Int J Clin Exp Pathol 2015;8(1):906-913
www.ijcep.com /ISSN:1936-2625/IJCEP0003509

Original Article

CREB1 gene polymorphisms combined with environmental risk factors increase susceptibility to major depressive disorder (MDD)

Peng Wang[1], Yanjie Yang[1], Xiuxian Yang[1], Xiaohui Qiu[1], Zhengxue Qiao[1], Lin Wang[1], Xiongzhao Zhu[2], Hong Sui[1], Jingsong Ma[1]

[1]*Department of Psychology, Public Health Institute, Harbin Medical University, 157 Baojian Road, Nangang, Harbin 150081, China;* [2]*Medical Psychological Institute, Second Xiangya Hospital, Central South University, Changsha, Hunan, China*

Received October 31, 2014; Accepted December 22, 2014; Epub January 1, 2015; Published January 15, 2015

Abstract: Major depressive disorder (MDD) is one of the most severe psychiatric disorders. The objective of this study was to explore the effects of *CREB1* gene polymorphisms on risk of developing MDD and the joint effects of gene-environment interactions. Genotyping was performed by Taqman allelic discrimination assay among 586 patients and 586 healthy controls. A significant impact on rs6740584 genotype distribution was found for childhood trauma (P = 0.015). We did not find an association of *CREB1* polymorphisms with MDD susceptibility. However, we found a significantly increased risk associated with the interactions of *CREB1* polymorphisms and drinking (OR = 11.67, 95% CI = 2.52-54.18; OR = 11.52, 95% CI = 2.55-51.95 for rs11904814; OR = 4.18, 95% CI = 1.87-9.38; OR = 5.02, 95% CI = 2.27-11.14 for rs6740584; OR = 7.58, 95% CI = 2.05-27.98; OR = 7.59, 95% CI = 2.12-27.14 for rs2553206; OR = 8.37, 95% CI = 3.02-23.23; OR = 7.84, 95% CI = 2.93-20.98 for rs2551941). We also noted that CREB polymorphisms combined with family harmony and childhood trauma conferred increased susceptibility for MDD. In conclusion, polymorphisms in the CREB gene may not be independently associated with MDD risk, but they are likely to confer increased susceptibility by interacting with environmental risk factors in the Chinese population.

Keywords: Polymorphism, *CREB1*, environmental risk factors, MDD, susceptibility

Introduction

CREB1 (cAMP response element-binding protein) is a transcription factor and plays an important role in neuronal signal transduction [1-3]. *CREB1* protein, encoded by the *CREB1* gene located on human chromosome 2q34, belongs to the leucine zipper family that serves as DNA-binding proteins [4]. The cAMP signal transduction pathway is induced by the activation of G-protein-coupled receptors and promoted through phosphorylation of the CREB protein [4, 5]. Zubenko et al. reported a clear association of the loci in 2q33-35 chromosomal region with mood disorders in women [6] and identified that *CREB1* predisposes to major depressive disorder (MDD) in a sex-specific manner [7]. An increasing body of literature confirmed that *CREB1* might be involved in suicide [8-10], and antidepressant response in patients suffering from MDD [11-13]. Recently, Zubenko et al. identified a significant contribution of genetic variations in *CREB1* to MDD in women [7]. Subsequent studies provided further support for the significant involvement of single nucleotide polymorphisms (SNP) at *CREB1* locus in suicidal behaviors, anger expression and MDD, including rs467590, rs7569963 and G(-656)A [14-16].

MDD is a well-known mental disease resulting in cognitive dysfunction [17]. Many groups have demonstrated data on the substantial importance of SNPs in candidate genes in MDD pathogenesis and antidepressant response [18-20]. Results from family, twins and epidemiological studies indicated that about 30% to 40% of MDD incidences result from genetic factors and environmental carcinogens [21, 22]. Caspi et al. showed that certain polymorphisms

Table 1. Characteristics of the controls and MDD patients

Variables	MDD/586	Controls/586	*P*
Age (years)	44.16 ± 0.56	42.93 ± 0.39	0.000
Gender			0.001
Female	421 (71.84%)	370 (63.14%)	
Male	165 (28.16%)	216 (36.86%)	
Marital status			0.720
Single	85 (14.51%)	78 (13.31%)	
Stable	464 (79.18%)	475 (81.06%)	
Separated or widow	37 (6.31%)	33 (5.63%)	
Smoking			0.019
No	84 (14.33%)	114 (19.45%)	
Yes	502 (85.67%)	472 (80.55%)	
Drinking			< 0.001
No	24 (4.10%)	111 (18.94%)	
Yes	562 (95.90%)	475 (81.06%)	
Family harmony			< 0.001
No	189 (32.25%)	21 (3.58%)	
Yes	397 (67.74%)	565 (96.42%)	
Working condition			0.330
Stable	11 (1.88%)	16 (2.73%)	
Unstable	575 (98.12%)	570 (97.27%)	
Childhood trauma			0.004
No	528 (90.10%)	554 (94.54%)	
Yes	58 (9.90%)	32 (5.46%)	

Table 2. Association between *CREB1* SNPs and MDD susceptibility

rs number	Genotype	MDD	Control	OR (95% CI)	OR[a] (95% CI)
rs11904814	TT	83	86	1	
	TG	300	287	1.08 (0.77-1.53)	1.12 (0.76-1.65)
	GG	203	213	0.99 (0.69-1.42)	1.04 (0.69-1.55)
rs6740584	TT	206	220	1	
	TC	299	282	1.13 (0.88-1.45)	1.15 (0.86-1.53)
	CC	81	84	1.03 (0.72-1.48)	1.00 (0.66-1.49)
rs2253206	GG	86	89	1	
	GA	293	286	1.06 (0.76-1.49)	1.08 (0.74-1.59)
	AA	207	211	1.02 (0.71-1.45)	1.04 (0.70-1.55)
rs2551941	AA	105	111	1	
	AT	293	281	0.87 (0.63-1.20)	1.12 (0.79-1.60)
	TT	188	194	0.76 (0.54-1.07)	1.04 (0.71-1.52)

[a]Adjusted by age, gender, marital status, smoking, drinking, family harmony, working condition and childhood trauma.

in the SLC6A4 gene regulate the effects of SLEs, including childhood maltreatment associated with MDD [23]. In recent years, a broad range of human genes and their interactions with exogenous variables have been identified to have an impact on the risk of developing MDD, such as FKBP5, CRHR1 and 5-HTTLPR [24-26]. However, few studies have previously focused on the joint effect of *CREB1* gene polymorphisms and environmental factors. Herein, we studied the association of *CREB1* SNPs with MDD and investigated the effects of common confounding factors in conjunction with these SNPs on the susceptibility to the disease.

Materials and methods

Participants

586 Chinese Han patients with MDD were recruited from Psychiatry Department of First Affiliated Hospital of Harbin Medical University. The patients were diagnosed by 2 experienced psychiatrists according to Diagnostic and Statistical manual of Disorders Fourth Edition (DMS-IV). All patients got more than 21 points in Hamilton's Depression Scale Test and received no antidepression treatment within 2 weeks before participation. We excluded the patients in case of the following conditions, brain organic mental disorders, other mental disease, and family history of genetic disease, mental retardation, dementia or physical disease. We also excluded the patients who provided insufficient information and accepted recent transfusion therapy. 586 unrelated controls were selected among the healthy individuals visiting the same hospital for physical examination and matched with cases in age (± 5 years), education and career. Their families had no substance dependent member, genetic diseases or interracial marriage in three generations. The baseline information is detailed in **Table 1**. The Research Ethics Committee of China

Table 3. Association between demographic factors and genotype distribution in MDD patients

Factor/genotype	rs11904814		*P*	rs6740584		*P*	rs2253206		*P*	rs2551941		*P*
	TT	TG/GG		TT	TC/CC		GG	GA/AA		AA	AT/TT	
Gender												
Female	62	359	0.533	149	272	0.847	62	359	0.956	76	345	0.893
Male	21	144		57	108		24	141		29	136	
Smoking												
No	11	73	0.762	23	61	0.107	13	71	0.823	13	71	0.529
Yes	72	430		183	319		73	429		92	410	
Drinking												
No	3	21	0.812	11	13	0.264	2	22	0.371	4	20	0.871
Yes	80	482		195	367		84	478		101	461	
Family harmony												
No	28	161	0.756	71	118	0.400	27	162	0.854	35	154	0.794
Yes	55	342		135	262		59	338		70	327	
Childhood trauma												
No	79	449	0.095	194	334	0.015*	82	446	0.078	99	429	0.113
Yes	4	54		12	46		4	54		6	52	

*indicate a significant ($P < 0.05$) difference.

Table 4. Interaction between drinking and *CREB1* genetic polymorphisms

Variable	Case	Control	OR (95% CI)	OR[a] (95% CI)
rs11904814				
TT and no drinking	3	23	1	1
TG or GG and no drinking	21	88	1.83 (0.50-6.67)	1.91 (0.41-8.97)
TT and drinking	80	63	9.74 (2.80-33.90)	11.67 (2.52-54.18)
TG or GG and drinking	482	412	8.97 (2.67-30.09)	11.52 (2.55-51.95)
rs6740584				
TT and no drinking	11	34	1	1
TC or CC and no drinking	13	77	0.52 (0.21-1.28)	0.61 (0.24-1.59)
TT and drinking	195	186	3.24 (1.60-6.58)	4.18 (1.87-9.38)
TC or CC and drinking	367	289	3.93 (1.96-7.88)	5.02 (2.27-11.14)
rs2553206				
GG and no drinking	2	24	1	1
GA or AA and no drinking	22	87	3.034 (0.666-13.825)	1.22 (0.32-4.59)
GG and drinking	84	65	15.51 (3.54-68.01)	7.58 (2.05-27.98)
GA or AA and drinking	478	410	13.99 (3.29-59.55)	7.59 (2.12-27.14)
rs2551941				
AA and no drinking	4	29	1	1
AT or TT and no drinking	20	82	1.77 (0.56-5.61)	1.33 (0.45-3.89)
AA and drinking	101	82	8.93 (3.02-26.43)	8.37 (3.02-23.23)
AT or TT and drinking	461	393	8.50 (2.96-24.40)	7.84 (2.93-20.98)

approved the study and all participants signed the informed consent form.

Measure of stressful life events

Life event scale (LES) proposed by Desen Yang and Yalin Zhang was used to evaluate stressful life events, such as serious illness, relationships, housing and social difficulties, relationship breakdowns, unemployment and financial crisis. This scale assessed four aspects of negative life events: when the life events occurred (absent = 1, 1 year earlier = 2, in a year = 3, chronicity = 4), how the life events were charac-

Table 5. Interaction between family harmony and *CREB1* genetic polymorphisms

Variable	Case	Control	OR (95% CI)	OR[a] (95% CI)
rs11904814				
TT and harmony	55	85	1	1
TT and no harmony	28	1	43.27 (5.72-327.28)	40.91 (5.40-309.81)
TG or GG and harmony	342	480	1.10 (0.76-1.58)	1.07 (0.74-1.55)
TG or GG and no harmony	161	20	12.41 (7.00-22.12)	12.71 (7.07-22.85)
rs6740584				
TT and harmony	135	213	1	1
TT and no harmony	71	7	16.00 (7.15-35.82)	16.77 (7.47-37.66)
TC or CC and harmony	262	352	1.17 (0.90-1.54)	1.24 (0.94-1.62)
TC or CC and no harmony	118	14	13.30 (7.34-24.10)	13.78 (7.59-25.01)
rs2253206				
GG and harmony	59	86	1	1
GG and no harmony	27	3	13.12 (3.80-45.24)	38.13 (5.04-288.68)
GA or AA and harmony	338	479	1.03 (0.72-1.47)	1.03 (0.72-1.47)
GA or AA and no harmony	162	18	13.12 (7.28-23.64)	11.69 (6.59-20.72)
rs2551941				
AA and harmony	70	105	1	1
AA and no harmony	35	6	8.75 (3.50-21.90)	14.55 (4.96-42.67)
AT or TT and harmony	327	460	1.07 (0.76-1.49)	1.13 (0.80-1.58)
AT or TT and no harmony	154	15	15.40 (8.36-28.35)	13.86 (7.69-24.97)

terized (good = 1, bad = 2), to what extent the respondent was affected (absent = 1, mild = 2, moderate = 3, severe = 4, extreme = 5), and how long the influence lasted (less than 3 months = 1, 3-6 months = 2, 6-12 months = 3, more than 12 months = 4). A 75% percentile (a score of 4) in controls was taken as a cutoff value to group the events into the high or low level categories.

Measure of child maltreatment

Self-reported childhood maltreatment including abuse and neglect was recorded according to childhood trauma questionnaire (CTQ). It comprises 28 items graded on a five-point Likert scale, with higher scores corresponding to higher degree of traumatic experience. The scores were critical evidence to measure the degree of maltreatment: none = 0, low = 1, moderate = 2, severe and above = 3.

DNA isolation and genotyping

Genomic DNA was isolated from blood samples using a MagNA Pure DNA Isolator (Roche, Indianapolis, IN). Extracted DNA was used for genotyping. We selected 4 tag SNPs (rs11904814, rs6740584, rs2551941, rs2253206) from the whole-gene region of *CREB1* using Haploview's program. Analyses of SNPs were performed using Taqman allelic discrimination assay on a 7900 system (Applied Biosystem Inc) according to the manufacturer's instructions. To ensure the allele discrimination accuracy, all samples were measured in triplicate, and the results yielded a 100% concordance rate.

Statistical analysis

Hardy-Weinberg equilibrium was evaluated for each polymorphism using χ^2 test in both patients and controls. T-test was used to assess age difference between cases and controls. χ^2-test was used to assess the between-group differences in gender, marital status, smoking, drinking, family harmony and working condition. Multi-factor variance analysis was performed to evaluate the association of demographic factors with genotype distribution. Logistic regression was used to test the SNP associations and the joint effects of gene-environment interactions. All analyses were carried out using SPSS 18.0. The values of $P < 0.05$ were considered statistically significant.

Table 6. Interaction between childhood trauma and *CREB1* genetic polymorphisms

Variable	Case	Control	OR (95% CI)	OR[a] (95% CI)
rs11904814				
TT and no trauma	79	84	1	1
TG or GG and no trauma	449	470	1.02 (0.72-1.42)	1.05 (0.75-1.48)
TT and trauma	4	2	2.13 (0.38-11.94)	2.37 (0.41-13.61)
TG or GG and trauma	54	30	1.91 (1.11-3.29)	1.43 (0.80-2.54)
rs6740584				
TT and no trauma	194	210	1	1
TC or CC and no trauma	334	344	0.69 (0.82-1.35)	1.05 (0.82-1.35)
TT and trauma	12	10	1.30 (0.55-3.08)	0.76 (0.34-1.70)
TC or CC and trauma	46	22	2.26 (1.31-3.90)	2.19 (1.16-4.15)
rs2253206				
GG and no trauma	82	83	1	1
GA or AA and no trauma	446	471	0.96 (0.69-1.34)	1.02 (0.73-1.42)
GG and trauma	4	6	0.68 (0.18-2.48)	2.19 (0.39-12.50)
GA or AA and trauma	54	26	2.10 (1.20-3.68)	1.37 (0.78-2.41)
rs2551941				
AA and no trauma	99	105	1	1
AT or TT and no trauma	429	449	1.01 (0.75-1.37)	1.04 (0.76-1.41)
AA and trauma	6	6	1.06 (0.33-3.40)	1.02 (0.32-3.28)
AT or TT and trauma	52	26	2.12 (1.23-3.66)	1.48 (0.83-2.65)

Results

Demographic and clinical data on study subjects

The characteristics of study subjects are listed in **Table 1**. The mean age was 44.16 in cases (male/female 28.2%/71.8%) and 42.93 in controls (male/female 36.9%/63.1%). A significant difference in gender distribution was detected between the two groups ($P = 0.002$). Most subjects were smokers (cases 85.7%, controls 80.6%) and alcohol drinkers (cases 95.9%, controls 81.1%). The cases were statistically different from controls both in alcohol consumption ($P < 0.001$) and tobacco smoking ($P = 0.019$). No significant difference was found in family harmony, marital status and working condition ($P > 0.05$).

Effect of CREB1 SNPs on MDD susceptibility

To evaluate the effects of *CREB1* SNPs, we performed logistic regression. The results indicated no association between *CREB1* polymorphisms and MDD susceptibility (**Table 2**). We then explored the effects of demographic factors on genotype distribution (**Table 3**) and the data showed that childhood trauma was significantly associated with genotype distribution of rs6740584 in MDD patients ($P = 0.015$).

Combined effects of SNPs and drinking, family harmony and childhood trauma

Considering that the SNPs of *CREB1* alone did not show any impact on MDD susceptibility, we analyzed the interactions between SNPs and drinking, family harmony and childhood trauma (**Table 4**). We found significantly increased risk of MDD associated with rs11904814 genotypes among drinkers (OR = 11.67, 95% CI = 2.52-54.18; OR = 11.52, 95% CI = 2.55-51.95). A similar trend was indicated for rs6740584, rs2253206 and rs2551941. These results demonstrated that drinking served as an important risk factor for MDD. We also found a significant role of family harmony in the risk of MDD. As shown in **Table 5**, lack of family harmony significantly promoted the development of MDD. In addition, we identified a 2.19-fold increased risk in relation to TC/CC genotypes of rs6740584 in conjunction with childhood trauma (OR = 2.19, 95% CI = 1.16-4.15, **Table 6**).

Discussion

As genetic polymorphisms are usually impossible to work alone in predisposing human diseases, analysis of gene-environment interactions is frequently used to test the combined effects conferred by genetic polymorphsims

and environment variables. It is reported that environmental factors such as emotional abuse, emotional and physical neglect are important components in the pathogenesis of depression [27, 28]. Either high- or low-predisposing genes always function in combination with many exogenous substances [29]. Rice et al. found that candidate genes exert strong effects on depressive symptoms, stronger in males than in females [30]. Grabe et al. also reported that interaction of TAT-haolotype of CRHR1 and childhood physical neglect has a role in MDD pathogenesis [31]. Actually, various environmental factors are involved in the etiology of MDD, including gender, age and marital status as substantiated by Benitez et al. [32], neighborhood environment (OR = 2.2, 95% CI = 1.2-3.9) as suggested by Kessler et al. [33], and low self-esteem family depression, childhood abuse, traumatic experiences education state as indicated by Blanco et al. [34]. These data highlight the important role of exogenous substances in the development of MDD and identification of the risk factors may contribute to an increased understanding of the mechanisms that underlie this disease.

In the present study, we explored the effects of SNPs in *CREB1* gene and gene-environment interactions on MDD susceptibility, and showed evidence of no association between MDD and *CREB1* SNPs, a finding that contradicts Zubenko et al., indicating that *CREB1* is a potential susceptibility locus for MDD [7], and Guo et al. reporting that rs6740584 of *CREB1* has an effect on selective attention and retrieval [35]. As expected, we found a significantly increased risk when both polymorphisms and exogenous variables were considered. This joint effect is supported by Perlis et al., who found a strong, gender-specific association between variation at *CREB1* locus and anger expression in MDD [15]. Although we cannot exclude the possibility that the lack of an association between *CREB1* polymorphisms and MDD susceptibility is a false negative finding, it seems likely that the polymorphisms at *CREB1* do not function alone in predisposing MDD, as suggested by Hettema et al. and Crisafulli et al. [36].

In addition, we evaluated the impact of demographic factors on the genotype distribution in MDD patients and only childhood trauma was identified as a regulatory factor of rs6740584 genotypes (P = 0.015). To obtain a more comprehensive understanding of MDD etiology, we assessed the association of MDD risk with gender, smoking, drinking, family harmony and childhood trauma (**Table 1**). A significant interaction was detected for drinking, family harmony and childhood trauma, which were found to increase genetic susceptibility to MDD by interplaying with various *CREB1* SNPs. Appel et al. uncovered interactions between physical abuse and rs1360780 in the FKBP5 gene and confirmed its role in depression susceptibility [24]. Moreover, significant interactions between stressful life events and 5-HTTPR and BDNF genotypes were observed in patients with depression [26]. A recent study carried out by Wong et al. provided further evidence supporting the impact of exogenous factors (smoking, marriage status, age, alcohol abuse and gender) on susceptibility to major depression [37]. The previous studies along with the present study suggest that MDD is a heterogeneous disease and both genetic variations and a large repertoire of exogenous variables may have modulating effects on the susceptibility.

In conclusion, presence of *CREB1* gene polymorphisms combined with exogenous factors including drinking, family harmony and childhood trauma may increase the risk of developing MDD. Further large-scale studies are warranted to identify the role of environment-genetic risk factors in the etiology of MDD, thus facilitating better understandings of MDD pathogenesis and subsequent preventive measures and treatment.

Acknowledgements

This research was supported by the National Natural Science Foundation of China (3127-1093, 81473054) to Prof. Yanjie Yang and the National Natural Science Foundation of China (81202213) to Xiuxian Yang.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yanjie Yang, Department of Psychology, Public Health Institute, Harbin Medical University, 157 Baojian Road, Harbin 150081, China. E-mail: yanjie1965@163.com

References

[1] De Cesare D, Fimia GM and Sassone-Corsi P. CREM, a master-switch of the transcriptional

cascade in male germ cells. J Endocrinol Invest 2000; 23: 592-596.
[2] Mayr B and Montminy M. Transcriptional regulation by the phosphorylation-dependent factor CREB. Nat Rev Mol Cell Biol 2001; 2: 599-609.
[3] Lonze BE and Ginty DD. Function and regulation of CREB family transcription factors in the nervous system. Neuron 2002; 35: 605-623.
[4] Sands WA and Palmer TM. Regulating gene transcription in response to cyclic AMP elevation. Cell Signal 2008; 20: 460-466.
[5] Mamdani F, Alda M, Grof P, Young LT, Rouleau G and Turecki G. Lithium response and genetic variation in the CREB family of genes. Am J Med Genet B Neuropsychiatr Genet 2008; 147B: 500-504.
[6] Zubenko GS, Maher B, Hughes HB 3rd, Zubenko WN, Stiffler JS, Kaplan BB and Marazita ML. Genome-wide linkage survey for genetic loci that influence the development of depressive disorders in families with recurrent, early-onset, major depression. Am J Med Genet B Neuropsychiatr Genet 2003; 123B: 1-18.
[7] Zubenko GS, Hughes HB 3rd, Stiffler JS, Brechbiel A, Zubenko WN, Maher BS and Marazita ML. Sequence variations in CREB1 cosegregate with depressive disorders in women. Mol Psychiatry 2003; 8: 611-618.
[8] Dwivedi Y, Rao JS, Rizavi HS, Kotowski J, Conley RR, Roberts RC, Tamminga CA and Pandey GN. Abnormal expression and functional characteristics of cyclic adenosine monophosphate response element binding protein in postmortem brain of suicide subjects. Arch Gen Psychiatry 2003; 60: 273-282.
[9] Odagaki Y, Garcia-Sevilla JA, Huguelet P, La Harpe R, Koyama T and Guimon J. Cyclic AMP-mediated signaling components are upregulated in the prefrontal cortex of depressed suicide victims. Brain Res 2001; 898: 224-231.
[10] Young LT, Bezchlibnyk YB, Chen B, Wang JF and MacQueen GM. Amygdala cyclic adenosine monophosphate response element binding protein phosphorylation in patients with mood disorders: effects of diagnosis, suicide, and drug treatment. Biol Psychiatry 2004; 55: 570-577.
[11] Dowlatshahi D, MacQueen GM, Wang JF and Young LT. Increased temporal cortex CREB concentrations and antidepressant treatment in major depression. Lancet 1998; 352: 1754-1755.
[12] Koch JM, Kell S, Hinze-Selch D and Aldenhoff JB. Changes in CREB-phosphorylation during recovery from major depression. J Psychiatr Res 2002; 36: 369-375.
[13] Yamada S, Yamamoto M, Ozawa H, Riederer P and Saito T. Reduced phosphorylation of cyclic AMP-responsive element binding protein in the postmortem orbitofrontal cortex of patients with major depressive disorder. J Neural Transm 2003; 110: 671-680.
[14] Perlis RH, Purcell S, Fava M, Fagerness J, Rush AJ, Trivedi MH and Smoller JW. Association between treatment-emergent suicidal ideation with citalopram and polymorphisms near cyclic adenosine monophosphate response element binding protein in the STAR*D study. Arch Gen Psychiatry 2007; 64: 689-697.
[15] Perlis RH, Purcell S, Fagerness J, Cusin C, Yamaki L, Fava M and Smoller JW. Clinical and genetic dissection of anger expression and CREB1 polymorphisms in major depressive disorder. Biol Psychiatry 2007; 62: 536-540.
[16] Zubenko GS and Hughes HB 3rd. Effects of the G(-656)A variant on CREB1 promoter activity in a glial cell line: interactions with gonadal steroids and stress. Am J Med Genet B Neuropsychiatr Genet 2008; 147B: 579-585.
[17] Zubenko GS and Hughes HB 3rd. Effects of the G(-656)A variant on CREB1 promoter activity in a neuronal cell line: interactions with gonadal steroids and stress. Mol Psychiatry 2009; 14: 390-397.
[18] Hammar A and Ardal G. Cognitive functioning in major depression--a summary. Front Hum Neurosci 2009; 3: 26.
[19] Angst J. The Prognosis of Antidepressive Treatments: Longitudinal and Genetic Studies. Anglo Ger Med Rev 1965; 2: 733-751.
[20] Pare CM, Rees L and Sainsbury MJ. Differentiation of two genetically specific types of depression by the response to anti-depressants. Lancet 1962; 2: 1340-1343.
[21] Serretti A, Franchini L, Gasperini M, Rampoldi R and Smeraldi E. Mode of inheritance in mood disorder families according to fluvoxamine response. Acta Psychiatr Scand 1998; 98: 443-450.
[22] Kendler KS, Walters EE, Neale MC, Kessler RC, Heath AC and Eaves LJ. The structure of the genetic and environmental risk factors for six major psychiatric disorders in women. Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. Arch Gen Psychiatry 1995; 52: 374-383.
[23] Kendler KS, Kessler RC, Walters EE, MacLean C, Neale MC, Heath AC and Eaves LJ. Stressful life events, genetic liability, and onset of an episode of major depression in women. Am J Psychiatry 1995; 152: 833-842.
[24] Appel K, Schwahn C, Mahler J, Schulz A, Spitzer C, Fenske K, Stender J, Barnow S, John U, Teumer A, Biffar R, Nauck M, Volzke H, Freyberger HJ and Grabe HJ. Moderation of adult depression by a polymorphism in the FKBP5 gene and childhood physical abuse in the gen-

eral population. Neuropsychopharmacology 2011; 36: 1982-1991.
[25] Ressler KJ, Bradley B, Mercer KB, Deveau TC, Smith AK, Gillespie CF, Nemeroff CB, Cubells JF and Binder EB. Polymorphisms in CRHR1 and the serotonin transporter loci: gene x gene x environment interactions on depressive symptoms. Am J Med Genet B Neuropsychiatr Genet 2010; 153B: 812-824.
[26] Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Kim YH and Yoon JS. Interactions between life stressors and susceptibility genes (5-HTTLPR and BDNF) on depression in Korean elders. Biol Psychiatry 2007; 62: 423-428.
[27] Kendler KS and Baker JH. Genetic influences on measures of the environment: a systematic review. Psychol Med 2007; 37: 615-626.
[28] Heim C and Binder EB. Current research trends in early life stress and depression: review of human studies on sensitive periods, gene-environment interactions, and epigenetics. Exp Neurol 2012; 233: 102-111.
[29] Meyer-Lindenberg A and Tost H. Neural mechanisms of social risk for psychiatric disorders. Nat Neurosci 2012; 15: 663-668.
[30] Rice F, Harold G and Thapar A. The genetic aetiology of childhood depression: a review. J Child Psychol Psychiatry 2002; 43: 65-79.
[31] Grabe HJ, Schwahn C, Appel K, Mahler J, Schulz A, Spitzer C, Fenske K, Barnow S, Lucht M, Freyberger HJ, John U, Teumer A, Wallaschofski H, Nauck M and Volzke H. Childhood maltreatment, the corticotropin-releasing hormone receptor gene and adult depression in the general population. Am J Med Genet B Neuropsychiatr Genet 2010; 153B: 1483-1493.
[32] Hernandez-Benitez CT, Garcia-Rodriguez A, Leal-Ugarte E, Peralta-Leal V and Duran-Gonzalez J. [Enviromental factors related to depressive disorders]. Rev Med Inst Mex Seguro Soc 2014; 52: 574-579.
[33] Kessler RC, Duncan GJ, Gennetian LA, Katz LF, Kling JR, Sampson NA, Sanbonmatsu L, Zaslavsky AM and Ludwig J. Associations of housing mobility interventions for children in high-poverty neighborhoods with subsequent mental disorders during adolescence. JAMA 2014; 311: 937-948.
[34] Blanco C, Rubio J, Wall M, Wang S, Jiu CJ and Kendler KS. Risk factors for anxiety disorders: common and specific effects in a national sample. Depress Anxiety 2014; 31: 756-764.
[35] Guo J, Liu Z, Dai H, Zhu Z, Wang H, Yang C, Xiao L, Huang Y and Wang G. Preliminary investigation of the influence of CREB1 gene polymorphisms on cognitive dysfunction in Chinese patients with major depression. Int J Neurosci 2014; 124: 22-29.
[36] Hettema JM, An SS, van den Oord EJ, Neale MC, Kendler KS and Chen X. Association study of CREB1 with Major Depressive Disorder and related phenotypes. Am J Med Genet B Neuropsychiatr Genet 2009; 150B: 1128-1132.
[37] Wong ML, Dong C, Andreev V, Arcos-Burgos M and Licinio J. Prediction of susceptibility to major depression by a model of interactions of multiple functional genetic variants and environmental factors. Mol Psychiatry 2012; 17: 624-633.