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ORIGINAL PAPER

Clinical and genetic factors associated with suicide in mood disorder patients

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Abstract Suicidality is a continuum ranging from ideation to attempted and completed suicide, with a complex etiology involving both genetic heritability and environmental factors. The majority of suicide events occur in the context of psychiatric conditions, preeminently major depression and bipolar disorder. The present study investigates clinical factors associated with suicide in a sample of 553 mood disorder patients, recruited within the 'Psy Pluriel' center, Centre Européen de Psychologie Médicale, and the Department of Psychiatry of Erasme Hospital (Brussels). Furthermore, genetic association analyses examining polymorphisms within COMT, BDNF, MAPK1 and CREB1 genes were performed in a subsample of 259 bipolar patients. The presence or absence of a previous suicide attempt and of current suicide risk were assessed. A positive association with suicide attempt was reported for younger patients, females, lower educated, smokers, those with higher scores on depressive symptoms and higher functional disability and those with anxiety comorbidity and familial history of suicidality in first- and second-degree relatives. Anxiety disorder comorbidity was the stronger predictor of current suicide risk. No associations were found with polymorphisms within COMT and BDNF genes, whereas significant associations were found with variations in rs13515 (MAPK1) and rs6740584 (CREB1) polymorphisms. From a clinical perspective, our study proposes several clinical characteristics, such as increased depressive symptomatology, anxiety comorbidity, functional disability and family history of suicidality, as correlates associated with suicide. Genetic risk variants in MAPK1 and CREB1 genes might be involved in a dysregulation of inflammatory and neuroplasticity pathways and are worthy of future investigation.

Keywords Depression · Bipolar · Mood disorder · Suicide · Single nucleotide polymorphism · Genetic association study

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Introduction

Mood disorders include major depressive (MDD) and bipolar (BD) disorders [1], common psychiatric conditions within the general population [2]. It has been estimated that up to 15 % of the population will experience at least one mood disorder episode during their lifetime [3], leading to moderate-to-severe impairment in working and social activities and accounting for a significant burden in terms of days lost. Although the majority of psychiatric diseases present an increased liability toward suicidal behavior [4], patients affected by mood disorders are exposed to the highest risk [5]: The mortality rates due to completed suicide are up to 15 % in MDD [6, 7] and 10 % in BD [4]. A strong relationship connects mood disorder episodes, in particular depressive states, with suicidal ideation and attempt [8]. Therefore, the assessment of suicidal risk and

the prevention of suicide attempt in patients suffering from mood disorders is crucial, even if an accurate evaluation often remains a challenge for psychiatrists.

Both retrospective and prospective studies have investigated suicidality in mood disorder patients, identifying several predisposing factors. The main demographic feature involved in increasing risk of suicide attempts is the female gender, whereas males are more likely to have a completed suicide [9–11]. Clinical factors that increase the risk of suicide attempt include: early onset of disease [12], high severity of depressive episodes [13], longer period of undiagnosed and untreated illness [14] and discontinuation of antidepressants [15]. A considerable number of studies relate suicide attempts and completions to feelings of hopelessness and higher scores on subjective depression levels [16–21]. Higher levels of suicidal tendencies have been suggested as the best predictor of completed suicide [18]. An increased likelihood of a suicide attempt has been described in persons who have experienced adverse life events [22] and use tobacco [8]. Among bipolar patients, additional risk factors for suicide attempts are the presence of rapid-cycling and mixed states [23] and depressive episodes at onset [24]; on the contrary, preponderance of manic episodes appears to be a risk-reducing factor [25]. A previous history of suicide attempt is the most reliable single predictor of future suicidal behavior (both attempted and completed suicide) in patients affected by mood disorders [20, 26–28]. Several comorbidities lead to an increased susceptibility toward suicidal conduct: anxiety disorders [23], eating disorders [29], alcohol and substance abuse [25, 30, 31], personality disorders [32] and anger-related/impulsive temperamental tracts [33]. Finally, in patients with positive anamnesis for a suicide attempt, a family history of mental illness [20] and suicidal behavior [28] is frequently found.

The heritability of completed suicide is about 40 % [34], with minor contribution of shared family environmental factors; nevertheless, the precise genetic predisposition has not been fully understood yet. Strong neurobiological evidence points toward serotonergic and noradrenergic dysfunction [35–37]. Dysregulation in serotonin (5-HT) neurotransmission also appears to be related to impulsive–aggressive behavior [38], which influences suicidal behavior as an intermediate phenotype [39]. Genetic studies have identified several candidate genes involved in the dopaminergic and other neurotransmitter pathways [40].

The catechol-O-methyltransferase (COMT) gene, located on chromosome 22, synthesizes an enzyme responsible for the degradation of catecholamines. The most studied variant (rs4680) involves a valine–methionine substitution at codon 158 (Val158Met), resulting in a high or low functional activity of the enzyme [41]. In particular, Val/Val genotypes present 40 % higher enzymatic activity compared with Met/Met genotypes [42]. COMT effects can be modulated by exposure to stress, particularly in the pathophysiology of depressed mood and related neurocognitive processes [43]. A meta-analysis conducted by Kia-Keating [44] found significant association between this variant and suicidal behavior. Nevertheless, more recent studies [45–48] reported no relationship between Val-158Met and suicide. Other researchers [49–52] explored the link between Val158Met and personality traits, such as novelty seeking/extraversion trait and violent behavior, with mixed results. While mostly rs4680 has been extensively investigated so far, other less examined variants within COMT gene could also alter the enzymatic efficiency in catabolizing catecholamines [53, 54].

Another commonly studied gene is the brain-derived neurotrophic factor (BDNF) gene, located on chromosome 11, and expressed in a high number of cerebral structures; it codes for a homodimeric protein which plays an important role in neuronal development and synaptic plasticity. BDNF has also been previously implicated in suicidal behavior [55]. A postmortem study detected reduced mRNA levels of BDNF in the prefrontal cortex and hippocampus of suicide subjects [56] and a meta-analysis reported significantly lower serum BDNF levels in depressed patients, compared with healthy controls [57]; furthermore, successful antidepressant treatment leads to an increment in BDNF secretion [58]. The valine-66-methionine polymorphism (rs6265), resulting in a modulation of BDNF activity-dependent secretion [59], has been observed to be associated with BD [60, 61], especially in patients with rapid cycling [62, 63]. Nevertheless, three studies and a meta-analysis [64–67] demonstrated a significant association between Met allele-carrying genotypes and a higher risk of suicide attempts in depressed patients. Another meta-analysis reported better response to selective serotonin reuptake inhibitors (SSRI) treatment in depressed patients with heterozygous genotypes for Val66Met, compared with homozygous genotypes [68]. A less studied polymorphism (rs11030101) within the BDNF gene has been previously associated with BD [69].

Two other, not well investigated, genes that could be implicated in the genetic susceptibility to suicide are the mitogen-activated protein kinase 1 (MAPK1) gene and the cyclic adenosine monophosphate response element-binding protein-1 (CREB1) gene. The MAPK1 gene, located on chromosome 22, encodes a member of the MAP kinase family. Of various MAPKs, extracellular signal-regulated kinase 1/2 (ERK1/2) is involved in neuronal proliferation and differentiation and synaptic plasticity [70, 71]. In addition, through the activation of nitric oxide and pro-inflammatory cytokines, it plays an important function in inflammatory processes [72]. Dysregulation in MAPK1 signaling pathway is involved in MDD and suicidal behavior [73]; an alteration of MAPK1 levels has been documented in the

frontal cortex of patients with schizophrenia, BD and MDD [74]. In rodents, decreased phosphorylation of ERK1/2 induced depressive-like behavior [75], while treatment with fluoxetine increased the activity of ERK1/2 signaling and led to an alleviation of depressive symptoms [76]. Other studies showed an involvement of MAPK1 in relation to antidepressants [77], mood stabilizers [78] and antipsychotics [79]. These findings suggest a possible role of MAPK1 pathway in response to depression and exposure to stress; in support of this hypothesis, BDNF may improve depressive symptoms through the stimulation of ERK1/2 signaling [80].

The CREB1 gene is situated on chromosome 2; it encodes a transcription factor member of the leucine zipper family of DNA-binding proteins, which is a downstream target of MAPK1 pathway [81]. There is a close association between MAPK1 and CREB1 as they are both involved in the regulation of neuronal plasticity and inflammatory pathways [82], which retain a fundamental role in the pathophysiology of MDD [75]. Furthermore, an association between CREB1 and response to antidepressants [83] and mood stabilizers [84] has been found. Most importantly, two studies have shown that in postmortem brains of suicide subjects there are a decreased mRNA expression and functional parameters of CREB [85, 86], thereby signaling that CREB-related genes may play an important role in suicide.

The aim of the present study was twofold. Firstly, we examined clinical factors associated with a history of suicide attempt in a sample of 553 mood disorder patients; the selection of variables subject to study was based on factors arising from the literature. Secondly, we investigated in a subsample of 259 bipolar patients the association between several polymorphisms within COMT, BDNF, MAPK1 and CREB1 genes and suicide attempt status; the selection of these candidate genes is based on previous data suggesting their involvement in pathophysiologic mechanisms underlying suicidal behavior. Two single nucleotide polymorphisms (SNPs) (rs4680 and rs174696) within the COMT gene were examined: The former one is located in the coding exon, while the latter one belongs to the intron. We also examined four SNPs (rs6265, rs11030101, rs11030104 and rs12273363) within the BDNF gene: The first is a functional polymorphism, while the second belongs to the 5′ untranslated region (5′-UTR); the other two SNPs are situated in the promoter region. Within the MAPK1 gene, we tested four SNPs (rs6928, rs13515, rs3810608 and rs8136867) for their association with suicide attempt status: The first two SNPs are placed in the 5′-UTR, while the latter two belong to the intronic sequence. We also examined four SNPs (rs889895, rs2254137, rs6740584 and rs2551922) within the CREB1 gene, all found in the intronic region.

Methods

Participants

The participants of the present study have been recruited between March 2004 and March 2009 within the 'Psy Pluriel' center, Centre Européen de Psychologie Médicale, and the Department of Psychiatry of Erasme Hospital (in- and outpatients) in Brussels. The assessment of mood disorder patients was completed using the software program 'COPE-Bipolar.COM' (Clinical Outcome Measures for Bipolar Disorder), consisting of structured examination tools and immediate data capture. It is composed of 10 modules: each of them is dedicated to essential elements of unipolar and bipolar disorders, such as sociodemographic characteristics, psychiatric antecedents, diagnosis and treatment, quality of life and functioning. Patients were included if they met DSM-IV criteria for a diagnosis of mood disorder (BD and/or MDD). Approximately 40 % of the patients had an illness onset during the previous 6 months before admission and were seeking treatment for the first time, whereas another 27 % of the sample had an illness onset of more than 5 years. Mental retardation, dementia, neurologic disorder and severe organic disease were exclusion criteria. Written informed consent was obtained from all participants in the study after local ethical committee approval was obtained. For a detailed description of the sample, see [87].

Assessments

Clinical interviews were conducted by specifically trained psychiatrists. Lifetime diagnosis, course of illness and comorbidities of patients were assessed on the basis of the Mini-International Neuropsychiatric Interview (MINI) [88]. Severity of mood symptoms of the most recent episode was assessed using the Hamilton Rating Scale for Depression (HDRS) [89], the Montgomery and Asberg Depression Rating Scale (MADRS) [90] and the Young Mania Rating Scale (YMRS) [91]. Severity of functional impairment subsequent to the psychiatric disease was assessed using the Sheehan Disability Scale (SDS) (Sheehan 1983). The presence or absence of a previous suicide attempt was established according to the MINI. Current suicidal risk was also assessed with the MINI interview and coded as present or absent. Psychiatric familial antecedents were screened for each patient: familial history of MDD and BD in first-degree relatives and familial history of suicide attempt in first- and second-degree relatives.

Genotyping Genomic DNA (gDNA) was purified from whole peripheral blood samples with an automated workstation (Maxwell, Promega) and checked for quality (260/280 ratio >1.6) and quantity (>15 ng/L) by a

small-scale spectrophotometer (Nanodrop, Thermo Scientific). The genotyping was performed using 20 ng of gDNA on a Sequenom MassARRAY platform (Sequenom, California, USA) together with the iPLEX assay (http://www.sequenom.com). Genotyping was then performed according to the manufacturer's standard protocols. MassARRAY Typer version 4.0 3.4 was used to read the extended mass and genotype calls. SNPs were selected following a series of criteria: relevant previous findings, MAF > 5 %, validated and tagging. For some SNPs, genotyping was performed by restriction fragment length polymorphism (RFLP), based on PCR followed by restriction enzyme analysis. Forward and reverse primers' sequences are available upon request. Genotyping success rate was above 95 %. Genotype data were available for 259 patients.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Science (SPSS, IBM 20.0); Chi-square (χ^2) tests and Student's *t* tests were used to compare groups with history or no history of suicide attempt(s) on a range of categorical and continuous variables. Logistic regressions were run to examine which factors were associated with current suicidal risk.

Results

Sociodemographic characteristics

The presence or absence of a suicide attempt was the main outcome of interest. Within our sample ($n = 553$), 221 patients (40 %) were affected by MDD, while 332 patients (60.0 %) were diagnosed with BD. The psychopathology groups did not significantly differ with regard to the proportion of suicide attempters: In the MDD group 77 (34.8 %) had a suicide attempt versus 136 (40.9 %) in the BD group [$\chi^2(1) = 2.1$, $p = 0.15$], so we merged the two groups in our analysis.

Sociodemographic features of the sample, stratified by suicide attempt status, are reported in Table 1. Suicide attempters were significantly younger than non-suicidal patients, and female patients were more likely to have attempted suicide in comparison with male ones. Mood disorder patients with low levels of education also had more suicide attempts compared with those with high educational background. Smoking habits (defined as the use of tobacco for a period of a month or more) were associated with suicide attempter status. The two groups did not significantly differ with regard to ethnicity or employment status, whereas a marginal significant difference ($p = 0.05$) was found with regard to marital status, wherein suicide attempters were less likely to be married or cohabiting.

Clinical characteristics

Clinical features of mood disorder episodes are described in Table 2a, stratified by suicide attempt status. Patients with positive anamnesis for suicide presented higher scores on HDRS and MADRS. Furthermore, we detected no association between suicide attempt and severity of the manic symptoms (YMRS). Suicide attempters also displayed poorer scores on functionality in working and studying activities, family and social life.

With regard to suicide attempt status and psychiatric comorbidities (Table 2b), we found an increased frequency of suicide attempters in mood disorder patients currently affected by anxiety disorders, in particular panic disorder, obsessive–compulsive disorder (OCD) and post-traumatic stress disorder (PTSD). The presence of any anxiety disorder was also associated with prior suicide attempts. With regard to physical disorders, there were no differences between suicide attempters and non-attempters on the prevalence of diabetes or thyroid disease (Table 2c). Finally, the presence of first- and second-degree relatives with suicidal behavior was associated with positive anamnesis for suicide attempt, whereas family history of bipolar or unipolar mood disorder was not (Table 2d).

As a last step, in a logistic regression model with age and gender as covariates, we tested which clinical factors are predictive of current suicidal risk. Due to high multicollinearity, three models were yielded, one including anxiety disorders as predictors, one with the rest of the clinical factors and one with the SDS, which highly correlated with the presence of both anxiety disorders and depressive symptoms and was entered in a regression as a single predictor. Besides age and gender, which were significant predictors, the presence of panic disorder, PTSD, severe depressive symptoms and high functional disability increased the odds of having a current suicide risk. Results are reported in Table 3. Mood disorder diagnosis (MDD or BD) was also entered as a predictor in all models but was not significant ($p > 0.6$) (data not shown).

Genetic analyses

Table 4 shows the frequency distributions of all SNPs of the four genes (COMT, BDNF, MAPK1 and CREB1) stratified by suicide attempt status. We found a significant association between MAPK1-rs13515 and suicide attempt status. Patients carrying the TT genotype were more likely to be suicide attempters, whereas the CC genotype was more frequent among non-attempters. Further analyses showed that this pattern was mainly observed in the male group, with significant differences between genotypes [$\chi^2(2) = 11.60$, $p = 0.003$], whereas in females differences did not approach significance ($p = 0.10$). Allelic analyses showed

Table 1 Sociodemographic characteristics stratified by suicide attempt status, in the whole sample (MDD and BD patients)

	Suicide attempt ($n = 213$)	No suicide attempt ($n = 340$)	t	df	p value
Age (mean ± SD)	45.99 ± 14.48	48.88 ± 13.75	−2.346	548	**0.019**
	N (%)	N (%)	χ^2	df	p value
Gender					
Females	150 (70.8 %)	192 (56.6 %)	11.042	1	**0.001**
Ethnicity					
Caucasian	204 (96.2 %)	325 (95.9 %)	1.131	4	0.889
Asian	2 (0.9 %)	2 (0.6 %)			
African	5 (2.4 %)	10 (2.9 %)			
North American	0 (0.0 %)	1 (0.3 %)			
Latin-American	1 (0.5 %)	2 (0.3 %)			
Education[a]					
Primary school	13 (6.3 %)	20 (6.0 %)	11.510	4	**0.021**
Secondary school	39 (18.8 %)	35 (10.4 %)			
Higher level secondary school	57 (27.4 %)	88 (26.2 %)			
Non-university higher education	48 (23.1 %)	113 (33.6 %)			
University	51 (24.5 %)	80 (23.8 %)			
Marital status					
Married/cohabiting	87 (41.0 %)	172 (50.7 %)	9.354	4	0.053
Widowed	6 (2.8 %)	11 (3.2 %)			
Separated	17 (8.0 %)	12 (3.5 %)			
Single	76 (35.8 %)	100 (29.5 %)			
Divorced	26 (12.3 %)	44 (13.0 %)			
Professional status					
Employed (full time)	62 (33.3 %)	135 (44.4 %)	9.312	5	0.097
Employed (part time)	23 (12.4 %)	34 (11.2 %)			
Unemployed	54 (29.0 %)	81 (26.6 %)			
Student	21 (11.3 %)	18 (5.9 %)			
Volunteer work	2 (1.1 %)	1 (0.3 %)			
Retired	24 (12.9 %)	35 (11.5 %)			
Smoking (for a month or more)	133 (63.9 %)	173 (51.0 %)	8.717	1	**0.003**

Significant p values are in bold

SD standard deviation, *df* degrees of freedom

[a] One patient was excluded due to the lack of information

that the T allele was significantly more frequent among suicide attempters (frequency = 53 %) than among non-attempters (frequency = 42 %), [$\chi^2(1) = 6.46$, $p = 0.01$]. All other SNPs of the MAPK1 gene were not associated with suicide attempt status.

With regard to the CREB1 gene, we also found a significant association: The TC genotype of the rs6740584 was more frequent in suicide attempters, whereas the CC genotype was more frequent in non-attempters (Table 4). Further analyses showed that this pattern was most prevalent in females, where we found significant genotype differences [$\chi^2(2) = 6.19$, $p = 0.045$], whereas in males differences did not reach significance ($p = 0.10$). Allelic analyses showed that the T allele of the same SNP was more frequent in suicide attempters, at the trend level of significance [$\chi^2(1) = 3.12$, $p = 0.08$]. The A allele of rs889895 was also more frequent among suicide attempters—the association reached only trend level of significance [$\chi^2(1) = 3.09$, $p = 0.08$]. No association was found between suicide attempt status and the COMT Val158Met polymorphism, and neither with rs174696. Associations with all BDNF polymorphisms were also not significant.

Discussion

The present study explored several clinical and genetic factors in relation to suicide attempt history or current suicidal risk. History of a prior attempt is still considered one of the

Table 2 Clinical characteristics, psychiatric comorbidities, physical diseases and family history stratified by suicide attempt status

	Suicide attempt ($n = 213$) Mean ± SD	No suicide attempt ($n = 340$) Mean ± SD	t	df	p value
a. Clinical characteristics					
Hamilton total score (21 items)	15.95 ± 9.10	13.73 ± 8.29	2.893	528	**0.004**
MADRS total score	19.91 ± 11.78	16.73 ± 10.71	3.202	528	**0.001**
YMRS total score	3.51 ± 5.81	4.11 ± 6.36	−1.097	530	0.273
Sheehan's Disability Scale	6.80 ± 2.29	6.11 ± 2.19	3.473	534	**0.001**
	N (%)	*N* (%)	χ^2	*df*	*p* value
b. Psychiatric comorbidities					
Panic disorder	40 (18.9 %)	37 (11.0 %)	6.643	1	**0.010**
Obsessive–compulsive disorder[a]	27 (13.1 %)	25 (7.5 %)	4.528	1	**0.033**
Social phobia	26 (12.3 %)	33 (9.8 %)	0.807	1	0.369
Post-traumatic stress disorder	22 (10.4 %)	14 (4.2 %)	8.225	1	**0.004**
Generalized anxiety disorder	66 (31.1 %)	98 (29.2 %)	0.239	1	0.625
Anorexia nervosa	2 (0.9 %)	0 (0.0 %)	3.166	1	0.075
Bulimia nervosa	4 (1.9 %)	7 (2.1 %)	0.028	1	0.867
Any anxiety disorder (current)	109 (51.2 %)	138 (40.6 %)	5.937	1	**0.015**
Alcohol abuse	48 (22.5 %)	83 (24.6 %)	0.294	1	0.587
Drug abuse	8 (3.8 %)	10 (3.0 %)	0.267	1	0.606
Mood disorder with psychotic features (lifetime)	81 (38.6 %)	107 (32.2 %)	2.284	1	0.131
c. Physical diseases					
Thyroid disease					
Hyperthyroidism	3 (1.4 %)	3 (0.9 %)	1.24	3	0.742
Hypothyroidism	23 (11.1 %)	29 (8.7 %)			
Thyroid goiter	3 (1.4 %)	4 (1.2 %)			
Diabetes	7 (3.4 %)	15 (4.5 %)	0.43	1	0.51
d. Familial history					
MDD in first-degree relatives[a]	128 (66.7 %)	183 (61.0 %)	1.617	1	0.204
BD in first-degree relatives[a]	51 (30.4 %)	72 (25.4 %)	1.284	1	0.257
Suicide attempt in first- and second-degree relatives[a]	58 (36.0 %)	59 (22.2 %)	9.664	1	**0.002**

Significant p values are in bold

df degrees of freedom, *SD* standard deviation, *MADRS* Montgomery–Asberg Depression Rating Scale, *YMRS* Young Mania Rating Scale

[a] Patients were excluded due to the lack of information. All disorders are assessed as current unless otherwise specified

best predictors of future suicide [28]. Our analyses add to the prior literature by confirming several associations of factors related to a suicidal profile in a relatively large sample of mood disorder patients.

More specifically, with regard to age, our findings are in line with prior research, demonstrating the presence of higher suicide rates in younger patients, in both MDD [92, 93] and BD [30, 94]. This can be explained by the association of early-onset affective disorders with more severe depressive symptoms and increased liability toward suicide [12], while in older patients somatic symptoms and cognitive decline prevail [93]. Female patients had a higher suicide attempt rate, in line with prior literature. In fact, women often present non-suicidal self-injury [10], while in men suicidal behavior is frequently characterized by violent methods and higher lethality [9]. In addition, bipolar women are more likely to display predominance of depressive polarity [9], a known risk factor for suicidality [28]. Nonetheless, another hypothesis has been proposed: Depressive status in females could be influenced by hormone–brain associations [95]. In particular, pubertal hormonal changes may contribute to sensitize brain structures toward neurobiological and behavioral repercussions of exposure to stress, which is known to be involved in the pathophysiology of depressive mood [96]. With regard to education, patients with lower education were more likely to report history of suicide; this is probably related to poorer social and occupational functioning, in conjunction

Table 3 Logistic regression models examining predictors of *current suicidal risk*

	B	SE	*p* value	OR	95 % CI for OR	
					Lower	Upper
Model 1: logistic regression including sociodemographics and anxiety disorders as predictors						
Age	**−0.014**	**0.007**	**0.033**	**0.986**	**0.973**	**0.999**
Gender	**0.441**	**0.193**	**0.022**	**1.555**	**1.064**	**2.270**
Education	0.022	0.079	0.783	1.022	0.875	1.194
Panic disorder	**1.276**	**0.358**	**<0.001**	**3.583**	**1.775**	**7.232**
Obsessive–compulsive disorder	0.810	0.414	0.051	2.248	0.998	5.062
Post-traumatic stress disorder	**1.099**	**0.557**	**0.049**	**3.001**	**1.007**	**8.942**
Model 2: logistic regression including sociodemographics, depressive symptoms and family history as predictors						
Age	**−0.022**	**0.009**	**0.012**	**0.979**	**0.962**	**0.995**
Gender	0.304	0.233	0.191	1.355	0.859	2.138
Education	0.053	0.096	0.577	1.055	0.874	1.273
Smoke	0.427	0.232	0.065	1.532	0.973	2.413
Hamilton total score	**0.106**	**0.015**	**<0.001**	**1.112**	**1.079**	**1.146**
Familial history of suicide attempt	0.156	0.269	0.562	1.168	0.690	1.978
Model 3: logistic regression including sociodemographics Sheehan's Disability Scale as predictor						
Age	**−0.019**	**0.007**	**0.005**	**0.981**	**0.968**	**0.994**
Gender	**0.405**	**0.194**	**0.037**	**1.500**	**1.025**	**2.194**
Education	0.074	0.080	0.354	1.077	0.921	1.259
Sheehan (mean)	**0.222**	**0.043**	**<0.001**	**1.248**	**1.147**	**1.358**

Significant predictors are in bold

with an earlier-onset mood disorder and early behavioral dysfunction [97]. Past suicide attempters were more likely to be current smokers, and this is also in line with other studies [8, 98].

With regard to clinical characteristics that are associated with suicide, we found higher depression severity in the suicide attempters group, consistently with recent literature [13, 20, 28] that indicates symptoms like hopelessness and longer periods spent in depressed mood as substantial risk factors for suicidality. In fact, suicide attempts in BD are more likely to occur during depressive and mixed phases of the illness [30]. Consistent with this, we did not observe any differences in the levels of manic symptoms. A higher degree of disability was observed in the suicide group, in line with other findings [99], and can be probably ascribed to a more severe clinical course of the disorder (including high comorbidity) and treatment-resistant traits. Indeed, patients with history of a suicide attempt were more likely to suffer from a comorbid panic disorder, PTSD and OCD. High disorder comorbidity in suicide samples has been reported before in both depressed and bipolar patients [20, 23]; in particular, OCD [28] and obsessive–compulsive personality traits [1] have been associated with suicidal behavior. Comorbidity with panic disorder and PTSD was also associated with a significant increase in current suicidal risk in our sample: Our findings are in line with a large-scale longitudinal study showing that patients affected by mood disorders and comorbid anxiety have an increased risk of a subsequent suicide attempt [100]. Mood disorder patients affected by comorbid anxiety are more susceptible to present earlier onset of symptoms [101], increased recurrence of depressive episodes [102] and severe depressive psychopathology [103]. Seeking auto-medication by means of alcohol and substance abuse [104, 105] may also elicit an additive risk on suicide outcome [101]. Finally, family history of suicide was associated indeed with a higher likelihood of having attempted suicide, in line with prior observations [106]. Interestingly, family history of BD or MDD was not associated with a suicide attempt status. Prior literature shows evidence of an increased frequency of psychiatric conditions in the family of patients who committed suicide [107, 108] and in the family of attempters [106]; our observations are in the same direction but did not reach statistical significance. Our sample size has adequate power; thus, we conclude that prior psychiatric family history is not strongly associated with suicide attempt status in mood disorder patients, but family history of suicide is. We should also note that in our sample the percentage of suicide attempters in the MDD and BD groups did not differ significantly, which is contrary to prior observations that show higher suicide attempter rates in BD patients [109, 110]; however, no differences between the two groups have also been found [111].

Turning to the associations with genetic polymorphisms, we found no association between the COMT Val158Met

Table 4 Distribution of genotypes on the four genes (COMT, BDNF, MAPK1 and CREB1) according to suicide attempt status

	Suicide attempt *N* (%)	No suicide attempt *N* (%)	χ^2	*p* value
COMT				
rs4680				
AA	23 (23.2 %)	39 (26.7 %)	1.202	0.548
GA	44 (44.4 %)	69 (47.3 %)		
GG	32 (32.3 %)	38 (26.0 %)		
rs174696				
CC	3 (2.9 %)	2 (1.4 %)	3.702	0.157
CT	41 (39.8 %)	44 (29.9 %)		
TT	59 (57.3 %)	101 (68.7 %)		
BDNF				
rs6265				
AA	3 (3.1 %)	5 (3.5 %)	0.379	0.827
GA	25 (25.8 %)	41 (29.1 %)		
GG	69 (71.1 %)	95 (67.4 %)		
rs11030101				
AA	25 (24.0 %)	38 (25.7 %)	0.791	0.673
TA	53 (51.0 %)	80 (54.1 %)		
TT	26 (25.0 %)	30 (20.3 %)		
rs11030104				
AA	63 (61.8 %)	85 (58.6 %)	0.248	0.883
AG	35 (34.3 %)	54 (37.2 %)		
GG	4 (3.9 %)	6 (4.1 %)		
rs12273363				
CC	3 (2.9 %)	3 (2.0 %)	0.259	0.878
TC	25 (24.0 %)	38 (25.7 %)		
TT	76 (73.1 %)	107 (72.3 %)		
MAPK1				
rs6928				
CC	31 (30.4 %)	42 (28.0 %)	1.091	0.580
GC	43 (42.2 %)	73 (48.7 %)		
GG	28 (27.5 %)	35 (23.3 %)		
rs3810608				
AA	18 (17.1 %)	17 (11.7 %)	1.872	0.392
AG	29 (27.6 %)	48 (33.1 %)		
GG	58 (55.2 %)	80 (55.2 %)		
rs13515				
CC	14 (13.3 %)	42 (28.4 %)	9.240	**0.010**
TC	70 (66.7 %)	88 (59.5 %)		
TT	21 (20.0 %)	18 (12.2 %)		
rs8136867				
AA	7 (7.6 %)	12 (8.6 %)	0.357	0.837
GA	23 (25.0 %)	39 (27.9 %)		
GG	62 (67.4 %)	89 (63.6 %)		
CREB1				
rs889895				
AA	63 (61.2 %)	71 (50.0 %)	3.003	0.223
AG	27 (26.2 %)	48 (33.8 %)		
GG	13 (12.6 %)	23 (16.2 %)		
rs2254137				
AA	32 (30.2 %)	42 (28.0 %)	5.202	0.074
CA	47 (44.3 %)	85 (56.7 %)		
CC	27 (25.5 %)	23 (15.3 %)		
rs6740584				
CC	7 (6.7 %)	31 (20.8 %)	9.694	**0.008**
TC	70 (67.3 %)	82 (55.0 %)		
TT	27 (26.0 %)	36 (24.2 %)		
rs2551922				
AA	1 (0.9 %)	0 (0.0 %)	1.576	0.455
GA	7 (6.6 %)	12 (7.9 %)		
GG	98 (92.5 %)	140 (92.1 %)		

Significant *p* values are in bold

polymorphism and history of suicide attempt, in line with negative findings from prior literature [45–48], supporting the hypothesis of an indirect modulation exerted by COMT through perhaps intermediate phenotypes that may increase the vulnerability toward suicidal behavior [39]. In fact, several studies linked rs4680 to anger, aggressive and violent temperamental traits [51, 52], reward dependence [45] and novelty seeking/extraversion [49].

We also did not find any associations with the BDNF gene polymorphisms. A view of the literature shows mixed results: Some studies provide evidence of association between suicide and reduced levels of serum BDNF [112], along with a decrease in BDNF mRNA expression [56, 113]. We found dissimilar results pertaining to the role of Val66Met in increasing suicidal risk [64, 65, 114, 115]. It has to be noted that although the majority of these studies point toward an association with suicidal behavior, negative studies are less likely to be published, resulting in publication bias.

To our knowledge, this is the first study suggesting an association of rs13515 (within MAPK1) and rs6740584 (within CREB1) polymorphisms with suicide attempt in a sample of bipolar patients. A study conducted by Dwivedi [73] offers an accurate insight of the physiopathologic mechanism involving MAPK1/ERK1 pathway. Previous research showed that expression and activation of extracellular signal-regulated kinase (ERK1/2) were lower in prefrontal cortex and hippocampus of suicide subjects affected by MDD [116]; the down-regulation was found to be associated with a decrease in ERK1/2 mRNA and protein levels. Studies conducted in rodents support these results, showing that the administration of a compound which blocks activation of ERK1/2 produces mood

disorder-related behavioral deficits [117], and that depressive-like behavior is related to decreased levels of ERK1/2 phosphorylation [75]. Our hypothesis is that a genetic variation of rs13515 within the 5′-UTR of MAPK1 gene, in particular the presence of TT genotype, could influence mRNA transduction, leading to a decrease in ERK1/2 synthesis. The subsequent down-regulation of MAPK/ERK1 signaling cascade may result in functional abnormalities within the prefrontal cortex and hippocampal regions of the brain, such as dysregulation in neuronal proliferation, synaptic plasticity and inflammatory responses.

The present report has several limitations. First of all, it is a cross-sectional study, not allowing for the deduction of causal relationships. Secondly, suicide risk was classified as a dichotomous trait, according to the presence or absence of a past suicide attempt. We chose to do so because history of a suicide attempt is a more stable risk trait [28] than current suicidal ideation, according to prior literature. However, we may have missed cases who have a high suicidal risk but have not performed an attempt before. Regarding the genetic results, the number of cases in our study may be low, therefore not providing enough power to detect significant associations, for example, with the BDNF/COMT genes. Also, major effects from single SNPs are unlikely [118]. Future meta-analyses will shed light on this matter. Positive results involving SNPs within MAPK1 and CREB1 genes (also the gender-specific findings) should be considered as preliminary and are worthy of future investigation. Finally, no correction for multiple testing was applied despite the high number of investigated variables; most results would not survive correction. However, given the exploratory nature of our study, we do not claim to report strong associations but only suggestive results which could be useful for further investigations or meta-analyses.

Conclusion

Suicidal behavior has a complex etiology, involving both genetic predisposition and exposure to environmental influences, aside from the presence of an underlying psychiatric diagnosis. Our study provided suggestive data of variants within MAPK1 and CREB1 genes associated with suicide attempt status, whereas associations with variations in the COMT and BDNF Val/Met polymorphisms were not replicated in this sample. From a clinical perspective, our study proposes several clinical characteristics, such as increased depressive symptomatology, anxiety comorbidity, functional disability and family history of suicidality, as correlates associated with a suicide attempt status in a large sample of mood disorder patients. Current suicidal risk was also predicted by most of these factors, but current anxiety comorbidity increased the odds most significantly. Clinicians may consider these determinants in their treatment agenda, in order to monitor such clinical factors and administer adequate therapeutic interventions to prevent recurrence of suicidal tendencies.

Compliance with ethical standards

Conflict of interest Prof. Serretti is or has been consultant/speaker for: Abbott, Angelini, Astra Zeneca, Clinical Data, Boheringer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Italfarmaco, Janssen, Lundbeck, Pfizer, Sanofi, Servier. Dr. Souery has received grant/research support from GlaxoSmithKline and Lundbeck and has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen and Lundbeck. Prof. Mendlewicz is a member of the Board of the Lundbeck International Neuroscience Foundation and of Advisory Board of Servier. The other authors report no conflict of interest.

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