Meta-analysis of 5-hydroxytryptamine transporter gene promoter region polymorphism and post-stroke depression

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Abstract
Objective: To investigate the relationship between 5-hydroxytryptamine transporter gene promoter region (5-HTTLPR) gene polymorphism and post-stroke depression (PSD).
Methods: We searched the CNKI, China Science and Technology Journal, China WanFang, PubMed, Embase, and Web of Science databases for studies of the relationship between 5-HTTLPR polymorphism and PSD. Data were evaluated using Stata software.
Results: The L allele was significantly related to the S allele (OR = 0.57, 95% confidence interval (CI) 0.49–0.65). The dominant genotype LL + LS was related to SS (OR = 0.48, 95%CI 0.39–0.59), the recessive genotype LL was related to LS + SS (OR = 0.39, 95%CI: 0.30–0.51), the homozygous genotype LL was related to SS (OR = 0.24, 95%CI 0.18–0.33), and the heterozygous genotype LS was related to SS (OR = 0.55, 95 CI 0.44–0.68). All the differences were significant. Ethnicity subgroup analysis showed significant differences among the five genotypes in both Asians and Caucasians. Hardy–Weinberg equilibrium (HWE) subgroup analysis showed that, after removal of a non-HWE-conforming control group, all five genotypes were significant and genotypes LL, LS + LL, and LS and L allele had beneficial effects on recovery from PSD. Conclusion: 5-HTTLPR gene polymorphism is strongly associated with PSD, and the LL, LS + LL, and LS genotypes and L allele may protect against this condition.

Keywords
5-hydroxytryptamine transporter gene promoter region, gene polymorphism, post-stroke depression, meta-analysis, genetic model, genetic risk
Introduction

Post-stroke depression (PSD) is a common complication in patients with stroke, with an incidence rate of about 30%.1 The common symptoms are depression, loss of interest, slow thinking, lack of initiative, insomnia, early awakening, hypodynamia, and feelings of despair, associated with anxiety and cognitive disorders. PSD results in delayed recovery of stroke patients, with serious effects on quality of daily life and significantly increased rates of disability and death. PSD is associated with not only psychological pressures on the patients’ families and caregivers,2 but is also economic burdens on the family and society, with mean annual total costs of managing stroke and depression per patient of US$72473 and US$7638, respectively.4 The mainstream research view currently holds that PSD is related to a combination of neurology,5 neuropsychiatry6 and geriatric psychiatry.7 The neurobiological mechanisms are mainly related to neurotransmitters,8 functional deficits in neuroanatomical structure,9 neuroendocrinology,8 nutritional status,10,11 neuropeptides (e.g. orexin),12 neurotrophins (e.g. brain-derived neurotrophic factor),13 neurovascular changes,14 hemodynamic changes,15 and the inflammatory response.16–18 Among the multiple pathogeneses of primary depression, a decrease in the 5-hydroxytryptamine neurotransmitter is a currently recognized hypothesis. However, whether the pathogenesis and susceptibility factors for PSD, as a type of secondary depression, are consistent with those for simple depression has been the focus of recent research. Previous studies showed that an increase in the S allele or deletion of the L allele in the region of the serotonin transporter gene linkage polymorphism region, 5-HTTLPR, is composed of a long allele (L) and a short allele (S) polymorphism insertion/deletion. This change greatly affects the transcriptional function of the gene, with the S allele conferring significantly weaker transcriptional ability than the L allele,20 resulting in low expression of serotonin (5-HT). 5-HTTLPR is associated with a vascular response, and the LL genotype has been shown to increase vascular tension during stress events, resulting in ischemia.21 Great progress has recently been made in elucidating the pathogenesis of PSD, but its detailed mechanism remains unclear. However, the role of gene polymorphisms in the pathogenesis of PSD has recently attracted wide attention, including the involvement of polymorphisms in the 5,10-methylenetetrahydrofolate reductase (MTHFR), serotonin receptor 2C (HTR2C), and 5-HTTLPR genes.22,23 Many studies24,25 have found an association between 5-HTTLPR polymorphism and PSD. A meta-analysis of five studies of 5-HTTLPR polymorphism and PSD by Mak et al.26 in 2013 suggested that the LL genotype might be a protective factor for PSD. However, more studies of the relationship have since emerged, with some different results.27 In the current study, we carried out a comprehensive re-analysis of the relevant research on the relationship between 5-HTTLPR polymorphism and PSD using a larger sample size, to provide suitable evidence to support clinical practice.

Materials and methods

Retrieval strategy

The China National Knowledge Infrastructure (CNKI), China WanFang Database, and China Science and
Technology Journal Database were searched for articles written in Chinese using the key words “5-HTTLPR” and “post-stroke depression”. PubMed, Web of Science, and Embase were searched for English articles using the terms “poststroke”, “depression”, “serotonin transporter”, and “gene polymorphism”, from the date of database construction up to September 2019. The study was performed according to the PRISMA guidelines and PROSPERO registration was pending at the time of publication.

**Inclusion and exclusion criteria**

The inclusion criteria were as follows: 1) articles on the relationship between 5-HTTLPR polymorphism and the pathogenesis of PSD; 2) inclusion of a control group of stroke patients without depression (non-PSD); 3) strict diagnostic criteria for stroke and PSD; and 4) specific values for 5-HTTLPR genotype. The exclusion criteria were as follows: 1) incomplete and inaccessible literature; 2) no case-control group or only normal subjects instead of stroke patients in the control group; 3) non-clinical literature; 4) review literature; and 5) duplicate publications.

**Literature quality evaluation**

The selected literature was read carefully and the quality of the papers was evaluated according to the Newcastle–Ottawa Scale (NOS). Papers with less than six stars were considered low-quality, and papers with at least six stars were considered high quality. Only high-quality papers were included in this study. Two reviewers independently assessed the quality of the studies according to uniform quality standards, extracted the data, and then cross-checked their findings. Different opinions were resolved by discussion or by a third party.

**Data extraction**

Relevant information was extracted from the studies, including publication date, first author, country, number of PSD cases, number of non-PSD cases, and the corresponding table of PSD genotype and non-PSD genotype.

**Statistical methods**

The meta-analysis was carried out using Stata 15.0 statistical software (StataCorp LP, College Station, TX, USA). The odds ratios (ORs) and 95% confidence intervals (CIs) for the five respective genetic groups were calculated, with non-PSD patients as the control group. The Q test was used to check the heterogeneity of the results for each study. If $I^2 \geq 50\%$ or $P \leq 0.05$, the results were considered to show heterogeneity and a random-effects model would be used to generalize findings beyond the included studies, by assuming that the selected studies were random samples from a larger population. If $I^2 < 50\%$, and $P > 0.05$, there was no heterogeneity and a fixed-effect model (FEM) was used for analysis. FEMs assume that the population effect sizes are the same for all studies. The significance of the combined OR value was analyzed using the Z test. Subgroup analyses were conducted according to ethnicity and whether or not the data conformed to the Hardy–Weinberg equilibrium (HWE). Publication bias was assessed by funnel plots, using the standard error of each study log (OR) to map its OR value. An asymmetric funnel plot suggested publication bias, which was then tested by Egger’s test, as described previously.

**Results**

**Basic data**

Nine articles met the inclusion criteria. There were 855 patients in...
the PSD group and 981 patients in the non-PSD group. The study selection procedure is shown in Figure 1. The characteristics of each study and the distribution of genotypes reported in the study are shown in Table 1.

**Allelic comparison**

The main results of the meta-analysis are displayed in Table 2 and Figure 2. The L allele was related to the S allele, with $I^2 = 0.0\%$, with no significant heterogeneity among the studies. A FEM was therefore used. The final results showed that the difference was statistically significant $(OR = 0.57, 95\%CI = 0.49–0.65, P < 0.01)$. Subgroup analysis according to race produced similar results, with significant differences for Caucasian and Asian alleles (Figure 2a). After removing an article in which the control group did not satisfy the HWE, the results still demonstrated a significant difference in allele differences (Table 3). All the analyses indicated that 5-HTTLPR gene polymorphism was associated with PSD, and that the L allele was a protective factor for PSD. The funnel plot was basically symmetrical (Figure 3a) and Egger’s test showed no significant effect, indicating that the publication bias was well controlled and the conclusion was reliable.

**Dominant genetic model**

The LL + LS genotype was related to the SS genotype, with $I^2 = 0.0\%$, and no significant heterogeneity among the studies. The FEM showed results showed that the difference was statistically significant $(OR = 0.48, 95\%CI = 0.39–0.59, P < 0.01)$. Subgroup analysis according to race showed similar results for Caucasians and Asians (Figure 2b). After removing an article in which the control group did not satisfy the HWE, the results still demonstrated a significant difference in dominant genetic models (Table 3). The results confirmed that 5-HTTLPR gene polymorphism was associated with PSD, and the LL + LS genotype was a protective factor for PSD, compared with the SS genotype. The funnel plot was basically symmetrical (Figure 3b) and Egger’s test

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**Figure 1.** Flow diagram of the study selection process.
showed no significant publication bias, indicating that the conclusion was reliable.

**Recessive genetic model**

The LL genotype was related to the LL + SS genotype, with $I^2 = 0.0\%$, and no significant heterogeneity among the studies. An FEM was used, and showed a significant difference (OR = 0.39, 95%CI = 0.30–0.51, $P < 0.01$). Subgroup analysis according to race produced the same results, indicating significant differences in recessive genetic models in Caucasians and Asians (Figure 2c). After removing an article in which the control group failed to satisfy the HWE, the difference in recessive genetic models remained statistically significant (Table 3). All the analyses confirmed the relationship between 5-HTTLPR gene polymorphism and PSD, and identified the LL genotype as a protective factor for PSD, compared with the LS + SS genotype. The funnel plot was basically symmetrical (Figure 3c) and Egger’s test showed no significant publication bias, demonstrating that the conclusion was reliable.

**Homzygous genetic model**

The LL genotype was related to the SS genotype, with $I^2 = 0.0\%$, and no significant heterogeneity among the studies. An FEM was therefore used, and showed a significant difference (OR = 0.24, 95%CI = 0.18–0.33, $P < 0.01$). Subgroup analysis of ethnicity confirmed a significant difference between homozygous models in Caucasians and Asians (Figure 2d). After removing an article in which the control group did not satisfy the HWE, the results still demonstrated a significant difference in homozygous models (Table 3). The 5-HTTLPR gene polymorphism was confirmed to be associated with PSD, and the LL genotype was a protective factor for PSD, compared with the SS genotype. The funnel plot was basically
symmetrical (Figure 3d) and Egger’s test indicated no publication bias, and the conclusion was therefore reliable.

**Heterozygote model**

The LS genotype was related to the SS genotype, with $I^2 = 0.0\%$, and no significant heterogeneity among the studies. An FEM was used and showed a significant difference (OR = 0.55, 95%CI = 0.44–0.68, $P < 0.01$). Subgroup analysis of race indicated significant differences in heterozygous models in both Caucasians and Asians (Figure 2e). After removing an article in which the control group did not meet the HWE, the results still demonstrated a significant difference in heterozygous models (Table 3). The analyses confirmed that the 5-HTTLPR gene polymorphism was associated with PSD, and that the LS genotype was a protective factor for PSD, compared with the SS genotype. The funnel plot was basically symmetrical (Figure 3e) and Egger’s test showed no significant publication bias, indicating that the conclusion was reliable.

**Sensitivity analysis**

The results of the sensitivity analysis are shown in Figure 4. Each study was excluded one by one, and the results showed no effects on each genetic model, indicating that all nine included articles were stable.

**Discussion**

Stroke, including cerebral infarction, is an important disease with a high incidence, mortality, and disability. Epidemiological studies showed that about 40% of stroke patients developed some degree of depression after acute incidents, making PSD a common and serious complication of cerebrovascular accident. Compared with stroke patients without PSD, stroke patients with PSD have worse self-care, survival, and emotional abilities, and higher mortality. The serotonin transporter (5-HTT) gene has been widely studied in
Figure 2. Forest plots for the five genetic models. (a) L vs. S; (b) LL+LS vs. SS; (c) LL vs. LS+SS; (d) LL vs. SS; (e) LS vs. SS. OR, odds ratio; CI, confidence interval.
relation to affective disorders and as the target of antidepressants and artificial intelligence systems for managing depression, as well as in other diseases. Schenkel et al. conducted a case-control study of 175 patients with temporal lobe epilepsy and showed that the *5-HTT* gene polymorphism was a risk factor for epilepsy and suicide. The *5-HTT* gene was also studied as a candidate gene in a Colombian patient with Alzheimer’s disease, but no association was found. The *5-HTT* gene was also studied as a candidate gene in a Colombian patient with Alzheimer’s disease, but no association was found. The *5-HTTLPR* polymorphism is located in the *5-HTT* promoter region and is caused by a 44-base-pair insertion/deletion, which affects the transcription rate of the *5-HTT* promoter. A previous study showed that the S allele polymorphism was associated with a lower transcription rate. Numerous studies have examined the effects of *5-HTTLPR* gene polymorphism and its interaction with the environment on depression, and the S allele or S/S genotype was shown to be a risk factor for PSD. However, clinical studies generally include small sample sizes, and further studies with larger sample sizes are needed to support this conclusion. The current study therefore applied a meta-analysis to analyze the relationship between *HTTLPR* gene polymorphism and PSD, to provide more evidence for clinical guidance.

Nine articles were included in this study, of which seven were conducted in Asians and two in Caucasians. The results showed a strong correlation between *HTTLPR* gene polymorphism and PSD, with significant differences in allele, dominant, recessive, homozygous, and heterozygous genetic models. The LL, LS, and SS genotypes and L allele had protective effects against PSD. Subgroup analysis according to ethnicity showed the same results. The same conclusion was also drawn after removing a control group that did not conform to the HWE. Funnel plots and Egger’s test showed no significant publication bias, and the results of heterogeneity tests showed that the $I^2$ for each model was much less than 50%, indicating good homogeneity among the studies. The results of sensitivity analysis demonstrated no significant change in the combination of genetic models, indicating good stability of the included literature. The conclusions of this study were therefore considered to be reliable. Mak et al. found that homozygous SS genotype was a risk factor for PSD, but there was no correlation between the

| Genetic model | HWE | n | OR   | 95%CI  | $P$ | $I^2$ | $P$ for heterogeneity | Model | $P$ for publication bias |
|---------------|-----|---|------|--------|-----|------|-----------------------|-------|------------------------|
| L vs. S       | Yes | 8 | 0.58 | 0.50–0.65 | $<0.01$ | 0 | 0.809 | FEM | 0.19 |
|               | No  | 1 | 0.36 | 0.18–0.72 | 0.004 | NA | NA | NA | NA |
| LL + LS vs. SS| Yes | 8 | 0.49 | 0.40–0.60 | $<0.01$ | 0 | 0.87 | FEM | 0.165 |
|               | No  | 1 | 0.35 | 0.12–1.01 | 0.051 | NA | NA | NA | NA |
| LL vs. LS + SS| Yes | 8 | 0.41 | 0.31–0.53 | $<0.01$ | 0 | 0.812 | FEM | 0.723 |
|               | No  | 1 | 0.23 | 0.08–0.63 | 0.005 | NA | NA | NA | NA |
| LL vs. SS     | Yes | 8 | 0.25 | 0.19–0.34 | $<0.01$ | 0 | 0.783 | FEM | 0.859 |
|               | No  | 1 | 0.14 | 0.04–0.47 | 0.001 | NA | NA | NA | NA |
| LS vs. SS     | Yes | 8 | 0.55 | 0.44–0.69 | $<0.01$ | 0 | 0.801 | FEM | 0.114 |
|               | No  | 1 | 0.56 | 0.16–1.91 | 0.355 | NA | NA | NA | NA |

HWE, Hardy–Weinberg equilibrium; OR, odds ratio; CI, confidence interval; FEM, fixed-effect model; NA, not applied.
heterozygous LS genotype and PSD. The conclusion regarding the homozygous genotype was consistent with the current study, though the results regarding the heterozygous genotype differed from our results. The current meta-analysis found that the heterozygous LS genotype was also associated with PSD, and was a protective factor for PSD. This conclusion was verified by subgroup and sensitivity analyses. The apparent discrepancy with the previous study may be related to the inclusion of more high-quality research in the present study.

This study had some limitations. The scope of the study was relatively narrow,
because most research was conducted in Asians, only two studies were carried out in Europe and the United States, and none in Africa and other countries. The applicability of the conclusions to other races therefore remains to be confirmed.

Furthermore, the numbers of studies and subjects included were small, with <1,000 patients in the PSD and non-PSD groups, respectively. Finally, we did not analyze the effects of gene linkage and gene–environment interactions on PSD.

Figure 4. Sensitivity analysis plots for the five genetic models. (a) L vs. S; (b) LL + LS vs. SS; (c) LL vs. LS + SS; (d) LL vs. SS; (e) LS vs. SS. CI, confidence interval.
In conclusion, the 5-HTTLPR gene polymorphism was strongly associated with PSD. The LL, LS + LL, and LS genotypes and L allele have protective effects against PSD, in both Asian and Caucasian populations. However, follow-up studies are needed to address the limitations of this study, such as the potential interactions among genes and between genes and the environment.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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