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Association between norepinephrine transporter T-182C polymorphism and major depressive disorder: A meta-analysis

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HIGHLIGHTS

- The association between the T-182C polymorphism and MDD was assessed by a meta-analysis.
- A total of 1779 cases and 1584 controls were included.
- No association was found between the NET T-182C polymorphism and MDD.

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ABSTRACT

The human norepinephrine transporter (NET) gene is one of the key candidates for genetic studies in major depressive disorder (MDD). The association between NET T-182C gene polymorphisms and MDD risk has been widely reported, but results were controversial and underpowered. The purpose of this study was to derive a more precise estimation of the relationship between NET T-182C polymorphisms and MDD risk through a meta-analysis. Relevant studies were identified from PubMed, Web of Science, Chinese Biomedical Database (CBM), Chinese National Knowledge Infrastructure (CNKI), Ovid and Wan Fang (Chinese) up to March 2013. Finally, seven studies containing 1779 cases and 1584 controls were included. The pooled odds ratio (OR) and 95% confidence interval (CI) were performed. The combined results showed that there was no significant difference between MDD group and control group in all comparison models (T vs. C: OR = 1.00, 95% CI = 0.83–1.22; TC + TT vs. CC: OR = 0.87, 95% CI = 0.55–1.36; TT vs. TC + CC: OR = 0.96, 95% CI = 0.76–1.20; TT vs. CC: OR = 1.09, 95% CI = 0.66–1.80). When stratifying for the race, there was still no significant difference in genotype distribution between MDD and controls. No publication bias was observed. Conclusively, the present meta-analysis did not suggest a confirmed association between the T-182C polymorphism of the NET gene and MDD.

1. Introduction

Major depressive disorder (MDD) is a psychiatric disorder characterized by persisting depressed mood, loss of interest or pleasure in normally enjoyable activities, psychomotor retardation and changes in sleep and appetite [9]. The estimated lifetime prevalence of MDD is more than 10%, and women are affected by MDD approximately twice as often as men [8,17]. It has a large impact on social health, with considerable direct and indirect costs [13]. The suicide rate is clearly higher in women with major depression than in the general population [16]. The World Health Organization (WHO) has predicted that MDD will be the second leading cause of disability worldwide by the year 2020 [11].

The etiology of MDD is diverse and complex, and both genetic and non-genetic factors contribute to the disorder [2,22]. Although, non-genetic factors, such as grief, stress, illness, and social support systems, have been linked to MDD [1,6,20], genetic factors have been considered to play an important role in MDD. Twin studies have indicated that the heritability of MDD is 0.36–0.70 [37] and the risk of MDD in first-degree relatives of probands is 2–4 times larger compared to the controls [35]. It indicates the closer the kinship is, the higher the prevalence will be. A number of genes, such as serotonin-transporter-linked polymorphic region (5-HTTLPR) [5], brain neurotrophic derived factor (BNDF) [3] and Dopamine D4 Receptor (DRD4) [41], have been proved to be associated with the MDD. Recently, the association between NET and MDD has received increasing research attention.

The NET gene, also called as SLC6A2, locates on chromosome 16q12.2 and spans approximately 45 kb containing 14 exons [28].

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A number of case–control studies have been conducted to quantify the effects of NET T-182C gene polymorphisms on MDD, but the results are not consistent. Three studies in Asia have reported that the polymorphisms of NET T-182C were not major susceptibility factors in the etiology of major depression disorder [7,10,15]. However, Ryu et al. have found a significantly lower frequency in TT genotype in patients with MDD than in normal controls [29]. Based on the assumption that CC genotype was associated with lesser susceptibility to major depressive disorder, Inoue et al. believed T-182C polymorphism may be partially related to the pathophysiology of major depressive disorder in the Japanese population [31]. To date, there were only two studies reporting the significantly differences between T-182C polymorphism and MDD, regardless of genotype or gene frequency [25,34].

It is essential to perform a quantitative synthesis of the evidence using rigorous methods. Therefore, we performed a comprehensive meta-analysis to evaluate the association between NET T-182C polymorphism and MDD.

2. Materials and methods

2.1. Search strategy

Electronic databases, including PubMed, Chinese Biomedical Database (CBM), Chinese National Knowledge Infrastructure (CNKI), Ovid and Wan Fang (Chinese) were used to retrieve articles published up to March 2013 for all genetic association studies evaluating the T-182C gene polymorphism and MDD in humans. We used the following key words: 'major depression', 'unipolar depression', 'major depressive disorder', 'MDD', 'norepinephrine transporter', 'NET', 'rs2242446', 'T182C' and 'T-182C'. Articles written in English or Chinese were included. No restrictions were placed on ethnicity, geographical area and other conditions. References of the original studies were also manually checked to make sure that all possible studies could be included in the meta-analysis.

2.2. Study selection

The inclusion criteria of literature were as follows: (a) the publication was a case–control study examining the association between NET T-182C polymorphisms and MDD; (b) the article had available genotype frequency in both cases and controls; (c) sufficient data calculating the value of odds ratio (OR) and 95% confidence interval (CI) were presented. We contacted the author to get the relevant information by e-mail or telephone if genotype frequency was not reported. Studies without data on allelic counts in cases and controls and studies containing patients with other serious disorders were excluded. In case of overlapping cases/controls existed in different studies, we retained only the studies with the largest sample size. The article selection procedure was shown in Fig. 1.

2.3. Data extraction

Two reviewers (Zhou YY and Song J) extracted the data independently according to the pre-specified selection criteria, and the results were reviewed by a third investigator (Su H). The following information was extracted: the first author name, publication year, country of origin, number of cases and controls, the genotype and allele frequency information, and the mean age of subjects. Different ethnicity descent was categorized as Asian and non-Asian.

2.4. Statistical analysis

We used crude ORs with their 95% CIs to assess the association between the NET gene polymorphism at T-182C and MDD. The pooled ORs were performed for the allele contrasts, dominant genetic model, recessive genetic model and homozygote comparison, respectively. Subgroup analysis was also performed by ethnicity for T-182C polymorphisms.

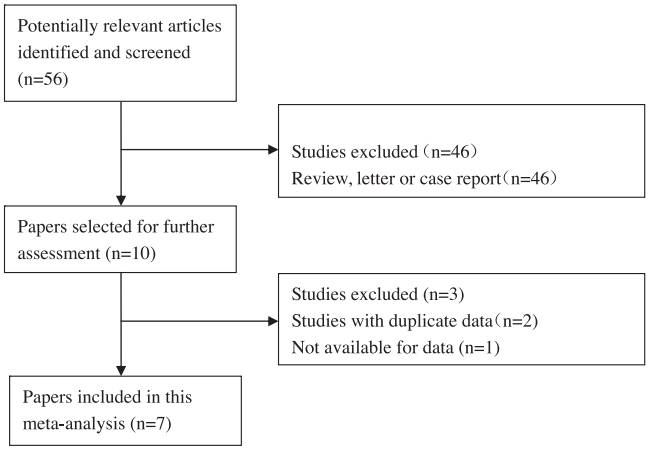

Fig. 1. The flow of the articles selection.

Statistical heterogeneity among studies was assessed using the Q-test and I^2 statistics [39]. We used the I^2 to measure the degree of heterogeneity (I^2 = 0–20%, no heterogeneity; I^2 = 20–50%, moderate heterogeneity; I^2 > 50%, obvious heterogeneity). Since Q-test is often underpowered to detect statistically significant heterogeneity, particularly when there are few trials in the analysis, the relatively conservative threshold of $P < 0.10$ was chosen to suggest statistically significant heterogeneity across trials [19].

The fixed effects model (if heterogeneity was not significant, $P \geq 0.10$) or random effects (if $P < 0.10$) model was used to pool the results [23]. Publication bias was assessed by the methods of Egger's linear regression test [33] and funnel plot. The significance of the pooled OR was determined by Z-test. Chi-square test was used for testing the Hardy–Weinberg equilibrium of genotypes in the control group of each study.

All P values were two-sided, and $P < 0.05$ was considered as statistically significant. Statistical calculations were all performed using STATA software package (version 11.0, College Station, TX).

3. Results

3.1. Eligible studies

A total of seven relevant studies concerning NET T-182C gene polymorphism and MDD were initially identified [7,10,15,25,29,31,34]. Among the 10 eligible articles, there were repetitive case–control studies for T-182C polymorphism in three publications [24,34,42], and we selected the most recently published study with the largest sample size for the meta-analysis [34]. Specific data of one study was not available [30]. In all eligible studies, six studies were conducted in Asians, and one study was in Caucasians. Our final pool of eligible studies included seven studies with 1779 cases and 1584 controls for T-182C polymorphism. The characteristics of the studies included in the meta-analysis are listed in Table 1.

3.2. Meta-analysis results

We tested the association between NET T-182C polymorphism and MDD by estimating the ORs and 95% CI. The main results of this meta-analysis and the heterogeneity test are shown in Table 2. The fixed effects model (if heterogeneity was not significant, i.e., $P \geq 0.10$) or random effects (i.e., $P < 0.10$) model was used to summarize the combined OR. Overall, we did not detect