5HTTLPR polymorphism and postpartum depression risk
A meta-analysis

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Objective: Postpartum depression (PPD) is an episode of major depressive disorder that affects women of childbearing age. 5-HTTLPR is 1 of the most extensively investigated polymorphisms in PPD. However, the previous results were inconsistent and inclusive. Hence, we performed a meta-analysis to precisely evaluate the association between 5-HTTLPR (L/S) polymorphism and PPD susceptibility.

Methods: The studies were retrieved through databases including PubMed, web of science, EMASE, and CNKI. The odd ratios (ORs) and 95% confidence interval (CIs) were applied for evaluating the genetic association between 5-HTTLPR (L/S) polymorphism and PPD risk.

Results: Six studies with 519 cases and 737 controls were enrolled in the present study. The frequencies of allelic (OR = 0.72, 95% CI = 0.60–0.85, \( P = .0001 \)) and dominant (OR = 0.57, 95% CI = 0.44–0.73, \( P = .0004 \)) models of 5-HTTLPR polymorphism significantly decreased in patients with PPD than those in the healthy controls. Subgroup analysis based on ethnicity revealed that the allelic (OR = 0.71, 95% CI = 0.60–0.85, \( P = .0001 \)) and dominant (OR = 0.51, 95% CI = 0.32–0.79, \( P = .003 \)) models of 5-HTTLPR polymorphism were significantly associated with PPD risk in Asian population (\( P > .05 \)). No evidence was observed between the recessive model of 5-HTTLPR polymorphism and PPD risk (\( P > .05 \)).

Conclusions: The allelic and dominant models of 5-HTTLPR polymorphism might be protective factors for PPD. To confirm these results, larger number of association studies or multicenter case–control studies are necessary in the future.

Abbreviations: CI = confidence interval, L = long allele, OR = odd ratio, PPD = postpartum depression, S = short allele.

Keywords: 5-HTTLPR, asian, polymorphism, postpartum depression
1. Introduction

Postpartum depression (PPD), characterized by depression, restlessness and irritability, is a serious emotional disorder either during pregnancy or within the first 6 months postpartum. The incidence of PPD is 9.2% to 15.0% in Chinese population and 3.5% to 33.0% in other populations.\[1-3\] Untreated and unresolved PPD leads to ramifications for the affected individual, their infant as well as their relationship with family members. Published reports have shown that physiological, psychological, individual characteristics such as lower serum 25[OH]D levels,\[4\] social factors and genetic factors may be important factors leading to PPD.\[5-8\] However, the exact mechanism of PPD is far from known.

Recent study has suggested that the serotonin (5-HT) system is involved in the pathogenesis of depression.\[9\] And the serotonin transporter (5-HTT) is located on its presynaptic membrane.\[10\] 5-HTTLPR, a 5-HTT-based functional polymorphism site, is a promoter-linked polymorphic region. It was revealed that the transcriptional activity may be regulated by this polymorphism in human.\[11,12\] The 5-HTTLPR gene polymorphism is consisted of 2 alleles, the short allele (S) and the long allele (L), formed by a 44-base pair insertion or deletion.\[13\] This polymorphism has been reported to affect the expression level of serotonin transporter in human, thereby affect the synaptic serotonin concentration in neurons.\[14,15\]

Several studies have shown that 5-HTTLPR may contribute to the occurrence of PPD, while the results were inconclusive. Zhang et al has shown that the L/L genotype of 5-HTTLPR polymorphism may reduce the risk of PPD in Chinese population.\[16\] However, Khabour et al has suggested that 5-HTTLPR (L/S) was not the susceptible factor for the development of PPD in Jordanian women.\[17\] Similar results were observed in other populations.\[18,19\]

Considered the inconsistent and inclusive results in individual studies, we conducted on a meta-analysis by including case-control studies in the electric databases to obtain more precise results of the genetic association between the 5HTTLPR polymorphism and PPD risk in the present study.

2. Methods

2.1. Patient and public involvement

There was no patient and public involvement in present meta-analysis. An ethical approval is not necessary for a meta-analysis.

2.2. Literature search strategy

The present study was accorded to the Cochrane collaboration definition and Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 guidelines for meta-analysis and systematic review.\[20\] Literature search was performed in databases including PubMed, web of science, EMASE, and CNKI. The searching terms were used as following: “serotonin transporter gene-linked polymorphic region” or “5HTTLPR” or “Solute Carrier Family 6 (Neurotransmitter Transporter), Member 4” or “solute carrier family 6” and “polymorphism” or “variant” or “single nucleotide polymorphism” or “single nucleotide polymorphism” and “postpartum depression” or “PPD.” No years and language were limited. The latest day was May 20, 2019. Related literature was retrieved manually.

2.3. Eligibility criteria

Inclusion criteria

(1) Cases-control designed study.
(2) The data of genotypes were available in case and control populations.
(3) Evaluated the association between 5HTTLPR (L/S) polymorphism and PPD risk.

Exclusion criteria

(1) Duplication, review, conference abstract, letter, case report.
(2) Unavailable genotype frequencies in case and control populations.

2.4. Data extraction and quality assessment

Xiang Q and Xiang J independently screened the included studies according to the eligibility criteria. The essential information including the first name of author, publication year, ethnicity, mean ages, genotyping methods, diagnostic criteria of PPD, number of cases and controls, state of Hardy-Weinberg Equilibrium in controls was extracted. Disagreement was solved by discussion. Newcastle-Ottawa Scale was used to evaluate the quality of individual study.\[21\] A study with a score of ≥6 was enrolled in the present study.

2.5. Methods for quantitative synthesis

STATA 12.0 (StataCorp, College Station, TX) and Revman 5 (Cochrane Collaboration, London, UK) software were used in quantitative synthesis. The pooled odd ratios (ORs) and 95% Confidence interval (CI) of the allelic (L vs S), dominant (LS+LL vs SS) and recessive (LL vs LS+SS) models of 5HTTLPR polymorphism and PPD risk were evaluated by Z test. P < .05 was significant difference. The statistical heterogeneity between studies was evaluated by a chi-square-based Cochrane Q test and Higgins I-squared statistic. F value more than 50% was regarded as significant heterogeneity among these studies and a random-effect model (Mantel-Haenszel) was used. Otherwise, a fixed model was used. Subgroup analysis was conducted on ethnicity of Asian and Caucasian. Sensitivity analysis which excluded the influence of a single study on the overall risk estimate by excluding one study at a time was confirmed. Begg funnel plots and Egger regression test were used to evaluate publication bias (P < .05 suggests bias).

3. Results

3.1. The characters of eligible studies

The Figure 1 has shown the flowchart of searching the publications through the databases. A total of 672 publications were retrieved. After screening the title, abstract, and context of each study, 247 were excluded for being duplicated records. 302 were excluded for being irrelevant articles. 117 were removed for being abstract, meeting, letters or reviews. Finally, 6 studies involving 519 patients with PPD and 737 healthy controls investigating the relationship between the 5HTTLPR polymorphism and PPD risk in all ethnic groups were enrolled in the present meta-analysis\[16-19,22,23\] (Fig. 1). Among these studies, 5
were in Asian, 1 was in Caucasian. The Newcastle-Ottawa Scale scores of the included studies were higher than 6 (Table 1 and Table s1, Supplemental Digital Content, http://links.lww.com/MD/E909).

### 3.2. Combined results

As presented in Table 2, the frequencies of the L allele (OR = 0.72, 95%CI = 0.60–0.85, \( P = .0001 \)) and dominant (OR = 0.57, 95% CI = 0.44–0.73, \( P = .004 \)) models of 5HTTLPR polymorphism were significantly lower in PPD population than those in the control group. No evidence supported the association between the recessive model of 5HTTLPR polymorphism and PPD susceptibility (\( P > .05 \)) (Fig. 2).

The effect of the 5HTTLPR polymorphism on PPD was further evaluated using stratification analysis on ethnicity. In the 5 studies consisting of 504 cases and 624 controls, the L allele (OR = 0.71, 95%CI = 0.60–0.85, \( P = .0001 \)) and dominant (OR = 0.51, 95% CI = 0.32–0.79, \( P = .003 \)) models of 5HTTLPR polymorphism significantly decreased PPD risk in Asian population (Table 2).

### 3.3. Test for heterogeneity

Significant between-study heterogeneity existed in the dominant model of 5HTTLPR polymorphism (\( I^2\% = 58\% \), \( P = .03 \)). However, this significant difference of heterogeneity was detected only in Asian population (\( I^2\% = 63\% \), \( P = .03 \)) in the subgroup analysis based on ethnicity. These heterogeneities in overall and subgroup analysis were conducted by Xiu et al[18] and Peng et al[22]. After removal of these 2 studies, the significant between-study heterogeneity disappeared (\( I^2\% = 29\% \), \( P = .24 \)), which indicate these 2 studies may mainly influence the results (Table 2).

### 3.4. Sensitive analysis and publish bias

The data showed that no individual study altered the pooled ORs qualitatively, which provided the evidence of the stability of the meta-analysis (Fig. 3). The shape of Begg funnel plots and Egger linear regression tests showed no publication bias (Fig. 4, Table 3).

### 4. Discussion

The level of serotonin in the synaptic cleft of neurons and the function of serotonin receptor plays an important role in the pathological process of depression, but whether the function is aggressive or low is still inconclusive.[24,25] The 5-HTT gene is a key factor in affecting risk of depression and other psychiatric conditions.
The human 5-HTT gene (also known as solute carrier family 6) is located on chromosome 17q11.1-q12. 5HTTLPR is located about 1kb upstream of the 5HTT gene transcriptional promoter, and contains a 44 base pair insertion (L allele) or deletion (S allele). Studies have shown that the S allele has lower transcriptional activity than the L allele and carriers of the S allele are more likely to fall into a state of long-term alertness, threatening and reflection, increasing their susceptibility to affective disorders. A previous study has reported that the 5-HTTLPR was a susceptible factor for the onset of depression after PM implantation. Many reports have revealed that the 5HTTLPR polymorphism was associated with schizophrenia, personality traits, mood disorders, obsessive-compulsive disorder, generalized anxiety and depression, while the results were inconclusive. Inconsistent results were also found between the 5HTTLPR polymorphism and PPD susceptibility.

### Table 2

The association between 5HTTLPR polymorphism and PDD risk.

| Genetic models | Subgroups | Number of studies | OR  | 95% CI  | P-value  | Model | P-value | I^2 (%) |
|----------------|-----------|-------------------|-----|---------|----------|-------|---------|---------|
| Allelic        | Total     | 6                 | 0.72 | [0.60, 0.85] | .0001 | F     | .23     | 27      |
|                | Asian     | 5                 | 0.71 | [0.60, 0.85] | .0001 | F     | .15     | 40      |
|                | Caucasian | 1                 | 0.83 | [0.39, 1.78] | .63   | –     | –       | –       |
| Dominant       | Total     | 6                 | 0.57 | [0.44, 0.73] | .004  | R     | .03     | 58      |
|                | Asian     | 5                 | 0.51 | [0.32, 0.79] | .003  | R     | .03     | 63      |
|                | Caucasian | 1                 | 1.31 | [0.27, 6.30] | .73   | –     | –       | –       |
| Recessive      | Total     | 6                 | 0.82 | [0.61, 1.10] | .19   | F     | .14     | 39      |
|                | Asian     | 5                 | 0.84 | [0.62, 1.14] | .27   | F     | .10     | 48      |
|                | Caucasian | 1                 | 0.51 | [0.14, 1.93] | .32   | –     | –       | –       |

Table 2: The association between 5HTTLPR polymorphism and PDD risk.

| Study or Subgroup | Experimental | Control | Total | Events | Total | Weight | Odds Ratio | M-H, Fixed, 95% CI | Odds Ratio | M-H, Fixed, 95% CI |
|-------------------|--------------|---------|-------|--------|-------|--------|------------|-------------------|------------|-------------------|
|                   | Events       | Total   |      |        |       |        |            |                   |            |                   |
| Xhabbour 2013     | 131          | 260     | 391  | 240    | 490   | 27.0%  | 0.95 [0.70, 1.29] |                   |            |                   |
| Liu 2016          | 119          | 310     | 429  | 148    | 290   | 30.1%  | 0.60 [0.43, 0.83] |                   |            |                   |
| Peng 2015         | 44           | 120     | 164  | 58     | 120   | 11.7%  | 0.82 [0.37, 1.94] |                   |            |                   |
| Zhang 2014        | 13           | 78      | 91   | 25     | 78    | 6.7%   | 0.42 [0.20, 0.91] |                   |            |                   |
| Zhang 2015        | 56           | 240     | 296  | 85     | 280   | 19.2%  | 0.70 [0.47, 1.03] |                   |            |                   |
| Zimmermann-Peruzzato 2012 | 16 | 30 | 46 | 131 | 226 | 4.6% | 0.83 [0.39, 1.78] |                   |            |                   |
| Total (95% CI)    | 1038         | 474     | 1512 | 1474   | 100.0% | 0.72 [0.66, 0.85] |                   |            |                   |
| Total events      | 379          | 695     | 1074 |        |        |        |            |                   |            |                   |
| Heterogeneity: Chi^2 = 6.84, df = 5 (P = 0.23); I^2 = 27% |                   |            |                   |            |                   |
| Test for overall effect: Z = 3.84 (P = 0.0001) |                   |            |                   |            |                   |

A

| Study or Subgroup | Experimental | Control | Total | Events | Total | Weight | Odds Ratio | M-H, Random, 95% CI | Odds Ratio | M-H, Random, 95% CI |
|-------------------|--------------|---------|-------|--------|-------|--------|------------|-------------------|------------|-------------------|
|                   | Events       | Total   |      |        |       |        |            |                   |            |                   |
| Xhabbour 2013     | 95           | 130     | 225  | 186    | 240   | 22.1%  | 0.79 [0.48, 1.29] |                   |            |                   |
| Liu 2016          | 86           | 155     | 241  | 109    | 145   | 22.1%  | 0.83 [0.55, 1.27] |                   |            |                   |
| Peng 2015         | 29           | 60      | 89   | 46     | 60    | 15.2%  | 0.27 [0.12, 0.59] |                   |            |                   |
| Zhang 2014        | 11           | 39      | 50   | 22     | 39    | 12.4%  | 0.30 [0.12, 0.79] |                   |            |                   |
| Zhang 2015        | 51           | 120     | 171  | 66     | 140   | 22.1%  | 0.83 [0.51, 1.35] |                   |            |                   |
| Zimmermann-Peruzzato 2012 | 13 | 15 | 28 | 94 | 113 | 6.0% | 1.31 [0.27, 6.30] |                   |            |                   |
| Total (95% CI)    | 519          | 737     | 1256 | 100.0% | 0.54 [0.35, 0.82] |                   |            |                   |
| Total events      | 284          | 523     | 807  |        |        |        |            |                   |            |                   |
| Heterogeneity: Tau^2 = 0.15; Chi^2 = 12.00, df = 5 (P = 0.03); I^2 = 58% |                   |            |                   |            |                   |
| Test for overall effect: Z = 2.96 (P = 0.004) |                   |            |                   |            |                   |

B

| Study or Subgroup | Experimental | Control | Total | Events | Total | Weight | Odds Ratio | M-H, Fixed, 95% CI | Odds Ratio | M-H, Fixed, 95% CI |
|-------------------|--------------|---------|-------|--------|-------|--------|------------|-------------------|------------|-------------------|
|                   | Events       | Total   |      |        |       |        |            |                   |            |                   |
| Xhabbour 2013     | 36           | 130     | 166  | 62     | 240   | 31.9%  | 1.10 [0.68, 1.78] |                   |            |                   |
| Liu 2016          | 33           | 155     | 188  | 39     | 145   | 32.2%  | 0.74 [0.43, 1.29] |                   |            |                   |
| Peng 2015         | 16           | 60      | 76   | 12     | 60    | 8.9%   | 1.45 [0.62, 3.41] |                   |            |                   |
| Zhang 2014        | 2            | 39      | 41   | 3      | 39    | 2.9%   | 0.50 [0.10, 2.39] |                   |            |                   |
| Zhang 2015        | 5            | 120     | 125  | 19     | 140   | 17.0%  | 0.09 [0.03, 0.23] |                   |            |                   |
| Zimmermann-Peruzzato 2012 | 3 | 15 | 48 | 37 | 113 | 7.0% | 0.51 [0.14, 1.93] |                   |            |                   |
| Total (95% CI)    | 519          | 737     | 1256 | 100.0% | 0.82 [0.61, 1.10] |                   |            |                   |
| Total events      | 95           | 172     | 267  |        |        |        |            |                   |            |                   |
| Heterogeneity: Chi^2 = 8.24, df = 5 (P = 0.14); I^2 = 39% |                   |            |                   |            |                   |
| Test for overall effect: Z = 1.32 (P = 0.19) |                   |            |                   |            |                   |

C

Figure 2. Forest plots of odds ratios for the association between 5HTTLPR and PPD. A: allelic model; B: dominant model; C: recessive model.
Figure 3. Sensitivity analyses between 5HTTLPR and PPD. A: allelic model; B: dominant model; C: recessive model.
Figure 4. Publication bias of literatures for 5HTTLPR were tested by Begg funnel plot and Egger test. A: allelic model; B: dominant model; C: recessive model.
Among the six included articles, only one study showed that the distribution of SS+SL genotype was higher in the case group than that in the control group. While others were in the opposite. The results of the 3 publications conducted by Zhang et al.,[22] Peng et al.,[23] and Xiu et al.[19] have revealed that the distribution of SS+SL genotype in control group was significantly higher than that in the case group. Therefore, we could not simply draw to the conclusion that the S allele or L allele is a predisposing factor for PPD.

Racial differences among different subjects may be one of the major factors that influence the relationship of SHTTLPR polymorphism with PPD. Subgroup analyses based on ethnicity has shown the significant association was only within Asian population. Different genetic background in the susceptibility to diseases may contribute to this inconsistent. Notable, only 1 study was conducted in Caucasian population. To confirm this result, larger number of subjects from multiple ethnicity is necessary in the future. In addition, the effects of psychology, physiology, and social environment on PPD should be considered. Nervousness and anxiety due to lack of knowledge about childbirth, the sex of the fetus, and the attitude of husband and family may cause a certain degree of mental burden on the mother.

Limitations should be considered. First, the number of study and subject included in the present study was relatively small, especially in Caucasian population, which may reduce the calculation power. Second, previous studies have adopted different criteria for the diagnosis of PPD, which may be an important influencing factor for the association between SHTTLPR polymorphism and PPD. Thirdly, further subtle adjusted analysis such as age, smoking, environmental factors, and other lifestyle, should be carried out if more detailed individual information was available.

In conclusion, our meta-analysis supports that the allelic and dominant models of SHTTLPR polymorphism might be protective factors for PPD in Asian. However, our results need to be confirmed by case-control studies with larger number of subjects.

Author contributions

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References

[1] Meltzer-Brody S. New insights into perinatal depression: pathogenesis and treatment during pregnancy and postpartum. Dialog in clin neurosci 2011;13:89–100.
[2] Hart AR, Farber KG, Chh K. Postpartum depression. N Engl J Med 2017;376:895.
[3] Di Florio A, Putnam K, Altensus M, et al. The impact of education, country, race and ethnicity on the self-report of postpartum depression using the Edinburgh Postnatal Depression Scale. Psych Med 2017;47:787–99.
[4] Fu CW, Liu JT, Wu WJ, et al. Association between serum 25-hydroxyvitamin D levels measured 24 hours after delivery and postpartum depression. BJOG 2015;122:1688–94.
[5] Cai FY, Kuang L, Wang W, et al. Prediction model for postpartum depression based on social psychological factors: establishment and evaluation. Acad J Second Military Med Univ 2017;38:476–81.
[6] Elbieta G, MaGorzata S, Arrur K, et al. Analysis of sociodemographic, psychological, and genetic factors contributing to depressive symptoms in pre-, peri- and postmenopausal women. Int J Environ Res Public Health 2018;15:712.
[7] Tian WT, Huang XJ, Liang GL, et al. Social and psychological survey on paroxysmal kinesigenic dyskinesia patients in China. Chin J Contemp Neurol Neurosurg 2017;17:590–6.
[8] Ghaedrahmati M, Kazemi A, Kheirabadi G, et al. Postpartum depression risk factors: a narrative review. J Edu Health Prom 2017;6:60.
[9] Robson MJ, Qunlan MA, Blakely RD. Immune system activation and depression: roles of serotonin in the central nervous system and periphery. Acs Chem Neurosci 2017;8:342–42.
[10] Artali G, Gil-Ad I, Weizman R, et al. Gonadal hormones and the pre-synaptic transporters for dopamine and serotonin in rat brain. Euro Neuropsychopharmacol 1996;109–109.
[11] Hranilovic S, Steflul D, Fura2 J. 5-HTTLPR. Bio Psych 2003;54: 844–9.
[12] Munafò MR, Freimer NB, Ng W, et al. 5-Hydroxy tryptamine transporter (SHTT) gene promoter region polymorphism in anxiety and depressive disorders. Med J Islamic Republic of Iran 2014;28: 127–127.
[13] Gotlib IH, Joormann J, Minor KI, et al. Hpa axis reactivity: a mechanism underlying the associations among 5-htrp, stress, and depression. Bio Psych 2008;63:847–51.
[14] Sugawara H, Bundo M, Ishigoska J, et al. Epigenetic regulation of serotonin transporter in psychiatric disorders. J Genet Genomics 2013;40:325–9.
[15] Kaufman J, Yang BZ, Douglas-Palumberi H, et al. Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifiers of depression in children. Bio Psych 2006;59: 673–80.
[16] Zhang X, Wang L, Huang F, et al. Evaluation of the promoter region polymorphism (5-HTTLPR) in the serotonin transporter gene in females with postpartum depression. Exp Ther Med 2015;9:245–9.
[17] Khabour OF, Amarneh BH, Bani Hani EA, et al. Associations between variations in TPH1, TPH2 and SLC6A4 genes and postpartum depression: a study in the jordanian population. Balkan J Med Genetics 2013;16:41–8.
[18] Zimmermann-Peruzzi JM, Almeida S, Lucion AB, et al. Evaluation of the 5-HTTLPR and 5-HTTVNTR polymorphisms in the serotonin transporter gene in women with postpartum depression. Neurosci Med 2012;3:6.
[19] Xiu L, Yang C, Area F. Research on correlations between anxiety during pregnancy and 5-HTTLPR polymorphism and postnatal depression. China Med and Pharm 2016;13:28–30.
[20] Liberati A, Altman DG, Tetzlaff J, et al. The prisma statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. J Clin Epidemiol 2009;62:339.
[21] Stang A. Critical evaluation of the Newcastle-ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Euro J Epidemiol 2010;25:603–5.

Table 3

| Polymorphism (minor allele) | Genetic model | Number of studies | P_egg | P_egg |
|-----------------------------|---------------|------------------|-------|-------|
| SHTTLPR (L)                 | Allelic       | 6                | .388  | .707  |
|                            | Dominant      | 6                | .690  | .452  |
|                            | Recessive     | 6                | .976  | .542  |
[22] Zhang X, Wang L, Li JF. Impact of 5-HTT gene-linked polymorphic region polymorphism and environmental factors on postpartum depression. Med J Wuhan University 2014;35:432–5.

[23] Peng TJ, Huang XW. Correlation analysis of 5HTTLPR polymorphism and social and environmental factors in postpartum depression. Chin J Clin Obstet Gynecol 2015;16:547–50.

[24] Yildiz G, Senturk MB, Yildiz P, et al. Serum serotonin, leptin, and adiponectin changes in women with postpartum depression: controlled study. Arch Gynecol Obstet 2017;295:853–8.

[25] Ji ES, Lee JM, Kim TW, et al. Treadmill exercise ameliorates depressive symptoms through increasing serotonin expression in postpartum depression rats. J Exerc Rehabil 2017;13:130–5.

[26] Yang Y, Fang M, Du X, et al. Lucky gene 5-HTTLPR and postpartum depression: a systematic review. Neuro Endocrinol Lett 2017;38:316–20.

[27] Schneider I, Kugel H, Redlich R, et al. Association of serotonin transporter gene AluJb methylation with major depression, amygdala responsiveness, 5-HTTLPR/rs25531 polymorphism, and stress. Neuropsychopharmacology 2017;43:1308–16.

[28] Ezaki N, Nakamura K, Sekine Y, et al. Short allele of 5-HTTLPR as a risk factor for the development of psychosis in Japanese methamphetamine abusers. Ann New York Acad Sci 2010;1139:49–56.

[29] Ming Q, Zhang Y, Yi J, et al. Serotonin transporter gene polymorphism (3-HTTLPR) L allele interacts with stress to increase anxiety symptoms in Chinese adolescents: a multiwave longitudinal study. BMC Psychiatry 2015;15:248.

[30] Xu H, Zhang Q, Hou X, et al. The effect of the polymorphisms of 5-HTTLPR on new onset of depression in patients who underwent pacemaker implantation. Psych Genetics 2014;24:70–4.

[31] Gu H, Liu C, Liu C, et al. The combined effects of the 5-HTTLPR and HTR1A rs6295 polymorphisms modulate decision making in schizophrene patients. Genes Brain Behavior 2013;12:133–9.

[32] Munafò MR, Freimer NB, Ng W, et al. 5-HTTLPR genotype and anxiety-related personality traits: a meta-analysis and new data. Am J Med Genet B Neuropsychiatr Genet 2010;150B:271–81.

[33] Eun TK, Jeong SH, Lee KY, et al. Association between the 5-HTTLPR genotype and childhood characteristics in mood disorders. Clin Psychopharmacol Neurosci 2016;14:88–95.

[34] Cavallini MC, Bella DD, Silprandti F, et al. Exploratory factor analysis of obsessive-compulsive patients and association with 5-HTTLPR polymorphism. Am J Med Genetics 2010;114:347–53.

[35] Narasimhan S, Hodge R, Doyle GA, et al. Association analysis between the 5-HTTLPR polymorphism in the SLC6A4 gene and generalized anxiety disorder. Psych Genetics 2011;21:267.

[36] Pezawas L, Meyer-Lindenberg A, Drabant EM, et al. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat Neurosci 2005;8:828–34.