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Association of FK506 binding protein 5 (*FKBP5*) gene rs4713916 polymorphism with mood disorders: a meta-analysis

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Feng X-L, Wang F, Zou Y-F, Li W-F, Tian Y-H, Pan F-M, Huang F. Association of FK506 binding protein 5 (*FKBP5*) gene rs4713916 polymorphism with mood disorders: a meta-analysis.

Background: Several studies have investigated the association of *FKBP5* gene polymorphisms with mood disorders, but findings are not always consistent. The aim of our study was to assess the association of *FKBP5* gene polymorphisms with mood disorders using a meta-analysis.
Methods: Data were collected from the following electronic databases: PubMed, Elsevier Science Direct, Cochrane Library, Chinese Biomedical Literature Database, China National Knowledge Infrastructure and Wanfang, with the last report up to March 2010. Meta-analysis was performed in a fixed/random effect model.
Results: We identified six studies using search, and one study was excluded because of unavailable data. One study contained data on two different ethnicities and we treated them independently. Thus, six separate studies (2655 cases and 3593 controls) were included in the meta-analysis. Meta-analysis was performed for three *FKBP5* gene polymorphisms (rs1360780, rs3800373 and rs4713916) in overall and Caucasian populations. We did not detect any association of *FKBP5* gene rs1360780 and rs3800373 polymorphisms with mood disorders ($p > 0.05$). However, a significant association of *FKBP5* gene rs4713916 polymorphism with mood disorders was found, and the heterozygous individual (GA genotype) was more susceptible to mood disorders in comparison to homozygous analogues (GG or AA genotype) [overall: GA vs. GG: OR (odds ratio) = 1.20, 95% CI (confidence interval) = 1.03–1.40, $p = 0.02$; GA vs. AA: OR = 1.44, 95% CI = 1.09–1.90, $p = 0.009$; Caucasian: GA vs. GG: OR = 1.22, 95% CI = 1.04–1.44, $p = 0.01$; GA vs. AA: OR = 1.43, 95% CI = 1.09–1.89, $p = 0.01$].
Conclusion: This meta-analysis shows that mood disorders are associated with *FKBP5* gene rs4713916 polymorphism, but not with rs1360780 and rs3800373.

Keywords: FK506 binding protein 5; genetic polymorphisms; meta-analysis; mood disorders

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Introduction

Mood disorders are the most common psychiatric disorders in modern society (1). The major symptoms of mood disorders include personality change, loss of appetite, fatigue, depression, aggression, anxiety and agitation. There are different types of mood disorders, based on their durations, prevalent features and severity of symptoms. The two main categories of mood disorders are unipolar disorder and bipolar disorder. Approximately 16 and 1% of the population are affected by unipolar and bipolar disorders, one or more times during their life time, respectively (2). Mood disorders have a large impact on social health, with a considerable amount of both direct and indirect costs (3–5). Twin, family and adoption studies have suggested that susceptibility to mood disorders is strongly influenced by genetic

factors (6). Beckman et al. (7) first conducted a case–control study on the relationship between genetic polymorphisms and mood disorders in 1978. Subsequently, many genetic association studies were conducted (8).

The fact that dysfunction of hypothalamic-pituitary-adrenal (HPA) axis was found in depressive patients has made the HPA axis an interesting candidate endophenotype for mood disorders (9,10). Recently, during their search for the genetic mechanisms underlying the HPA dysfunction in mood disorders, many researchers focused on genes involved in HPA-axis regulation. Among these, FK506 binding protein 5 (FKBP5) gained growing interest. FKBP5 is a member of the immunophilin protein family, which in humans is encoded by the *FKBP5* gene. It is a co-chaperone of hsp-90, and is involved in the regulation of the HPA system by adaptive changes in the glucocorticoid receptor (GR), and plays a role in immunoregulation and basic cellular processes involving protein folding and trafficking (11). *FKBP5* gene is located on chromosome 6p21, a chromosomal region associated with bipolar disorder and psychosis (12).

Several single nucleotide polymorphisms (SNPs) in FKBP5 have been found (13). These SNPs have been associated with increased FKBP5 protein expression, and variation in the correlation between plasma cortisol levels and peripheral blood FKBP5 mRNA expression, indicating that the alleles of these polymorphisms are associated with differences in GR sensitivity (14). In healthy controls, the alleles are associated with a relative GR resistance (15). Taking these facts into account, one could speculate that FKBP5 alleles associated with a slower return to baseline of stress-induced cortisol levels also increase the risk for stress-related psychiatric disorders (13). Currently, there is evidence for the impact of FKBP5 in mood disorders. Several studies have investigated the association of *FKBP5* gene polymorphisms with mood disorders, but findings are not always consistent (14,16–20). There are several possible explanations for this discordance, such as small sample size, ethnic background, different types of mood disorders and publication bias.

Meta-analysis is a statistical procedure for combining the results of several studies to produce a single estimate of the major effect with enhanced precision, and it is considered a powerful tool for summarising inconsistent results from different studies (21). This method also helped in the investigation of a possible association between *FKBP5* gene polymorphisms and mood disorders. Therefore, it is necessary to perform a comprehensive meta-analysis to evaluate the association between *FKBP5* gene polymorphisms and mood disorders.

Methods

Identification of eligible studies

All studies examining the association of *FKBP5* gene polymorphisms with mood disorders were carefully selected. Data were collected from the following electronic databases: PubMed, Elsevier Science Direct, Cochrane Library, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI) and Wanfang (Chinese). The key word 'FKBP5' was used for searching. Meanwhile, additional literature was collected from cross-references within both original and review articles. We recruited data only from the full-published paper and not from any meeting or conference abstracts. No language restrictions were applied. A study was included in the current meta-analysis if (a) it was published up to March 2010; (b) it was a case–control study; (c) patients were diagnosed by psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders IV criteria (DSM-IV) or the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). We excluded the study in which family members had been studied because the analysis is based on linkage considerations. When a study reported the results on different sub-populations/ethnicities, we treated them independently. Additionally, an independent search was done by two investigators with the same method. The contents of abstracts were reviewed independently by two investigators to determine if they met the eligibility criteria for inclusion.

Data extraction

Two investigators independently extracted the data with the standard protocol and the result was reviewed by a third investigator. From each study, we extracted the first author's name, year of publication, source of publication, racial ancestry, type of diseases, polymorphisms, the number of cases and controls and the available genotype and allele frequency information from the *FKBP5* gene. In addition, if original genotype frequency data was unavailable in relevant articles, a request for additional data was sent to the corresponding author.

Meta-analysis methods

Meta-analysis was performed for polymorphisms that had been investigated in at least two studies. We examined the relationship between the allele, as well as genotypes, and susceptibility to mood disorders. The odds ratio (OR) and its 95% confidence interval (CI) were estimated for each study. The degree of

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heterogeneity between the study results was assessed by the Q-test based on Chi-squared statistic (22). A significant Q-statistic ($p < 0.10$) indicated heterogeneity across studies. We also measured the effect of heterogeneity by another measure, $I^2 = 100\% \times$ (Q−df)/Q (23). The pooled OR was obtained by Mantel–Haenszel method in the fixed effect model and by DerSimonian–Laird method in the random effect model (24,25). The pooled OR was performed by weighting individual ORs by the inverse of their variance, and the significance of the pooled OR was determined by the Z-test.

Additionally, Chi-squared test was used to determine if the observed frequencies of genotypes conformed to Hardy–Weinberg equilibrium expectations.

Evaluation of publication bias

Publication bias was investigated with the funnel plot. Funnel plot asymmetry was further assessed by the method of Egger's linear regression test (26). Analyses were performed using the software Review Manager 4.2 (Cochrane Collaboration, http://www.cc-ims.net/RevMan/relnotes.htm/) and Stata version 10 (StataCorp LP, College Station, Texas). A p value less than 0.05 was considered statistically significant, and all the p values were two sided.

Results

Characteristics of eligible studies

The characteristics of studies investigating the association of *FKBP5* gene polymorphisms with mood disorders are presented in Table 1 (14,16–20). There were 323 papers relevant to the searching word. The study selection process is shown in Fig. 1. The six separate studies studied five different polymorphisms (rs1360780, rs3800373, rs4713916, rs755658 and rs1334894) in the *FKBP5* gene. Only three of these polymorphisms were investigated in more than two studies. Thus, meta-analysis was performed for three polymorphisms [rs1360780 (16–20), rs3800373 (16, 18,20), rs4713916 (16,18,20)]. The six separate studies consisted of five Caucasian and one Black population. The distribution of the genotype in control population was in Hardy–Weinberg equilibrium in these studies ($p > 0.05$).

Meta-analysis

The summary of the meta-analysis for *FKBP5* gene polymorphisms with mood disorders is shown in Table 2.

Analysis for FKBP5 gene rs1360780 polymorphism. We did not detect any association of *FKBP5* gene rs1360780 polymorphism with mood disorders in the overall population (T vs. C: OR = 1.04, 95% CI = 0.95–1.14, $p = 0.37$; CT + TT vs. CC: OR = 1.07, 95% CI = 0.89–1.29, $p = 0.46$; TT vs. CC + CT: OR = 0.94, 95% CI = 0.78–1.15, $p = 0.56$; TT vs. CC: OR = 1.01, 95% CI = 0.83–1.23, $p = 0.94$; CT vs. CC: OR = 1.09, 95% CI = 0.89–1.34, $p = 0.40$). We performed group-specific meta-analysis in the Caucasian population. No statistically significant association was established for *FKBP5* gene rs1360780 polymorphism in the Caucasian population (T vs. C: OR = 1.04, 95% CI = 0.94–1.13, $p = 0.46$; CT + TT vs. CC: OR = 1.05, 95% CI = 0.85–1.30, $p = 0.63$; TT vs. CC + CT: OR = 0.93, 95% CI = 0.76–1.14, $p = 0.51$; TT vs. CC: OR = 0.99, 95% CI = 0.80–1.22, $p = 0.94$;

Table 1. Characteristics of studies investigating the association of *FKBP5* gene polymorphisms with mood disorders

ID	Study	Year	Ethnic group	Diseases	Polymorphisms	Sample size		Frequencies of genotypes	HWE of genotype of control (p value)
						Case	Control		
1	Zobel et al. (16)	2010	Caucasian	UD	rs3800373/rs755658/rs1360780/ rs1334894/rs4713916	268	284	Available	>0.05
2	Lavebratt et al. (17)	2010	Caucasian	UD/dysthymia/mixed anxiety depression	rs1360780	457	2286	Available	>0.05
3	Lekman et al. (18)	2008	Caucasian	UD	rs1360780/rs4713916/rs3800373	1256	634	Available	>0.05
4	Lekman et al. (18)	2008	Black	UD	rs1360780/rs4713916/rs3800373	267	105	Available	>0.05
5	Papiol et al. (19)	2007	Caucasian	UD	rs1360780	159	96	Available	>0.05
6	Gawlik et al. (20)	2006	Caucasian	UD/BD	rs4713916/rs1360780/rs3800373	248	188	Available	>0.05
7	Binder et al. (14)	2004	Caucasian	UD/BD/ dysthymia	rs734369/rs1883637/rs3807050/rs3800374/ rs3800373/rs755658/rs992105/rs4713899/ rs737054/rs3777747/rs1591365/rs1360780/ rs2143404/rs4713902/rs1334894/rs1475774/ rs2092427/rs4713908/rs3800372/rs4713916/ rs4713921/rs2766534	294	339	NA	NA

BD, bipolar disorder; HWE, Hardy–Weinberg equilibrium; NA, not available; UD, unipolar depression.

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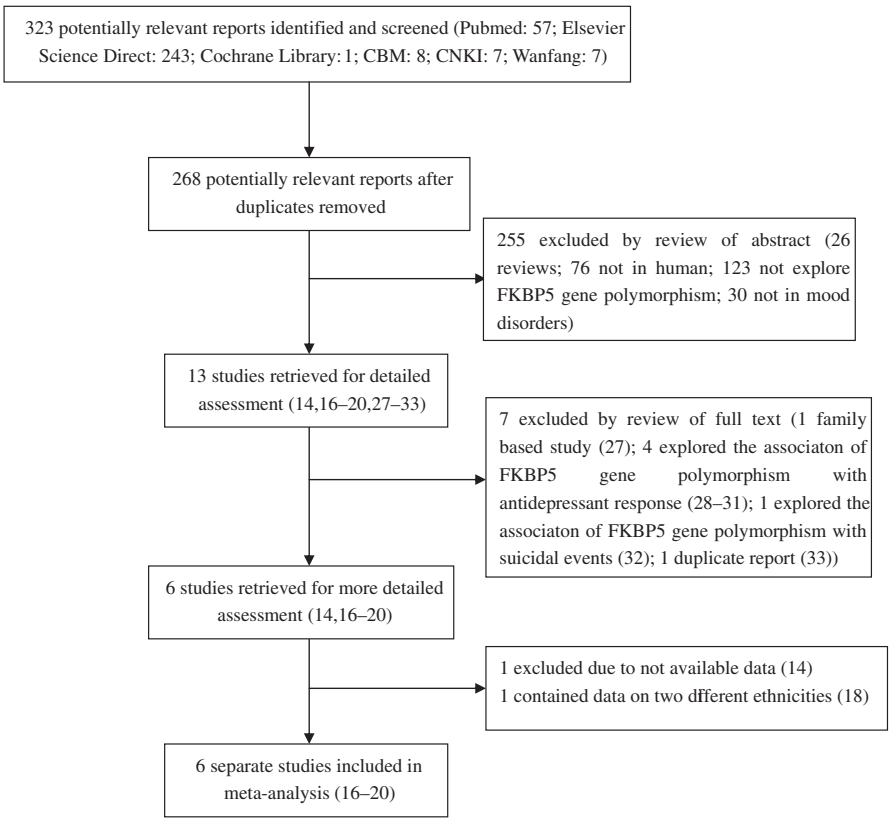

Fig. 1. Flow diagram of the study selection process.

CT vs. CC: OR = 1.07, 95% CI = 0.85–1.35, $p = 0.56$).

Analysis for FKBP5 gene rs3800373 polymorphism. We did not detect the association of *FKBP5* gene rs3800373 polymorphism with mood disorders in the overall population (C vs. A: OR = 1.04, 95% CI = 0.82–1.32, $p = 0.75$; AC + CC vs. AA: OR = 1.12, 95% CI = 0.81–1.55, $p = 0.51$; CC vs. AA + AC: OR = 0.91, 95% CI = 0.71–1.17, $p = 0.46$; CC vs. AA: OR = 0.84, 95% CI = 0.43–1.65, $p = 0.61$; AC vs. AA: OR = 1.15, 95% CI = 0.85–1.56, $p = 0.37$). We also did not detect the association of *FKBP5* gene rs3800373 polymorphism with mood disorders in the Caucasian population (C vs. A: OR = 0.98, 95% CI = 0.73–1.32, $p = 0.90$; AC + CC vs. AA: OR = 1.03, 95% CI = 0.70–1.52, $p = 0.86$; CC vs. AA + AC: OR = 0.86, 95% CI = 0.66–1.14, $p = 0.29$; CC vs. AA: OR = 0.70, 95% CI = 0.30–1.63, $p = 0.40$; AC vs. AA: OR = 1.08, 95% CI = 0.75–1.55, $p = 0.68$).

Analysis for FKBP5 gene rs4713916 polymorphism. An association of *FKBP5* gene rs4713916 polymorphism with mood disorders was found in the overall population when examining the contrast of GA versus GG (OR = 1.20, 95% CI = 1.03–1.40, $p = 0.02$), and the forest plot of the distribution of the ORs is shown in Fig. 2a. However, we did not find the association when examining the contrast of A versus G (OR = 0.97, 95% CI = 0.76–1.25, $p = 0.83$), GA + AA versus GG (OR = 1.08, 95% CI = 0.82–1.41, $p = 0.58$), AA versus GG + GA (OR = 0.67, 95% CI = 0.40–1.14, $p = 0.14$) and AA versus GG (OR = 0.72, 95% CI = 0.38–1.35, $p = 0.30$).

The association of *FKBP5* gene rs4713916 polymorphism with mood disorders was found in the Caucasian population when examining the contrast of GA versus GG (OR = 1.22, 95% CI = 1.04–1.44, $p = 0.01$), and the forest plot of the distribution of the ORs is shown in Fig. 2b. Similarly, no statistically significant association was found when examining the contrast of A versus G (OR = 0.98, 95% CI = 0.73–1.32, $p = 0.91$), GA + AA versus GG (OR = 1.11, 95% CI = 0.80–1.62, $p = 0.54$), AA versus GG + GA (OR = 0.68, 95% CI = 0.38–1.21, $p = 0.19$) and AA versus GG (OR = 0.73, 95% CI = 0.37–1.45, $p = 0.37$).

Evaluation of publication bias

The results of Egger's linear regression test are shown in Table 3. It has been shown that there was

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Table 2. Meta-analysis of *FKBP5* gene polymorphisms and mood disorders association

Polymorphisms	Comparisons		Sample size		Number of studies	Test of association				Test of heterogeneity		
			Case	Control		OR (95% CI)	*Z*	*p* value	Model	χ^2	*p* value	I^2 (%)
rs1360780	Overall	T vs. C	5248	7012	6	1.04 (0.95–1.14)	0.90	0.37	F	8.02	0.16	37.6
		CT + TT vs. CC	2624	3506	6	1.07 (0.89–1.29)	0.74	0.46	R	10.67	0.06	53.1
		TT vs. CC + CT	2624	3506	6	0.94 (0.78–1.15)	0.58	0.56	F	4.44	0.49	0.0
		TT vs. CC	1466	2132	6	1.01 (0.83–1.23)	0.08	0.94	F	5.21	0.39	3.9
		CT vs. CC	2355	3195	6	1.09 (0.89–1.34)	0.84	0.40	R	11.38	0.04	56.0
	Caucasian	T vs. C	4714	6802	5	1.04 (0.94–1.13)	0.74	0.46	F	7.79	0.10	48.6
		CT + TT vs. CC	2357	3401	5	1.05 (0.85–1.30)	0.48	0.63	R	10.38	0.03	61.5
		TT vs. CC + CT	2357	3401	5	0.93 (0.76–1.14)	0.66	0.51	F	4.31	0.37	7.2
		TT vs. CC	1330	2074	5	0.99 (0.80–1.22)	0.08	0.94	F	4.94	0.29	19.1
		CT vs. CC	2133	3107	5	1.07 (0.85–1.35)	0.58	0.56	R	11.15	0.02	64.1
rs3800373	Overall	C vs. A	4024	2326	4	1.04 (0.82–1.32)	0.31	0.75	R	11.11	0.01	73.0
		AC + CC vs. AA	2012	1163	4	1.12 (0.81–1.55)	0.66	0.51	R	11.65	0.009	74.3
		CC vs. AA + AC	2012	1163	4	0.91 (0.71–1.17)	0.73	0.46	F	3.45	0.33	13.1
		CC vs. AA	1224	690	4	0.84 (0.43–1.65)	0.51	0.61	R	15.51	0.001	80.7
		AC vs. AA	1822	1051	4	1.15 (0.85–1.56)	0.90	0.37	R	9.34	0.03	67.9
	Caucasian	C vs. A	3496	2126	3	0.98 (0.73–1.32)	0.12	0.90	R	9.46	0.009	78.9
		AC + CC vs. AA	1748	1063	3	1.03 (0.70–1.52)	0.17	0.86	R	9.86	0.007	79.7
		CC vs. AA + AC	1748	1063	3	0.86 (0.66–1.14)	1.05	0.29	F	2.63	0.27	23.9
		CC vs. AA	1095	634	3	0.70 (0.30–1.63)	0.84	0.40	R	13.07	0.001	84.7
		AC vs. AA	1604	966	3	1.08 (0.75–1.55)	0.41	0.68	R	8.05	0.02	75.2
rs4713916	Overall	A vs. G	4078	2422	4	0.97 (0.76–1.25)	0.22	0.83	R	10.07	0.02	70.2
		GA + AA vs. GG	2039	1211	4	1.08 (0.82–1.41)	0.55	0.58	R	7.47	0.06	59.9
		AA vs. GG + GA	2039	1211	4	0.67 (0.40–1.14)	1.47	0.14	R	7.16	0.07	58.1
		AA vs. GG	1193	752	4	0.72 (0.38–1.35)	1.04	0.30	R	9.25	0.03	67.6
		GA vs. GG	1890	1096	4	1.20 (1.03–1.40)	2.34	0.02	F	4.70	0.20	36.1
	Caucasian	A vs. G	3544	2212	3	0.98 (0.73–1.32)	0.11	0.91	R	9.83	0.007	79.7
		GA + AA vs. GG	1772	1106	3	1.11 (0.80–1.62)	0.62	0.54	R	6.93	0.03	71.2
		AA vs. GG + GA	1772	1106	3	0.68 (0.38–1.21)	1.31	0.19	R	6.92	0.03	71.1
		AA vs. GG	975	667	3	0.73 (0.37–1.45)	0.89	0.37	R	8.93	0.01	77.6
		GA vs. GG	1624	991	3	1.22 (1.04–1.44)	2.48	0.01	F	4.00	0.14	50.0

F, fixed effect model; R, random effect model.

no publication bias (all $p > 0.05$). For the association of *FKBP5* gene rs4713916 polymorphism with mood disorders in the overall and Caucasian populations, Egger's linear regression test provided no evidence of publication bias (overall: $t = -0.69$, $p = 0.564$; Caucasian: $t = -0.26$, $p = 0.839$).

Discussion

Mood disorders are common psychiatric disorders with a complex aetiology that likely involves multiple genes in addition to non-genetic influences (1,6). An impaired signalling by cortisol-activated GR, leading to a weakened negative feedback regulation, appears to be one significant biological abnormality observed in mood disorders (10). FKBP5 is an important regulator of the GR activity (34). HPA axis also plays a role in other pathomechanisms of depression, such as inflammatory background or neurodegeneration (35,36). Therefore, FKBP5 may play a role in the pathophysiology of mood disorders, and appears to be a good candidate for studies on the pathogenesis of mood disorders. Several studies have investigated the association of *FKBP5* gene polymorphisms with mood disorders (14,16–20). A positive result has been reported in patients with unipolar depression as compared to controls in the STAR*D study (18). However, This finding is not supported by other studies (14,17,19,20). The negative results from these studies might be related to the lack of power (37). Recently, Zobel et al. (16) reported a positive result in patients with unipolar depression. Thus, we performed a meta-analysis to assess the association of *FKBP5* gene polymorphisms with mood disorders.

In this study, we retrieved six separate studies that included data from 2655 cases and 3593 controls to evaluate the association between *FKBP5* gene polymorphisms and mood disorders. A meta-analysis was performed for three *FKBP5* gene polymorphisms (rs1360780, rs3800373 and rs4713916) in the overall and Caucasian populations. A significant association of *FKBP5* gene rs4713916 polymorphism with mood disorders was found in the overall and Caucasian populations. However, we did not find the association

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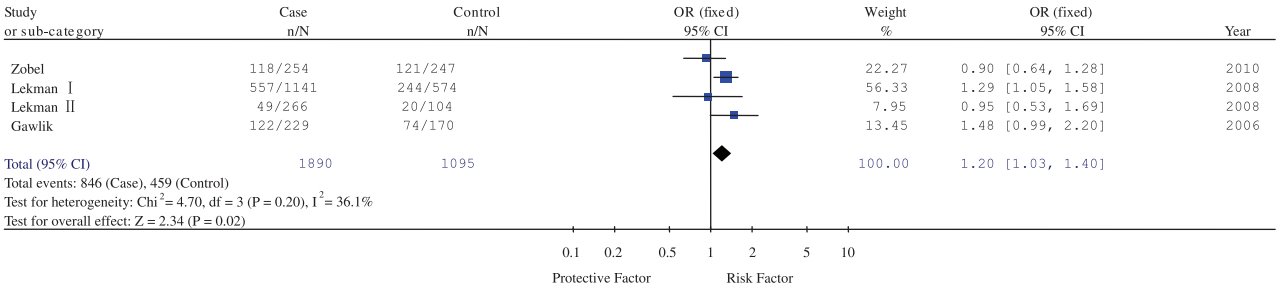
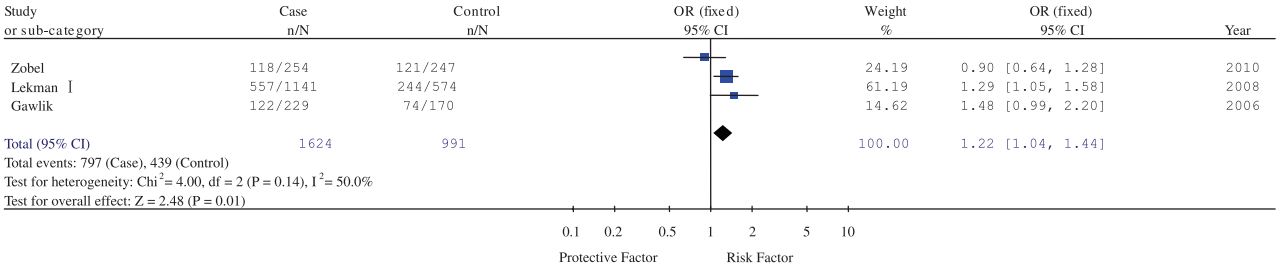
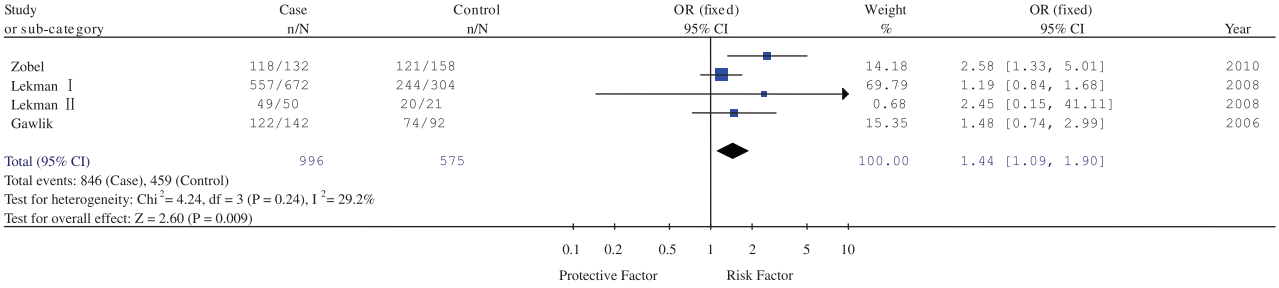


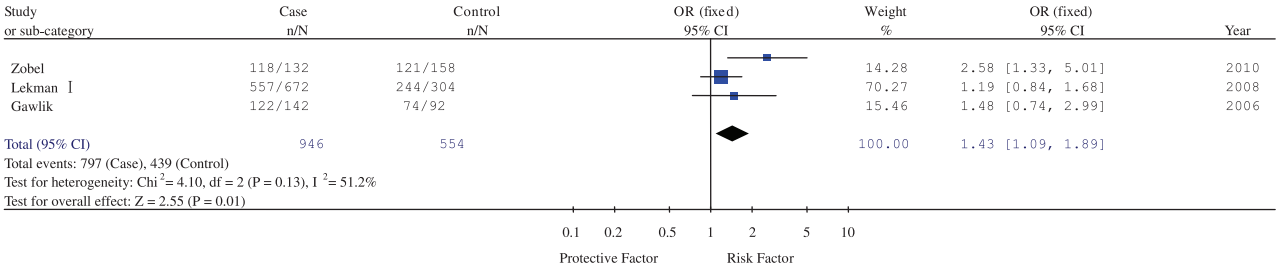
(a) rs4713916: GA vs GG Overall



(b) rs4713916: GA vs GG Caucaisan



(c) rs4713916: GA vs AA Overall



(d) rs4713916: GA vs AA Caucaisan

Fig. 2. Forest plots for statistically significant meta-analysis.

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Table 3. Egger's linear regression test to measure the funnel plot asymmetric

Polymorphisms		*Y* axis intercept: a (95% CI)				
		T vs. C	CT + TT vs. CC	TT vs. CC + CT	TT vs. CC	CT vs. CC
rs1360780	Overall	−0.43 (−5.02 ~ 4.15)	−0.64 (−5.68 ~ 4.40)	0.42 (−3.04 ~ 3.88)	−0.01 (−3.76 ~ 3.73)	−0.77 (−5.97 ~ 4.42)
	Caucasian	−0.88 (−7.48 ~ 5.71)	−1.27 (−8.66 ~ 6.10)	0.31 (−4.54 ~ 5.17)	−0.29 (−5.50 ~ 4.91)	−1.41 (−0.90 ~ 6.24)
		C vs. A	AC + CC vs. AA	CC vs. AA + AC	CC vs. AA	AC vs. AA
rs3800373	Overall	−0.23 (−16.15 ~ 15.68)	0.13 (−15.38 ~ 15.65)	−0.83 (−9.25 ~ 7.58)	−0.74 (−12.55 ~ 11.07)	0.21 (−13.75 ~ 14.17)
	Caucasian	−2.24 (−73.31 ~ 68.81)	−2.05 (−76.57 ~ 72.45)	−1.69 (−29.39 ~ 26.00)	−2.08 (−42.92 ~ 38.75)	−1.66 (−71.26 ~ 67.94)
		A vs. G	GA + AA vs. GG	AA vs. GG + GA	AA vs. GG	GA vs. GG
rs4713916	Overall	−1.73 (−12.49 ~ 9.03)	−1.63 (−11.49 ~ 8.22)	−1.50 (−8.04 ~ 5.04)	−1.60 (−9.29 ~ 6.08)	−1.28 (−9.34 ~ 6.77)
	Caucasian	−3.06 (−69.37 ~ 63.24)	−1.92 (−60.67 ~ 56.83)	−3.42 (−41.32 ~ 34.48)	−3.53 (−51.30 ~ 44.22)	−0.96 (−48.36 ~ 46.43)

All $p > 0.05$.

of *FKBP5* gene rs1360780 and rs3800373 polymorphisms with mood disorders. To our knowledge, the present meta-analysis is the first to assess the association between *FKBP5* gene polymorphisms and mood disorders.

In our study, we found that the *FKBP5* gene rs4713916 polymorphism GA genotype increased the risk of mood disorders in comparison to GG genotype. We further examined the contrast of GA versus AA, and found that GA genotype also increased the risk of mood disorders in comparison to AA genotype in the overall and Caucasian populations (overall: OR = 1.44, 95% CI = 1.09–1.90, $p = 0.009$; Caucasian: OR = 1.43, 95% CI = 1.09–1.89, $p = 0.01$). Egger's linear regression tests showed that there was no publication bias (overall: $t = 1.09$, $p = 0.391$; Caucasian: $t = 1.48$, $p = 0.379$). The result indicates that the heterozygous individual (GA genotype) is more susceptible to mood disorders in comparison to homozygous analogues (GG or AA genotype). Homozygosity for the minor allele T of SNP rs1360780, located <200 bp from a functional response element for progesterins and glucocorticoids in intron 2, has been associated with increased FKBP5 mRNA and protein expression (14). Increased FKBP5 activity would imply reduced GR activity and less efficient termination of stress, leading to an increased risk of stress-related psychiatric disorders (13). The promoter SNP rs4713916 is located in a putatively functional region (18). Therefore, our results seem to support the assumption that heterozygous individual (GA genotype) of SNP rs4713916 may have higher FKBP5 mRNA and protein expression than homozygous analogues (A/A or G/G genotype). However, to date, the function of the *FKBP5* gene rs4713916 polymorphism is unclear. Further studies on the function of the *FKBP5* gene rs4713916 polymorphism and the association between the polymorphism and mood disorders are required. In addition, whether SNPs in strong linkage disequilibrium (LD) with it in other functional parameters is conferring the susceptibility to mood disorders is unknown (14).

Several specific details merit consideration in this meta-analysis. First, significant between-study heterogeneity was detected, and may be distorting the meta-analysis. A second consideration is that only published studies were included in the meta-analysis, and so publication bias may have occurred. A third consideration is that we could not do subgroup analysis by types of mood disorders because of unavailable data. These results should be interpreted with caution because different types of mood disorders may have different causes. A fourth consideration is that our results are based on unadjusted estimates and a more precise analysis could be performed if individual data were available. Finally, meta-analysis remains a retrospective research that is subject to the methodological deficiencies of the included studies.

In conclusion, our meta-analysis shows that there is a lack of association of *FKBP5* gene rs1360780 and rs3800373 polymorphisms with mood disorders. There is an association between *FKBP5* gene rs4713916 polymorphism and mood disorders, and the heterozygous individual (GA genotype) is more susceptible to mood disorders in comparison to homozygous analogues (GG or AA genotype). More studies based on larger sample size, case–control design and stratified by ethnicity are still needed in future research.

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