Genetic linkage study for bipolar disorders on chromosomes 17 and 18 in families with a high expression of mental illness from the Balearic Islands

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Genetically, bipolar disorder is a complex genetic illness, in which both genes and environmental factors play an important role in pathogenesis. Linkage studies have reported suggestive evidence for genomic regions, especially on chromosome 18, but in most cases they have been inconclusive. A total of 12 pedigrees, from the islands of Majorca and Minorca (Balearic Archipelago), with a high expression of mental illness, have been studied. A scan of 29 polymorphic short tandem repeat markers was performed, spanning chromosomes 17 and 18 for bipolar and other affective disorder susceptibility loci. Narrow (only bipolar I disorder) and broad (bipolar plus other affective disorders) diagnosis criteria were employed. The loci D18S63, D18S452, D18S53, D18S61, D18S1161 and D17S831 showed LOD score values of less than −2. Thus, the positive linkage found by other authors on the regions 18p11.2 and 18p11.3 has not been reproduced in the families studied. The data obtained in chromosome 17 suggested two possible regions that could contain a bipolar disorder susceptibility gene: 17q11 (D17S1857, D17S798) and especially 17q24-qter (D17S949, D17S928). The maximum significant linkage was to D17S949 (17q24), following a recessive mode of inheritance. We have also found a positive LOD score value for D18S478 marker located in the region 18q12. *Psychiatr Genet* **16:145–151**

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Introduction

In psychiatric clinical practice, a family history of manic-depressive or related affective disorders is frequently found in patients with bipolar disorders. These, as well as disabling diseases of variable expression, are relatively common, and they have apparent phenotypic and etiologic heterogeneity (Fallin *et al.*, 2004). Estimates of lifetime prevalence for bipolar disorder I (BPI) have been reported to vary between 0.4 and 1.6% and for bipolar disorder II (BPII) the prevalence has been reported to be ~0.5%, although some controversy exists, as other estimates can be as high as 5%, depending on the diagnostic criteria used (Akiskal, 2002).

Genetically, bipolar disorders are a complex genetic illness, in which both genes and environmental factors play an important part role in pathogenesis (Craddock and Jones, 1999). Evidence from family, twin, and adoption studies strongly supports a genetic component of bipolar disorder, with heritability estimates of 58–74% (Tsuang and Faraone, 1990) and risk to first-degree relatives of 5–10% (Craddock and Jones, 1999). The mean age at onset is 28 years; however, onset has also been observed in children, and in adults in their sixth and seventh decades (Stone, 1989; Goodwin and Jamison, 1990). Relatives of probands with earlier ages at onset appear to have an increased risk for bipolar disorder (Weissman *et al.*, 1984; Coryell *et al.*, 2001; Grigorou-Serbanescu *et al.*, 2001; Todd, 2002). Occasionally, families may exist in which a single gene plays the major role in determining susceptibility, but in the majority of cases the illness involves the interaction of multiple genes or more complex genetic mechanisms, such as dynamic mutation or imprinting (Craddock *et al.*, 1995; Fallin *et al.*, 2004).

Analyses using mathematical modelling suggest bipolar susceptibility genes are likely to have modest effect sizes. This is consistent with results of linkage studies that: (1) find no evidence for common susceptibility genes of major effect; and (2) identify several broad genomic regions of interest, including chromosomes 1, 3, 4p16, 5q,

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6q16, 6q22, 8q24, 9p, 10q, 11, 12q, 13q, 14q, 16p, 17q25, and 22q12 (Fallin *et al.*, 2004). Berrettini *et al.* (1994) introduced linkage of bipolar disorder to the pericentromeric region on chromosome 18. The 18p linkage was replicated by Stine *et al.* (1995) who also reported suggestive evidence for a locus on 18q21. Since then, numerous studies have centred on different regions of chromosome 18, which has become the candidate to contain the susceptibility genes for bipolar disorder (Bowen *et al.*, 1999; Baron and Knowles, 2000; McMahon *et al.*, 2001; McInnes *et al.*, 2001; Escamilla, 2001; Reyes *et al.*, 2002; Schulze *et al.*, 2003; Fallin *et al.*, 2004, among others). Methodological issues and nonreplication again demonstrated that these findings, in most cases, are not conclusive (Bailer *et al.*, 2002). Family studies are consistent with the widely accepted view that different mental illnesses, such as schizophrenia and bipolar disorder, exhibit independent modes of inheritance, although some regions that are reported as positive for linkage in relation to schizophrenia overlap regions of positivity for affective disorder, especially on chromosome 18 where region 18p11.2 has been implicated (Berrettini *et al.*, 1994, 1997; Stine *et al.*, 1995; Nöthen *et al.*, 1999). In this study, families with high prevalence of affective illness were chosen.

Majorca and Minorca Islands form, together with Ibiza, the Balearic Archipelago (Western Mediterranean Sea). They have been inhabited since 5500 years ago and different people throughout their history have contributed to the genetic pool of the actual population. In particular, there have been contributions from the Romans in the III century BC and the Catalans in the early XIII century. The Balearic populations have not received any remarkable contribution of foreign genes for the last seven centuries, until very recently when the tourist boom promoted an active immigration, principally from mainland Spain, but also from other European countries. The distribution of the population was in closed families living in small and partially isolated localities. The familiar transmission of mental illness was popularly known in the villages. For these reasons, we consider that this population could be a good candidate for the study of the genetic component of bipolar disorders.

Therefore, the purpose of the present work was to study linkage of chromosomes 17 and 18 to bipolar disorder and other affective disorders in 12 families with a high expression of mental illness, from Majorca and Minorca islands, Spain.

Materials and methods

Sample

From 2000 to 2003, all the patients with DSM-IV diagnostic criteria of BPI admitted to the psychiatric unit of Son Dureta University Hospital (Palma, Majorca), with positive familiar antecedents of mental illness, were invited to participate in the study. The patient's pathology was assessed by using the Spanish version of Diagnostic Interview for Genetics Studies revised for DMS-IV (Nurnberger *et al.*, 1994; M. Roca, F. Cañellas, M.J. Serrano, in preparation). This is a semi-structural interview to elicit information about the lifetime history of psychiatric symptoms and behaviours. The Diagnostic Interview for Genetics Studies was specially designed for genetic studies.

The family history method was used to obtain information about affective disorders in families. The details regarding affective illness in the relatives were collected using the Familiar Interview for Genetic Studies (Maxwell, 1992). The key informants were either first-degree relatives (parents, siblings, or offspring), or spouses. Families in which the proband (a BPI patient) had to have two or more first or second-degree relatives who suffered from psychiatric illness were chosen. A total of 12 pedigrees with at least one BPI patient in each were studied.

The study was approved by relevant local ethical committees, and all participants provided written informed consent.

We used two criteria for the definition of affected: (1) narrow, only BPI; and, (2) broad, BPI and II, plus schizoaffective disorder and recurrent major depression, grouped following criteria similar to that of other authors (i.e. Bowen *et al.*, 1999). In addition, we decided to include two patients (II-10 family B1 and II-4 family B10; see Table 2) who had only one psychotic episode when they were very young, and they have been asymptomatic for the rest of their lives; brief psychotic disorder was the clinical status assigned to them. When the examination was performed, they had cognitive deficits and we were unable to make a clear diagnosis using Familiar Interview for Genetic Studies and familiar information. The rest of the patients were considered to be unaffected in the analysis.

Fifteen millilitres of total blood was taken by a vacutainer with ethylenediamine tetraacetic acid and/or buccal swabs were obtained. They were stored at $-20^{\circ}C$ until used in the study.

Genotyping

DNA was organically extracted from peripheral blood and buccal swabs were obtained following a phenol/chloroform standard protocol and were quantified spectrophotometrically.

Twenty-nine polymorphic short tandem repeat markers, spanning chromosomes 17 and 18, were analysed using panels 23 and 24 (Linkage Mapping Set Version 2, Foster

Table 1 Markers used in the current study and intermarker distances

Marker	Intermarker distance (cM)	No. alleles	Range (pb)	Heterozygosity
D17S849	0.0	6	256–266	0.769
D17S831	6.0	12	105–129	0.754
D17S938	9.0	11	230–260	0.782
D17S1852	8.0	11	289–311	0.827
D17S799	10.0	10	188–206	0.741
D17S921	5.0	7	198–212	0.772
D17S1857	7.0	8	160–174	0.734
D17S798	12.0	8	298–318	0.587
D17S1868	15.0	11	244–268	0.691
D17S787	10.0	10	141–171	0.714
D17S944	8.0	8	320–336	0.712
D17S949	11.0	9	213–231	0.737
D17S785	12.0	10	168–190	0.796
D17S784	12.0	9	229–245	0.717
D17S928	11.6	14	68–98	0.870
D18S59	0.0	11	152–172	0.873
D18S63	6.0	12	78–106	0.800
D18S452	11.0	11	123–143	0.825
D18S464	13.9	6	303–313	0.558
D18S53	9.0	13	157–175	0.860
D18S478	13.1	9	245–261	0.618
D18S1102	10.0	8	86–100	0.727
D18S474	10.0	11	125–145	0.837
D18S64	13.8	10	323–343	0.765
D18S68	12.0	10	269–291	0.745
D18S61	11.0	12	211–237	0.965
D18S1161	11.0	12	219–225	0.873
D18S462	7.0	11	292–312	0.821
D18S70	6.0	11	108–128	0.855

City, California, USA) from ABI PRISM (Foster City, California, USA). The genetic map of the markers was facilitated by Applied Biosystems (Foster City, California, USA).

Polymerase chain reaction amplification was achieved in a GeneAmp PCR System 2400 (Perkin-Elmer) according to the manufacturer's recommendations. Electrophoresis was carried out on an ABI Prism 310 DNA Sequencer. Amplified samples mixed with formamide, and the internal standard size (GS-400HD ROX), were denatured at 97°C for 5 min before the run. GeneScan 3.1.2 Analysis software (Foster City, California, USA) was used for the interpretation of the results.

Statistical analyses

In addition to the families studied, a healthy sample of Balearic Islands population ($n = 100$) was genotyped for the markers. This sample, in Hardy–Weinberg equilibrium, was used for determining the allelic frequencies and the degree of heterozygosity, calculated by means of the GENEPOP software (Laboratiore de Genetique et Environment, Montpellier, France) (see Table 1 for detailed marker properties).

Parametric analyses

Multipoint parametric LOD score analyses both under homogeneity and allowing for heterogeneity were performed using the GENEHUNTER package (The Rockefeller University, New York, New York, USA) (Kruglyak *et al.*, 1996). We examined both autosomal dominant and recessive modes of transmission for the putative affective disorder susceptibility locus. The genetic parameters used in the analysis were similar to those indicated by Bowen *et al.* (1999). These parameters reflect the following assumptions: (1) population lifetime prevalence of 1% for diagnostic criterion 1 and 6% for category 2 (Bowen *et al.*, 1999); (2) penetrance of 50% for the disease gene homozygote in the dominant and recessive models and also for the heterozygote in the dominant models; and (3) phenocopy rates of 10% for category 1 and 50% for category 2.

Non-parametric analyses

Non-parametric analyses using the non-parametric linkage (NPL_{all}) statistic were carried out using the GENEHUNTER package according to both diagnostic categories 1 and 2. This is a multipoint non-parametric method of analysis and under some circumstances has a power to detect linkage similar to that of parametric analysis under the correct model. The NPL_{all} statistic provides a measurement for simultaneous sharing of a marker allele between all affected individuals in a pedigree and has been shown to perform better than the NPL_{pairs} statistic, which provides a measurement of pairwise sharing (Kruglyak *et al.*, 1996).

Results

Clinical features

The pedigrees of the 12 families that were studied are indicated in Fig. 1. The families included a total of 164 individuals, of which 32 have died, 81 were healthy and 51 presented different mental disorders. Those affected by BPI are indicated in black and the other pathologies are marked in grey. In the affective disorders, the most predominant was bipolar disorder with 22 affected individuals: 20 affected by BPI and two by BPII. Thirteen patients were affected by recurrent major depression and seven suffered single episode depression. Schizoid personality disorder, schizophrenia and drug addiction were only observed once. Four persons were affected by schizoaffective disorder and two by brief psychotic disorder. Women represented a slightly greater percentage (60%) of the patients. In 22% of the cases, the patients had attempted suicide of which five were violent. The mean age for the onset of disease was 29.9 years.

Table 2 shows the position in the pedigree and the status of the individuals with different pathologies. We have also indicated sex, age of onset and the cases involving suicide, which are shown as violent or nonviolent. Owing to the choice of families with a high expression of mental illnesses, the ratio between healthy and affected indivi-

Table 2 Clinical characteristics of the affected individuals

Family	Position	Status	Affected		Sex	Age at onset (years)	Suicide
			1	2			
B1	II-10	Brief psychotic disorder	No	Yes	M	18	V
	II-11	Bipolar disorder	Yes	Yes	F	15	–
	III-1	Schizoaffective disorder	No	Yes	F	20	V
	III-3	Bipolar disorder	Yes	Yes	F	21	NV
	III-4	Bipolar disorder	Yes	Yes	M	19	V
	III-6	Single episode major depression	No	No	M	48	–
	III-7	Recurrent major depression	No	Yes	F	38	–
	III-8	Single episode major depression	No	No	F	–	–
	III-9	Single episode major depression	No	No	F	17	–
	III-11	Recurrent major depression	No	Yes	F	27	–
	IV-1	Schizoid personality disorder	No	No	M	16	–
B2	I-1	Bipolar disorder	Yes	Yes	M	40	–
	II-3	Bipolar disorder	Yes	Yes	F	42	–
	III-1	Single episode major depression	No	No	F	12	–
B3	III-7	Bipolar disorder	Yes	Yes	F	30	NV
	IV-8	Bipolar disorder	Yes	Yes	F	23	NV
B5	I-2	Recurrent major depression	No	Yes	F	40	–
	II-2	Bipolar disorder	Yes	Yes	F	35	–
	II-3	Schizoaffective disorder	No	Yes	F	27	–
B6	II-2	Bipolar disorder	Yes	Yes	M	–	–
	III-1	Recurrent major depression	No	Yes	F	16	NV
B7	II-2	Recurrent major depression	No	Yes	F	–	–
	II-3	Single episode major depression	No	No	M	–	–
	III-2	Single episode major depression	No	No	M	29	–
	IV-2	Bipolar disorder	Yes	Yes	F	23	–
B8	II-2	Bipolar disorder	Yes	Yes	F	54	–
	II-6	Bipolar disorder	Yes	Yes	F	23	–
	III-2	Recurrent major depression	No	Yes	F	24	–
B9	II-3	Recurrent major depression	No	Yes	M	–	–
	II-6	Recurrent major depression	No	Yes	F	–	–
	III-1	Recurrent major depression	No	Yes	M	–	–
	III-3	Bipolar disorder	Yes	Yes	M	21	–
	III-5	Schizoaffective disorder	No	Yes	M	–	–
	III-7	Recurrent major depression	No	Yes	M	–	–
	IV-2	Drugs addiction	No	No	F	–	–
B10	II-4	Brief psychotic disorder	No	Yes	M	16	–
	III-1	Bipolar disorder	Yes	Yes	F	48	–
	III-2	Bipolar disorder	Yes	Yes	M	23	–
	III-3	Bipolar disorder	Yes	Yes	M	43	–
B11	I-2	Bipolar disorder	Yes	Yes	F	15	NV
	II-1	Bipolar disorder II	No	Yes	M	24	–
	II-2	Recurrent major depression	No	Yes	F	16	V
B12	II-1	Recurrent major depression	No	Yes	F	–	–
	II-5	Recurrent major depression	No	Yes	F	70	–
	II-6	Single episode major depression	No	No	F	72	–
	III-1	Schizophrenia	No	No	M	–	–
	III-2	Bipolar disorder II	No	Yes	M	40	–
	III-4	Bipolar disorder	Yes	Yes	M	34	–
B14	II-2	Bipolar disorder	Yes	Yes	F	–	–
	II-3	Bipolar disorder	Yes	Yes	F	–	V
	II-6	Schizoaffective disorder	No	Yes	M	–	NV

M, male; F, female; V, violent; NV, nonviolent.

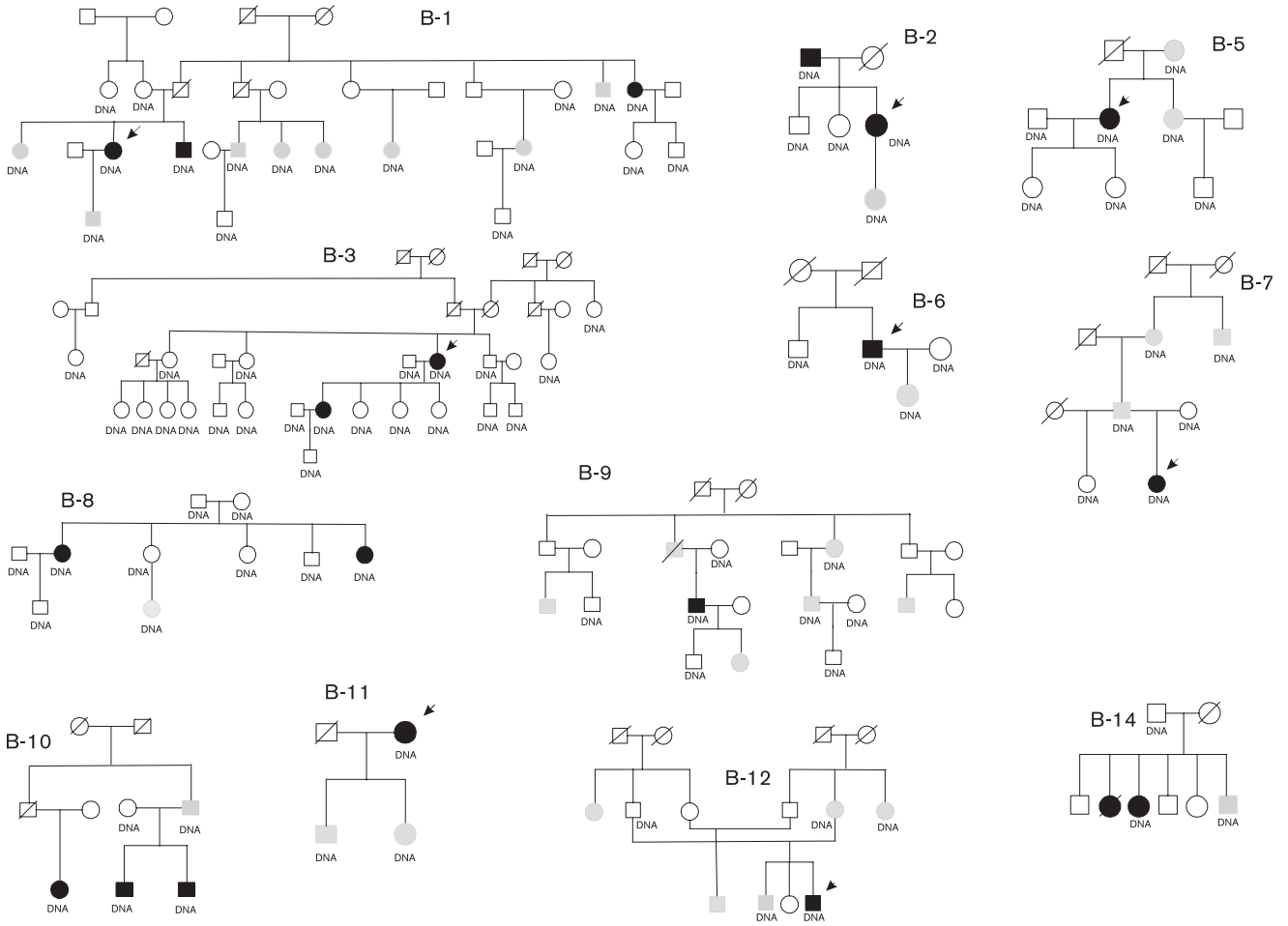
duals was 4.05 (following the criterion 1 definition of affected) and 1.98 (by criterion 2). The sex distribution was similar (13 females and nine males) for those affected by bipolar disorder and clearly displaced towards females in recurrent major depression patients (10 females and three males). The remaining pathologies did not show any particular distribution by sex. The mean age at onset was 30.7 years for bipolar disorder and 26.8 years for recurrent major depression.

Parametric analyses

The results of the multipoint heterogeneity linkage analyses at zero recombination between bipolar disorder and each of the 29 markers, for both dominant and recessive genetic models, and for the 1 and 2 diagnostic models, indicated that none of the tests were statistically significant. Despite this, we have detected, at chromosome 17, the LOD score values (Fig. 2a) for D17S1857 (1.7), D17S798 (1.6) D17S949 (2.1) and D17S928 (1.5) markers, with the assumption of recessive mode of transmission and criterion 1. The marker D17S831 showed values lower than -2 for all criteria and mode of inheritance.

At chromosome 18, the LOD score for D18S478 marker showed a positive value around 1. Figure 2b shows the

Fig. 1



Pedigrees of the 12 families studied. Bipolar patients are indicated in black. Those affected by other pathologies are indicated in grey.

graphical representation of the LOD scores that allowed the linkage between affective disorders and five markers in chromosome 18 to be rejected.

Nonparametric analyses

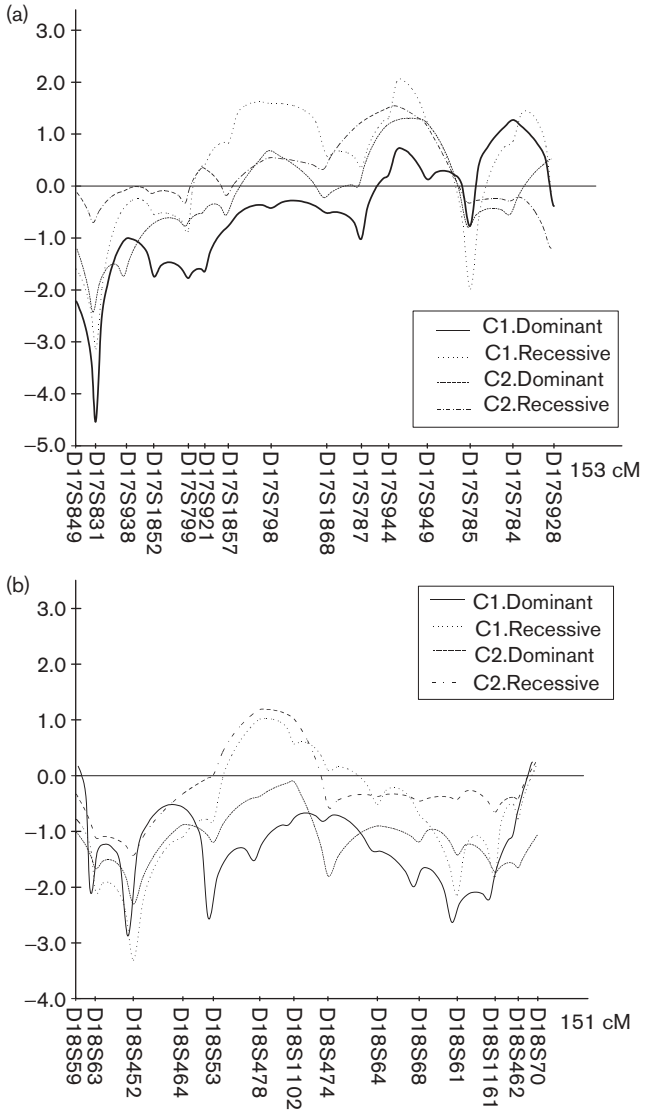
Single-point NPL_{all} results for 1 and 2 diagnostic models are represented in Fig. 3. The maximum single-point NPL_{all} score was 1.55 ($P = 0.04$) with diagnostic model 2 at D17S949. Although it was the only significant value observed, which could be a consequence of the multiple tests carried out, statistically, it disappears when Bonferroni correction was applied. It is interesting to point out that the marker D17S949 corresponds with the maximum LOD score value detected (2.1).

Discussion

We have performed a scan of chromosomes 17 and 18 for bipolar disorder susceptibility loci among insular families with a high mental illness expression. This condition limited the number of possible families to analyse but introduced insularity as an interesting aspect. Numerous studies have been carried out in recent years with outbred populations and a few with more specific populations (i.e. Ashkenazi). The Balearic Archipelago, with a population of fewer than 800 000 individuals, has a reduced number of families that have a high number of mental patients, but if a loci involved in the disease can be detected we can presuppose there is a high degree of founder effect.

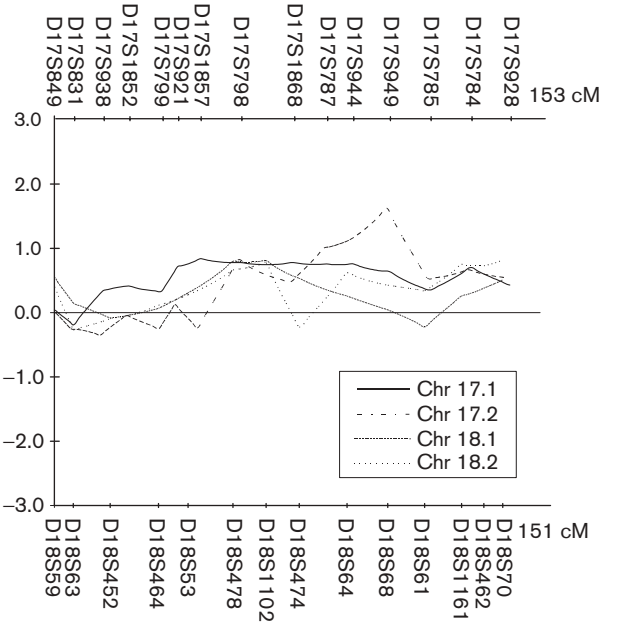
Phenotype identification and classification is a fundamental feature in the genetic study of bipolar disorders. It is necessary to bear in mind the difficulties in the study related to mental disorders because of diagnosis instability, as our results show, two diagnostic changes in 3 years of follow up. In addition, healthy young individuals could be considered as normal in cases in which they are carrying genes of vulnerability, which are not yet expressed. Moreover, we must not obviate the gene-by-environment interaction evidenced in any mental ill-

Fig. 2



(a) LOD score values detected at chromosome 17 following criteria 1 and 2 for diagnosis, and dominant or recessive transmission. (b) LOD score values detected at chromosome 18 following criteria 1 and 2 for diagnosis, and dominant or recessive transmission.

Fig. 3



Values of NPL_{all} obtained for chromosomes 17 and 18, following criteria 1 and 2 for diagnosis.

nesses (Caspi *et al.*, 2003). Some studies have included several diagnostic categories, such as BPI, BPII, recurrent depression and schizoaffective disorders, as being affected by linkage analyses, whereas other studies have focused only on BPI. In our work, we have introduced both criteria (one narrow, only BPI, and two broad, BPI and BPII plus schizoaffective disorder and recurrent major depression), with a few very similar results.

The chromosomal localization of the markers D17S831 (17p13.3) and, at chromosome 18, D18S63 (18p11.3), D18S452 and D18S53 (18p11.2), D18S61 and D18S1161 (18q22) could allow one to discard these regions as carriers of a gene for affective disorder in the families studied. The 18p11.3 region was described as a positive linkage by McInnes *et al.* (2001), and region 18p11.2 has also been presented as a positive linkage in numerous studies (Berrettini *et al.*, 1994; Stine *et al.*, 1995; Nöthen *et al.*, 1999; Segurado *et al.*, 2003). These linkages have not been reproduced in the families studied here. Moreover, the lack of linkage with the two markers located in region 18q22 does not confirm the linkage findings established by Schulze *et al.* (2003) and McMahon *et al.* (1997, 2001).

The data obtained in chromosome 17 suggested two possible regions that could contain a susceptibility gene: 17q11 (D17S1857, D17S798) and especially 17q24-qter (D17S949, D17S928). The maximum significant linkage was to D17S949 (17q24), following a recessive mode of inheritance and taking into account only the bipolar disorder patients (criteria 1). Other authors (Ewald *et al.*, 1997; Fallin *et al.*, 2004) have showed evidence for one bipolar disorder locus on 17q24-25.

Several recent studies have suggested the presence of a bipolar disorder susceptibly locus on the 18q12 region (i.e. Maziade *et al.*, 2005; Walss-Bass *et al.*, 2005). We have also found a positive LOD score value for D18S478 marker located in this region.

The linkage study on chromosomes 17 and 18 carried out in families from the Balearic Archipelago, with a high expression of mental illnesses, replicates recent signifi-

cant linkage findings detected on 17q24 and 18q12. The positive linkage found by other authors on the regions 18p11.2 and 18p11.3, however, has not been reproduced in this study.

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