introduce a certain amount of bias, especially in the estimation of the AO in patients with long duration of the illness. However, as no other means of determining the AO in large patient samples exists, we tried to minimize the bias by using several sources of information on AO in each case, and computing an interrater agreement coefficient.

Differential recall of past symptoms between males and females is unlikely to account for our findings, since the diagnosis of the AO was not based purely on the proband interview. AO was corroborated with both male and female relatives of the proband and also with the medical records.

What is more, if a psychological bias had caused the results, then the bias would have affected all FH-groups equally.

A fourth limitation of the study is the small proportion of directly investigated proband relatives in the German sample. Despite its size, however, this sample still produced significant results, which replicated those of the Romanian sample.

The results of our study have implications for the molecular and clinical research of bipolar disorder. They emphasize the importance of the role of the interaction between gender and FH-type among other sources of heterogeneity of the AO in this disorder.

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