



Case–control association study of 14 variants of CREB1, CREBBP and CREM on diagnosis and treatment outcome in major depressive disorder and bipolar disorder

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ABSTRACT

Some evidence suggests an association between genetic variants within the cyclic adenosine monophosphate (cAMP) response element-binding protein (*CREB*), CREB binding protein (*CREBBP*) and cAMP response element-modulator (*CREM*) and several psychiatric disorders. The present study investigated whether some single nucleotide polymorphisms (SNPs) within these genes could be associated with major depressive disorder (MDD) and bipolar disorder (BD) and whether they could predict clinical outcomes in Korean inpatients treated with antidepressants and mood stabilizers, respectively. The sample comprised 145 patients with MDD, 132 patients with BD and 170 psychiatrically healthy controls. Participants were genotyped for 14 SNPs within *CREB1*, *CREBBP* and *CREM*. Baseline and final clinical measures, including the Montgomery-Åsberg Depression Rating Scale and Young Mania Rating Scale for patients with MDD and BD, respectively, were recorded. All p-values were 2-tailed, and statistical significance was conservatively set at the 0.006 level in order to reduce the likelihood of false positive results. We failed to observe any association of the 14 SNPs genotypes or alleles with clinical improvement, response and remission rates as well as final outcomes in any of such disorders. Our findings suggest that the 14 SNP under investigation in our study do not influence diagnosis and treatment response in patients with MDD and BD. However, taking into account the several limitations of our study, further research is needed to draw more definitive conclusions.

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1. Introduction

CREB1 (cAMP response element-binding protein) is a transcription factor activated by the phosphorylation of a key serine residue by a kinase stimulated by cyclic adenosine monophosphate (cAMP), calcium, growth factors and stress signals. Such phosphorylation allows for the recruitment of CREBBP (CREB binding protein), a large co-activator that activates the transcription of genes containing the cAMP response element (CRE) in their promoters (De Cesare et al., 2000; Mayr and Montminy, 2001; Lonze and Ginty, 2002).

The gene coding for CREB1, located on chromosome 2q34, is of particular interest for psychiatric research because its product plays a key role into neuronal (and other cellular) signal transduction, and it has been implicated in synaptogenesis, neural connections, and long-term

potentiation (LTP) (Silva et al., 1998). Indeed, several studies showed that CREB1 is implicated in major depressive disorder (MDD) (Zubenko et al., 2003), although negative results have been reported as well (Burcescu et al., 2005; Hettema et al., 2009), and in bipolar disorder (BD) (Mamdani et al., 2008). In addition, CREB1 might play an important role in the neurobiology of suicide (Dwivedi et al., 2003; Young et al., 2004), as shown by observations suggesting that its signaling cascade is up-regulated in brains of depressed suicides and that this alteration is not related to antidepressant treatments (Odagaki et al., 2001). Also, CREB1 has been found to be associated with the mechanism of action of antidepressant treatments (Dowlatshahi et al., 1998) and with antidepressant response in patients suffering from MDD (Koch et al., 2002; Yamada et al., 2003; Wilkie et al., 2007). Furthermore, recent studies have shown that some genetic polymorphisms within *CREB1* could be associated with treatment resistance (Serretti et al., 2011) and with lithium response in patients with BD (Mamdani et al., 2008).

CREBBP is encoded by a gene located on chromosome 16p13.3. This protein has an intrinsic histone acetyltransferase activity and also acts as a scaffold to stabilize additional protein interactions with the transcription complex. Mutations in *CREBBP* cause Rubinstein-Taybi syndrome

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(RTS) (Murata et al., 2001; Bartsch et al., 2005; Sharma et al., 2010), and chromosomal translocations involving this gene have been associated with acute myeloid leukemia (Shigeno et al., 2004). Genetic and pharmacological studies in a variety of organisms have demonstrated that, among other functions, CREB–CREBBP signaling regulates LTP, a cellular mechanism that underlies memory formation (Silva et al., 1998; Kandel, 2001). In accordance with such observation, Beglopoulos and Shen showed that reduced CREB–CREBBP activity might contribute to the pathogenesis of sporadic Alzheimer's disease (AD), whereas elements which enhance CRE-dependent gene expression might be beneficial for the treatment of AD (Beglopoulos and Shen, 2006). More recently, polymorphisms within *CREBBP* were studied in well-characterised BD and early onset MDD population and correlated with treatment outcomes showing, however, no influence on antidepressant response (Wilkie et al., 2007).

CREBBP can also interact with CREM (cAMP response element-modulator), a protein that is highly homologous to CREB (Laurance et al., 1997). CREM, which is encoded by a gene located on chromosome 10p11, is a nuclear transcription factor that mediates cAMP action by binding to CRE in the promoter regions of cAMP-dependent genes (Foulkes et al., 1991). It plays a key physiological and developmental role within the hypothalamic-pituitary-gonadal axis (Sassone-Corsi, 1998). Several studies provided evidence for a susceptibility locus for panic disorder within *CREM* (Domschke et al., 2003; Hamilton et al., 2004). Moreover, CREM knock-out mice exhibit significantly less anxiety behavior than wild-type mice (Maldonado et al., 1999) and mice that lack both CREB and the CREB family member CREM in the postnatal forebrain exhibit age-dependent neurodegeneration (Mantamadiotis et al., 2002). Note also that the lack of *CREB1/CREM* in neural tissue leads to increased synaptogenesis and spontaneous neural network activity specifically at early developmental stages where they are required for neural activity-dependent synaptogenesis, refinement, and plasticity (Aguado et al., 2009). Overall, such findings suggest that several genetic variants in *CREB*, *CREBBP* and *CREM* could play an important role in the aetiology of several psychiatric disorders as well as in the response to some of their treatments.

On the basis of such observations, the primary aim of the present paper is to investigate whether specific single nucleotide polymorphisms (SNPs) within *CREB1* (rs2709377 and rs6740584), *CREBBP* (rs2239317, rs2239316, rs3025702, rs130021, rs130005, rs129974 and rs9392) and *CREM* (rs1148247, rs4934735, rs12775799, rs6481941 and rs16935888) could be associated with MDD and BD in an independent sample of Korean in-patients and whether the same variants could predict clinical outcome in such groups of patients treated with antidepressants and mood stabilizers respectively.

2. Experimental procedure

2.1. Subjects

The sample under investigation in the present study comprised 145 in-patients suffering from MDD and 132 in-patients with BD during an acute manic episode who were consecutively recruited at the Department of Psychiatry of the Catholic University of Korea College of Medicine, Seoul, Korea. Patients were eligible for inclusion if they had a documented clinical diagnosis of MDD or BD according to the DSM-IV criteria, as assessed by the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998).

There was not any particular restriction with regard to treatments, concomitant comorbidities and first vs. following episodes of disease. However, patients were excluded if they had current severe or unstable medical and neurological conditions, current treatment with a long-acting antipsychotic, concomitant alcohol and substance abuse disorders and if they were not of Korean ethnicity. The choice not to use excessively tight inclusion and exclusion criteria was motivated by the decision to include a sample of subjects that could be representative of usual psychiatric in-patients in Korea. A further sample of 170 Korean psychiatrically healthy subjects, who underwent the same assessment as psychiatric patients to exclude possible psychiatric disorders and who derived from the same location as the psychiatric patients included in the present study, was also included to compare genotype and allelic frequencies among the three populations of subjects under investigation.

All patients admitted to the hospital were assessed for the severity of illness at baseline and at discharge by means of psychometric questionnaires specific for each disorder under investigation. More in detail, MDD severity was assessed by means of

the Hamilton Rating Scale for Depression (HAMD) (Hamilton, 1960) whereas mania severity in patients with BD was assessed by means of the Young Mania Rating Scale (YMRS) (Young et al., 1978). Scorers were trained with the specific instruments with good inter-rater reliability ($\kappa > 0.8$). Additionally, the following clinical and demographic variables were recorded: gender, age, clinical subtypes, age at onset, familiar history of psychiatric disorders, lifetime suicide attempts, duration of admission, drugs at discharge and use of concomitant anxiolytics. The study protocol was approved by the institutional review board (approval number HC10TISI0031). All patients (18–65 years old) provided written informed consent before participating into the study.

2.2. Outcome measures

The main outcome measures of the present study were: 1) differences between genotype and allelic frequencies in patients with MDD, BD and healthy control subjects and 2) influences of the SNPs under investigation on clinical improvement in the two groups of psychiatric patients mentioned above separately analyzed. Further outcomes of interest comprised the effects of included SNPs on clinical and demographic variables mentioned above as well as on response and remission rates. Both continuous and categorical analyses were performed. In accordance with previous studies, response was *a priori* defined as a $\geq 50\%$ reduction of symptoms from baseline to discharge (Hirschfeld et al., 2004; Riedel et al., 2010). Remission was defined as a HAMD score ≤ 7 at discharge for patients with MDD (Riedel et al., 2010) and as a YMRS score ≤ 12 for patients with BD (Perlis et al., 2006).

2.3. DNA analysis

Genomic DNA was extracted from blood by standard methods and quantified. The high-throughput genotyping method using pyrosequencer (Biotage AB, Sweden) was used for genotyping two SNPs (rs2709377 and rs6740584) within *CREB1*, seven SNPs (rs2239317, rs2239316, rs3025702, rs130021, rs130005, rs129974, and rs9392) within *CREBBP* and five SNPs (rs1148247, rs4934735, rs12775799, rs6481941 and rs16935888) within *CREM* (Table 1). PCR primers (Bioneer, Daejeon, Korea) and sequencing primers (Bioneer, Daejeon, Korea) used for the pyrosequencing assay were designed by using the Pyrosequencing Assay Design Software v1 (Biotage AB, Sweden) and one primer of each primer set was biotinylated.

2.4. Statistical analysis

Statistical analyses were performed using the 'Statistica' package (StatSoft, 1995). Differences in the allelic and genetic frequencies between healthy subjects and patients with MDD and BD as well as effects of such variants on response rates and further categorical outcomes were calculated using χ^2 statistics. The influence of the SNPs under investigation and continuous outcomes was calculated using analysis of variance (ANOVA). Clinical improvement on MADRS total scores was calculated according to the following formula:

$$\left(\frac{\text{HAMD}_{\text{final}} - \text{HAMD}_{\text{baseline}}}{\text{HAMD}_{\text{baseline}}} \right) \times 100$$

The same formula was adapted to calculate the improvement measured by the YMRS as well. In case of positive findings, clinical variables correlated with the outcome measures under investigation were added as covariates, so as to investigate possible stratification effects. Haploview 3.2 was used to generate a linkage disequilibrium (LD) map and to test for Hardy-Weinberg equilibrium (HWE) (Barrett et al., 2005). Tests for associations using multi-marker haplotypes were performed using the statistics environment "R" (<http://www.R-project.org>), package "haplo.score", to compare clinical and socio-demographic outcomes among different haplotypes. Permutations ($n = 10,000$) were performed to estimate the global significance of the results for all haplotypes analyses and to validate the expectation-maximization values. All p -values were 2-tailed, and statistical significance was conservatively set at the 0.006 level (corresponding to the Bonferroni correction for the 8 blocks of SNPs under investigation) in order to reduce the likelihood of false positive results.

2.5. Power analysis

With these parameters we had a sufficient power (0.80) to detect a small-medium effect size ($\omega = 0.185$) that, as an example, corresponded to an odds ratio of 2.12 between the two groups of patients and the group of controls, and to detect medium-large ($d = 0.3$) effect sizes for patients with MDD and BD, respectively, carrying the GG genotype of rs129974 as compared with those carrying the GT genotype (Cohen, 1988). Such effect sizes corresponded to the possibility of detecting final differences on both the HAMD and the YMRS of 2 points.

3. Results

3.1. Socio-demographic features of MDD and BD patients and controls

Socio-demographic features such as gender, age and further clinical and socio-demographical variables are reported in Table 2. For

Table 1
CREB1, *CREBBP* and *CREM* SNPs considered in this study.

SNP ID	Position	Distance	Alleles	Location
<i>CREB1</i>				
rs2709377	208393907 (−26453)	−35444	A/T	Promoter
rs6740584	208429351 (8992)		C/T	Intron
<i>CREBBP</i>				
rs2239317	3920740 (9178)	6745	C/G	Intron
rs2239316	3913995 (15923)		A/G	Intron
rs3025702 (69278)	3860640	53355	A/G	Coding exon
rs130021	3832471 (97447)		A/G	Intron
rs130005 (101570)	3828348	4123	A/G	Intron
rs129974	3795292 (134626)		G/T	Coding exon
rs9392	3775169 (154749)	20123	G/A	3' UTR
<i>CREM</i>				
rs1148247	35496946 (70183)	216	G/A	Intron
rs4934735	35496730 (69967)		A/G	Intron
rs12775799	35488264 (61501)	8466	C/T	Intron
rs6481941	35440141 (13378)		G/A	Intron
rs16935888	35432405 (5642)	7736	T/C	Intron

* Absolute chromosomal position. The relative position to the start codon is given in parenthesis. All data from www.snpper.chip.org.

control subjects only data about gender and age were collected. There were significant differences among the three groups of subjects with regard to age and gender (gender: $\chi^2 = 6.25$, $p = 0.04$; age: $F = 5.25$, $p = 0.005$). In particular, among patients with MDD, we observed a significantly lower proportion of male patients as compared with patients with BD and healthy controls. In addition, patients with BD were significantly younger than patients with MDD. Therefore, age and gender were added as covariates in case-control analyses. There were no associations between any of the SNPs under investigation and baseline clinical variables.

3.2. Hardy Weinberg equilibrium (HWE) and linkage disequilibrium for *CREB1*, *CREBBP* and *CREM* SNPs

One out of 14 SNPs under investigation was not polymorphic in the present study (rs2709377 in *CREB1*) and was therefore systematically excluded from the present study. The large majority of SNPs under investigation were in HWE in the whole sample (rs2239317: $p = 0.88$, rs2239316: $p = 0.43$, rs3025702: $p = 0.79$, rs130021: $p = 0.21$, rs130005: $p = 0.98$, rs129974: $p = 0.76$, rs9392: $p = 0.87$, rs1148247: $p = 0.56$, rs4934735: $p = 1.0$, rs12775799: $p = 1.0$, rs6481941: $p = 1.0$, rs16935888: $p = 1.0$), with rs6740584 being the

only exception ($p = 4.3649E-28$). Strong LD was observable between rs129974, rs130005 and rs130021, between rs130021 and rs3025702, between rs3025702 and rs2239316, and between rs2239316 and rs2239317 within *CREBBP* and between all SNPs within *CREM* (Figs. 1 and 2). Patients and healthy controls separately analyzed yielded similar results (data not shown).

3.3. Differences between genotype and allelic frequencies in MDD and BD patients and in healthy controls

There were no significant differences between allelic and genotype frequencies in MDD and BD patients and healthy controls (Table 3; all p -values > 0.006).

3.4. Influence of *CREB1*, *CREBBP* and *CREM* variants on clinical improvement in MDD and in BD patients

We did not observe any significant association between the genetic variants under investigation in the present study and HAMD and YMRS scores in patients with MDD and BD respectively (Table 4; all p -values > 0.006). The haplotype analysis focusing on the sliding windows haplotypes mentioned above did not find any significant association either.

3.5. Influence of *CREB1*, *CREBBP* and *CREM* variants on response and remission rates and further clinical and socio-demographic variables

We did not observe any significant association between alleles and genotypes under investigation and clinical and socio-demographic variables. Furthermore, none of the haplotypes under investigation was associated with any of such measures.

4. Discussion

The present article explored whether specific SNPs within *CREB1*, *CREBBP* and *CREM* could be associated with MDD and BD and whether the same variants could predict clinical outcomes. In addition we explored whether such variants could be associated with several clinical and socio-demographic variables of our sample. We found no significant differences between allelic and genotype frequencies in MDD and BD patients and healthy controls. Our inability to detect an association between common variants in the

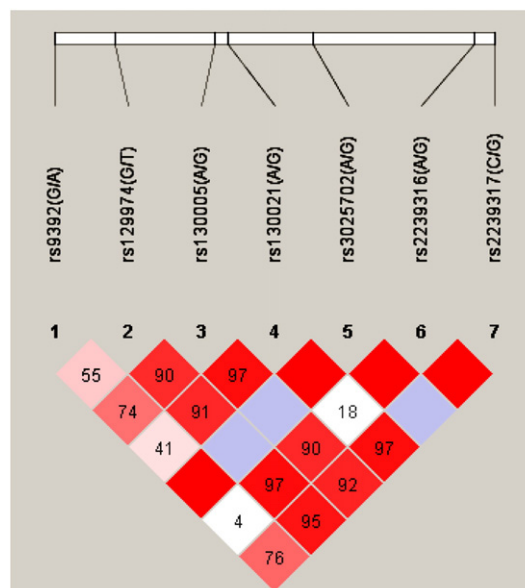


Fig. 1. Linkage disequilibrium of *CREBBP* SNPs under investigation in the present study.

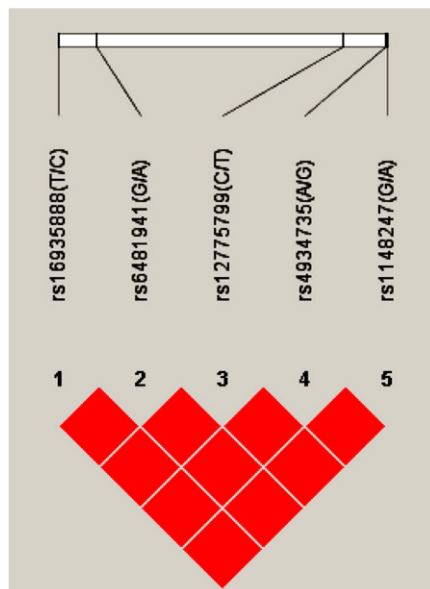


Fig. 2. Linkage disequilibrium of *CREM* SNPs under investigation in the present study.

CREB1 and MDD and BD is consistent with the null findings reported in previously published association studies of *CREB1* and liability to mood disorders (Burcescu et al., 2005; Mamdani et al., 2008; Hettema et al., 2009). However, such finding is in contrast with previous studies in which *CREB1* variants contributed to the pathophysiology of MDD (Zubenko et al., 2003; Liu et al., 2010). Possible explanations for the discrepancy of these findings could be that in other studies an association was found for women but not for men or to further differences across the studies in terms of ethnicity, study design and SNPs under investigation. Moreover, we did not observe any significant association between the genetic variants under investigation and response or remission in patients with MDD and BD, and the haplotype analyses did not find any significant association as well. Unlike our results, the majority of previous studies showed an association between these genes, in particular *CREB1*, and action of antidepressant treatment (Dowlatshahi et al., 1998), and with antidepressant response in MDD patients (Koch et al., 2002; Yamada et al., 2003; Wilkie et al., 2007). Moreover, our group (Serretti et al., 2011) and Mamdani and colleagues (Mamdani et al., 2008) showed an association between some polymorphisms within *CREB1* and treatment resistance as well as lithium response in BD patients. Note, however, that negative findings have been observed as well, as shown by the results of Wilkie and colleagues showing no influence of some polymorphisms within *CREBBP* on antidepressant response in MDD and BD patients (Wilkie et al., 2007).

Because of the dearth of studies specifically dealing with the present topic, particularly with regard to *CREM*, we could make a preliminary suggestion that the genetic variants under investigation in the present study could be associated neither with MDD and BD nor with response to their treatments. However, several limitations should be taken into account before definitive conclusions are drawn from the present study.

First of all, the limited sample size of our study could raise concerns as to whether negative findings observed in this study could simply reflect the lack of power to detect small differences such as those that are likely to be associated with single SNPs. Second, the use of several drugs with different mechanisms of action for each cohort of patients makes it impossible to draw definitive conclusions with regard to the influence of the SNPs under investigation on specific drugs or classes of drugs. Also, the duration of hospitalization

in the present study could be considered as insufficient to ascertain a lack of response and remission, though this time frame is consistent with common clinical practice (Zimmerman et al., 2002). Furthermore, we obtained only limited information about some clinical and socio-demographic variables which was particularly evident with regard to familiar history of psychiatric disorders in patients with BD, and it is therefore unclear whether additional information could have altered our results.

In conclusion our findings suggest that the SNPs under investigation in our study do not influence diagnosis and response to treatments in patients with MDD and BD who were naturalistically treated with antidepressants and mood stabilizers, respectively. However, taking into account the limitations of the present study, further research is needed to confirm our findings in larger samples, in out-patients and in patients treated with specific drugs or classes of drugs.

Table 2
Clinical and demographic characteristics of the subjects.

Clinical and demographic characteristics of the sample	MDD (n = 145)	BD (n = 132)	Healthy controls (n = 170)
Gender			
Males	75(52%)	87(66%)	105(62%)
Females	70(48%)	45(34%)	65(38%)
Age	41.37 ± 14.07	36.35 ± 11.60	38.83 ± 12.80
HAMD			
Baseline	28.21 ± 6.52		
Discharge	13.70 ± 8.01		
YMRS			
Baseline		33.27 ± 9.09	
Discharge		19.80 ± 5.25	
Response			
Yes	88(61%)	33(25%)	
No	57(39%)	99(75%)	
Remission			
Yes	35(24%)	10(8%)	
No	110(76%)	122(92%)	
Clinical subtypes			
MDD/BD without PF	105(72%)	73(55%)	
MDD/BD with PF	11(8%)	57(43%)	
Dysthymia	4(3%)	-	
MDD NOS	5(4%)	-	
Missing value	20(13%)	2(2%)	
Age at onset	38.08 ± 13.29	26.58 ± 10.19	
Familiar history of psychiatric disorders			
Yes	30(21%)	42(32%)	
No	92(63%)	35(26%)	
Missing values	23(16%)	55(42%)	
Suicide attempts			
Yes	36(25%)	22(17%)	
No	92(63%)	89(67%)	
Missing value	17(12%)	21(16%)	
Duration of admission (days)	32.31 ± 20.55	33.66 ± 21.07	
Drug			
Paroxetine	40(27%)	-	
Venlafaxine	35(24%)	-	
Fluoxetine	23(16%)	-	
Mirtazapine	21(14%)	-	
Lithium	-	41(31%)	
Valproate	-	56(42%)	
Other	3(3%)	5(4%)	
Missing value	23(16%)	30(23%)	
Concomitant anxiolytics			
Alprazolam	30(21%)	5(4%)	
Lorazepam	73(50%)	82(62%)	
Clonazepam	3(2%)	3(3%)	
Buspiron	4(3%)	7(5%)	
None	35(24%)	35(26%)	

HAMD = Hamilton Rating Scale for Depression; YMRS = Young Mania Rating Scale; MDD = Major depressive disorder; BD = Bipolar disorder; PF = psychotic features, NOS, Not Otherwise Specified.

Table 3
Differences between genotype and allelic frequencies among subjects in the present study.

MDD	BD	Healthy subjects	χ^2	p-value
<i>Genotype frequencies</i>				
<i>CREB1</i>				
rs6740584			1.15	0.89
CC:106(73%)	CC:91(69%)	CC:121(71%)		
TC:21(15%)	TC:22(17%)	TC:23(14%)		
TT:18(12%)	TT:19(14%)	TT:26(15%)		
<i>CREBBP</i>				
rs2239317			2.95	0.81
CC:66(46%)	CC:59(45%)	CC:85(50%)		
CG:64(44%)	CG:61(46%)	CG:69(41%)		
GG:15(10%)	GG:12(9%)	GG:15(9%)		
rs2239316			4.56	0.34
AA:58(40%)	AA:59(45%)	AA:59(35%)		
AG:66(46%)	AG:61(46%)	AG:89(52%)		
GG:21(14%)	GG:12(9%)	GG:22(13%)		
rs3025702			3.33	0.50
AA:133(92%)	AA:126(95%)	AA:159(93%)		
AG:12(8%)	AG:6(5%)	AG:10(6%)		
GG:0(0%)	GG:0(0%)	GG:1(1%)		
rs130021			4.55	0.34
AA:39(27%)	AA:48(36%)	AA:57(34%)		
AG:77(53%)	AG:56(43%)	AG:74(43%)		
GG:29(20%)	GG:28(21%)	GG:39(23%)		
rs130005			1.95	0.75
AA:67(46%)	AA:58(44%)	AA:87(51%)		
AG:64(44%)	AG:61(46%)	AG:66(39%)		
GG:14(10%)	GG:13(10%)	GG:17(10%)		
rs129974			2.03	0.73
GG:102(70%)	GG:93(70%)	GG:115(68%)		
TG:40(28%)	TG:33(25%)	TG:50(29%)		
TT:3(2%)	TT:6(5%)	TT:5(3%)		
rs9392			3.02	0.55
GG:46(32%)	GG:35(26%)	GG:59(35%)		
AG:69(47%)	AG:71(54%)	AG:83(49%)		
AA:30(21%)	AA:26(20%)	AA:28(16%)		
<i>CREM</i>				
rs1148247			3.23	0.52
AG:65(44%)	AG:56(42%)	AG:84(49%)		
GG:67(46%)	GG:58(44%)	GG:71(42%)		
AA:13(9%)	AA:18(14%)	AA:15(9%)		
rs4934735			7.57	0.11
AA:70(48%)	AA:73(55%)	AA:102(60%)		
AG:63(44%)	AG:47(36%)	AG:62(36%)		
GG:12(8%)	GG:12(9%)	GG:6(4%)		
rs12775799			10.47	0.11
CC:69(48%)	CC:72(55%)	CC:102(60%)		
TC:64(44%)	TC:48(36%)	TC:62(36%)		
TT:12(8%)	TT:12(9%)	TT:6(4%)		
rs6481941			7.95	0.24
GG:68(47%)	GG:70(53%)	GG:98(58%)		
AG:63(44%)	AG:48(36%)	AG:65(38%)		
AA:13(9%)	AA:13(11%)	AA:7(4%)		
rs16935888			4.19	0.38
TT:85(59%)	TT:82(62%)	TT:114(67%)		
TC:51(35%)	TC:44(33%)	TC:52(31%)		
CC:9(6%)	CC:6(5%)	CC:4(2%)		
<i>Allele frequencies</i>				
<i>CREB1</i>				
rs6740584			0.88	0.64
C:233(80%)	C:204(77%)	C:265(78%)		
T:57(20%)	T:60(23%)	T:75(22%)		
<i>CREBBP</i>				
rs2239317			0.90	0.64
C:196(68%)	C:179(68%)	C:239(71%)		
G:94(32%)	G:85(32%)	G:99(29%)		
rs2239316			3.18	0.20
A:182(63%)	A:179(68%)	A:207(61%)		
G:108(37%)	G:85(32%)	G:133(39%)		
rs3025702			1.53	0.46
A:278(96%)	A:258(98%)	A:328(96%)		
G:12(4%)	G:6(2%)	G:12(4%)		
rs130021			0.95	0.62
A:155(53%)	A:152(58%)	A:188(55%)		
G:135(47%)	G:112(42%)	G:152(45%)		

Table 3 (continued)

MDD	BD	Healthy subjects	χ^2	p-value
rs130005			0.92	0.63
A:198(68%)	A:177(67%)	A:240(71%)		
G:92(32%)	G:87(33%)	G:100(29%)		
rs129974			0.36	0.83
G:244(84%)	G:219(83%)	G:280(82%)		
T:46(16%)	T:45(17%)	T:60(18%)		
rs9392			2.06	0.36
G:161(56%)	G:141(53%)	G:201(59%)		
T:129(44%)	T:123(47%)	T:139(41%)		
<i>CREM</i>				
rs1148247			0.77	0.68
G:199(69%)	G:172(65%)	G:226(66%)		
A:91(31%)	A:92(35%)	A:114(33%)		
rs4934735			5.70	0.06
A:203(70%)	A:193(73%)	A:266(78%)		
G:87(30%)	G:71(27%)	G:74(22%)		
rs12775799			6.15	0.05
C:202(70%)	C:191(73%)	C:266(22%)		
T:88(30%)	T:71(27%)	T:74(22%)		
rs6481941			4.84	0.09
G:199(69%)	G:188(72%)	G:261(77%)		
A:89(31%)	A:74(28%)	A:79(23%)		
rs16935888			3.66	0.16
T:221(76%)	T:208(79%)	T:280(82%)		
C:69(24%)	C:56(21%)	C:60(18%)		

MDD = Major depressive disorder; BD = Bipolar disorder.

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Table 4
Demographic and clinical variables stratified according to *CREB1*, *CREBBP* and *CREM* genotypes.

Genotypes	Females (%) [*]	Age (years)	Age at onset (years)	Positive familial history of psychiatric disorders (%) [*]	Suicide attempts	Baseline Hamilton scores	Final Hamilton scores	Baseline YMRS scores	Final YMRS scores
Major depressive disorder									
<i>CREB1</i>									
rs6740584									
CC	52(49%)	42.13±14.19	37.90±13.70	23(22%)	28(26%)	28.79±6.38	13.99±7.76	-	-
TC	11(52%)	42.14±11.47	38.38±9.71	2(9%)	5(24%)	24.90±6.33	11.95±7.92	-	-
TT	7(39%)	35.73±17.88	38.87±15.64	5(28%)	3(17%)	26.93±6.67	13.33±9.68	-	-
<i>CREBBP</i>									
rs2239317									
CC	35(53%)	39.15±13.40	35.50±12.40	12(18%)	15(23%)	26.98±6.61	12.59±6.64	-	-
CG	30(47%)	43.37±14.17	40.38±12.47	15(23%)	17(27%)	29.16±6.26	14.13±8.82	-	-
GG	5(33%)	42.31±18.22	39±18.98	8(53%)	4(27%)	29.53±6.77	15.54±9.42	-	-
rs2239316									
AA	28(48%)	41.87±15.27	39.16±14.22	13(22%)	16(28%)	28.33±6.31	13.93±8.56	-	-
AG	34(51%)	42.28±13.86	38.15±12.51	14(21%)	16(24%)	27.85±6.67	13.53±7.96	-	-
GG	8(38%)	36.44±12.16	34.12±12.96	3(14%)	4(19%)	27.06±7.00	12.62±6.21	-	-
rs3025702									
AA	63(47%)	41.37±14.64	38.01±13.50	26(19%)	35(26%)	28.04±6.51	13.58±8.14	-	-
AG	7(58%)	41.70±9.87	39±11.12	4(33%)	1(8%)	26.90±6.90	13.70±6.20	-	-
rs130021									
AA	23(59%)	37.17±11.32	35.83±11.03	9(23%)	7(18%)	22.23±6.77	13.46±6.46	-	-
AG	39(51%)	42.26±40	38.19±12.73	16(21%)	22(29%)	29.33±6.39	13.08±8.43	-	-
GG	8(28%)	44.96±17.86	41.04±17.39	5(17%)	7(24%)	27.85±6.46	15.29±8.71	-	-
rs130005									
AA	34(51%)	40.05±13.21	37.15±12.58	11(16%)	14(21%)	27.47±6.88	12.73±6.54	-	-
AG	31(48%)	42.54±14.56	38.81±12.72	16(25%)	18(28%)	28.25±6.12	14.02±8.95	-	-
GG	5(36%)	42.31±18.22	39±18.98	3(21%)	4(29%)	28.77±6.95	15.54±9.42	-	-
rs129974									
TT	1(33%)	33±14.14	24.50±6.36	1(33%)	2(67%)	26±2.83	13±5.66	-	-
TG	21(52%)	40.95±13.70	38.35±13.85	7(17%)	8(20%)	28.38±7.15	12.70±8.34	-	-
GG	48(47%)	41.76±14.63	38.27±13.12	22(22%)	26(25%)	27.83±6.34	13.96±7.93	-	-
rs9392									
AA	13(43%)	42.30±16.24	38.33±15.72	8(27%)	9(30%)	26.81±6.74	13.48±8.24	-	-
AG	35(51%)	44±13.03	39.98±12.27	11(16%)	15(22%)	28.47±6.26	13.73±8.60	-	-
GG	22(48%)	36.62±14.01	34.87±12.83	11(24%)	12(26%)	27.90±6.84	13.42±6.92	-	-
<i>CREM</i>									
rs1148247									
AA	5(38%)	44.44±16.11	40.89±13.86	2(15%)	3(23%)	27.33±6.42	14.78±9.86	-	-
AG	31(48%)	42.29±14.67	37.70±14.49	13(20%)	20(31%)	27.57±7.62	13.62±8.60	-	-
GG	34(51%)	40.05±13.76	38.05±12.09	15(22%)	13(19%)	28.43±5.30	13.37±7.15	-	-
rs4934735									
AA	38(54%)	40.31±14.65	37.36±13.14	13(19%)	18(26%)	27.52±6.76	13.33±8.32	-	-
AG	26(41%)	43±13.97	39.19±13.73	13(21%)	14(22%)	27.90±6.74	13.78±7.77	-	-
GG	6(50%)	39.17±14.49	36.42±12.57	4(33%)	4(33%)	30.42±3.23	14±7.97	-	-
rs12775799									
TT	6(50%)	39.17±14.49	36.42±12.57	4(33%)	4(33%)	30.42±3.23	14±7.97	-	-
TC	26(41%)	43.12±13.88	39.30±13.64	13(20%)	14(22%)	27.88±6.68	13.59±7.83	-	-
CC	38(55%)	40.15±14.72	37.22±13.20	13(19%)	18(26%)	27.53±6.82	13.50±8.28	-	-
rs6481941									
AA	7(54%)	38.85±13.92	35.38±12.60	5(38%)	4(31%)	30.84±3.46	13.92±7.63	-	-
AG	25(40%)	43.19±13.93	39.59±13.58	12(19%)	14(22%)	27.81±6.66	13.69±7.81	-	-
GG	38(56%)	40.05±14.83	37.07±13.27	13(19%)	18(26%)	27.47±6.86	13.59±8.31	-	-
rs16935888									
TT	48(56%)	39.60±14.31	36.76±13.08	15(18%)	23(27%)	27.12±6.76	12.70±7.81	-	-
TC	18(35%)	44.28±14.06	40±13.87	12(23%)	10(20%)	28.85±6.44	14.87±8.16	-	-
CC	4(44%)	41.78±14.64	39.44±12.15	3(33%)	3(33%)	30.44±3.43	14.55±8.57	-	-
Bipolar disorder									
<i>CREB1</i>									
rs6740584									
CC	31(34%)	37.08±11.01	27.08±9.90	28(31%)	15(16%)	-	-	33.44±8.57	18.52±5.16
TC	8(36%)	35.90±14.00	25.33±10.82	9(41%)	4(18%)	-	-	32.38±9.38	19±6.14
TT	6(32%)	36.44±11.68	26.67±10.75	5(26%)	3(16%)	-	-	30.94±9.98	-
<i>CREBBP</i>									
rs2239317									
CC	18(30%)	37.81±13.14	26.94±9.60	18(30%)	9(15%)	-	-	-	19.66±5.62
CG	24(39%)	36.07±10.65	26.96±10.64	20(33%)	12(20%)	-	-	-	19.84±4.58
GG	9(75%)	35.54±8.12	24.36±10.46	4(33%)	1(8%)	-	-	31.92±8.96	19.18±5.55
								34.77±8.89	
								27.73±5.95	
rs2239316									
AA	39(66%)	34.11±10.21	25.96±10.59	20(34%)	9(15%)	-	-	-	19.74±4.58
AG	23(38%)	38.00±11.79	27.21±9.69	17(28%)	10(16%)	-	-	33.41±8.74	19.62±5.08
GG	10(83%)	43.72±13.81	27.91±10.64	5(42%)	3(25%)	-	-	32.45±8.85	19.91±7.76
								32.54±10.59	

Table 4 (continued)

Genotypes	Females (%) ^a	Age (years)	Age at onset (years)	Positive familial history of psychiatric disorders (%) ^a	Suicide attempts	Baseline Hamilton scores	Final Hamilton scores	Baseline YMRS scores	Final YMRS scores
rs3025702									
AA	42(33%)	36.47±11.39	26.75±10.33	39(31%)	20(16%)	-	-	-	19.83±5.04
AG	38(50%)	42.83±14.55	26±5.06	3(50%)	2(33%)			32.64±8.66	17.17±6.18
								37.50±12.77	
rs130021									
AA	13(27%)	36.14±12.71	26.44±9.34	14(29%)	6(12%)	-	-	-	19.23±6.12
AG	23(41%)	37.08±10.71	28.08±10.78	18(32%)	12(21%)			31.81±9.28	20.08±4.58
GG	9(32%)	37.26±11.67	24.59±10.00	10(36%)	4(14%)			34.71±8.91	19.74±4.35
								31.15±7.88	
rs130005									
AA	16(28%)	37.58±13.15	26.33±9.38	18(31%)	8(14%)	-	-	-	19.48±5.66
AG	25(41%)	36.60±10.59	27.67±10.80	20(33%)	13(21%)		31.94±8.9	19.80±4.92	
GG	4(31%)	34.25±8.94	23.92±10.09	4(31%)	1(8%)		34.25±8.94	20.17±3.49	
							30.50±7.88		
rs129974									
TT	1(17%)	47.40±12.22	30.20±8.70	1(17%)	-	-	-	-	16.00±7.68
TG	9(27%)	36.60±11.17	26.03±9.76	7(21%)	5(15%)			26.60±12.60	19.77±6.26
GG	35(38%)	36.23±11.52	26.76±10.38	34(37%)	17(18%)			32.63±8.41	19.90±4.45
								33.34±8.81	
rs9392									
AA	4(15%)	38.21±9.87	23.25±9.26	6(23%)	2(8%)	-	-	-	20.96±4.75
AG	29(41%)	36.15±10.77	27.71±10.03	6(23%)	13(18%)			33.04±7.83	18.89±5.89
GG	12(34%)	37.03±14.41	27.29±10.69	13(37%)	7(20%)			32.88±9.37	20.45±4.29
								32.77±8.92	
CREM									
rs1148247									
AA	5(28%)	37.35±12.79	43.93±30.41	6(33%)	3(17%)	-	-	-	21.18±3.56
AG	18(32%)	36.60±11.17	24.79±9.21	15(27%)	8(14%)				19.60±5.63
GG	22(38%)	37.33±12.66	27.49±10.01	21(36%)	11(19%)			32.29±10.74	19.31±4.97
								32.43±7.81	
								33.55±9.43	
rs4934735									
AA	22(30%)	37.94±12.50	27.29±11.24	25(34%)	14(19%)	-	-	-	19.62±5.29
AG	17(36%)	34.16±8.64	25.30±8.28	13(28%)	6(13%)			33.48±8.91	19.37±5.19
GG	6(50%)	40.20±14.80	28.90±9.37	4(33%)	2(17%)			31.81±9.35	21.70±3.06
								33.40±6.91	
rs12775799									
TT	6(50%)	40.20±14.80	28.90±9.37	4(33%)	2(17%)	-	-	-	21.70±3.06 q
TC	17(36%)	34.16±8.64	25.30±8.29	13(28%)	6(13%)			33.40±6.91	19.37±5.19
CC	22(31%)	38.00±12.58	27.46±11.24	25(35%)	14(19%)			31.81±9.35	19.64±5.32
								33.61±8.92	
rs6481941									
AA	6(46%)	39.91±14.07	27.73±9.71	4(31%)	2(15%)	-	-	-	21.27±3.23
AG	19(40%)	34.91±10.14	25.51±8.16	14(29%)	7(15%)			32.18±7.70	19.51±5.20
GG	20(29%)	37.48±12.08	27.24±11.39	24(34%)	13(19%)			32.19±9.19	19.58±5.35
								33.53±9.02	
rs16935888									
TT	24(29%)	37.72±12.25	27.28±11.02	30(37%)	17(21%)	-	-	-	19.85±5.15
TC	17(39%)	34.54±9.22	25.44±8.47	10(23%)	4(9%)			33.38±8.72	19.15±5.27
CC	4(67%)	39.50±16.10	28.00±8.51	2(33%)	1(17%)			31.49±9.33	21.33±3.44
								35.67±8.33	

^aThe percentages are referred to the males/females ratio, to the positive/negative history of psychiatric disorders' and to positive/negative history of suicide attempts' ratios respectively relative to each genotype. HAMD = Hamilton Rating Scale for Depression; YMRS = Young Mania Rating Scale; MDD = Major depressive disorder; BD = Bipolar disorder; PF = psychotic features.

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