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META-ANALYSIS

Association of interleukin-10 polymorphisms with risk of irritable bowel syndrome: A meta-analysis

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Abstract

AIM: To clarify the current understanding of the association between interleukin-10 (*IL-10*) polymorphisms and the risk of irritable bowel syndrome (IBS).

METHODS: We searched for studies in any language recorded in PubMed, Embase and Cochrane library before August 2013. The associations under allele contrast model, codominant model, dominant model, and recessive model were analyzed. The strengths of the association between *IL-10* polymorphisms and IBS risk were estimated using odds ratios (OR) with 95% confidence interval (CI). Fixed effects model was used to pool the result if the test of heterogeneity was not significant, otherwise the random-effect model was selected.

RESULTS: Eight case-control studies analyzing three single-nucleotide polymorphisms rs1800870 (-1082 A/G), rs1800871 (-819C/T), and rs1800872 (-592A/C) of the *IL-10* gene, which involved 928 cases and 1363 controls, were eligible for our analysis. The results showed that rs1800870 polymorphisms were associated with a decreased risk of IBS (GG+GA *vs* AA: OR = 0.80, 95%CI: 0.66-0.96), (AA+GA *vs* GG: OR = 0.68, 95%CI: 0.52-0.90). Subgroup analysis revealed such association only existed in Caucasian ethnicity (AA+GA *vs* GG, OR = 0.70, 95%CI: 0.55-0.89). The *rs1800872* polymorphisms were associated with an increased risk of IBS in Asian ethnicity (CC *vs* GG: OR = 1.29, 95%CI: 1.01-1.16). There were no associations between rs1800871 polymorphisms and the IBS risk.

CONCLUSION: The results suggest that IL-10 rs1800870 confers susceptibility to the risk of IBS in Caucasian ethnicity, and the rs1800872 may associate with IBS risk in Asians. However, no significant associations are found between rs1800871 and IBS risk.

Key words: Interleukin-10; Irritable bowel syndrome; Gene polymorphism; Case-control; Meta-analysis

Core tip: Interleukin-10 (*IL-10*) polymorphisms have been identified as a biomarker causally associated with occurrence of irritable bowel syndrome (IBS) and receives extensive interest. However, its relationship with IBS remains obscure. In this paper, after combing the data from 8 case-control studies with 928 cases and 1363 controls, the authors found that the IL-10 rs1800870 confers susceptibility to the risk of IBS in Caucasian ethnicity, and the rs1800872 may associate with IBS risk in Asians. However, no significant associations are found between rs1800871 and IBS risk.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a type of functional gastrointestinal disorder that has a multi-factorial origin. The exact pathophysiology leading to the occurrence of IBS is largely unknown, although inflammatory reactions are believed to play an important role in its pathogenesis. In some animal studies, researchers have found that inflammatory responses can alter the function of gut smooth muscles, enteric nerves, and interstitial cells of Cajal[1-3]. Moreover, IBS patients show an increase in the number of inflammatory cells in the gut[4-6]. The clustering of IBS in families and the results from twin studies have also provided evidence for a role of hereditary factors in the propensity of developing IBS[7,8].

Cytokines are important modulators of immune responses and inflammatory reactions and play a central role in intestinal inflammation[9]. The production of cytokines can be affected by genetic polymorphisms within the coding and promoter regions of cytokine genes[10,11]. Therefore, a genetic predisposition for the high or low production of a particular cytokine may affect disease susceptibility and clinical outcome[12,13]. Interleukin 10 (IL-10), also known as a human cytokine synthesis inhibitory factor, is an anti-inflammatory cytokine capable of inhibiting the synthesis of proinflammatory cytokines, such as interferon-γ, IL-2, IL-3, and tissue necrosis factor-α, which are produced by macrophages and regulatory T-cells[14]. Several studies have shown that serum IL-10 levels are significantly lower in IBS patients than in normal controls, suggesting that altered IL-10 levels may be involved in the pathogenesis of IBS and may be an IBS biomarker[15-17].

Some reports[18-21] have also indicated a significant association between *IL-10* polymorphisms and IBS risk; however, other studies[13,22-24] have failed to find such associations. Generally, this disparity may be partly due to ethnic differences or to the limited numbers of subjects involved in the studies. Therefore, the relationship between IBS risk and *IL-10* polymorphisms is not confirmed and needs further study with a large, genetically homogenous sample. The current study is a comprehensive meta-analysis performed to further evaluate the associations between *IL-10* polymorphisms and the risk of IBS.

MATERIALS AND METHODS

Search strategy and study selection

All methods were based on the guidelines proposed by the Human Genome Epidemiology Network for systematic reviews of genetic association studies, and followed the PRISMA guidelines[25]. A systematic literature search was performed using PubMed, Embase, the Cochrane Library, Google Scholar databases, Chinese National Knowledge Infrastructure (CNKI), and conference abstracts to identify published studies evaluating genetic association between *IL-10* polymorphisms and IBS risk published prior to August 2013; letters and abstracts were included. The Medical Subject Headings and text words used for the search were "interleukin-10" or "IL-10", "polymorphism," and "irritable bowel syndrome" or "IBS". Search results were limited to human studies. All languages were searched, and the retrieved articles were translated, when necessary. The references of the identified publications were searched for additional studies, and the MEDLINE option for searching for related articles was used to examine all relevant articles.

Inclusion and exclusion criteria

Studies were included if they (1) examined the association between *IL-10* polymorphisms and IBS risk; (2) had a case-control design; and (3) contained sufficient information on genotype frequency. To achieve adequate statistical power, only single-nucleotide polymorphisms (SNPs) reported in > 2 publications were selected. For studies describing results from the same or overlapping groups of subjects or controls, but reported in > 1 publication, only the largest published data set was included.

Studies were excluded if they did not evaluate the association between *IL-10* polymorphisms and the risk of IBS or if the genotype and allele frequency was inadequately reported, and such data could not be obtained by contacting the authors. Studies reporting associations with SNPs described by fewer than 3 publications were also excluded. In the event of duplicate publications, the smaller data set was excluded.

Data extraction

Two investigators independently extracted data from the identified publications, including the first author's name, year of publication, source of publication, diagnostic criteria for IBS, method of genotyping, number of cases and controls, genotype frequency, and allele frequency. Discrepancies in data extraction were resolved by repeating the study review and discussing the results.

Statistical analysis

Associations found with the allele contrast, codominant, dominant, and recessive models were analyzed. The strengths of the associations between *IL-10* polymorphisms and risk of IBS were estimated using odds ratios (OR) with 95% confidence interval (CI). We assessed the heterogeneity among the studies using the Cochran's Q-test. We also calculated the inconsistency index I^2 to quantify heterogeneity[26]. A fixed effects model ($P > 0.05$) was used to pool the results if a heterogeneity test was not significant, otherwise a random-effects model was

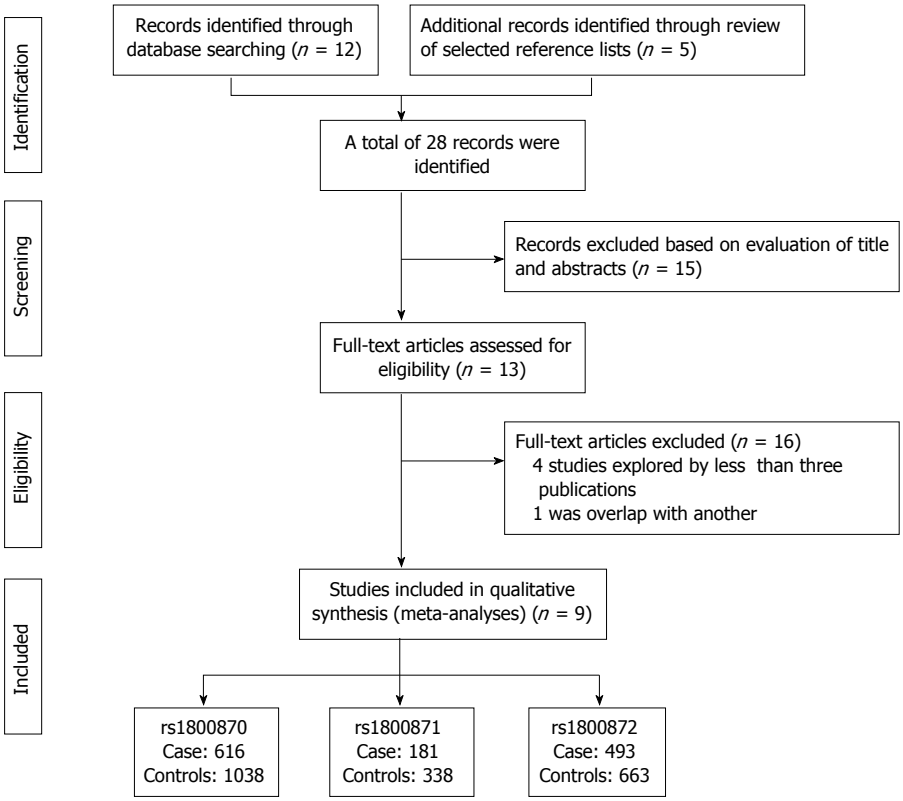


Figure 1 Flow chart of study selection.

used ($P < 0.05$)[27,28]. Subgroup analyses were performed to investigate narrower subsets of studies.

A Hardy-Weinberg equilibrium (HWE) was applied to the control population to evaluate data quality. The HWE analysis for genotype distribution among control populations was performed using a Chi-squared test. Further, a sensitivity analysis was performed to exclude studies that were not in HWE[29]. An asymmetric plot was used to suggest possible publication biases. Publication bias was examined using the Begg's and Egger's tests for each SNP publication[30,31]. All statistical tests were two-sided, and a P value < 0.05 was considered statistically significant. STATA, version 11.2 (Stata, College Station, TX, United States), was used for all statistical analyses.

RESULTS

Study selection process

The initial search yielded 28 studies; 15 were excluded because they were review articles, animal studies, or non-case-control design studies. After screening the full text of the remaining 13 studies, an additional 5 studies were excluded; of these, 4 explored SNPs reported by < 3 studies and one[19] did not provide sufficient genotype frequency data, even after contacting the original authors. Thus, a total of 8 case-control studies[18-24,32], involving 928 cases and 1363 controls, were included in the present meta-analysis. The studies analyzed 3 *IL-10* SNPs, rs1800870 (1082 A/G), rs1800871 (819 C/T), and rs1800872 (592 A/C). Figure 1 provides a summary of the selection process.

Characteristics of included studies

One study selected IBS patients using the Rome I criteria, 3 used the Rome II criteria, and the other 4 studies used the Rome III criteria. Patients from 4 studies[18-21] were Caucasians, and 4 studies involved Asians[22-24,32]. The characteristics of the 8 studies and the results of the HWE test for the distribution of the genotype in the control population are shown in Table 1.

IL-10 rs1800870 and IBS risk

Seven studies[13,18,20-24], involving 616 IBS subjects and 1038 controls, analyzed the association between the *IL-10 rs1800870* polymorphism and IBS risk. The distribution of the controls in 2 studies[20,21] deviated from the HWE. Overall, the GG+GA *vs* AA (OR = 0.80, 95%CI: 0.66-0.96, $P = 0.018$) and AA+GA *vs* GG (OR = 0.68, 95%CI: 0.52-0.90, $P = 0.007$) models presented a decreased risk of IBS. Little heterogeneity was found in the AA+GA *vs* GG model ($I^2 = 0.0\%$, $P = 0.542$) by the I^2 test and Q-test; however, there was significant heterogeneity in the GG+GA *vs* AA ($I^2 = 79.4\%$, $P = 0.000$) model. There were no significant associations between the GG *vs* AA ($P = 0.523$) and G *vs* A ($P = 0.892$) models and IBS risk. Egger's and Begg's tests suggested little publication bias in the 4 models (all, $P > 0.05$) (Table 2, Figure 2A). In the sensitivity analysis, after removing 2 studies[20,21] in which the controls deviated from the

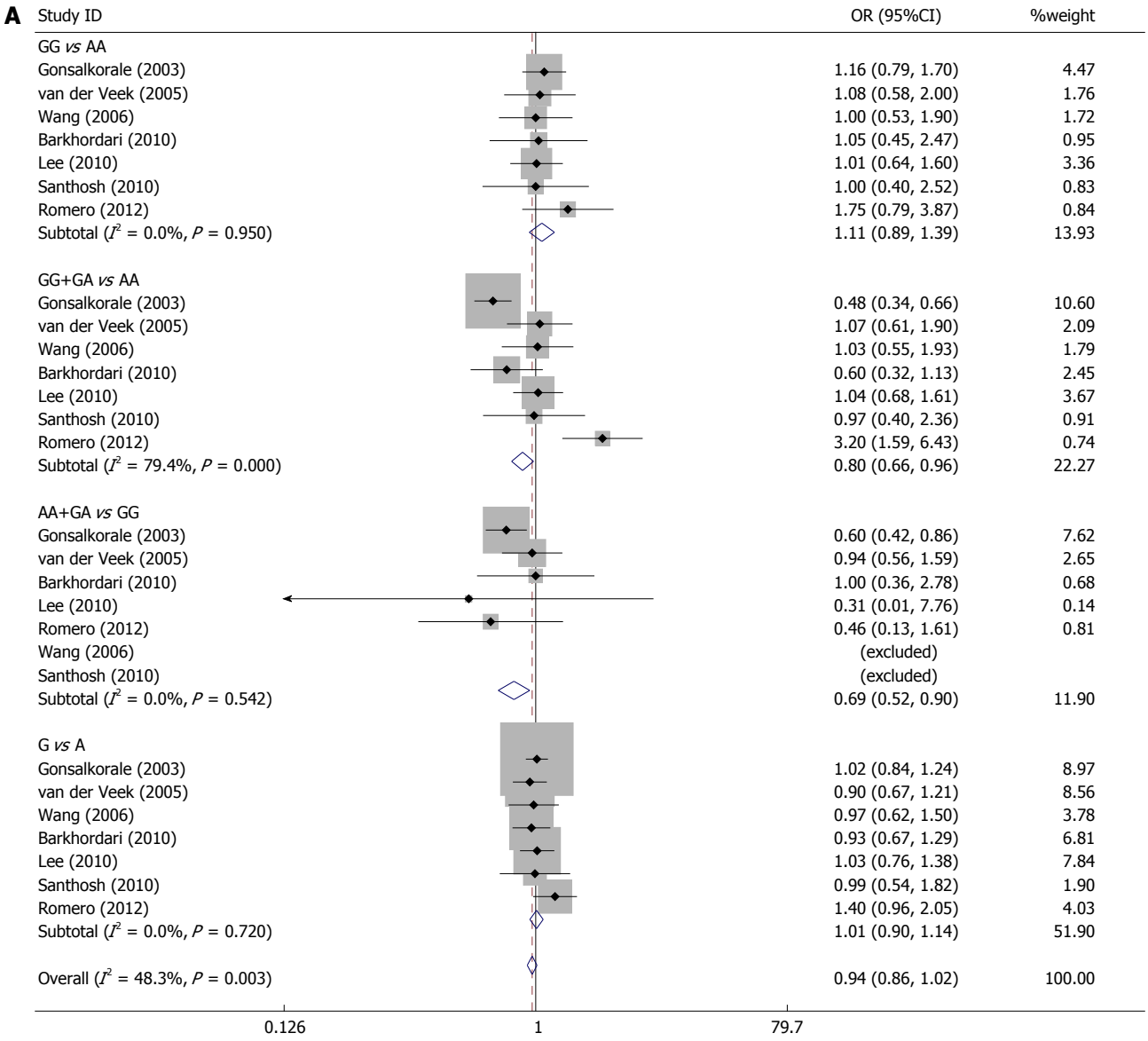
Table 1 Characteristic of individual studies in the meta-analysis

Ref.	Year	Country/ethnicity	SNP of *IL-10*	IBS/controls	Genotyping methods	Diagnostic criteria	HWE of control
Gonsalkorale *et al*[21]	2003	United Kingdom	rs1800870	230/450	PCR-SSP	RomeI	0.000
van der Veek *et al*[13]	2005	Netherlands	rs1800870	111/128	PCR-RFLP	Rome Ⅱ	0.707
Wang *et al*[24]	2006	China	rs1800870	43/41	PCR-RFLP	Rome Ⅱ	0.678
Barkhordari *et al*[18]	2010	Iran	rs1800870	70/140	PCR-SSP	Rome Ⅲ	0.041
Lee *et al*[22]	2010	South Korea	rs1800870	94/88	PCR-RFLP	Rome Ⅲ	0.707
Santhosh *et al*[23]	2010	Indian	rs1800870	23/20	PCR-SSP	Rome Ⅱ	0.717
Romero-Valdovinos *et al*[20]	2012	Mexico	rs1800870	45/173	PCR-RFLP	Rome Ⅲ	0.000
Wang *et al*[24]	2006	China	rs1800871	43/41	PCR-RFLP	Rome Ⅱ	0.619
Barkhordari *et al*[18]	2010	Iran	rs1800871	70/140	PCR-SSP	Rome Ⅲ	0.907
Santhosh *et al*[23]	2010	China	rs1800871	23/20	PCR-SSP	Rome Ⅱ	0.662
Romero-Valdovinos *et al*[20]	2012	Mexico	rs1800871	45/173	PCR-RFLP	Rome Ⅲ	0.920
Wang *et al*[24]	2006	China	rs1800872	43/41	ARMS-PCR	Rome Ⅱ	0.619
Barkhordari *et al*[18]	2010	Iran	rs1800872	70/140	PCR-RFLP	Rome Ⅲ	0.97
Jiang *et al*[32]	2010	China	rs1800872	312/325	PCR-SSP	Rome Ⅲ	0.255
Santhosh *et al*[23]	2010	Indian	rs1800872	23/20	PCR-SSP	Rome Ⅱ	0.438
Romero-Valdovinos *et al*[20]	2012	Mexico	rs1800872	45/173	PCR-RFLP	Rome Ⅲ	0.018

SNP: Single nucleotide polymorphism; HWE: Hardy-Weinberg equilibrium; IBS: Irritable bowel syndrome; PCR: Polymerase chain reaction; SSP: Sequence specific primer; RFLP: Restriction fragment length polymorphism; ARMS: Amplification refractory mutation system.

Table 2 Summary odds ratios of polymorphisms with irritable bowel syndrome risk

	P value	OR (95%CI)	I^2	*P* heterogeneity	Begg' test	Egger test
rs1800870						
GG *vs* AA	0.338	1.11 (0.89-1.39)	0.0%	0.950	1.000	0.694
Caucasian[13,18,20,21]	0.228	1.19 (0.90-1.58)	0.0%	0.776		
Asian[22-24]	0.963	1.01 (0.71-1.42)	0.0%	0.999		
GG+GA *vs* AA	0.018	0.80 (0.66-0.96)	79.4%	0.000	1.000	0.200
Caucasian	0.003	0.70 (0.55-0.89)	88.5%	0.000		
Asian	0.860	1.03 (0.74-1.43)	0.0%	0.990		
AA+GA *vs* GG	0.007	0.68 (0.52-0.90)	0.0%	0.542	1.000	0.899
Caucasian	0.008	0.69 (0.52-0.91)	0.0%	0.415		
Asian	0.478	0.31 (0.01-7.76)	-	-		
G *vs* A	0.815	1.01 (0.90-1.14)	0.0%	0.720	0.764	0.773
Caucasian	0.799	1.02 (0.89-1.16)	17.1%	0.306		
Asian	0.976	1.00 (0.80-1.260	0.0%	0.974		
rs1800871						
AA *vs* GG	0.698	0.90 (0.53-1.54)	0.0%	0.440	0.308	0.326
Caucasian[18,20]	0.205	0.56 (0.23-1.37)	22.6%	0.255		
Asian[23,24]	0.530	1.25 (0.62-2.54)	0.0%	0.969		
AA+GA *vs* GG	0.969	0.99 (0.61-1.60)	32.4%	0.218	0.308	0.146
Caucasian	0.182	0.58 (0.26-1.29)	0.0%	0.365		
Asian	0.252	1.45 (0.77-2.76)	0.0%	0.364		
GG+GA *vs* AA	0.651	0.92 (0.64-1.33)	0.0%	0.720	0.734	0.080
Caucasian	0.985	1.00 (0.68-1.49)	0.0%	0.906		
Asian	0.219	0.54 (0.20-1.45)	0.0%	0.967		
A *vs* G	0.496	1.09 (0.85-1.38)	0.0%	0.809	1.000	0.924
Caucasian	0.939	1.01 (0.75-1.37)	0.0%	0.631		
Asian	0.314	1.23 (0.83-1.82)	0.0%	0.671		
rs1800872						
CC *vs* AA	0.989	1.00 (0.77-1.19)	0.0%	0.456	0.806	0.506
Caucasian[18,20]	0.379	0.73 (0.37-1.47)	41.6%	0.191		
Asian[23,24,32]	0.730	1.05 (0.80-1.38)	0.0%	0.466		
CC+CA *vs* AA	0.028	1.29 (1.03-1.62)	0.0%	0.717	0.221	0.196
Caucasian	0.417	1.27 (0.71-2.26)	0.0%	0.573		
Asian	0.042	1.29 (1.01-1.66)	0.0%	0.410		
AA+CA *vs* CC	0.833	0.97 (0.72-1.31)	60.2%	0.040	0.806	0.384
Caucasian	0.578	1.13 (0.72-1.71)	3.2%	0.310		
Asian	0.382	0.82 (0.53-1.27)	76.0%	0.016		
C *vs* A	0.112	1.12 (0.97-1.28)	0.0%	0.863	0.086	0.266
Caucasian	0.614	1.12 (0.97-1.28)	0.0%	0.669		
Asian	0.114	1.14 (0.97-1.33)	0.0%	0.618		



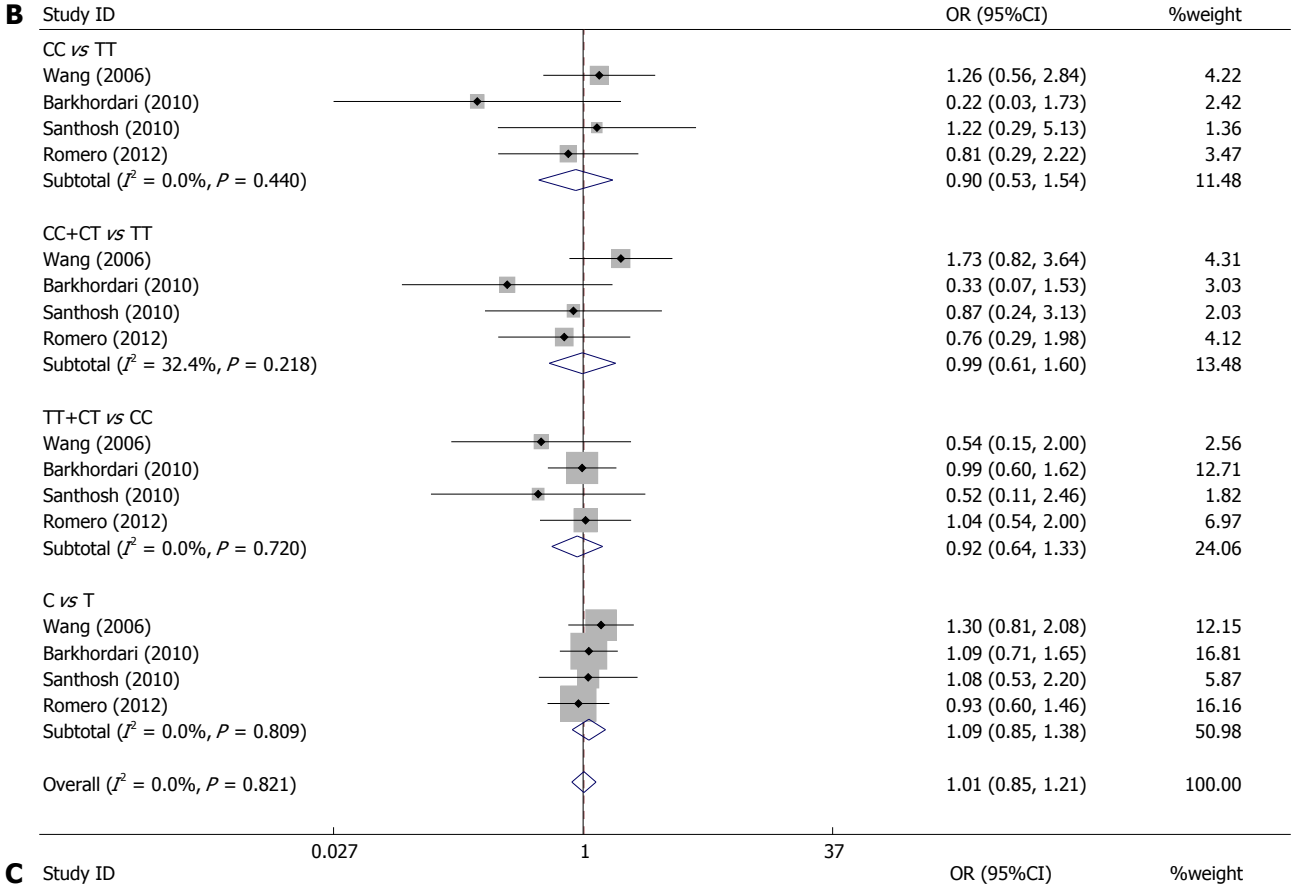
HWE, significant associations with the GG+GA *vs* AA model were no longer observed, and the heterogeneity became negligible (data not shown); the associations remained for the AA+GA *vs* GG (OR = 0.69, 95%CI: 0.52-0.91, P = 0.008) model. Subgroup analysis revealed associations between the *IL-10 rs1800870* polymorphisms and IBS risk in Caucasians[18,20,21] (P = 0.003), but not in Asians[22-24] (P = 0.860) (Table 2).

IL-10 rs1800871 and IBS risk

Four studies[18,20,23,24], involving 493 IBS subjects and 663 controls, analyzed the associations between the *IL-10 rs1800871* polymorphisms and IBS risk; the distribution of controls in the studies fulfilled the HWE. In the meta-analysis, no significant associations were observed for any of the 4 models: AA *vs* GG (P = 0.698), AA+AG *vs* GG (P = 0.969), GG+AG *vs* AA (P = 0.651), and A *vs* G (P = 0.496). Either significant heterogeneity or publication bias was found associated with each of the 4 models (all, P > 0.05). A sensitivity analysis, after excluding studies in turn, indicated that the null associations remained (data not shown). Further, subgroup analyses did not find any associations between the *IL-10 rs1800871* polymorphisms and IBS risk, regardless of ethnicity[18,20,23,24] (Table 2, Figure 2B).

IL-10 rs1800872 and IBS risk

Five studies[18,20,23,24,32], involving 181 IBS subjects and 338 controls, analyzed the associations between IL-10 rs1800872 polymorphisms and IBS risk; the distribution of the controls in the studies fulfilled the HWE. The meta-analysis demonstrated that the CC+CA *vs* AA model was associated with susceptibility to IBS (OR = 1.29, 95%CI: 1.03-1.62, P = 0.028). However, significant associations were not found between the other 3 models, CC *vs* AA (P = 0.989), AA+CA *vs* CC (P = 0.833), and C *vs* A (P = 0.112), and IBS risk. Either significant heterogeneity or publication bias was found in each of the 4 models (all, P > 0.05). A sensitivity analysis, after removing each study sequentially, demonstrated that the results remained similar to the initial results. Subsequent subgroup analyses showed associations between rs1800872 and IBS risk



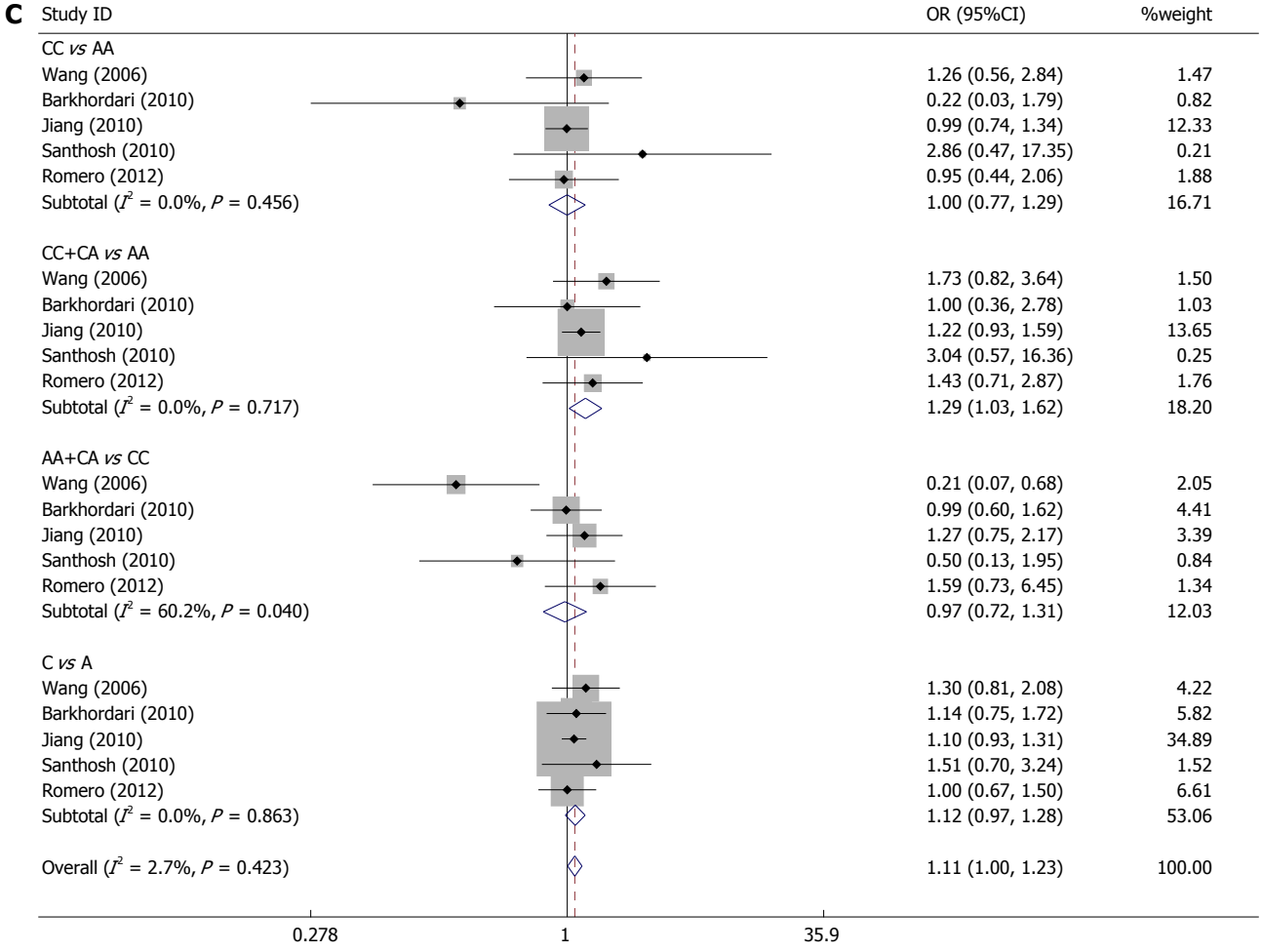


Figure 2 Meta-analysis. A: Interleukin-10 (*IL-10*) *rs1800870* polymorphisms and irritable bowel syndrome risk; B: *IL-10 rs1800871* polymorphisms and IBS risk; C: *IL-10 rs1800872* polymorphisms and IBS risk.

in Asians[23,24,32] (P = 0.042), but not in Caucasians[18,20] (P = 0.417) (Table 2, Figure 2C).

DISCUSSION

The gene encoding IL-10 is located on chromosome 1q31-1q32, and has 3 confirmed biallelic polymorphisms in the promoter region, *i.e.*, rs1800870, rs1800871, and rs1800872. A genetic predisposition for low IL-10 production is associated with the development of IBS[33-35], and previous studies have shown that IL-10 SNPs and some haplotypes are associated with an increased IBS risk[5,13,18,23]. Likewise, production of the anti-inflammatory cytokine IL-10 is also associated with SNPs at specific positions.

The A allele of rs1800870 has been reported to be associated with lower production of IL-10 and an accordingly stronger inflammatory response[36]. More recently, Bashashati *et al*[37] reported the results of a meta-analysis that showed that the A/G of rs1800870 conferred susceptibility to IBS. However, their study only included 5 studies, and most of the included subjects were Caucasians. When considering the disparity in genetic factors among different racial groups, it is difficult to conclude that rs1800870 was associated with IBS risk, without adjusting for ethnicity and sample size. In the present study, although the overall meta-analysis results showed the presence of significant associations between rs1800870 and IBS risk in the GG+GA *vs* AA (P = 0.018) and AA+GA *vs* GG (P = 0.007) models, a subgroup analysis revealed that such association existed only for Caucasians, and not for Asians. This disparity between the two ethnicities might be explained by variations in allelic frequencies between the ethnic groups. This was possible since the frequency of the rs1800870 A allele is associated with significantly higher production of IL-10 in Caucasians than in Asians. Moreover, another study showed that the frequency of the high producer *IL-10* genotype is much higher in the Irish population than in Africans or Singaporean Chinese[38]. In the present study, 4[13,18,20,21] of the 8 included studies analyzed Caucasian subjects, and the frequency of the *rs1800870 GG* genotype in controls was higher than that observed in Asian subjects. The present meta-analysis results confirmed the association of rs1800870 and IBS risk, but also demonstrated that the association varies according to ethnicity.

The role of rs1800871 in IL-10 production is incompletely understood. Although some studies have reported that rs1800871 is associated with several diseases, such as endometriosis[39] and periodontitis[40], the association between rs1800871 and IBS has remained controversial[18,20,23,24]. In our study, the overall results and the results of the subgroup analysis failed to show a significant association between rs1800871 and IBS risk, regardless of the examined ethnicity. This observation indicates similar distribution of rs1800871 among both IBS patients and controls, supporting the observation that the genetic make-up for IL-10 production levels does not differ between IBS patients and normal subjects[13,18,24]. Although a direct link between rs1800871 and IL-10 production levels has not been established, previous reports have suggested that rs1800871 polymorphisms are in linkage disequilibrium with rs1800871 polymorphisms; that the haplotypes for rs1800870, rs1800871 and rs1800872 are common in Caucasians; and that the GCC/GCC haplotypes are commonly associated with high IL-10 production, whereas the *ATA/ATA* genotype is associated with low IL-10 production[41]. Because only limited data are available in the included studies, further studies are required to perform a haplotype analysis to explore the associations between rs1800871 haplotypes and other SNPs with IBS.

With regard to rs1800872, studies have reported that the presence of rs1800872 confers susceptibility to some diseases such as leprosy[42] and hepatocellular carcinoma[43]. In studies investigating the association of IL-10 with IBS risk, Santhosh *et al*[23] reported that the C allele was much lower in individuals with IBS than among normal controls (41.3% *vs* 73.5%), in an Indian population. Wang *et al*[24] found similar results in a Chinese population (IBS *vs* controls, 9.3% *vs* 17.1%). However, a Mexican study[18] failed to show a significant difference between IBS patients and normal controls with respect to the C allele (72.51% *vs* 71.1%); similar results were reported in 2 other studies[19,20]. In the present meta-analysis, we found that CC+CA *vs* AA was associated with an increased IBS risk, and the sensitivity analysis further confirmed this association. However, the subgroup analysis revealed that only Asians demonstrated this association. Although 5 studies were included in the present analysis, the sample size was relatively small; hence, these results should be interpreted with caution.

The present comprehensive meta-analysis demonstrated an association between *rs1800871* and *rs1800872* polymorphisms and IBS risk, and that the *rs1800872* polymorphism conferred susceptibility to IBS. In addition, although Bashashati *et al*[37] reported a meta-analysis demonstrating that rs1800870 conferred susceptibility to IBS, we expanded this finding to show that this association existed in Caucasians but not in Asians, which had not been previously reported. The present study also involved a sensitivity analysis demonstrating that the distribution of controls deviated from the HWE, guaranteeing the reliability of the results. The Begg's and Egger's test results did not show a significant publication bias in the eligible as well as the non-English studies, which also attests to the robustness of the results.

Some limitations to this meta-analysis require careful consideration. First, because only limited data were available, we did not analyze the association between *IL-10* polymorphisms and different types of IBS, *e.g.*, diarrhea or constipation. Thus, the associations between different types of IBS require further investigation. Second, other factors such as genetic and environmental factors, which also may affect susceptibility to IBS, were not adjusted in the present studies. Hence, a well-designed study is warranted to account for potential confounders and to provide a more precise association. Third, also because

of the limited number of available studies, the subgroup analysis of rs1800872 involved comparatively few studies; thus, its association with IBS needs to be confirmed by a study involving a larger number of subjects.

In conclusion, the present meta-analysis suggests that the *rs1800870* polymorphism of IL-10 may represent an increased risk of IBS in Caucasians, but not in Asians. Similarly, *rs1800872* polymorphisms may represent an increased risk of IBS in Asians, but future studies are necessary to reinforce these findings. The present study failed to find an association between rs1800871 and IBS risk, regardless of ethnicity.

COMMENTS

Background

Cytokines are important modulators in the immune responses and inflammatory reaction, which play a central role in intestinal inflammation.

Research frontiers

Interleukin-10 (*IL-10*) polymorphisms have been identified as a biomarker causally associated with occurrence of irritable bowel syndrome (IBS) and receives extensive interest. However, its relationship with IBS remains obscure.

Innovations and breakthroughs

This is the first paper conducting a comprehensive meta-analysis to investigate the association of *IL-10* polymorphisms with IBS risk. The authors showed that IL-10 rs1800870 is associated with IBS risk in Caucasian ethnicity, and rs1800872 associate with IBS risk in Asians.

Applications

This study furthers the understanding of the association of *IL-10* polymorphisms with IBS risk.

Peer review

The study deals with the important topic related to the association between single nucleotide polymorphisms of genes coding for inflammation-linked factors with pathogenesis of chronic inflammatory diseases such as IBS.

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