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Original Article

Association between HTR2A T102C polymorphism and major depressive disorder: a meta-analysis in the Chinese population

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Abstract: Although a number of studies have been conducted on the association between HTR2A T102C polymorphism and major depressive disorder (MDD) in Chinese, this association remains elusive and controversial. To clarify the effects of HTR2A T102C polymorphism on the risk of MDD, a meta-analysis was performed in the Chinese population. Related studies were identified from PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) till 5 May 2015. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the strength of the associations. Statistical analyses were conducted with Version 10.0 STATA statistical software. A total of 12 case-control studies including 1444 MDD cases and 1445 controls were involved in this meta-analysis. Overall, no significant association with MDD risk was provided in the Chinese population (C vs. T: OR=0.97, 95% CI: 0.81-1.17, 95%; CC vs. TT: OR=0.95, 95% CI: 0.65-1.37; CC+TC vs. TT: OR=0.96, 95% CI: 0.75-1.12; CC vs. TT+TC: OR=0.94, 95% CI: 0.78-1.12). In subgroup analyses stratified by geographic area and source of controls, no significant association was found in any of the subgroups. In conclusion, this meta-analysis indicate that the HTR2A T102C polymorphism is not associated with susceptibility to MDD in Chinese population.

Keywords: Meta-analysis, HTR2A-T102C, polymorphism, major depressive disorder

Introduction

Major depressive disorder (MDD) is the most common psychiatric disorder, and is the second leading cause of disease burden worldwide [1]. It is one of the causes of disability in association with diabetes, stroke, and coronary heart disease, which could reduce health-related quality of life scores [2-7]. A meta-analysis of the data from the WHO World Mental Health (WMH) Survey suggested that the 12-month MDD prevalence rate in the mainland Chinese population was 2.3%, was lower than those in developed countries (4.0-10.4%) and was similar to that in Japan (2.2%) [8]. Accumulated evidence suggests that both environmental and genetic factors are involved in the etiology of MDD although the pathogenesis of MDD remains unknown [9]. It is estimated that the heritability of MDD was about 30-40% [10]. In recent years, several common low-penetrant genes have been identified as potential MDD susceptibility genes. An important one is the serotonin 2A receptor (HTR2A, also known as 5-HT2A), which plays a particularly important role in prefrontal cortical function though binding to the neurotransmitter serotonin, according to both pharmacologic and physiologic data [11, 12]. Several polymorphisms in HTR2A have been identified, among which the T102C (or rs6313, exon-1 of HTR2A) single nucleotide polymorphism has been extensively studied. An association between HTR2A T102C polymorphism and depressive disorders was first reported by Zhang and co-workers in 1997 among the Japanese population [13]. As a con-

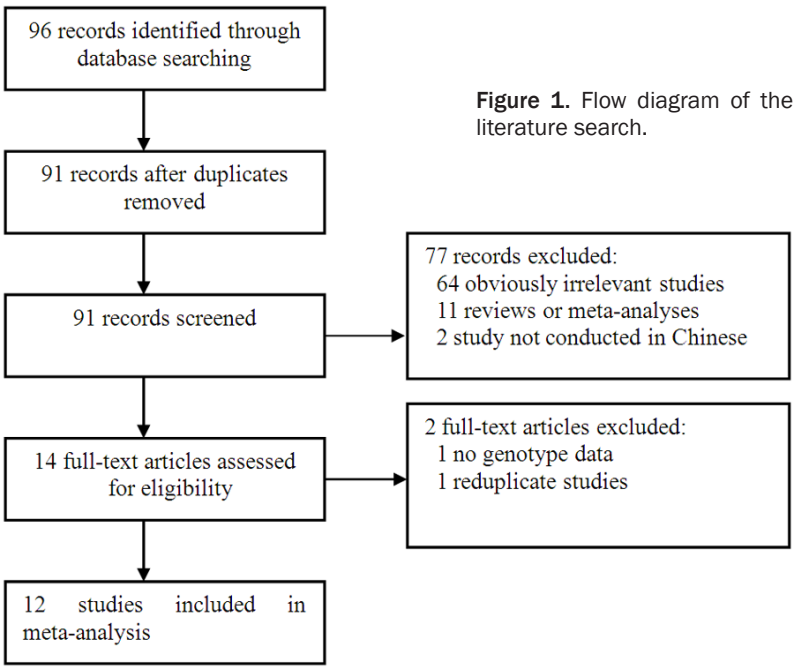

Figure 1. Flow diagram of the literature search.

sequence, many studies analyzed the influence of MTHFR C677T polymorphism on depression risk, however, no clear consensus was reached. Recently, two meta-analyses [14, 15] also conclude that HTR2A T102C polymorphism does not seem to be capable of modifying MDD risk. Given the different genetic background between the Chinese and non-Chinese populations, it is necessary to investigate this association in Chinese. In addition, we performed subgroup analysis stratified by geographic area and the source of control population to explore the possible effects of the gene-environment interactions with respect to MDD risk.

Materials and methods

Search strategy and study selection

We conducted a systematic literature search for published articles regarding the association of HTR2A T102C polymorphism and MDD risk. The studies were searched in PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) till 5 May 2015, using the combination of following terms: (1) serotonin 2A receptor gene or HTR2A or 102T/C or 5-HT2A; (2) depression or major depressive disorder; (3) polymorphism or variant or variation; and (4) Chinese or China or Taiwan. The search was performed without any restrictions on language and focused on studies conducted in humans. In addition to the electronic database search, all reference lists of retrieved articles were reviewed manually to identify additional articles. In our meta-analysis, studies were included if the following criteria were met: (1) case-control or cohort studies describing the association of the HTR2A T102C polymorphism and MDD, (2) all patients with the diagnosis of MDD confirmed by the ICD, DSM-IV criteria or Chinese classification of mental disorders (CCMD) systems, (3) clear description of HTR2A T102C polymorphism in MDD patients and controls, (4) all participants were Chinese. The reasons for exclusion of studies were: (1) duplicate publications, (2) incomplete data, (3) no control, (4) meta-analyses, letters, reviews, or editorial articles.

Data extraction

Information was extracted carefully from all eligible publications independently by two authors, based on the inclusion criteria above. Disagreements were resolved through a discussion between the two authors, and if consensus was not achieved the decision was made by all the reviewers. The title and abstract of all potentially relevant articles were screened to determine their relevance. Full articles were also scrutinized if the title and abstract were ambiguous. The following data were extracted from the identified studies: the first author, publication year, source of controls, geographic area, sample size, HTR2A T102C genetic polymorphism in cases and controls. If data from any category were not reported in the primary study, we did not contact the author to request the information.

Statistical analysis

STATA statistical package (version 10, STATA, College Station, TX) was used for statistical analysis. The χ^2-test was used for Hardy-Weinberg equilibrium (HWE) of genotypes in the con-

Table 1. Characteristics of studies included in the meta-analysis

References	Geographic area	Source of controls	Cases number	Controls number	Cases			Controls			HWE	
					TT	TC	CC	TT	TC	CC	χ^2	*P*
Jiang 1999	Shanghai	PB	72	81	22	31	19	24	38	19	0.27	0.601
Tsai 1999	Taiwan	PB	79	96	26	44	9	36	50	10	1.48	0.224
Wang 2002	Jiangsu	PB	125	109	40	65	20	38	53	18	0.00	0.947
Xie 2002	Hunan	PB	42	97	9	23	10	26	51	20	0.30	0.584
Cai 2004	Shanghai	PB	79	102	25	43	11	30	46	26	0.95	0.329
Xu 2006	Shanghai	PB	281	219	73	132	76	64	99	56	1.96	0.161
Liu 2008	Shaxi	PB	375	374	110	186	79	92	196	86	0.88	0.349
Li 2009	Guangdong	PB	123	122	62	48	13	45	54	23	0.88	0.348
Tang 2011	Jiangsu	PB	58	37	22	29	7	13	21	3	1.87	0.172
Wu 2011	Sichuan	PB	41	66	4	24	13	22	37	7	2.19	0.139
Chen 2011	Guangdong	HB	97	72	33	44	20	12	35	25	0.00	0.966
Guo 2014	Henan	PB	72	70	18	28	26	19	29	22	2.20	0.155

HB, hospital-based; PB, population-based.

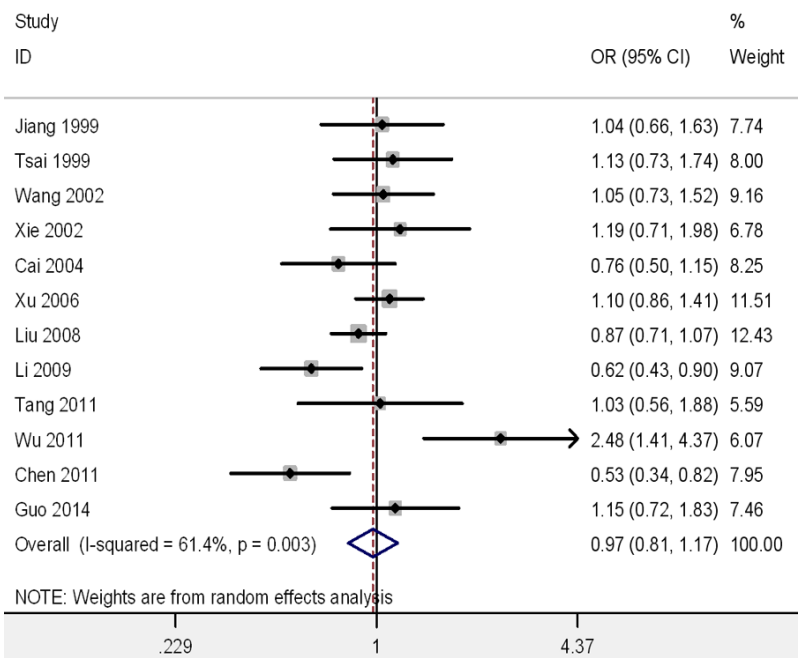

Figure 2. The forest plots of all selected studies on the association between HTR2A T102C polymorphism and MDD risk in Chinese.

trol group of each reviewed study and the heterogeneity of rare allele frequencies in control groups among all studies. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association between the HTR2A T102C polymorphism and MDD risk. The significance of the pooled OR was determined by the Z test. Dependent on the results of heterogeneity test among individual studies, the fixed-effect model (Mantel-Haenszel) or random-effect model (DerSimonian and Laird) was selected to summarize the combined ORs and their 95% CIs. Sensitivity analysis was conducted to verify stability of the meta-analysis using both models (the fixed effect model and random effect model). Begg's funnel plots and Egger's linear regression test were used to assess publication bias. In addition to the comparison among all subjects, we also performed stratification analyses by geographical locations and source of controls. All the *p*-values were two-sided, a *p*-value <0.05 was considered statistically significant.

Results

Description of included studies

We identified 96 articles that examined the association between HTR2A T102C polymorphism and risk of MDD. However, after screening of the titles and abstracts of all 96 articles, 82 were excluded. Of the 14 potentially relevant articles [16-29] identified for full study retrieval, one article [16] was excluded due to no genotype data, one [17] was excluded because it

Table 2. Main results in the total and subgroup analysis

Analysis model	Study groups	n	Random-effect model	Fixed-effect model	Heterogeneity	
			OR (95% CI)	OR (95% CI)	χ^2	P
C vs. T	Total analysis	12	0.97 (0.81-1.17)	0.95 (0.86-1.05)	28.49	0.003
	PB	11	1.02 (0.86-1.21)	0.98 (0.88-1.10)	21.24	0.019
	South China	10	0.98 (0.78-1.23)	0.97 (0.85-1.10)	27.16	0.001
	North China	2	0.92 (0.75-1.13)	0.91 (0.76-1.10)	1.09	0.279
CC vs. TT	Total analysis	12	0.95 (0.65-1.37)	0.90 (0.73-1.12)	27.44	0.004
	PB	11	1.04 (0.73-1.47)	0.97 (0.78-1.21)	20.82	0.022
	South China	10	0.97 (0.60-1.57)	0.93 (0.72-1.21)	26.26	0.002
	North China	2	0.84 (0.58-1.22)	0.84 (0.58-1.22)	0.99	0.319
CC+TC vs. TT	Total analysis	12	0.96 (0.75-1.12)	0.93 (0.79-1.10)	20.73	0.036
	PB	11	1.00 (0.80-1.25)	0.98 (0.83-1.15)	15.30	0.122
	South China	10	0.98 (0.73-1.33)	0.98 (0.81-1.19)	19.29	0.023
	North China	2	0.83 (0.62-1.12)	0.83 (0.62-1.12)	0.71	0.398
CC vs. TT+TC	Total analysis	12	0.95 (0.73-1.23)	0.94 (0.78-1.12)	18.99	0.061
	PB	11	1.01 (0.78-1.30)	0.98 (0.81-1.18)	15.31	0.121
	South China	10	0.94 (0.67-1.33)	0.93 (0.74-1.16)	18.32	0.032
	North China	2	0.95 (0.70-1.30)	0.95 (0.70-1.30)	0.66	0.417

PB, Population-based, South China including Taiwan, Jiangsu, Shanghai, Hunan, Guangdong, Sichuan; North China including Henan, Shanxi.

concerned subjects included in an expanded study [26]. Finally, 12 case-control studies [18-29] met the inclusion criteria. The publication year of involved studies ranged from 1999 to 2014. The flow chart of study selection is shown in **Figure 1**. In total, 1444 MDD cases and 1445 controls were involved in this meta-analysis, which evaluated the relationship between HTR2A T102C polymorphism and MDD risk in Chinese. The characteristics of the included studies are summarized in **Table 1**.

Meta-analysis results and subgroup analysis

Based on OR and 95% CI, no significant association with MDD risk was provided in overall analysis. The OR and 95% CI in four genetic models were: C vs. T model (OR=0.97, 95% CI: 0.87-1.17, P=0.769) (**Figure 2**); CC vs. TT model (OR=0.95, 95% CI: 0.65-1.37, P=0.770); CC+TC vs. TT model (OR=0.96, 95% CI: 0.75-1.12, P=0.709); CC vs. TT+TC model (OR=0.94, 95% CI: 0.78-1.12, P=0.692) (**Table 2**). Ten studies (997 patients and 1001 controls) performed in South China and 2 studies (447 patients and 444 controls) conducted in North China were included for further analysis by geographical locations. No significant association with the T102C polymorphism was found both in South China and North China (**Table 2**). The population-based group, including 11 studies consisting of 1347 cases and 1373 controls, indicated that no significant association existed between the T102C SNP and increased risk of MDD (**Table 2**).

Sensitive analysis and bias diagnosis

To validate the credibility of outcomes in this meta-analysis, a sensitivity analysis was performed by the comparison between random-effects model and fixed-effects model. All the results were not materially altered (**Table 2**). Hence, results of the sensitivity analysis suggest that the data in this meta-analysis are relatively stable and credible. The Begg's funnel plot and Egger's test were performed to access the publication bias of literatures. As showed in **Figure 3A**, the shape of the funnel plots revealed obvious asymmetry. However, the Egger's test indicated no publication bias in the 12 reviewed studies (**Figure 3B**, t=0.41, *P*=0.690).

Discussion

The current meta-analysis performed a systematic evaluation between the HTR2A T102C polymorphism and susceptibility to MDD based on a total of 12 independent studies contain-

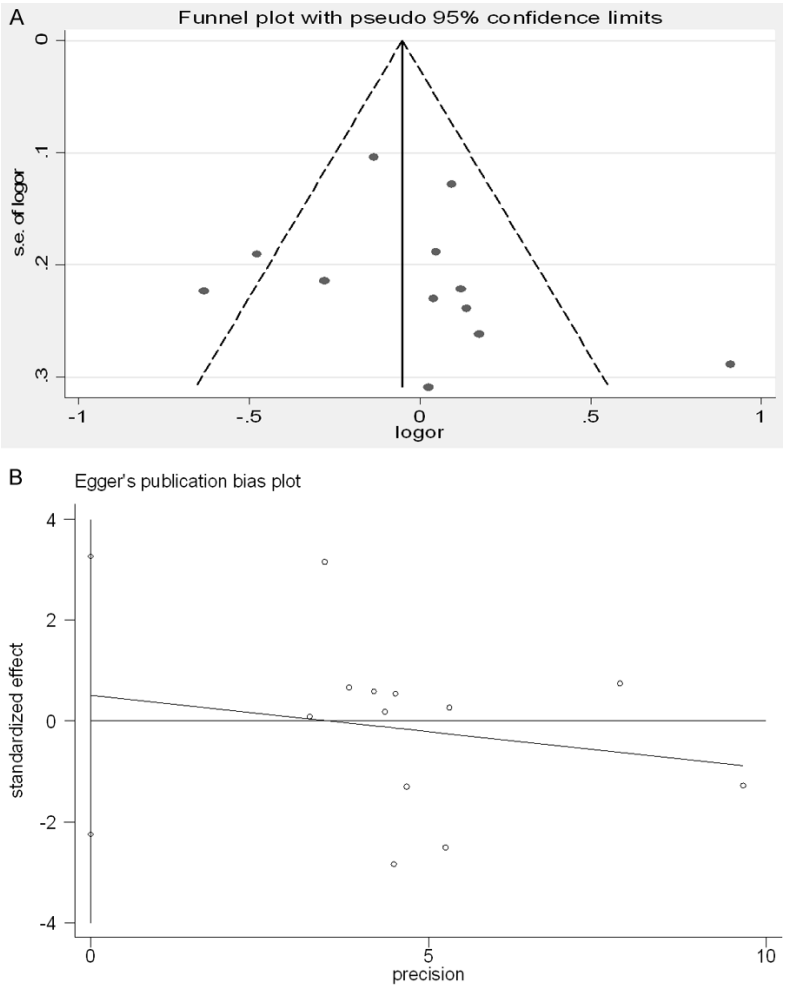

Figure 3. Publication bias evaluation on the association between HTR2A T102C polymorphism and MDD risk in Chinese (A: Funnel plot, B: Egger's test).

ing 1444 cases and 1445 control subjects in the Chinese population. However, no statistical significance was detected in the overall data analysis for MDD. Our results were similar to the previous meta-analysis which reported that the HTR2A T102C polymorphism was not directly associated with depressive disorders [14, 15, 30]. Thus, it confirmed that there were no significant associations between the HTR-2A T102C polymorphism and increased risk of MDD. To eliminate the effects of gene-environment interactions with respect to MDD risk, we also conducted subgroup analyses by dividing the samples into subgroups according to geographic area and the source of controls, but no significant association was found in any of the subgroups. Compared to the previous studies, our meta-analysis included a larger number of studies which were conducted in the Chinese population. Therefore, our study has higher statistical power than other meta-analyses conducted in other ethnic groups.

The characteristic of meta-analysis is to combine comparable studies to increase the sample size and statistical power and draw a more reliable result. However, the result of meta-analysis may be influenced by some factors such as publication bias, method of sampling, different genetic backgrounds of subjects, different protocols and quality of analysis. We obeyed the inclusion criteria strictly to reduce selection bias. Funnel plot and Egger's linear regression test were used to assess publication bias. In addition, our inclusion of non-English language reports, were important in minimizing a major potential threat to the validity of any meta-analysis-publication bias and the related threat of a language bias. The impact of different genetic background was lessened by means of including the studies performed in the Chinese population only, and the test of HWE for distribution of the genotypes in control groups suggested that there was no significantly different genetic background among the participants. Finally, the sensitivity analysis had been performed to confirm the reliability and stability. Therefore, the 12 studies would seem to be comparable in all respects relevant to our meta-analysis.

Some limitations of this meta-analysis should be addressed. First, observational studies are susceptible to various biases (e.g. recall bias in case-control studies) because of their retrospective nature. Therefore, recall bias could invalidate the results from this meta-analysis. Another potential limitation was that our results were based on unadjusted estimates. More precise analyses can be conducted if individual

data were available, which would allow for the adjustment by other covariates including age, sex, race and other factors. Finally, heterogeneity can interfere with the interpretation of the results of a meta-analysis. Although we minimized this likelihood by performing a careful search of published studies and subgroup analyses, significant inter-study heterogeneity nevertheless existed in some comparisons.

In conclusion, our meta-analysis failed to find a significant association between the HTR2A T102C polymorphism and MDD in the Chinese population. Concerning MDD with multifactorial etiology, to further evaluate gene-gene and gene-environment interactions on HTR2A T102C polymorphism and MDD, larger studies in selected populations with different environmental background or other risk factors are required. Such studies may eventually lead to have a better, comprehensive understanding of the association between the HTR2A T102C polymorphism and MDD risk.

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Disclosure of conflict of interest

None.

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