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Association between the serotonin transporter linked polymorphic region and lifelong premature ejaculation

An updated meta-analysis of case–control studies

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Abstract

Previous studies on the association between serotonin transporter linked polymorphic region (5-HTTLPR) polymorphism and premature ejaculation (PE) have led to inconsistent results. The purpose of the present meta-analysis was to examine whether 5-HTTLPR polymorphism is associated with PE susceptibility.

All eligible studies were searched and acquired from PubMed, Embase, Science Direct, CNKI, and Wanfang databases according to inclusion and exclusion criteria. Odds ratios (ORs) with 95% confidence intervals (CIs) were computed to assess the strength of the association between 5-HTTLPR polymorphism and PE. In addition, heterogeneity test, publication bias and sensitivity analysis were also conducted.

Firstly, the association were observed in 8 studies (L vs S: OR = 0.74, 95% CI = 0.63–0.87; LL vs SS: OR = 0.61, 95% CI = 0.44–0.83; SL vs SS: OR = 0.73, 95% CI = 0.55–0.96; LL + SL vs SS: OR = 0.67, 95% CI = 0.52–0.86; LL vs SL + SS: OR = 0.72, 95% CI = 0.55–0.92). When the 2 studies not in Hardy–Weinberg equilibrium (HWE) were omitted, a positive association could only be observed between the 5-HTTLPR polymorphism and PE in allele contrast model (L vs S: OR = 0.81, 95% CI = 0.67–0.98). In the stratified analysis by subgroup, significantly associations were also found between PE and 5-HTTLPR polymorphism in Caucasians but not Asians (L vs S: OR = 0.79, 95% CI = 0.63–0.98; LL + SL vs SS: OR = 0.67, 95% CI = 0.46–0.96).

Our meta-analysis demonstrated that the 5-HTTLPR polymorphism was associated with the susceptibility to PE in the Caucasian population. Compared with S allele, L allele is likely to be less susceptible to PE.

Abbreviations: 5-HT = serotonin, 5-HTTLPR = serotonin transporter linked polymorphic region, APE = acquired premature ejaculation, CI = confidence intervals, ED = erectile dysfunction, HWE = Hardy–Weinberg equilibrium, ISSM = International Society for Sexual Medicine, L = long, LPE = lifelong premature ejaculation, NOS = Newcastle-Ottawa scale, OR = odds ratio, PE = premature ejaculation, S = short, SLC6A4 = The solute carrier family 6 member 4 gene, SSRIs = selective serotonin reuptake inhibitors.

Keywords: meta-analysis, polymorphism, premature ejaculation, serotonin transporter linked polymorphic region

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Ethics and dissemination: This meta-analysis is based solely on a secondary study of published literatures and does not require ethics committee approval.

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1. Introduction

It is widely accepted that premature ejaculation (PE) is the most common sexual dysfunction in men, even more than erectile dysfunction (ED).[1] The prevalence of premature ejaculation varies by different areas and diverse definitions, and nearly 20% to 40% of adult men suffer from this embarrassing disease.[2,3] In general, PE is divided into lifelong PE (LPE) and acquired PE (APE). The patients with LPE complain the most serious symptoms and have the strongest willingness to visit a doctor. According to the latest definition by the International Society for Sexual Medicine (ISSM),[4] we need to consider 3 main factors when dealing with LPE patients: an intravaginal ejaculatory latency time (IELT) of $\leq$1 minute; the inability to delay ejaculation; and negative personal consequences, such as frustration, anxiety, depression, and/or avoiding sexual intimacy. However, the etiology of PE is not yet clear. Studies have indicated that genetic,[5,6] endocrine,[7] neurological,[8] psychological,[9] and other factors may be related to the occurrence of PE. Results from twins study indicated PE is a moderately inherited disease, with 28% hereditary effect.[10] In recent decades, the use of selective serotonin reuptake inhibitors (SSRIs) which delay both adult rats[11,12] and men[13] ejaculation suggests that neurotransmitter serotonin (5-HT) participates in the

process of ejaculation regulation. As a result, 5-HT transporter (5-HTT), which is a membrane bound protein in presynaptic neuron and reuptakes 5-HT in the synaptic cleft, has become the best breakthrough point for PE genetic research.[14]

1.1. The solute carrier family 6 member 4 (SLC6A4) is the gene encoding 5-HTT.

Over the past decade, there has been an increasing emphasis on the role of the promoter polymorphisms of *SLC6A4*, which is known as 5-HTT gene-linked polymorphic region (5-HTTLPR).[15] Insertion or deletion of a 44 base-pairs produced 2 alleles called long (L) and short (S), which could affect the transcription and expression of the SLC6A4 gene, and lead to a different number of 5-HTT proteins.[16] Many studies have been conducted to explore the relationship between 5-HTTLPR polymorphism and PE susceptibility in different ethnic groups.[17–24] However, they reached inconsistent and even contradictory conclusions. Therefore, the relationship between the 2 remains uncertain.

A recent meta-analysis of 6 studies conducted in 2013, which concerning the relationship between 5-HTTLPR polymorphism and PE suggested that 5-HTTLPR polymorphism was significantly associated with PE, and L allele may play a protective role in the pathogenesis of PE.[25] However, another critical meta-analysis published in 2014 provided conflicting results.[26] As the studies performed by Safarinejad[17] and Luo et al[20] were not consistent with Hardy–Weinberg equilibrium (HWE). It is generally known that meta-analysis is able to combine and review the results from previous studies. In order to avoid the limitations above, we performed this updated meta-analysis aiming to further evaluate the association of 5-HTTLPR polymorphism with PE susceptibility.

2. Methods

2.1. Search strategy

We performed a comprehensive and thorough search through the PubMed, Embase, Science Direct, CNKI (Chinese), and Wanfang (Chinese) databases up to December 31, 2018. The keywords of retrieve were ("premature ejaculation" or "rapid ejaculation" or "ejaculatory function" or "PE") and ("polymorphism" or "variant" or "mutation" or "5-HTTLPR") and ("serotonin" or "5-hydroxytryptamine" or "5-HT") without language restriction. The research design was limited to humans. All eligible studies were inspected carefully.

2.2. Inclusion and exclusion criteria

Studies should meet all of the following inclusion criteria: examined the association between 5-HTTLPR polymorphism and LPE susceptibility; case–control studies in design; and with clear original data of genotype frequencies of cases and controls. We also excluded studies that met the following criteria: incomplete data availability; noninclusion of their own data, such as review articles and comments; and duplicate of previous publication.

2.3. Quality assessment

Two independent investigators (NY and YH) evaluated the quality of the included studies according to the Newcastle-Ottawa scale (NOS).[27]

Quality evaluation of non-randomized studies mainly includes the following 3 aspects: selection of participants, comparability of groups, and exposure assessment. As well, HWE in controls for each study was examined by the chi-square test, while $P < .05$ was considered disequilibrium. A study of high quality was considered that the point according to NOS got at least 7 points, and its control group should not departure from HWE at the same time.

2.4. Data extraction

Data from each of the included studies were carefully extracted by 2 independent investigators (YH and HZ). When there were disagreements, we would reached a consensus finally by discussion. The following information was collected from each included study: the name of first author, the year of publication, ethnicity, source of control, genotyping method, the number of cases and controls, frequency of 5-HTTLPR polymorphism in cases and controls.

2.5. Statistical analysis

In this meta-analysis, the pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the association between 5-HTTLPR polymorphism and the risk of PE. Five genetic models were performed in this meta-analysis: allelic model (L vs S), homozygote comparison (LL vs SS), heterozygote comparison (SL vs SS), dominant model (LL + SL vs SS), and recessive model (LL vs SL + SS) (SS, homozygotes for the common allele; SL, heterozygotes; LL, homozygotes). Chi-square test and I^2 test were used to examine the heterogeneity of these genetic models. In addition, the effect of heterogeneity was quantified by the I^2 value.[28] $I^2 \leq 50\%$ was defined as acceptable, while $I^2 > 50\%$ indicated a high heterogeneity.

When $P < .05$ and/or $I^2 > 50\%$, we should choose the random effects model,[29] otherwise, a fixed effects model was applied.[30] Not only the comparison among all subjects, we also conducted stratification analyses by ethnicity and source of controls.

Sensitivity analyses were performed to assess the stability of the results; that is to say, every single study in the meta-analysis was removed each time to reflect the influence of the individual data set to the pooled ORs. In the end, Begg funnel plot and Egger regression test were used to evaluate the potential publication bias. All analyses were performed using STATA 12.0 (Stata Corp, College Station, TX). For all statistical analyses, a 2-sided P value $<.05$ was considered as statistically significant.

3. Results

3.1. Study characteristics

The flow of study identification, inclusion, and exclusion process is shown in Fig. 1. A total of 106 literatures were identified by retrieving 5 databases or by hand. At first, 67 papers were removed because of duplicate publication. After scanning by title and abstract, 27 articles were excluded (10 articles lacked 5-HTTLPR polymorphism, and 10 were letters, reviews, or meta-analysis, 7 were on other diseases). After the full-text evaluation, another 4 articles were excluded for incomplete genotype data. Finally, we got 8 eligible articles for the present meta-analysis, which included 7 in English and 1 in Chinese. The detailed characteristics of all included studies were shown in Table 1. There were 2 studies based on the Asian population and 6 studies

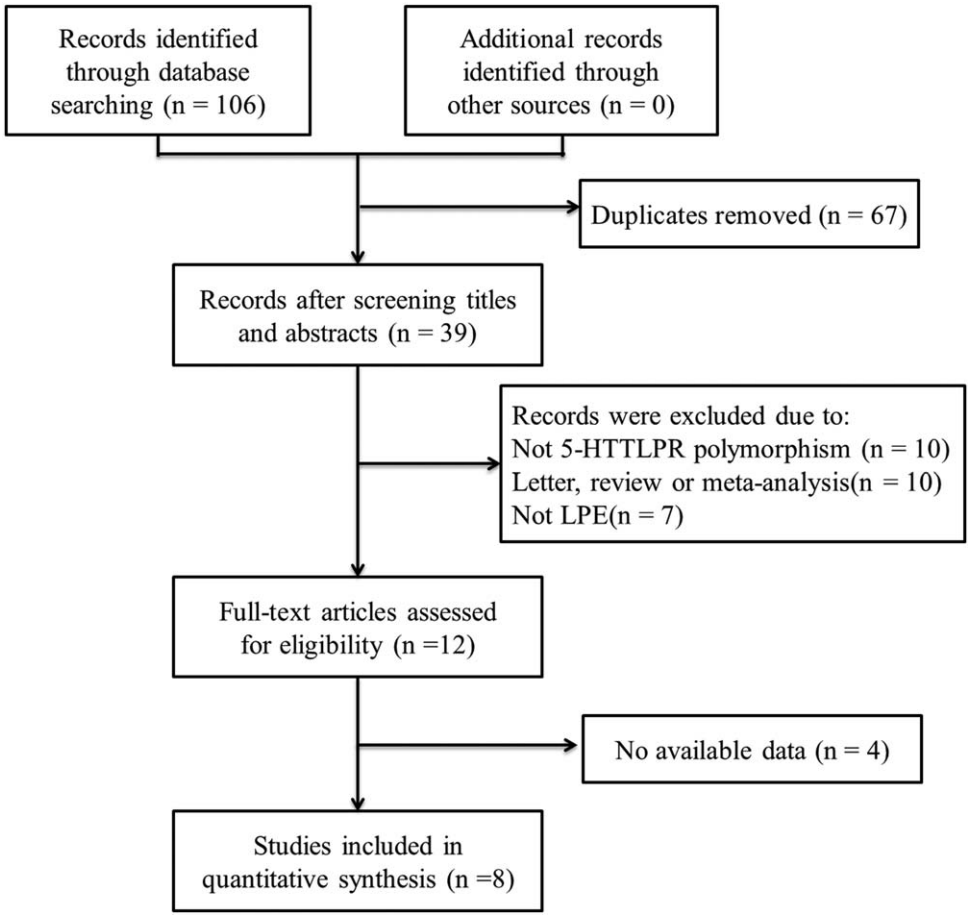

Figure 1. Flowing chart of selection publications in the current meta-analysis.

conducted on the Caucasian population. Besides, the source of control was divided into 2 types, which were population-based or hospital-based. The genotype distribution of the control group was consistent with HWE apart from 2 studies.[17,20] The quality score of each enrolled study was also presented in Table 1.

3.2. Quantitative synthesis

Meta-analysis for 5-HTTLPR polymorphism with PE was performed in 8 studies firstly with a total of 655 cases and 587 controls. Among which, 6 studies in HWE and 2 studies not in HWE were involved in the meta-analysis. As shown in Table 2, associations were observed in overall population (L vs S: OR = 0.74, 95% CI = 0.63–0.87; LL vs SS: OR = 0.61, 95% CI = 0.44–0.83; SL vs SS: OR = 0.73, 95% CI = 0.55–0.96; LL + SL vs SS: OR = 0.67, 95% CI = 0.52–0.86; LL vs SL + SS: OR = 0.72, 95% CI = 0.55–0.92). Because of ethnic differences in the 5-HTTLPR genotype distribution, the studies on Asians and Caucasians were independently analyzed. There seemed to be some relationship through subgroup analysis when regarding ethnicity as well as source of control (Table 3).

To further strengthen our conclusions, reanalysis was performed by removing the 2 studies not in HWE. These 6 articles left consisted of 454 cases and 415 controls. In the overall

Table 1

Characteristics of the eligible studies in this meta-analysis.

Study ID	Year	Country	Ethnicity	Genotyping method	Source of control	Case			Control			HWE	NOS
						SS	SL	LL	SS	SL	LL		
Safarinejad[17]	2009	Iran	Caucasian	PCR	PB	29	29	24	17	30	35	**No**	8
Janssen et al[18]	2009	Netherlands	Caucasian	PCR	HB	19	43	27	24	41	27	Yes	9
Obzek et al[19]	2009	Turkey	Caucasian	PCR	PB	37	21	11	20	37	12	Yes	8
Luo et al[20]	2011	China	Asian	PCR	HB	61	34	24	34	31	25	**No**	7
Zuccarello et al[21]	2012	Italy	Caucasian	PCR	PB	18	49	22	16	51	33	Yes	9
Jern et al[22]	2013	Finland	Caucasian	PCR	PB	5	15	13	5	16	12	Yes	8
Huang et al[23]	2016	China	Asian	PCR	HB	35	61	18	31	48	22	Yes	8
Salem et al[24]	2016	Egypt	Caucasian	PCR	HB	19	25	16	2	8	10	Yes	7

HB = hospital-based; HWE = Hardy–Weinberg equilibrium (in control), $P < 0.05$ was shown in bold; NOS = the Newcastle–Ottawa Scale; PB = population-based; PCR = polymerase chain reaction.

Table 2

Stratified analysis of the 5-HTTLPR polymorphism and PE (8 publications).

Variables	Group	Case/Control	Allelic (L vs S)			Homozygous (LL vs SS)			Heterozygous (SL vs SS)		
			OR (95% CI)	I^2	P_h	OR (95% CI)	I^2	P_h	OR (95% CI)	I^2	P_h
	Overall	655/587	0.74 (0.63–0.87)	39.4	.116	0.61 (0.44–0.83)	8.1	.368	0.73 (0.55–0.96)	37.6	.129
Ethnicity	Caucasian	422/396	0.74 (0.60–0.90)	51.1	.069	0.60 (0.41–0.89)	31.5	.199	0.66 (0.46–0.94)	42.9	.119
	Asian	233/191	0.76 (0.58–1.00)	23.2	.254	0.61 (0.36–1.03)	0.0	.573	0.84 (0.54–1.31)	44.8	.129
Source of control	HB	382/303	0.80 (0.64–0.99)	59.8	.059	0.67 (0.44–1.02)	45.3	.140	0.89 (0.62–1.29)	31.3	.224
	PB	273/284	0.68 (0.54–0.87)	4.2	.372	0.53 (0.33–0.85)	0.0	.691	0.55 (0.36–0.84)	25.3	.260

Variables	Group	Case/Control	Dominant (LL + SL vs SS)			Recessive (LL vs SL + SS)		
			OR (95% CI)	I^2	P_h	OR (95%CI)	I^2	P_h
	Overall	655/587	0.67 (0.52–0.86)	40.9	.106	0.72 (0.55–0.92)	0.0	.683
Ethnicity	Caucasian	422/396	0.62 (0.45–0.86)	48.0	.087	0.74 (0.54–1.00)	0.0	.456
	Asian	233/191	0.75 (0.50–1.12)	44.0	.181	0.66 (0.42–1.06)	0.0	.959
Source of control	HB	382/303	0.80 (0.57–1.11)	50.8	.107	0.72 (0.50–1.02)	2.8	.387
	PB	273/284	0.53 (0.36–0.78)	2.1	.382	0.71 (0.49–1.04)	0.0	.632

I^2: 0–25, means no heterogeneity; 25–50, means modest heterogeneity; and >50, means high heterogeneity.

5-HTTLPR = serotonin transporter linked polymorphic region; CI = confidence interval; HB = hospital-based; OR = odds ratio; PB = population-based; PE = premature ejaculation; P_h = *P*-value of heterogeneity test.

analysis, there were significant differences compared with the former OR and 95% CI when the 2 studies were omitted. As we can see, when the 2 studies were omitted, the ORs of the homozygous model (LL vs SS), heterozygous model (SL vs SS), dominant model (LL + SL vs SS), and recessive model (LL vs SL + SS) of 5-HTTLPR polymorphism, which were significant previously, became insignificant. Results were presented at Table 3. Meanwhile, a positive association could only be observed between the 5-HTTLPR polymorphism and PE in allele contrast model (L vs S: OR = 0.81, 95% CI = 0.67–0.98). In the results from a subgroup analysis by ethnicity subgroup, significantly decreased associations were also found between LPE risk and 5-HTTLPR polymorphism in Caucasians but not Asians (L vs S: OR = 0.79, 95% CI = 0.63–0.98; LL + SL vs SS: OR = 0.67, 95% CI = 0.46–0.96). When a stratification analysis was performed by source of control, we also identified a decreased susceptibility of PE in the population-based studies (L vs S: OR = 0.74, 95% CI = 0.55–0.98; SL vs SS: OR = 0.55, 95% CI = 0.33–0.90; LL + SL vs SS: OR = 0.55, 95% CI = 0.34–0.88).

3.3. Sensitivity analysis

Sensitivity analysis was applied to assess the impact of the independent studies which caused obvious heterogeneity by removing one study at a time. After excluding the studies not fulfill HWE, none of left studies affected the pooled OR value, indicating the results of our meta-analysis were reliable (Fig. 2).

3.4. Evaluation of publication bias

Begg funnel plot and Egger test were further performed to examine the publication bias risk in our research. No publication bias was identified in different alleles of 5-HTTLPR polymorphism ($P = .452$ for Begg test, $P = .348$ for Egger test). Besides, no

Table 3

Stratified analysis of the 5-HTTLPR polymorphism and PE after removing 2 studies not in HWE (6 publications).

Variables	Group	Case/Control	Allelic (L vs S)			Homozygous (LL vs SS)			Heterozygous (SL vs SS)		
			OR (95% CI)	I^2	P_h	OR (95% CI)	I^2	P_h	OR (95% CI)	I^2	P_h
	Overall	454/415	**0.81 (0.67–0.98)**	42.6	.121	0.69 (0.47–1.02)	15.0	.318	0.79 (0.57–1.11)	51.1	.069
Ethnicity	Caucasian	340/314	**0.79 (0.63–0.98)**	52.7	.076	0.68 (0.44–1.07)	32.0	.208	0.69 (0.46–1.02)	53.3	.073
	Asian	114/101	0.89 (0.60–1.30)	–	–	0.72 (0.33–1.59)	–	–	1.13 (0.61–2.08)	–	–
Source of control	HB	263/213	0.88 (0.68–1.14)	65.1	.057	0.76 (0.45–1.27)	57.6	.094	1.07 (0.68–1.67)	12.5	.319
	PB	191/202	**0.74 (0.55–0.98)**	7.1	.341	0.61 (0.34–1.11)	0.0	.682	**0.55 (0.33–0.90)**	50.1	.135

Variables	Group	Case/Control	Dominant (LL + SL vs SS)			Recessive (LL vs SL + SS)		
			OR (95% CI)	I^2	P_h	OR (95% CI)	I^2	P_h
	Overall	454/415	0.75 (0.55–1.02)	50.2	.074	0.77 (0.57–1.06)	0.0	.560
Ethnicity	Caucasian	340/314	**0.67 (0.46–0.96)**	54.9	.065	0.80 (0.57–1.14)	0.0	.443
	Asian	114/101	1.00 (0.56–1.79)	–	–	0.67 (0.34–1.34)	–	–
Source of control	HB	263/213	0.95 (0.63–1.44)	47.7	.148	0.75 (0.49–1.14)	33.1	.224
	PB	191/202	**0.55 (0.34–0.88)**	32.5	.227	0.81 (0.51–1.28)	0.0	.650

I^2: 0–25, means no heterogeneity; 25–50, means modest heterogeneity; and >50, means high heterogeneity.

The values shown in bold indicate that statistically significant associations were observed between the paired groups.

5-HTTLPR = serotonin transporter linked polymorphic region; CI = confidence interval; HB = hospital-based; HWE = Hardy–Weinberg equilibrium; OR = odds ratio; PB = population-based; PE = premature ejaculation; P_h = *P*-value of heterogeneity test.

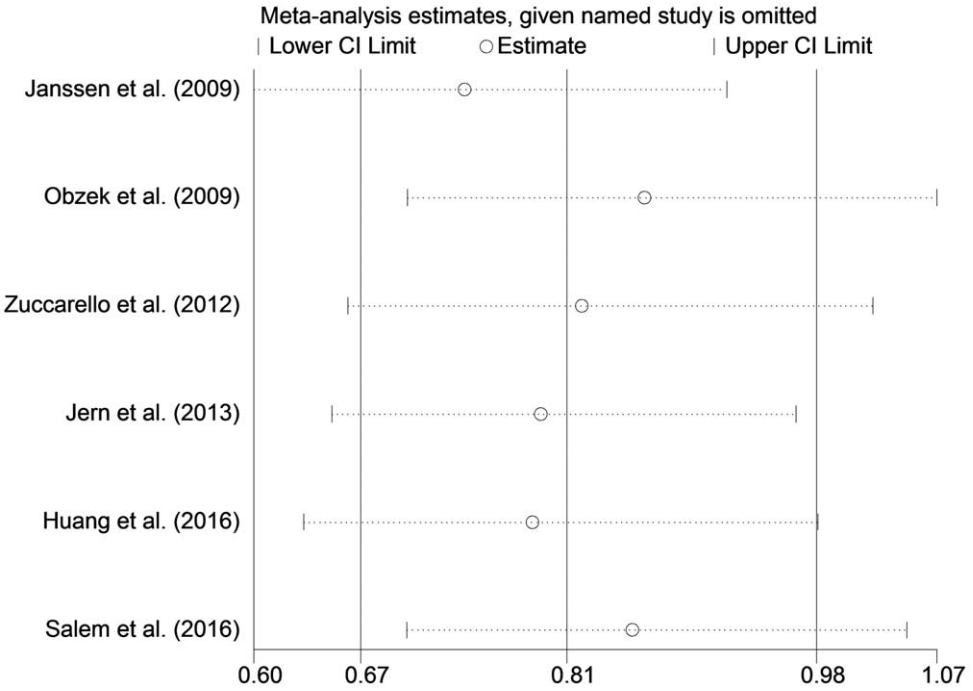

Figure 2. Sensibility analysis in studies of the association between the 5-HTTLPR polymorphism and PE susceptibility assessed by deleting one single case–control study at each time from inclusion pooled. 5-HTTLPR = serotonin transporter linked polymorphic region; PE = premature ejaculation.

obvious asymmetry was noticed according to the shape of Begg funnel plot (Fig. 3).

4. Discussion

The exact pathogenesis of PE is not clear so far. Many studies suggested that genetic factors may be associated with the onset of PE, especially for LPE. A genetic etiology was first suggested in 1943, when Schapiro[31] observed that the PE seems to be familial. As is known to all, neurotransmission 5-HT plays an important role in the regulation of ejaculation. 5-HTTLPR polymorphisms can affect the transcription and expression of 5-HTT and further affect 5-HT concentration. Then, the association between 5-HTTLPR polymorphism and PE had been thoroughly explored.[17–24] Unfortunately, these results were inconsistent and inconclusive, and thus a systematic review and meta-analysis was of great value. In the present meta-analysis, our findings showed that the 5-HTTLPR polymorphism was related to the susceptibility of PE in the Caucasian population. Compared with S allele according to the allele contrast mode (L vs S), L allele was likely to be less susceptible to PE. Meanwhile, in the studies whose controls were from population-based, significant association was also found.

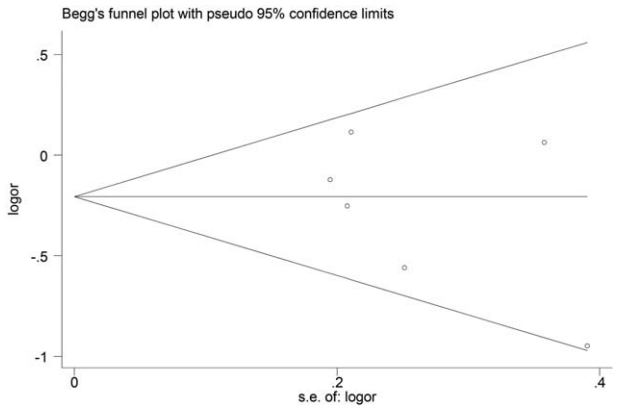

Figure 3. Publication bias examinations by Begg funnel plots and Egger test of alleles (L vs S).

The association between 5-HTTLPR polymorphism and PE had been reported in different population with different results. In detail, Janssen et al[18] performed a prospective study in Dutch Caucasian men. They found there was no significant difference in the 5-HTTLPR alleles and genotypes between the LPE patients and controls. A second study performed in Turkish men, Ozbek et al[19] evaluated the genotypes of 5-HTTLPR in 70 PE patients and 70 controls. They found the S allele was significantly more frequent in PE patients than in controls. In China, Luo et al[20] investigated the relationship between 5-HTTLPR and PE in a Han population. The results showed S allele was significantly higher in LPE group than in control group. Different from the above, a case–control study in China by Huang et al[23] found no significant difference in the frequencies of biallelic 5-HTTLPR allelic or genotypic polymorphisms between LPE patients and controls. The rs25531 is a single-nucleotide polymorphism (SNP) in L allele, which further leads to an A/G polymorphism. Thus, it provided a functional triallelic polymorphism as S, LG, and LA. The results by Huang et al[23] indicated triallelic 5-HTTLPR polymorphism was related to LPE in Chinese population. Meanwhile, Jern et al[22] reassessed the effects of 5-HTTLPR on ejaculatory function in a large, population-based sample from Finland twins. No significant association was found between the 5-HTTLPR polymorphism and PE. Another study in Italy by

Zuccarello et al[21] indicated that no difference exists in 5-HTTLPR polymorphism frequency between PE patients and controls. Moreover, a study by Salem et al[24] found no significant association between the 5-HTTLPR polymorphism and Egyptian patients with LPE.

As far as we know, it is very common that significant findings from genetic association studies fail to replicate between different cohorts.[32] The effect of 5-HTTLPR polymorphism on the ejaculatory function may be quite complicated. On the one hand, gene frequencies of 5-HTTLPR polymorphism vary significantly among different races and ethnicities. As the S allele is much more prevalent in Asians than in Caucasians,[33,34] suggesting that ethnic differences may be a confounding factor in association studies of the 5-HTTLPR genotype, we conducted separate analyses for both populations to avoid biased conclusions. Significant association was found between 5-HTTLPR and the risk of PE in Caucasians. On the other hand, it may have a synergistic effect together with other polymorphisms on ejaculation such as STin2 VNTR,[21,35] 5-HT1A receptor, 5-HT1B receptor, 5-HT2C receptor, or other genes possibly indicated as involved in the pathogenesis of PE.[36–38]

The results of our meta-analysis were a little different from the previous meta-analyses and had several advantages. Firstly, this meta-analysis was the latest one and has the largest sample size. Besides, this meta-analysis performed by 5 genetic models demonstrated that the allelic model and dominant model can play a potential role in PE susceptibility. Last but not least, it was the first meta-analysis performed by removing the 2 studies not in HWE. So the result of our meta-analysis would be more convincing. However, some limitations had been identified in this meta-analysis. First, the sample size of the stratified analyses was rather small, especially for Asians, which reduced the reliability of our results. Therefore, we needed more research from Asian populations. Second, previous studies lacked detailed information on the individual level, such as age and duration of relationship. Third, as a complex ejaculatory disorder, PE could be caused by the interaction of genetic and environmental factors, so more studies exploring gene–gene and gene–environment interactions in PE are needed in future.

In conclusion, this meta-analysis indicated that 5-HTTLPR polymorphism was associated with a decreased susceptibility to PE in Caucasians. Compared with S allele, L allele is likely to be less susceptible to PE. More well-designed and large sample studies are warranted to confirm this conclusion, to definitively clarify the genetic etiology of PE, or to analyze other linked genes.

Author contributions

Conceptualization: Nan Ye, Yuanyuan Huang, Guangyuan Li.
Data collection, collation and statistical: Nan Ye, Yuanyuan Huang, Huaiming Zhao.
Quality assessment: Nan Ye, Yuanyuan Huang.
Software: Yuanyuan Huang.
Writing – original draft: Nan Ye, Yuanyuan Huang, Huaiming Zhao, Guangyuan Li.
Writing – review: Guangyuan Li.

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