Systematic Review and Meta-Analysis

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Association between NR3C1 rs41423247 polymorphism and depression

A PRISMA-compliant meta-analysis

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Abstract

Background: A dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis is closely related to the occurrence of depression. The glucocorticoid receptor, also known as the *nuclear receptor* subfamily *3,* group C, member 1 (*NR3C1)*, provides negative feedback to the HPA axis by binding to glucocorticoids. Some studies have demonstrated an association between the *NR3C1* rs41423247 polymorphism and depression, but results from other studies have been controversial.

Method: In this study, the association between the *NR3C1* rs41423247 polymorphism and depression was evaluated by a meta-analysis using the RevMan 5.3 software, and the Stata 10.0 software was used for sensitivity analysis and publication bias test. According to the inclusion criteria, related studies in databases were retrieved and screened.

Results: In total, 9 articles were selected, including 1630 depressed patients and 3362 controls. The meta-analysis showed that homozygous *mutation* of *NR3C1* rs41423247 was associated with depression in the total population (OR = 0.77, 95% CI = 0.64–0.94, *P* = .01) and in Caucasians (OR = 0.78, 95% CI = 0.63–0.96, *P* = .02).

Conclusion: This meta-analysis demonstrates that the *NR3C1* rs41423247 *homozygous mutation* may be a risk factor for depression.

Abbreviations: BDNF = brain derived neurotrophic factor, CI = confidence interval, GC = glucocorticoid, GR = glucocorticoid receptor, HPA = hypothalamic-pituitary-adrenal, NR3C1 = nuclear receptor subfamily 3, group C, member 1, OR = odds ratio, SNP = single nucleotide polymorphism.

Keywords: depression, glucocorticoid receptor, meta-analysis, polymorphism

Key Points

1. This is the first meta-analysis of the association between *NR3C1* rs41423247 polymorphism and depression.
2. Only about one-third of depressed patients achieved remission with antidepressant treatment, and these findings will help discover new therapeutic targets.

Editor: Zelena Dora.

Funding sources: This study was supported by funds from Science and Technology Program of Guangdong Province (2013A022100035, 2017A020212002)

The authors have no conflicts of interest to disclose.

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Medicine (2018) 97:39(e12541)

Received: 1 April 2018 / Accepted: 31 August 2018

http://dx.doi.org/10.1097/MD.0000000000012541

1. Introduction

Depression is an affective disorder characterized mainly by a persistent low mood state. The prevalence of depression is high, with more than 298 million depressed patients worldwide in 2010, and depression is the major cause of years lived with disability.[1,2] The pathogenesis of depression is complex, including genetic factor, environmental factor, and their interaction.[3] A meta-analysis of 5 high-quality family studies indicated that first-degree relatives of depressed patients had an increased risk of depression (OR = 2.84).[4] In addition, the heritability of depression was estimated to be 38% in a large-sample twin study.[5] These evidences suggest that heredity is a critical factor in the occurrence of depression.

A large number of clinical studies have shown that patients with depression have persistent hypothalamic-pituitary-adrenal (HPA) axis hyperactivity and high glucocorticoid (GC) concentration.[6] When an organism is subjected to stress, it will make an adaptive change that the HPA axis be activated, and thereby causing an increase in the secretion of GC from the adrenal cortex. Glucocorticoid receptors (GRs) play an important role in mediating the action of GCs. Activated GR transduces a negative feedback signal to the hypothalamus and pituitary. When the function of GR is impaired, the negative feedback decreases, resulting in persistent high GC concentration levels in the blood. Previous study demonstrated that the knockout of GR in forebrain induced depression-like behavior in male mice.[7] Alternatively, strengthened GR function may also lead to depressive symptoms. Preliminary clinical trials have found that the GR antagonist RU486 can improve cognitive function and mood in patients with bipolar disorders.[8]

GRs are encoded by the *NR3C1 (nuclear receptor* subfamily *3*, group C, member 1) gene. Cuzzoni et al[9] had found the *NR3C1* rs41423247 (C/G) polymorphism was associated with high sensitivity to GC, and may affect the occurrence of depression by altering the function of GRs. Some studies demonstrated that the *NR3C1* rs41423247 polymorphism was associated with the risk of depression,[10–13] while other studies found no correlation between the two.[14–18] In order to increase the statistical test power, and to provide evidence for further studies on the pathogenesis of depression, we performed a meta-analysis on the association between the *NR3C1* rs41423247 polymorphism and depression.

2. Methods

2.1. Search strategy

We searched Pubmed, ScienceDirect, Cochrane library, Wan Fang Data, and the China National Knowledge Infrastructure for relevant studies published before March 7, 2018. The following combination of search terms was used: "Glucocorticoid receptor or GR or NR3C1," "polymorphism or variant or mutation" AND "depression or depressive disorder or mood disorders or depressive symptoms." Taking PubMed, for example, the search criteria were: (Glucocorticoid receptor[Title/Abstract] OR GR [Title/Abstract] OR NR3C1[Title/Abstract]) AND (polymorphism*[Title/Abstract] OR variant[Title/Abstract] OR mutation[Title/Abstract]) AND (depression[Title/Abstract] OR depressive disorder[Title/Abstract] OR mood disorders[Title/Abstract] OR depressive symptoms[Title/Abstract]). Additional literature was identified by manually retrieving the references in relevant publications.

2.2. Inclusion criteria and qualitative evaluation

The inclusion criteria for the different studies were as follows: the study should have investigated the association between the *NR3C1* rs41423247 polymorphism and depression; it should have been a case–control study; and it should have provided the genotype or allele frequencies of rs41423247 in the depressed group and controls.

A study was excluded if it fulfilled any of the following exclusion criteria: If the study was a review; included animals as subjects; demonstrated that the genotype distribution in the control group does not correspond to the Hardy–Weinberg equilibrium; and was a duplicate case sample (i.e., a study with a larger sample population).

Evaluation criteria: Newcastle–Ottawa scale (NOS) (http://www.ohri.ca/) of the case–control study was used. The total score possible was 9 points. The scoring items included the definition and selection of subjects, intergroup comparability, and exposure factor.

2.3. Data extraction

The following data were extracted from each article: author, year of publication, ethnicity and country of subjects, method of SNP test, the number of depressed patients and controls, and the genotype distribution of *NR3C1* rs41423247. Data extraction was conducted independently by 2 researchers.

2.4. Statistical analysis

Statistical analyses were performed using the RevMan 5.3 software (http://community.cochrane.org/) and Stata 10.0 software (StataCorp, College Station, TX). The Hardy–Weinberg equilibrium of genotypes in the control groups were evaluated by the chi-square (χ^2) test. A P-value $<.05$ was considered to be statistically significant. The heterogeneity was tested by χ^2-based Q statistic, and $P<.05$ indicated that heterogeneity existed among the eligible studies.[19] When heterogeneity was present, we selected a random effects model. Otherwise, a fixed effects model was selected to calculate the pooled odds ratio (OR) with the corresponding 95% CI. The Z-test was adopted to determine the pooled OR. The sensitivity analysis was conducted to test the stability of the combined ORs. We performed a stratified analysis by sampling different ethnicities, and studies with Caucasians samples were analyzed in subgroups. The publication bias was evaluated according to the Begg's and Egger regression tests, where $P<.05$ indicated no obvious bias.

2.5. Ethical approval

Since no human subject was involved, this study does not need an application for ethical review.

3. Results

3.1. Characteristics of each study

A total of 245 studies were identified through the literature search. We excluded 236 studies for specific reasons, which are described in Figure 1, and a total of 9 studies were included.[10–18] A study was excluded for a lack of allelic or genotype frequencies after contacting the author who investigated and revealed a lack of correlation between the *NR3C1* rs41423247 polymorphism and depression.[20] The 9 studies in this meta-analysis included 1,630 depressed patients and 3362 healthy controls. For each study, the genotype distribution of the control groups corresponded to Hardy-Weinberg equilibrium, and the NOS quality scores were greater than 5 points (Table 1), which showed that the studies were of high quality. Details of the selected studies are presented in Table 1, which include ethnicity, country, SNP detection method, sample size, and the genotype distribution.

3.2. Meta-analysis for NR3C1 rs41423247

Allelic model (G vs C): for all of the selected studies, the heterogeneity test showed significant heterogeneity ($I^2=77\%$, $P<.0001$), and the random effects model was selected. The overall effects test showed no significant differences in allele frequencies between the depression and control groups (OR = 0.91, 95% CI = 0.74–1.12, $P=.38$) (Fig. 2). In order to reduce racial differences, 3 studies were excluded for non-Caucasians subjects, and 6 studies were analyzed to evaluate the association between the *NR3C1* rs41423247 polymorphism and depression in Caucasians (Table 1). A heterogeneity test showed significant heterogeneity ($I^2=79\%$, $P=.0003$), and the random effects model was selected. The overall effect test showed no significant differences in allele frequencies between the depression and control groups in Caucasians (OR = 0.82, 95% CI = 0.65–1.03, $P=.38$) (Fig. 2).

Dominant genetic model (GG + GC vs CC): for the 9 studies included, the heterogeneity test showed better homogeneity ($I^2=32\%$, $P=.16$), and the selected fixed effects model was selected. The overall effects test showed that the CC genotype frequency in depressed patients was significantly higher than that of the individuals of the control group (OR = 0.77, 95% CI = 0.64–0.94, $P=.01$), suggesting that the CC genotype might be a risk

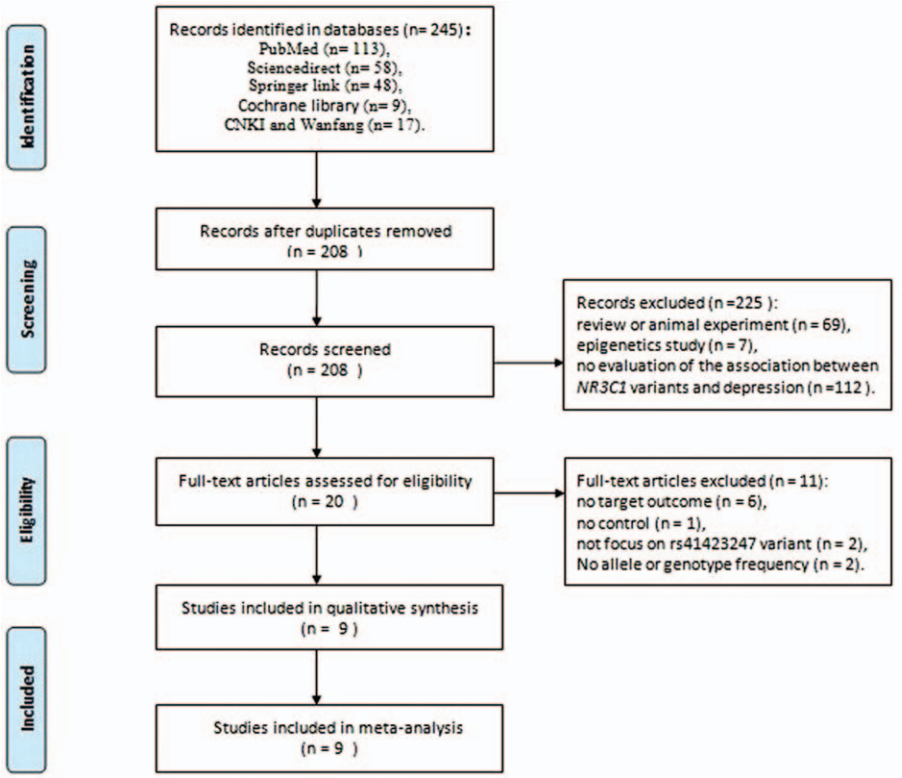

Figure 1. Literature screening process.

factor for susceptibility to depression (Fig. 3). For the further subgroup analyses on studies with Caucasians only, the heterogeneity test showed better homogeneity ($I^2 = 52\%$, $P = .07$), and the fixed effects model was selected. The overall effects test showed a significant difference in the CC genotype frequency between the depression and control groups (OR = 0.78, 95% CI = 0.63–0.96, $P = .02$), and the CC genotype may be a risk factor for depression in Caucasians (Fig. 3).

3.3. Sensitivity analysis

Because a small sample study was included, we conducted a sensitivity analysis. The results showed that there was no significant change in the combined ORs when excluding one of the selected studies (Fig. 4), and which indicated that the sensitivity was low and the combined ORs was relatively robust.

3.4. Publication bias

No evidence for obvious publication bias was found for the allelic model (Begg's $z = 0.31$ and $P = .754$; Egger's $t = 0.75$ and $P = .478$), and consistent results were found with the dominant genetic model (Begg's $z = 0.52$ and $P = .602$; Egger's $t = -1.08$ and $P = .318$).

Table 1

Characteristics of eligible studies on the association between the NR3C1 rs41423247 polymorphism and depression.

First author, year	Country	Ethnicity	Outcomes	Sample size (cases/ controls)	Genotype						NOS score
					Depression group (n)			Control group (n)			
					GG	GC	CC	GG	GC	CC	
Rossum, 2006[10]	Mixed	Caucasian	Recurrent depression	170/374	67	75	28	163	174	37	6
Krishnamurthy, 2008[11]	Mixed	Mixed	MDD	52/29	25	17	10	9	18	2	6
Zobel, 2008[14]	Germany	Caucasian	Recurrent depression	322/298	116	156	50	139	123	36	6
Lee, 2009[12]	Korea	Asian	MDD	83/105	58	21	4	50	50	5	8
Bet, 2009[15]	Netherlands	Caucasian	Depressive symptom	219/678	97	97	25	289	304	85	5
Szczepankiewicz, 2011[16]	Poland	Caucasian	MDD	193/721	67	100	26	306	325	90	5
Leszczynska, 2013[17]	Poland	Caucasian	Melancholic depression	129/721	65	48	16	306	325	90	5
Gałecka, 2013[13]	Poland	Caucasian	Recurrent depression	181/149	42	108	31	70	70	9	8
Hu, 2011[18]	China	Asian	MDD	281/287	164	106	11	169	108	10	8

GC = genotype is heterozygous mutation of NR3C1 rs41423247, MDD = major depressive disorder, NOS = Newcastle–Ottawa scale.

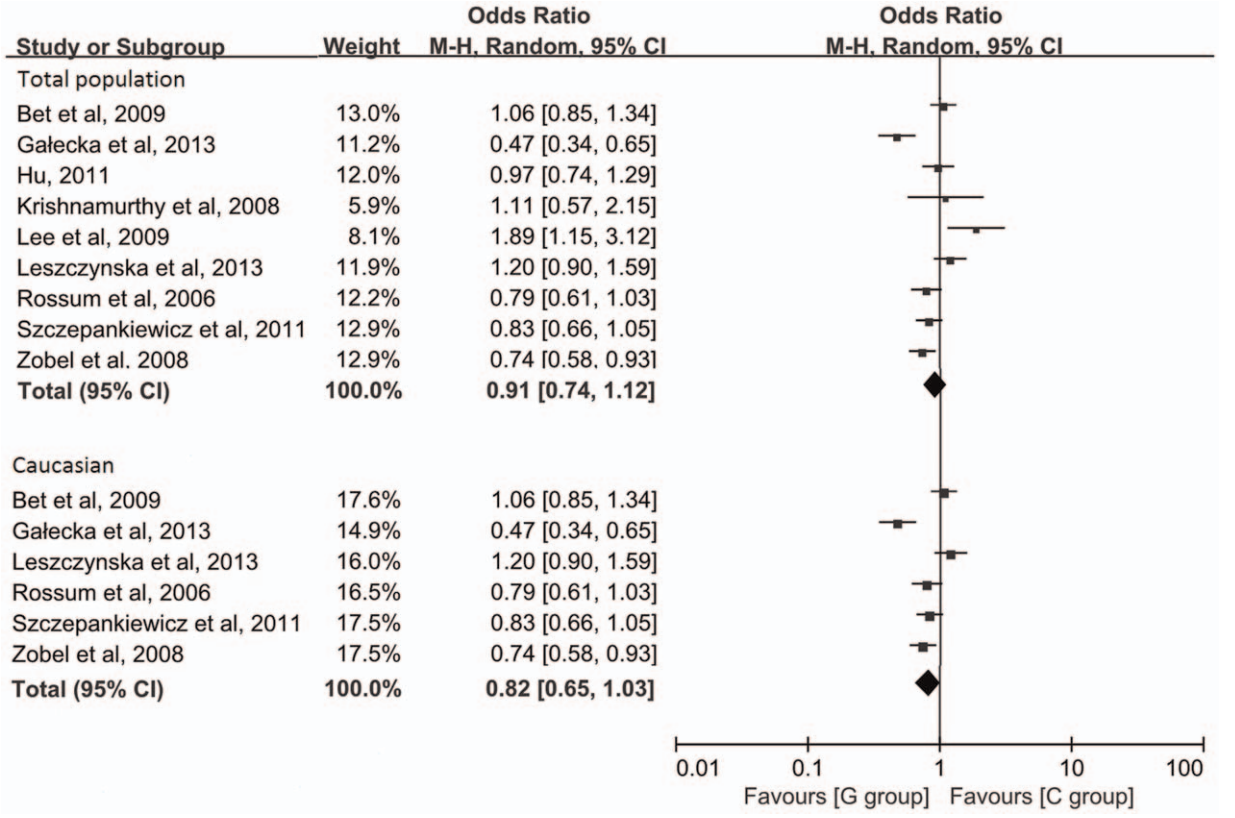

Figure 2. Forest plot of meta-analysis for *NR3C1* rs41423247 allele (G vs C). CI = confidence interval; M-H = Mantel–Haenszel.

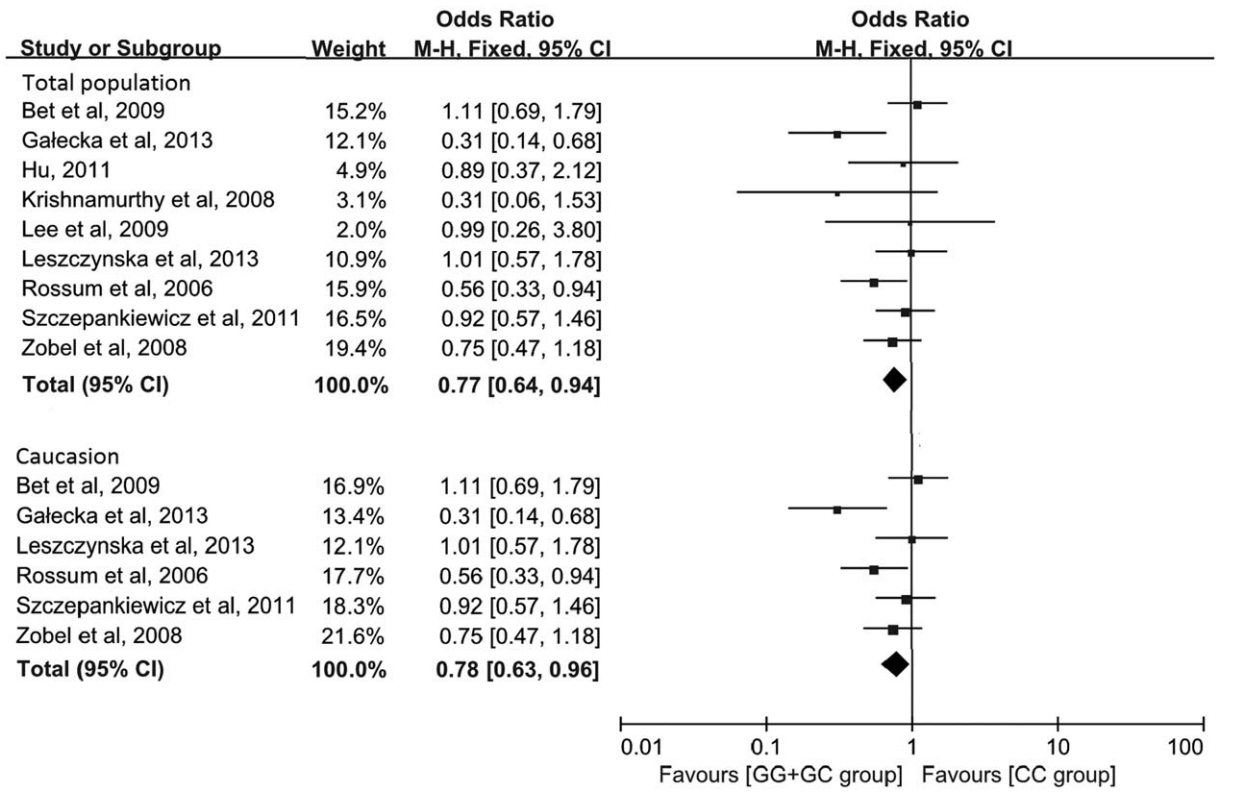

Figure 3. Forest plot of meta-analysis for *NR3C1* rs41423247 genotype (GG+GC vs CC).

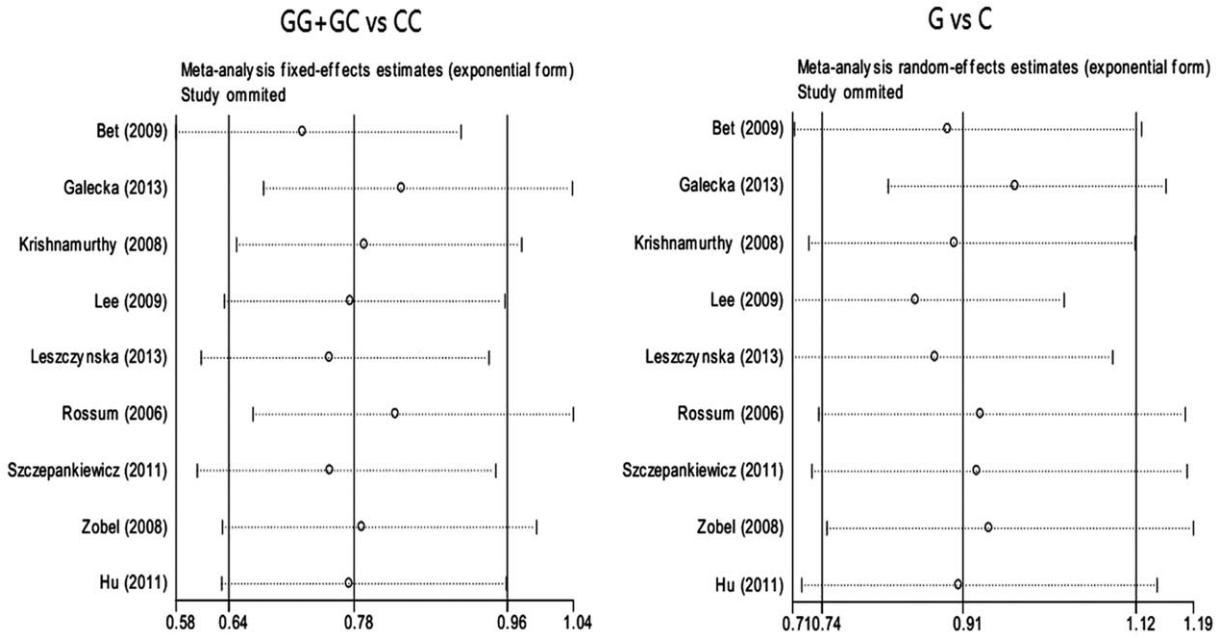

Figure 4. Sensitivity analysis of the pooled effect on the relationship between rs41423247 variant and depression in allelic and dominant genetic models.

4. Discussion

Glucocorticoid receptors are distributed in various tissues and are abundantly expressed in the hippocampus. It affects the function of the nervous system by delivering GC signals. Chen et al[21] found that administration of GC agonists to mouse neuronal cells reduced BDNF mRNA expression by about 30%, whereas treatment with GR antagonist RU486 could eliminate this effect. Additionally, Chmielarz et al[22] reported that blocking the activation of GR in the mouse noradrenergic system caused a significant upregulation of BDNF in the hippocampus and induced depression-like behavior in female mice. Thus, GRs dysfunction may be an important cause of stress-induced depression.

To the best of our knowledge, this is the first meta-analysis to evaluate the association between the *NR3C1* rs41423247 polymorphism and depression. The forest plot of dominant genetic model showed a pooled OR value of 0.77 (ranging from 0.64 to 0.94), which helped us find that the frequency of CC genotype in the depression group was significantly higher than that of the control group ($P = .01$). In the stratified analysis, we found similar results in Caucasian populations (OR = 0.78, 95% CI = 0.63–0.96). This is consistent with results from previous individual studies.[10,11,13] The total cases and controls from the 9 studies were 1630 and 3362, respectively, and the number of total cases reached a sample size required for sufficient statistical test power. However, the weak correlation between the *NR3C1* rs41423247 polymorphism and depression was easily influenced by other important risk factors of depression. For example, compared with that in men, the prevalence of depression in females was significantly higher,[1] while the gender ratios among the 9 included studies were significantly different, which may affect the reliability of the statistical results. A previous study has shown that cocaine addicts carrying the *NR3C1* rs41423247 C allele have higher levels of depressive symptoms during early rehabilitation.[23] In addition, Engineer et al[24] found that the *NR3C1* rs41423247 polymorphism was associated with an increased risk of postpartum depression, indicating that the role of the rs41423247 polymorphism on depression can also be affected by stress. Lu et al[25] provided evidence showing that childhood trauma may increase the risk of depression by heightening the reactivity of the HPA axis. Genetic variations can account for 40% of the population that are susceptible to depression,[26] while the remaining 60% can be attributed to the environment, personality, and other factors. Currently, there has been minimal research on the interaction between the environment and the rs41423247 polymorphism; therefore, for future studies, gene-environmental and gender-specific researches are necessary.

There were also some limitations to our study. First, target outcomes for all of the selected individual studies included multiple phenotypes of depression, such as depression, depression subtypes, and depressive symptoms, which may affect the accuracy of the results of this meta-analysis.[3] Because of the insufficient number of selected studies, we failed to analyze the association between a depression subtype and the rs41423247 polymorphism. In addition, no gender-specific allele frequency data could be used, and gender factors were not controlled. Besides, the number of controls in one study was too small such that it was not possible to obtain a true-effects estimate for the study.[11]

In conclusion, this meta-analysis suggests that the *NR3C1* rs41423247 homozygous mutation can be considered to be a risk factor for depression.

Acknowledgments

We sincerely thank Dr Lin Hui for providing statistical advice.

Author contributions

Conceptualization: Huacheng Yan, Lei Shi.
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Validation: Chongfa Lai.
Writing – original draft: Qiuju Peng.
Writing – review & editing: Huacheng Yan, Yuguan Wen.

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