

Association between polymorphisms in the serotonin transporter gene-linked polymorphic region and risk for irritable bowel syndrome in China: evidence based on a meta-analysis

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Abstract

Objective: The association between mutations in the serotonin transporter gene-linked polymorphic region (5-HTTLPR) and irritable bowel syndrome (IBS) differs between populations. This meta-analysis was designed to assess the relationship between 5-HTTLPR polymorphisms and IBS in a Chinese population.

Methods: Relevant published studies from PubMed, Embase, Web of Science, the Cochrane Library, and China National Knowledge Infrastructure databases were accessed prior to May 2018. Odds ratios (ORs) with 95% confidence intervals (CIs) were pooled using STATA software.

Results: A total of 754 IBS cases and 578 healthy controls in six studies were included in this meta-analysis. Significant results were obtained between 5-HTTLPR polymorphisms and IBS risk among studies with the genotype distribution of controls in Hardy–Weinberg equilibrium (L vs. S, OR = 1.41, 95% CI: 1.11–1.79; LL vs. SS, OR = 2.17, 95% CI: 1.16–4.08; LL vs. LS + SS, OR = 2.29, 95% CI: 1.25–4.20). In subgroup analyses, 5-HTTLPR polymorphisms were significantly associated with increased IBS-C risk in China; however, no risk was observed for IBS-D and IBS-M.

Conclusion: This meta-analysis clearly indicates that 5-HTTLPR polymorphisms are associated with an increased risk of IBS in the Chinese population, especially IBS-C.

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Keywords

5-HTTLPR, polymorphism, irritable bowel syndrome, meta-analysis, Chinese population, IBS-C

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Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by recurrent abdominal pain occurring at least 1 day per week during the last 3 months and accompanied by a change in bowel habits.^{1,2} According to different bowel behaviors, IBS can be divided into four subtypes: IBS-C (constipation-predominant), IBS-D (diarrhea-predominant), IBS-M (mixed), and IBS-U (unspecified); IBS-D is the major subtype.³ The high prevalence of IBS in Europe (14%–28%)⁴ and China (0.82%–11.5%)^{5,6} adversely impacts the quality of life and increases medical expenses among affected patients.^{7,8}

Although the etiology of IBS remains largely unknown, multiple genetic variations have been shown to affect its development.^{9–13} Of these, polymorphisms in the serotonin transporter gene-linked polymorphic region (5-HTTLPR) have been most widely evaluated in patients with IBS. 5-HTTLPR short (14 repeats) and long variation (16 repeats) polymorphisms were shown to influence the activity of the serotonin reuptake transporter,^{14,15} and are very likely to be related to IBS development. However, the potential relationships between 5-HTTLPR polymorphisms and IBS risk in the Chinese population are conflicting.

Meta-analyses based on individual studies with small sample sizes have a lower statistical power. Additionally, a lack of repeatability may also result from inconsistent genetic heritability or lifestyle contexts. Therefore, we conducted the present study

to determine the role of 5-HTTLPR polymorphisms in IBS risk in a Chinese population.

Materials and methods

Identification and selection of studies

We evaluated the association between 5-HTTLPR polymorphisms and IBS risk by searching PubMed, Embase, Web of Science, the Cochrane Library, and China National Knowledge Infrastructure databases prior to May 2018 using the following search terms: (“irritable bowel syndrome” or “IBS”) and (“serotonin” or “5-hydroxytryptamine” or “5-HT”) and “polymorphism” and (“Chinese” or “China”). The search was not restricted by language or publication status. At least two independent reviewers screened the potentially relevant articles, and disagreements were resolved by discussion or input from a third reviewer if needed.

The inclusion criteria were as follows: (1) studies examining the relationship between 5-HTTLPR polymorphisms and IBS risk; (2) a case–control study design; (3) sufficient data regarding genotype frequency; and (3) Chinese ethnicity. The exclusion criteria were as follows: (1) overlapping literature; (2) unextractable data; (3) study design other than case–control; and (4) abstract or review article types.

Data extraction

Potentially relevant studies and extracted data from identified publications, including

the first author's name, publication year, geographic area, source of controls, sample size, and available genotype information from 5-HTTLPR polymorphisms, were screened by two investigators. We studied the titles and abstracts for each retrieved document first, then read the full papers if the titles and abstracts did not determine if the study met the inclusion criteria. Data discrepancies in extraction were resolved by discussion between the two investigators. In this meta-analysis, the quality of individual studies was assessed according to the nine-star Newcastle–Ottawa Scale.¹⁶

Statistical analysis

Odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the strength of association between 5-HTTLPR polymorphisms and IBS risk to the model. L versus S, LL versus SS, LL versus (LS + SS), and (LL + LS) versus SS were examined for IBS risk. The comprehensive test of heterogeneity, as well as the Hardy–Weinberg equilibrium (HWE) in controls, was tested by I-squared based on Q and the df.¹⁷ When $P_{\text{heterogeneity}} < 0.1$ or $I^2 > 50\%$, a random effects meta-analysis model was applied to estimate the pooled ORs; otherwise the fixed effects model was adopted. The entire calculated ORs were analyzed by the Z-test. Both effects models of each pooled OR were computed for the sensitivity assay. The funnel plot was used to assess potential publication bias and Egger's test was applied to evaluate funnel plot asymmetry. We also performed a subgroup investigation according to geographic area, IBS subtype, and HWE in controls to evaluate the relationship between 5-HTTLPR and IBS risk. All statistical analyses were performed using Stata version 12 (StataCorp LP, College Station, TX, USA), and $P < 0.05$ was considered significant.

Results

Research characteristics

Three hundred sixty-seven publications that assessed the relationship between 5-HTTLPR polymorphisms and IBS were identified. Six studies^{18–23} met the inclusion criteria and were used in this meta-analysis. The publication years included for this meta-analysis ranged from 2004 to 2014. Figure 1 reveals the detailed screening information. A total of 754 IBS cases and 578 healthy controls were included in the current study, which assessed the relationship between 5-HTTLPR polymorphisms and IBS risk among the Chinese population. The main characteristics of the six studies are listed in Table 1.

Overall analysis

No significant associations were observed between 5-HTTLPR and IBS risk among the four models (L vs. S, OR = 0.90, 95% CI: 0.40–2.02; LL vs. SS, OR = 1.15, 95% CI: 0.36–3.71; LL vs. LS + SS, OR = 1.19, 95% CI: 0.34–4.14; LL + LS vs. SS, OR = 0.83, 95% CI: 0.45–1.52; Table 2). There was significant heterogeneity among the tested models ($P < 0.05$). Sensitivity analysis indicated consistent results for the fixed and random effects models. When evaluating publication bias, the shape of the funnel plot revealed obvious asymmetry (Figure 3). However, Egger's test indicated that there was no evidence of obvious publication bias in all included studies ($t = 0.13$, $P = 0.900$, Figure 4).

Subgroup analysis

Subgroups were designated according to geographic area and HWE in controls. The data indicated that 5-HTTLPR polymorphisms were not related to IBS risk among populations from north China and south China. Positive associations among

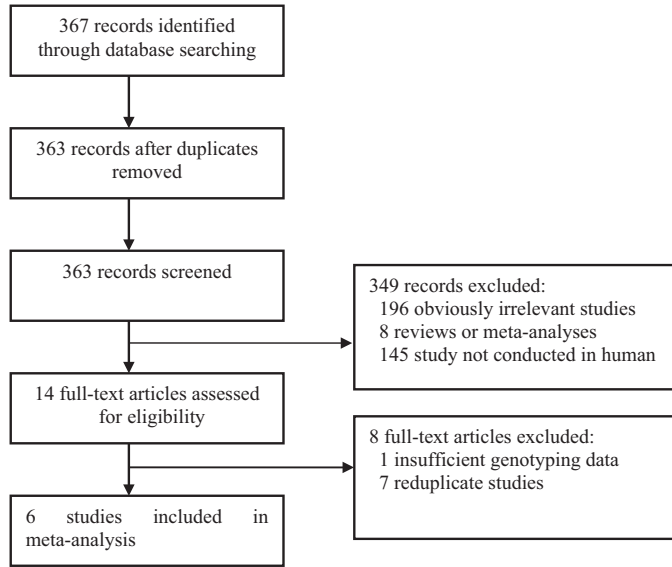


Figure 1. Flow diagram of the literature search.

Table 1. Characteristics of studies included in the meta-analysis.

Reference	Geographic area	IBS subtype	Case number	Control number	Cases			Controls			HWE		Quality score
					SS	LS	LL	SS	LS	LL	χ^2	P	
Wang 2004	Tianjin	IBS-C, IBS-D, IBS-M	78	44	21	25	32	10	17	17	1.89	0.169	7
Zhang 2006	Fujian	IBS-C, IBS-D, IBS-M	145	48	64	49	32	24	20	4	0.00	0.954	8
Li 2007	Guangzhou	IBS-C, IBS-D, IBS-M	87	96	46	27	14	55	34	7	0.30	0.586	8
Wang 2012	Tianjin	IBS-C, IBS-D, IBS-M	254	120	97	67	90	49	35	36	20.15	0.000	8
Zhang 2012	Jiangxi	IBS-C	84	103	43	20	21	59	36	8	0.56	0.453	8
Yuan 2014	Yunnan	IBS-C, IBS-D, IBS-M	106	167	45	31	30	20	8	139	108.32	0.000	8

HWE, Hardy–Weinberg equilibrium; IBS, irritable bowel syndrome; IBS-C, constipation-predominant; IBS-D, diarrhea-predominant; IBS-M, mixed.

studies with controls in HWE in three analysis models were demonstrated (L vs. S, OR = 1.41, 95% CI: 1.11–1.79; LL vs. SS, OR = 2.17, 95% CI: 1.16–4.08; LL vs. LS + SS, OR = 2.29, 95% CI: 1.25–4.20;

Figure 2). Next, IBS-C, IBS-D, and IBS-M subgroups were analyzed from the data in five studies. The L allele and LL genotype were significantly correlated with increased risk of IBS-C in China; however,

Table 2. Association of the 5-HTTLPR polymorphism with IBS susceptibility.

Analysis model	n	OR _r (95% CI)	OR _f (95% CI)	P _h
L vs. S				
Total analysis	6	0.90 (0.40–2.02)	0.84 (0.71–0.99)	0.000
North China	2	1.12 (0.86–1.46)	1.12 (0.86–1.46)	0.523
South China	4	0.83 (0.22–3.06)	0.70 (0.57–0.87)	0.000
In HWE	4	1.41 (1.11–1.79)	1.41 (1.11–1.79)	0.398
IBS-C	5	1.84 (1.48–2.30)	1.84 (1.48–2.30)	0.740
IBS-D	4	0.87 (0.67–1.14)	0.87 (0.67–1.14)	0.678
IBS-M	4	1.05 (0.67–1.65)	1.07 (0.78–1.48)	0.142
LL vs. SS				
Total analysis	6	1.15 (0.36–3.71)	0.87 (0.66–1.16)	0.000
North China	2	1.17 (0.74–1.84)	1.17 (0.74–1.84)	0.5360
South China	4	1.23 (0.16–9.12)	0.72 (0.50–1.03)	0.000
In HWE	4	2.17 (1.16–4.08)	2.20 (1.36–3.55)	0.016
IBS-C	5	2.88 (1.90–4.39)	2.90 (1.93–4.35)	0.391
IBS-D	4	0.83 (0.51–1.35)	0.83 (0.51–1.35)	0.896
IBS-M	4	1.12 (0.44–2.84)	1.15 (0.63–2.12)	0.152
LL vs. LS+SS				
Total analysis	6	1.19 (0.34–4.14)	0.80 (0.63–1.03)	0.000
North China	2	1.23 (0.83–1.83)	1.23 (0.83–1.83)	0.745
South China	4	1.22 (0.13–10.98)	0.60 (0.43–0.83)	0.000
In HWE	4	2.29 (1.25–4.20)	2.24 (1.44–3.47)	0.008
IBS-C	5	3.00 (2.07–4.35)	3.04 (2.10–4.39)	0.639
IBS-D	4	0.91 (0.58–1.41)	0.91 (0.58–1.41)	0.935
IBS-M	4	0.98 (0.38–2.49)	0.97 (0.56–1.67)	0.095
LL+LS vs. SS				
Total analysis	6	0.83 (0.45–1.52)	0.85 (0.67–1.07)	0.000
North China	2	1.04 (0.70–1.55)	1.04 (0.70–1.54)	0.498
South China	4	0.77 (0.30–1.57)	0.76 (0.57–1.01)	0.000
In HWE	4	1.17 (0.85–1.62)	1.17 (0.85–1.61)	0.825
IBS-C	5	1.43 (1.04–1.96)	1.44 (1.06–1.96)	0.391
IBS-D	4	0.82 (0.57–1.19)	0.82 (0.57–1.19)	0.610
IBS-M	4	1.18 (0.75–1.85)	1.18 (0.75–1.85)	0.716

5-HTTLPR, serotonin transporter gene-linked polymorphic region; IBS, irritable bowel syndrome; OR_r, Odds ratio for random effects model; OR_f, Odds ratio for fixed effects model; CI, confidence interval; P_h, P value for heterogeneity test; South China including Fujian, Guangzhou, Jiangxi, Yunnan; HWE, Hardy–Weinberg equilibrium.

no associations existed between 5-HTTLPR polymorphisms and the risk of IBS-D or IBS-M (Table 2).

Discussion

A number of studies have been published to analyze the relationship between 5-HTTLPR polymorphisms and risk of IBS; however, no comprehensive definitive

conclusion has been established. Based on a previous meta-analysis,²⁴ no association was detected between 5-HTTLPR polymorphisms and IBS, but mainstream patients among the Asian population were shown to be short allele homozygous (64%). Subgroup analysis based on participant region or population showed a reduced 5-HTTLPR polymorphism effect on IBS risk in Americans and Asians.²⁵ Individual

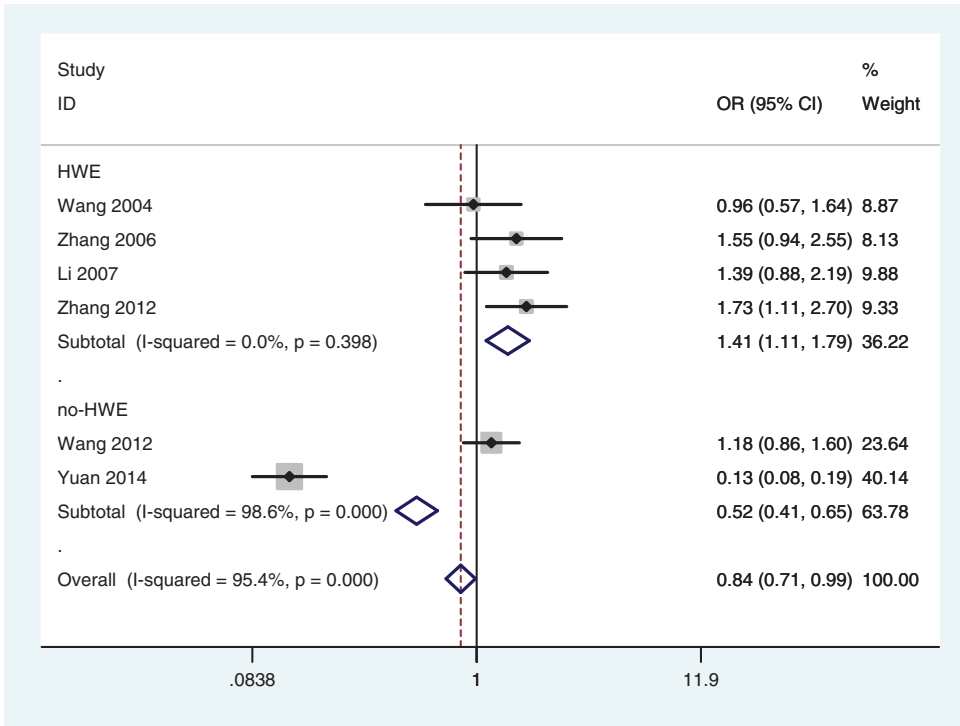


Figure 2. Forest plots of all selected studies about the association between 5-HTTLPR polymorphisms on IBS risk in a Chinese population under the allele model. 5-HTTLPR: serotonin transporter gene-linked polymorphic region; IBS: irritable bowel syndrome.

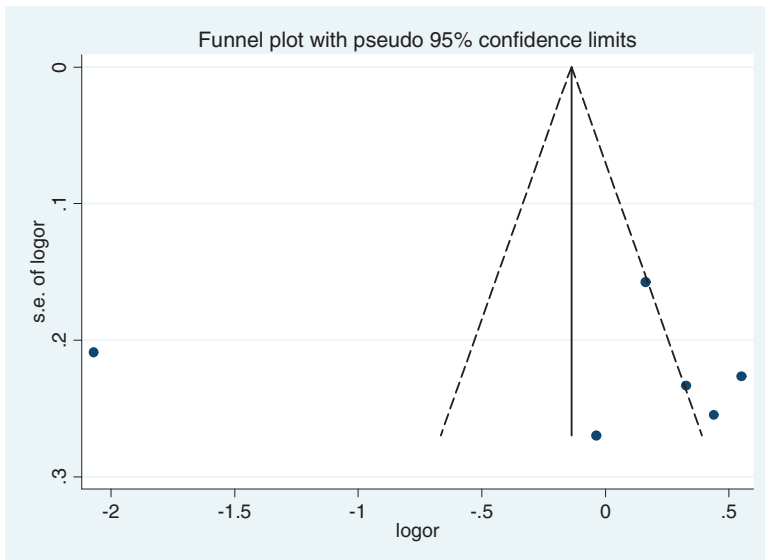


Figure 3. Publication bias assessment with Begg's funnel plot.

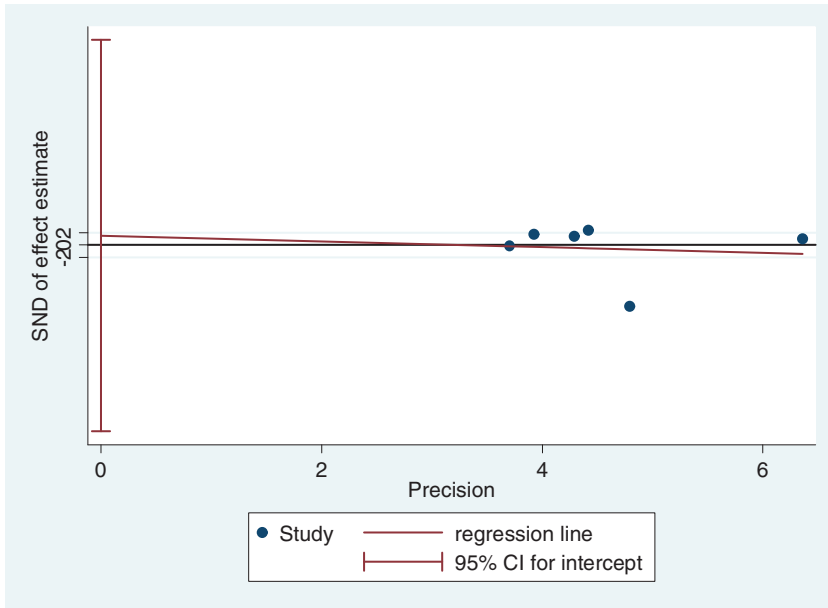


Figure 4. Egger's linear regression.

studies are capable of generating diverse results reflecting regional variability and individuals in different populations, or the limited number of cases studied in each analysis. Additionally, unique cultures and lifestyles of diverse ethnic groups may lead to different genetic traits. To reduce these effects, we conducted the current meta-analysis to further survey the relationship between 5-HTTLPR polymorphisms and IBS in the Chinese population.

The current study consisted of six investigations, including 754 IBS cases and 578 healthy controls. The overall analysis indicated that 5-HTTLPR polymorphisms were not associated with IBS risk among the Chinese population. Considering the effect of geographic background, IBS subtype, and HWE in controls on the results, we also performed subgroup analysis with respect to these factors. Positive relationships between 5-HTTLPR polymorphisms and IBS risk were also found among studies with controls in HWE. Furthermore, the L allele and LL genotype were significantly

associated with increased IBS-C risk in China. No associations between 5-HTTLPR polymorphisms and the risk of IBS-D or IBS-M were shown. Our results are consistent with the previously published meta-analysis conducted by Zhang et al.,²⁶ which indicated that the association between 5-HTTLPR with IBS-C is population-dependent and that a positive relationship only exists in the east Asian population, not in the Caucasian population.

One important 5-HTTLPR polymorphism feature is that the variation may be significant between different groups and/or races.²⁷ A strength of this study is that the association between 5-HTTLPR mutations and IBS risk is pooled only in the Chinese population. Heterogeneity is fairly common in meta-analyses among genetic association studies. When considering all of the eligible data, we found heterogeneity between studies. Although the heterogeneity was effectively decreased after subgroup analysis by geographic area, IBS subtype, and HWE in controls, there are some limitations in our meta-

analysis that require discussion. First, only studies published in English and Chinese languages were included, and related articles published in other languages and indexed in other databases were excluded. Second, we could not perform other subgroup analyses, such as those based on age, gender, and duration of disease because of data limitation in original papers. Finally, the pathogenesis of IBS is considered multifactorial so a single genetic variant may not predict the risk of IBS.

Conclusion

The results of this meta-analysis clearly showed a positive correlation between 5-HTTLPR polymorphisms and the increased risk of IBS in a Chinese population, especially IBS-C. However, because of limitations in this meta-analysis, further studies with different backgrounds are required to validate this association and to investigate potential gene–gene and gene–environment interactions between 5-HTTLPR polymorphisms and IBS susceptibility.

Abbreviations

5-HTTLPR: serotonin transporter gene linked polymorphic region; IBS: irritable bowel syndrome; OR: odds ratio; CI: confidence interval; HWE: Hardy–Weinberg equilibrium.

Authors' contributions

Bianfang YU1, Qinggang LI, and Xin DONG designed, collected, and analyzed the data. Zhan-bo Jia and Li-ping Wang drafted the manuscript and approved submission.

Availability of data and materials

All data are included in the study.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics approval and consent to participate

Not applicable.

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