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Original Article

Association of angiotensin-converting enzyme insertion/deletion polymorphism with panic disorder risk: a meta-analysis

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Abstract: Many studies have focused on the relationship between angiotensin-converting enzyme (*ACE*) gene insertion/deletion (I/D) polymorphism and panic disorder risk, but the results remain inconsistent. Thus, a meta-analysis was carried out to derive a more precise estimation of the association between *ACE* I/D polymorphism and panic disorder risk. Relevant publications were searched in several widely used databases and five studies were included in the meta-analysis. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of the association between *ACE* I/D polymorphism and panic disorder risk. Significant associations between *ACE* I/D polymorphism and panic disorder risk were observed in overall meta-analysis for DD versus II (OR = 0.58, 95% CI = 0.40-0.84) and DD versus DI+II (OR = 0.51, 95% CI = 0.33-0.80), in Caucasian subgroup, and also in male subgroup. However, no such panic disorder risk variation was detected in the Asian subgroup or in the female subgroup. According to the results of our meta-analysis, the *ACE* I/D polymorphism probably associates with panic disorder risk especially in males, with the I allele acting as a risk factor.

Keywords: Angiotensin-converting enzyme, polymorphism, panic disorder, risk, meta-analysis

Introduction

Panic disorder (PD) is an anxiety disorder with a life-time prevalence of 1-3% and rates higher in women than in men [1]. It is characterized by sudden attacks of intense fear. Family and twin studies indicate a genetic contribution to PD [2-4]. Segregation studies suggest that this genetic contribution is complex and there is not a simple pattern of inheritance [5]. Therefore, PD is considered a genetically complex disorder [6].

The renin-angiotensin system (RAS) plays an important role in brain [7]. The angiotensin-converting enzyme (*ACE*) gene encodes a key enzyme in RAS, which converts angiotensin I to the potent vasoconstrictor angiotensin II [8-10]. An insertion/deletion (I/D) polymorphism has been reported to locate in intron 16 of the *ACE* gene, and ACE level is higher in subjects with D allele than those with I allele [11]. This polymorphism is reported to be associated with psychiatric diseases including major depressive disorder (MDD) and bipolar disorder (BD) [12].

In this study, we investigated the association between *ACE* I/D polymorphism and panic disorder risk. In the past decade, several studies have focused on the relationship between *ACE* I/D polymorphism and panic disorder risk, but the results of those individual studies provided limited information and could not draw a convincible conclusion [6, 13-16]. Therefore, we performed a meta-analysis with a relatively large sample size of 5 studies (441 cases and 930 controls in all) to provide a more reliable conclusion of the relationship between *ACE* I/D polymorphism and panic disorder risk.

Materials and methods

Literature search, selection, and data collection

In this study, we searched papers published before Sep 9, 2014 according to the keywords "angiotensin-converting enzyme"/"angiotensin I converting enzyme"/"ACE", "panic disorder", and "polymorphism"/"polymorphisms"/"variati

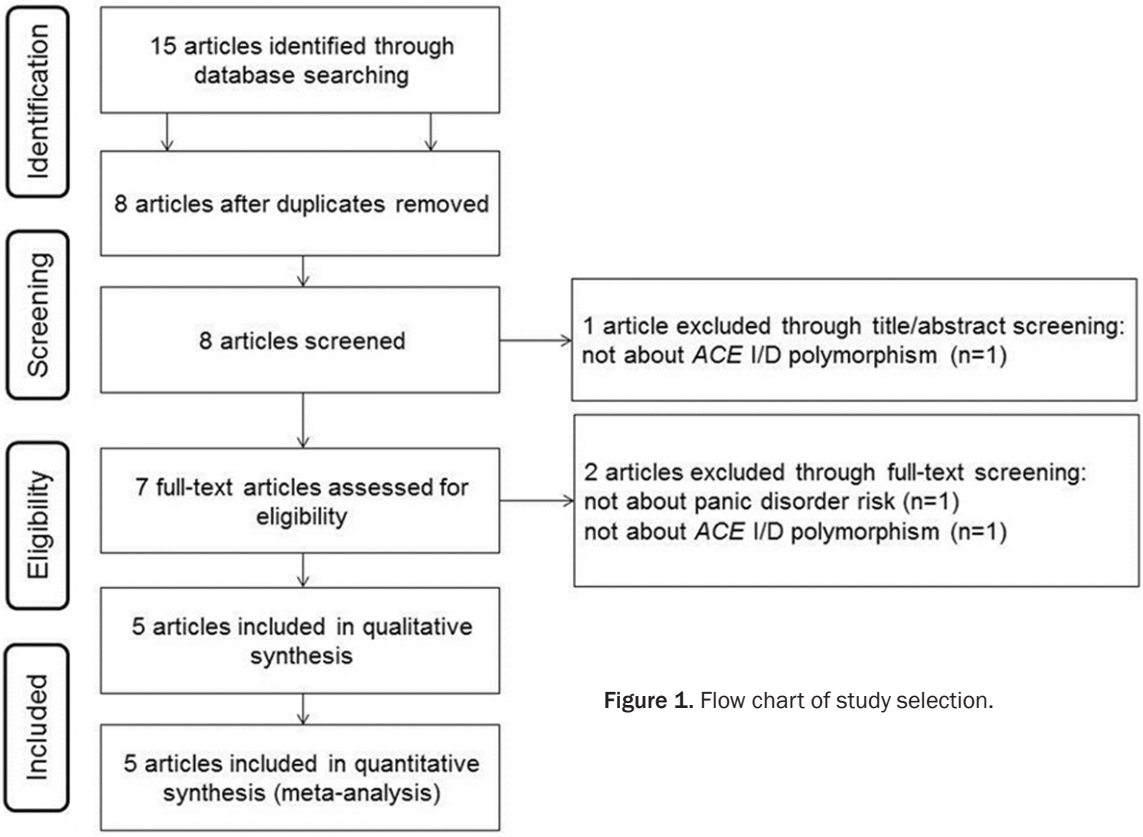

Figure 1. Flow chart of study selection.

on"/"variations"/"variant"/"variants"/"genotype"/"genotypes" in PubMed, Web of Science, and OVID independently. The papers obtained were further selected for the meta-analysis and our selection criteria were: (a) full text English-written study; (b) study providing complete case and control data about the relationship between *ACE* I/D polymorphism and panic disorder risk; (c) studies sharing the same sample of cases and controls were compared and the most complete study from them was included in our meta-analysis.

In this study, two investigators independently collected data from each eligible paper. The data were composed of first author, published year, country of origin, ethnicity, and numbers of cases and controls. Through checking between the two investigators, a final data collection was determined. Hardy-Weinberg equilibrium (HWE) was also tested by χ^2 test for the control group of each eligible study, and when χ^2 test reported a *P* value of more than 0.05, the control group genotypes were consistent with HWE.

Meta-analysis methods

According to the data collected from each eligible paper, we performed both the overall meta-analysis and the subgroup meta-analysis based on ethnicity, gender, and HWE in controls, to evaluate the relationship between *ACE* I/D polymorphism and panic disorder risk. In the overall as well as the subgroup meta-analysis, pooled odds ratios (ORs) and 95% confidence intervals (CIs) for dominant, recessive, and codominant genetic models were all calculated by fixed effects model or random effects model. The model chosen was based on the heterogeneity test. For the heterogeneity test, we performed the χ^2-based *Q*-test in this study [17]. When *Q*-test reported a *P* value of more than 0.10, fixed effects model was used to calculate the pooled ORs [18], otherwise random effects model was used [19].

Publication bias was also tested using the Begg's funnel plot and the Egger's test [20]. If the funnel plot was asymmetric and the Egger's test reported a *P* value of less than 0.05, the publication bias probably exists.

Table 1. Studies and data included in this meta-analysis

First author	Published year	Country of origin	Ethnicity	Sample size (case/control)	Cases DD/DI/II	Controls DD/DI/II	P_{HWE} [a]
Olsson [13]	2004	Sweden	Caucasian	72/435	10/42/20	128/216/91	0.994
Shimizu [14]	2004	Japan	Asian	101/184	12/48/41	24/79/81	0.496
Bandelow [15]	2010	Germany	Caucasian	102/102	15/67/20	26/53/23	0.685
Bayoglu [6]	2012	Turkey	Turkish	123/168	41/57/25	71/68/29	0.077
Gulec-Yılmaz [16]	2014	Turkey	Turkish	43/41	5/26/12	18/13/10	0.029

[a]*P* value for Hardy-Weinberg equilibrium test in each control group.

In this study, we used the software Stata version 13.1 (Stata Corporation, College Station, TX, USA) to carry out the meta-analysis.

Results

Studies and data included in this meta-analysis

Through searching and selection, a final list of 5 studies [6, 13-16] was collected for meta-analysis (see **Figure 1**). All 5 studies collected were case-control studies with various ethnicities (1 study of Asians, 2 studies of Caucasians, and 2 studies of Turkish). The control groups of the eligible studies were in Hardy-Weinberg equilibrium ($P > 0.05$) except for one study [16]. The information of these 5 studies and the numbers of cases and controls with different genotypes reported in each study were all presented in **Table 1**. In total, the 5 eligible studies provided 441 cases and 930 controls about the relationship between *ACE* I/D polymorphism and panic disorder risk.

Overall and subgroup meta-analysis results

In this study we performed both the overall meta-analysis and the subgroup meta-analysis based on ethnicity, gender, and HWE in controls. The detailed results of our meta-analysis are shown in **Table 2**. The results of the overall meta-analysis provided evidence of the association between *ACE* I/D polymorphism and panic disorder risk (OR = 0.58, 95% CI = 0.40-0.84 for DD versus II; OR = 0.51, 95% CI = 0.33-0.80 for DD versus DI+II, see **Table 2**; **Figures 2** and **3**). In the subgroup meta-analysis based on HWE in controls, significant associations between *ACE* I/D polymorphism and panic disorder risk were also detected (see **Table 2**). In the subgroup analysis based on ethnicity, significant association was observed in Caucasians but not in Asians (see **Table 2**). The stratified meta-analysis based on gender further showed that *ACE* I/D polymorphism was significantly associated with panic disorder risk in males (OR = 0.22, 95% CI = 0.10-0.47 for DD versus II; OR = 0.51, 95% CI = 0.28-0.93 for DI versus II; OR = 0.39, 95% CI = 0.22-0.70 for DD+DI versus II; OR = 0.36, 95% CI = 0.20-0.66 for DD versus DI+II, see **Table 2**), while no such significant association except an opposite weak association for the DI versus II model (OR = 1.64, 95% CI = 1.01-2.66) was detected in females (see **Table 2**). In summary, according to the results of our meta-analysis, the *ACE* I/D polymorphism probably associates with panic disorder risk especially in males, with the I allele acting as a risk factor.

Publication bias test results

The results of Begg's funnel plot (see **Figure 4**) and Egger's test showed no publication bias for DD versus II ($P = 0.280$), for DI versus II ($P = 0.336$), for DD+DI versus II ($P = 0.791$), and for DD versus DI+II ($P = 0.190$) in the overall meta-analysis.

Discussion

In this study, the results of our overall meta-analysis suggest that the *ACE* I/D polymorphism probably associates with panic disorder risk, with the I allele acting as a risk factor. It is reported that ACE degrades substance P, a neurotransmitter belonging to the tachykinin neuropeptide family [21], and increased substance P level has been shown to produce anxiogenic-like responses [22, 23]. Therefore, subjects with *ACE* I allele have lower ACE level and increased SP concentration, which could lead to the induction of anxiogenic-like responses. In addition, the *ACE* I/D polymorphism accounts for 47% of the variance of serum ACE concen-

Table 2. Detailed results of the meta-analysis

Meta-analysis groups	No. of studies	Sample size (case/control)	DD versus II		DI versus II		DD+DI versus II		DD versus DI+II	
			OR (95% CI)	P^a	OR (95% CI)	P^a	OR (95% CI)	P^a	OR (95% CI)	P^a
Overall analysis	5	441/930	0.58 (0.40, 0.84)[c]	0.251	1.13 (0.85, 1.51)	0.747	0.93 (0.71, 1.23)	0.632	0.51 (0.33, 0.80)[b,c]	0.098
Ethnicity										
Asian	1	101/184	0.99 (0.45, 2.17)	-	1.20 (0.71, 2.02)	-	1.15 (0.70, 1.88)	-	0.90 (0.43, 1.88)	-
Caucasian	2	174/537	0.47 (0.26, 0.85)[c]	0.303	1.09 (0.69, 1.71)	0.286	0.87 (0.56, 1.35)	0.219	0.44 (0.27, 0.71)[c]	0.600
Gender										
Male	3	109/299	0.22 (0.10, 0.47)[c]	0.526	0.51 (0.28, 0.93)[c]	0.971	0.39 (0.22, 0.70)[c]	0.993	0.36 (0.20, 0.66)[c]	0.406
Female	3	188/406	0.96 (0.55, 1.67)	0.498	1.64 (1.01, 2.66)[c]	0.311	1.38 (0.87, 2.19)	0.305	0.68 (0.45, 1.03)	0.789
HWE in controls										
Yes	4	398/889	0.63 (0.43, 0.93)[c]	0.356	1.10 (0.81, 1.48)	0.707	0.94 (0.71, 1.26)	0.472	0.59 (0.43, 0.81)[c]	0.364
No	1	43/41	0.23 (0.06, 0.85)[c]	-	1.67 (0.57, 4.86)	-	0.83 (0.31, 2.21)	-	0.17 (0.05, 0.51)[c]	-

[a]*P* value for heterogeneity test. If $P > 0.1$, ORs were calculated using fixed effects model, otherwise the random effects model was used; [b]ORs calculated using random effects model; [c]Results which are statistically significant.

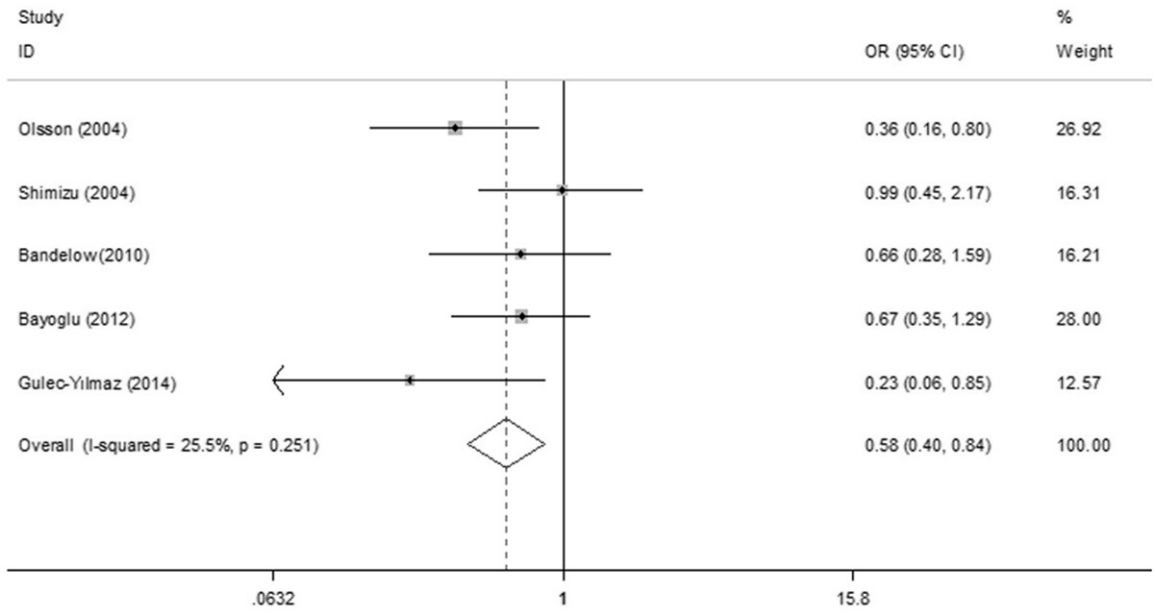

Figure 2. Forest plot for DD versus II of the overall meta-analysis using fixed-effects model. OR: Odds ratio; CI: Confidence interval.

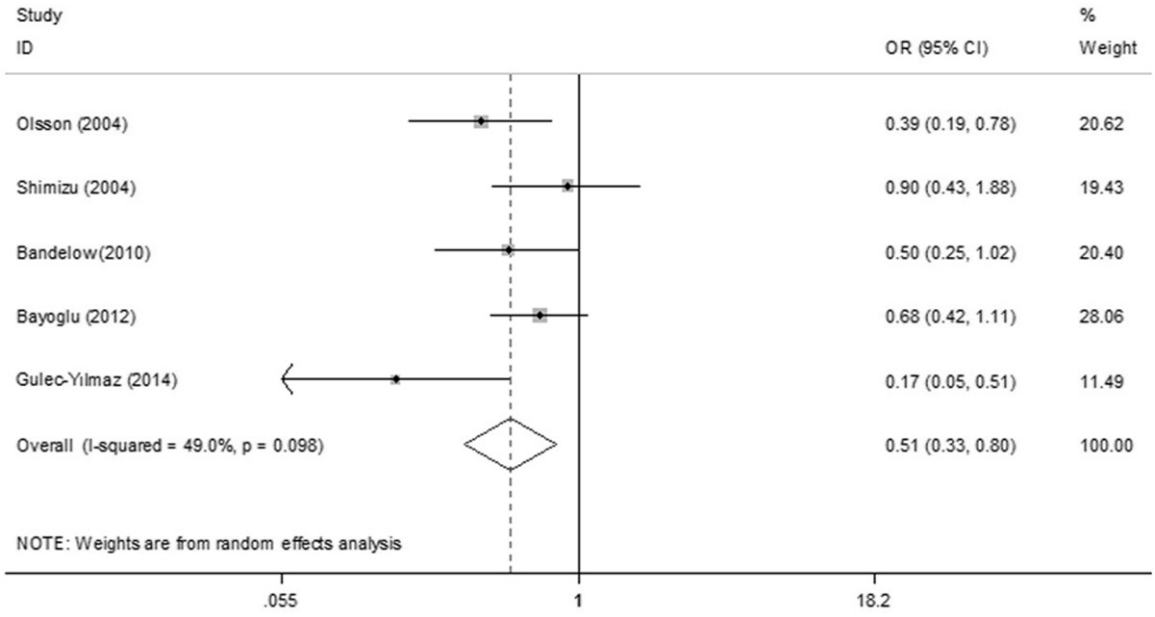

Figure 3. Forest plot for DD versus DI+II of the overall meta-analysis using random-effects model. OR: Odds ratio; CI: Confidence interval.

tration [11], hence combined effects of this polymorphism with other variants involved in the modulation of ACE levels and environmental factors probably exist.

In the subgroup meta-analysis based on gender, the *ACE* I allele was found to be associated with panic disorder in males only, suggesting a potential male-specific effect of this allele in the pathogenesis of panic disorder. In another study, Baghai et al. reported that the *ACE* I allele significantly influenced therapeutic outcome in female major depressed patients only [24]. Further research on the gender-effect of

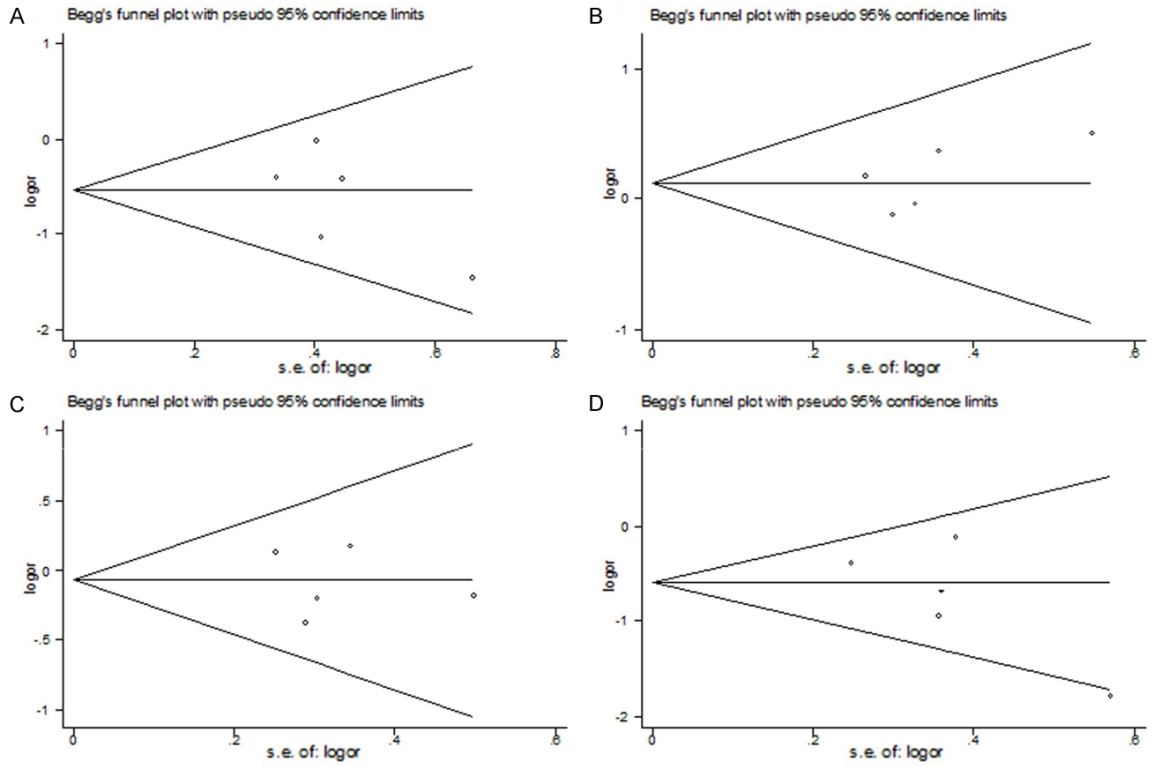

Figure 4. Begg's funnel plots of *ACE* I/D polymorphism and panic disorder risk for DD versus II (A), DI versus II (B), DD+DI versus II (C) and DD versus DI+II (D). logor: Logarithm of odds ratios; s.e.: Standard error.

the *ACE* I/D polymorphism specific to different psychiatric diseases is required in the future.

In the stratified meta-analysis based on ethnicity, significant association between *ACE* I/D polymorphism and panic disorder risk was observed in Caucasians, however, no obvious association existed in Asians. This result is not that convincible because of the insufficient data available at present for each subgroup, and the exact roles of *ACE* I/D polymorphism in different ethnicities will require further research.

In addition, all the results of our meta-analysis should be considered prudently due to the existence of several limitations. One limitation is the insufficient sample size used in our meta-analysis especially in the subgroup analysis based on ethnicity and gender. A second limitation is the lack of case-control data adjustment according to detailed individual information such as age and lifestyle in our meta-analysis. The third limitation is that the exact molecular basis of the association between the *ACE* I/D polymorphism and panic disorder risk is still not clear enough at present and needs further investigation. Hence, in order to achieve a more convincible conclusion, further analysis using larger sample size and adjusted individual data is required, and further functional research should also be performed.

In conclusion, supported by a meta-analysis with a total of 5 studies (441 cases and 930 controls in all), our study indicates that the *ACE* I/D polymorphism probably associates with panic disorder risk especially in males, with the I allele acting as a risk factor. Although there are some limitations, our meta-analysis can still provide valuable information for studying the relationship between the *ACE* I/D polymorphism and panic disorder risk.

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Disclosure of conflict of interest

None.

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