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Association between IL-1β polymorphisms and gastritis risk

A meta-analysis

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Abstract

Background: *Helicobacter pylori (H. pylori)* infection of the human stomach regularly leads to chronic gastric inflammation. The cytokine gene interleukin (IL)-1β has been implicated in influencing the pathology of inflammation induced by *H. pylori* infection. Currently, several studies have been carried out to investigate the association of *IL-1β-511* (rs16944) and *IL-1β-31* (rs1143627) polymorphisms with gastritis risk; however, the results are inconsistent and inconclusive. To assess the effect of *IL-1β* polymorphisms on gastritis susceptibility, we conducted a meta-analysis.

Methods: Up to March 15, 2016, 2205 cases and 2289 controls were collected from 12 published case–control studies. Summarized odds ratios and corresponding 95% confidence intervals (CIs) for *IL-1β-511* and *IL-1β-31* polymorphisms and gastritis risk were estimated using fixed- or random-effects models when appropriate. Heterogeneity was assessed by chi-squared-based Q-statistic test, and the sources of heterogeneity were explored by subgroup analyses and logistic meta-regression analyses. Publication bias was evaluated by Begg funnel plot and Egger test. Sensitivity analyses were also performed.

Results: The results provided evidences that the single nucleotide polymorphisms (SNPs) in *IL-1β-31* might be associated with the gastritis risk, especially in the Caucasian population, while SNPs in the *IL-1β-511* might not be.

Conclusion: Our studies may be helpful in supplementing the disease monitoring of gastritis in the future, and additional studies to determine the exact molecular mechanisms might inspire interventions to protect the susceptible subgroups.

Abbreviations: CI = confidence interval, HWE = Hardy–Weinberg equilibrium, IL = interleukin, OR = odds ratio, PCR = polymerase chain reaction.

Keywords: gastritis, IL-1β, polymorphism, risk assessment, single nucleotide

1. Introduction

Helicobacter pylori (*H. pylori)* infection of the human stomach regularly leads to chronic gastric inflammation. This infection first induces chronic superficial (nonatrophic) gastritis, which can progress through chronic atrophic gastritis, and finally toward gastric carcinoma. However, many *H. pylori* colonized individuals never develop these pathologies, implying that besides bacterial factors, genetic characteristics of the host as well as the environmental factors may be involved in the gastric pathological course.[1,2]

Epidemiological studies have indicated that the inflammation induced by *H pylori* infection was regulated by several interleukins (ILs), including proinflammatory cytokine *IL-1β*. *IL-1β* acts as an inhibitor of gastric acid secretion and plays important roles in initiating and amplifying the inflammatory responses to *H pylori* infection, yet finally allowing expansion of *H pylori* colonization from the gastric antrum to the corpus, leading to further progression of severe atrophic gastritis.[3]

Two allelic variants *IL-1β-511* (rs16944) and *IL-1β-31* (rs1143627) locate in the promoter region of the *IL-1β* gene, and they have been proved to affect the expression level of *IL-1β*.[4] Currently, several studies have been carried out to investigate the association between *IL-1β* promoter polymorphisms and gastritis risk; however, the results are inconsistent and inconclusive.[5–8]

Until recently, there has been no meta-analysis assessing the association between *IL-1β* promoter polymorphisms and gastritis risk. Therefore, we carried out a meta-analysis on all published case–control studies to estimate the overall gastritis risk of *IL-1β-511* and *IL-1β-31* polymorphisms and to investigate heterogeneity between the individual studies as well as the existence of potential publication bias. The association between *IL-1β* promoter polymorphisms and gastritis risk in *H pylori* infected patients was also evaluated.

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2. Materials and methods

This study was carried out in accordance with the checklist proposed by Systematic Review and Meta-Analysis (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

2.1. Selection of published studies

We searched the MEDLINE and Embase databases (the last search on March 15, 2016) using Pubmed and Ovid search engines for all articles on the association between *IL-1β* gene polymorphisms and gastritis risk. The following terms were used: "IL-1β, or IL-1β or IL-1 beta" and "gastritis" and "polymorphism or variant or variation." Additional eligible studies were identified by hand searching of references of retrieved articles. For inclusion, a study had to meet the following criteria: it had to be a case–control or case–cohort study; the study evaluated the association between *IL-1β-511* and/or *IL-1β-31* polymorphisms and gastritis risk; original data for odds ratios (ORs) calculation was reported; and records were published in English. The major exclusion criteria were as follows: not a case–control study;[4,9,10] no original data available for ORs.[11,12] The publication that was a deviation from Hardy–Weinberg equilibrium (HWE) was excluded.[13–15] The publication year of eligible studies ranged from 2002 to 2014. No contacts with authors were carried out.

A total of 69 relevant articles were retrieved from MEDLINE database. After title and abstract screening, 49 publications which did not investigate the association between gastritis risk and the polymorphisms of interest were excluded; and then, the remaining 20 publications were carefully reviewed according to the criteria described in "Section 2." Another 6 publications were further removed, among which, 1 publication was not a case–control study,[9] 4 had no original data for ORs,[7,12,16,17] and 1 did not evaluate the association between *IL-1β-511* and/or *IL-1β-31* polymorphisms and gastritis risk.[11] After the evaluation of deviation from HWE, 2 studies were removed because of deviation from HWE in controls[13,15] (Fig. S1, http://links.lww.com/MD/B536). Finally, 12 case–control studies were included in this meta-analysis, including 2205 cases and 2289 controls.[8,18–28] Among them, 8 articles studied the association between the *IL-1β-31* polymorphism and gastritis risk, and 12 articles studied the association between the *IL-1β-511* polymorphism and gastritis risk. Ethical approval and informed patient consent was not required as this study was a literature review and had no direct patient contact or influences on patient care.

2.2. Data extraction

Two investigators (XS and ZL) independently extracted the following data: the first author's name, year of publication, country of the first author, patient ethnicity, source of control groups, numbers of cases and controls, genotyping methods, matching variables, minor allele frequency in controls, and the number of *H pylori* infected persons. A 3rd investigator (SL) checked the data further and solved the inconsistency, if any, through discussion together. Different ethnicity descents were categorized as Asian, Caucasian, and mixed (Mexico) populations.

2.3. Quality score assessment

The quality of included studies were assessed using the Newcastle–Ottawa Scale.[29] A "☆" rating system was used to judge the quality of the included studies. The score of each study was ranked by the total number of "☆" given. WY and GD assessed the quality of the studies independently, and the inconsistencies were resolved in a consensus meeting with all authors. Studies with a score ≥5 were considered to be of high quality.

2.4. Statistical analysis

Deviation from HWE in the control group was examined by χ^2 test. $P < 0.05$ was considered to be statistically significant. The strength of relationship association between *IL-1β* polymorphisms and gastritis risk was assessed using the pooled OR with 95% confidence intervals (CIs). The significance of the pooled OR was determined using the Z test, with $P < 0.05$ considered statistically significant. We evaluated the risk using the allele model, the homozygous model, the heterozygous model, the dominant model, and the recessive model. The statistical heterogeneity within studies was detected with the Chi-squared based Q test and I^2 metric (0%–25%, no heterogeneity; 25%–50%, moderate heterogeneity; 50%–75%, large heterogeneity; and 75%–100% extreme heterogeneity). When $P > 0.05$ or $I^2 < 50\%$, the fixed-effects model was used (the DerSimonian and Laird method). Otherwise, the random-effects model was selected (the Mantel–Haenszel method). If any apparent heterogeneity existed, logistic meta-regression would be used to explore the sources of heterogeneity: ethnicities, genotyping methods (if one method contains only one study, it was merged into the "other" group), source of control (hospital-based studies and population-based studies), and sample size (<200 and ≥200 subjects). Subgroup analysis based on ethnicity, source of controls, genotype method was performed. Funnel plots and Egger linear regression were used to evaluate publication bias. Sensitivity analyses were performed to assess the stability of the results by excluding one study at a time. All analyses were done using STATA software, version 10.0 (STATA Corp., College Station, TX). All graphs were obtained also by STATA software. All the *P* values were 2-sided.

3. Results

3.1. Characteristics of studies

We identified 12 articles using the above search terms, including 2205 cases and 2289 controls, concerning *IL-1β-511* and/or *IL-1β-31* polymorphisms of *IL-1β* gene and gastritis risk. The study characteristics were summarized in Tables 1 and 2. There were 6 studies of Caucasian descendents, 5 studies of Asian descendents, and 1 mixed population of Mexican descendents. Several genotyping methods were used, including Taq-Man, polymerase chain reaction (PCR)-restriction fragment length polymorphism, pyrosequencing, Taqman, dual fluorescence PCR, Single Strand Conformation Polymorphism Analysis of PCR Products, and primer extension and mass spectrometry. Nevertheless, only 25% (3/12) of these studies included described genotyping quality control measures, such as blindness to the case–control status, a different genotyping assay to confirm the data, and random repetition of a portion of samples.

The study quality was assessed using the Newcastle–Ottawa Scale. Most studies scored 5, with all studies being of high quality in terms of selection and exposure. However, on comparability, only 3 studies included cases comparable with the controls (Supplementary Table S1, http://links.lww.com/MD/B536).

Table 1

Characteristics of literatures on IL-1β-31 polymorphism included in the meta-analysis.

Reference	Country of first author	Ethnicity	Source of control	Sample size (case/control)	*H. pylori* infected cases (case/control)	Genotyping methods	Matching criteria	C allele frequency in controls	Case–control study
Furuta, 2002[18]	Japan	Asian	HB	264/227	264/0	PCR-RFLP	—	0.464	Yes
Sugimoto, 2006[21]	Japan	Asian	PB	164/172	164/0	PCR-RFLP	—	0.497	Yes
Ryberg, 2008[24]	Sweden	Caucasian	–	12/16	11/0	Pyrosequencing	–	0.312	Yes
Cheng, 2010[25]	Taiwan	Asian	PB	154/176	64/65	PCR-RFLP	–	0.423	Yes
Martínez-Carrillo, 2010[26]	Mexico	Mixed	HB	100/102	91/64	PCR-RFLP	–	0.716	Yes
Li, 2010[27]	China	Asian	PB	81/64	–	Dual fluorescence PCR	–	0.478	Yes
Wex, 2010[28]	Germany	Caucasian	HB	142/94	122/61	RFLP or by primer extension and mass spectrometry	–	0.320	Yes
Kulmambetova, 2014[8]	Kazakhstan	Caucasian	HB	301/246	216/0	Sequencing	–	0.449	Yes

HB = hospital-based, PB = population-based, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.

3.2. Quantitative synthesis

The mean frequencies of minor allele in controls varied between different populations. The mean frequency of *IL-1β-31C* allele was 0.47 for Asian, 0.36 for Caucasian, and 0.72 for Mexican. The mean frequency of *IL-1β-511T* allele was 0.47 for Asian, 0.35 for Caucasian, and 0.71 for Mexican (Tables 1 and 2).

The evaluations of the association of *IL-1β-31* polymorphism with gastritis risk are shown in Table 3. There was no evidence of any association between *IL-1β-31* polymorphism and gastritis risk in overall analysis under any genetic comparisons (Table 3). However, when stratified by ethnicity, significantly elevated risks were observed in the Caucasian population in 3 genetic comparisons (C vs T: OR = 1.24, 95% CI 1.01–1.51; CC vs TT: OR = 1.60, 95% CI 1.05–2.44; recessive model: OR = 1.44, 95% CI 1.00–2.06), while no associations were found in any comparison models in the Asian population. Interestingly, decreased risk was observed in the mixed population (C vs T: OR = 0.53, 95% CI 0.35–0.80; CC vs TT: OR = 0.28, 95% CI 0.11–0.73; recessive model: OR = 0.43, 95% CI 0.24–0.77) (Table 3 and Fig. 1). Hence, the limitation of this study must be considered, as there is only one study with a mixed population, which only provided 100 cases and 102 controls. No associations were found in any comparison when stratified by source of control or genotype method.

No significant association was found between *IL-1β-511* polymorphism and gastritis risk in overall analyses or any subgroup analyses (Supplementary Table S2, http://links.lww.com/MD/B536).

The data of patients infected with *H pylori* were also extracted. The evaluations of the association of *IL-1β-31* or IL-1β-511 polymorphisms with gastritis risk were carried out between *H pylori* infected patients and control groups[8,18,20,21,24,25] or *H pylori* noninfected controls.[8,18,20,21,24,25] No significant association was found in any comparison model of either polymorphism site.

Table 2

Characteristics of literatures on IL-1β-511 polymorphism included in the meta-analysis.

Reference	Country of first author	Ethnicity	Source of control	Sample size (case/control)	*H. pylori* infected cases (case/control)	Genotyping methods	Matching criteria	T allele frequency in controls	Case–control study
Furuta, 2002[18]	Japan	Asian	HB	264/227	264/0	PCR-RFLP	–	0.460	Yes
Machado, 2003[19]	Portugal	Caucasian	PB	221/306	218/300	PCR-SSCP	–	0.342	Yes
Li, 2006[20]	China	Asian	HB	129/264	–	PCR-RFLP	Age-, gender-	0.475	Yes
Sugimoto, 2006[21]	Japan	Asian	PB	164/172	164/0	PCR-RFLP	–	0.494	Yes
Lahner, 2008[22]	Italy	Caucasian	HB	110/110	110/55	Taqman	Age, gender	0.350	Yes
Gao, 2008[23]	Germany	Caucasian	PB	527/530	401/282	Pyrosequencing	5-year age, gender	0.315	Yes
Ryberg, 2008[24]	Sweden	Caucasian	–	12/16	11/0	Pyrosequencing		0.313	Yes
Cheng, 2010[25]	Taiwan	Asian	PB	154/176	64/65	PCR-RFLP	–	0.418	Yes
Martínez-Carrillo, 2010[26]	Mexico	Mixed	HB	100/102	91/64	PCR-RFLP	–	0.711	Yes
Li, 2010[27]	China	Asian	PB	81/46	–	Dual fluorescence PCR	–	0.478	Yes
Wex, 2010[28]	Germany	Caucasian	HB	142/94	122/61	RFLP or by primer extension and mass spectrometry	–	0.324	Yes
Kulmambetova, 2014[8]	Kazakhstan	Caucasian	HB	301/246	216/0	Sequencing	–	0.463	Yes

HB = hospital-based, PB = population-based, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, PCR-SSCP = Single Strand Conformation Polymorphism Analysis of Polymerase Chain Reaction Product.

Table 3

Stratified analyses of the IL-1β-31 polymorphism on gastritis risk.

	n*	Cases/controls	OR (95%CI)	P†	P (I^2)‡
Total	8	1218/1079			
C versus T			0.995 (0.82–1.21)§	0.958	0.020 (58.0%)
CC versus TT			1.03 (0.71–1.49)§	0.880	0.054 (49.4%)
TC versus TT			1.01 (0.83–1.23)	0.924	0.723 (0.00%)
CC/TC versus TT			1.03 (0.86–1.24)	0.735	0.267 (20.5%)
CC versus TT/TC			1.01 (0.74–1.36)§	0.976	0.057 (48.9%)
Ethnicity					
Asian	4	663/621			
C versus T			1.01 (0.86–1.18)	0.945	0.697 (0.00%)
CC versus TT			1.02 (0.74–1.40)	0.902	0.654 (0.00%)
TC versus TT			0.96 (0.74–1.25)	0.779	0.912 (0.00%)
CC/TC versus TT			0.98 (0.77–1.25)	0.875	0.815 (0.00%)
CC versus TT/TC			1.04 (0.79–1.37)	0.768	0.735 (0.00%)
Caucasian	3	455/356			
C versus T			**1.24 (1.01–1.51)**	0.037	0.405 (0.00%)
CC versus TT			**1.60 (1.05–2.44)**	0.028	0.609 (0.00%)
TC versus TT			1.16 (0.84–1.60)	0.360	0.413 (0.00%)
CC/TC versus TT			1.25 (0.93–1.70)	0.143	0.347 (5.6%)
CC versus TT/TC			**1.44 (1.00–2.06)**	0.049	0.832 (0.00%)
Mixed	1	100/102			
C versus T			**0.53 (0.35–0.80)**	0.002	–
CC versus TT			**0.28 (0.11–0.73)**	0.009	–
TC versus TT			0.58 (0.23–1.48)	0.257	–
CC/TC versus TT			0.42 (0.17–1.01)	0.053	–
CC versus TT/TC			**0.43 (0.24–0.77)**	0.004	–
Source of control					
PB	3	399/394			
C versus T			0.997 (0.82–1.22)	0.973	0.493 (0.00%)
CC versus TT			1.00 (0.67–1.51)	0.984	0.447 (0.00%)
TC versus TT			0.95 (0.68–1.32)	0.741	0.780 (0.00%)
CC/TC versus TT			0.96 (0.70–1.32)	0.815	0.634 (0.00%)
CC versus TT/TC			1.04 (0.73–1.47)	0.841	0.529 (0.00%)
HB	4	807/669			
C versus T			0.94 (0.67–1.32)§	0.737	0.003 (78.6%)
CC versus TT			0.95 (0.49–1.82)§	0.869	0.009 (74.0%)
TC versus TT			1.03 (0.80–1.31)	0.840	0.472 (0.00%)
CC/TC versus TT			0.99 (0.69–1.42)§	0.943	0.096 (52.8%)
CC versus TT/TC			0.95 (0.56–1.63)§	0.861	0.006 (75.6%)
Genotype method					
PCR-RFLP	3	582/575			
C versus T			1.01 (0.85–1.18)	0.954	0.488 (0.00%)
CC versus TT			1.02 (0.73–1.43)	0.907	0.444 (0.00%)
TC versus TT			0.95 (0.73–1.25)	0.718	0.805 (0.00%)
CC/TC versus TT			0.97 (0.75–1.26)	0.827	0.641 (0.00%)
CC versus TT/TC			1.05 (0.79–1.40)	0.732	0.539 (0.00%)
Sequencing	3	413/364			
C versus T			1.01 (0.48–2.11)§	0.987	0.001 (86.7%)
CC versus TT			0.96 (0.24–3.91)§	0.960	0.003 (83.0%)
TC versus TT			1.15 (0.80–1.64)	0.450	0.202 (37.5%)
CC/TC versus TT			1.05 (0.41–2.66)§	0.920	0.031 (71.2%)
CC versus TT/TC			0.92 (0.33–2.55)§	0.868	0.002 (83.8%)
Other	2	223/140			
C versus T			1.01 (0.74–1.38)	0.958	0.983 (0.00%)
CC versus TT			1.07 (0.55–2.09)	0.849	0.914 (0.00%)
TC versus TT			0.97 (0.61–1.55)	0.899	0.738 (0.00%)
CC/TC versus TT			0.99 (0.64–1.54)	0.964	0.815 (0.00%)
CC versus TT/TC			1.05 (0.58–1.92)	0.870	0.773 (0.00%)

CI = confidence interval, OR = odds ratio.

* Number of comparisons.

† *P* value of Z test for pooled OR. The OR values with statistical significance were shown in bold ($P < 0.05$).

‡ *P* value of Q test for heterogeneity test.

§ Random-effects model was used when *P* value for heterogeneity test <0.05; otherwise, fixed-effects model was used.

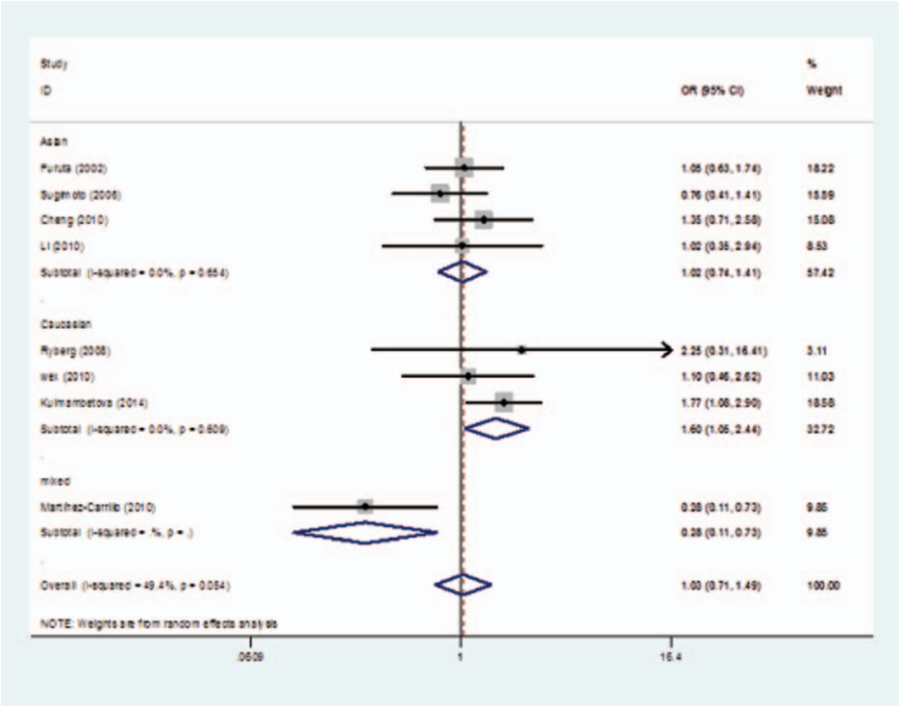

Figure 1. Forest plot of gastritis risk associated with the CC genotypes compared with the TT genotype in interleukin (IL)-1β-31 polymorphism in subgroup analysis of "ethnicity."

3.3. Evaluation of heterogeneity

There was heterogeneity among studies in overall comparisons and also subgroup analyses in *IL-1β-31* polymorphism. To explore sources of heterogeneity, we evaluated the following variables by meta-regression: ethnicities, source of control, study quality, genotyping methods, and sample size.

For the *IL-1β-31* polymorphism, there was significant heterogeneity in overall comparisons of allele model ($P=0.02$), homozygous model ($P=0.054$), and dominant model ($P=0.057$). Interestingly, when stratified by "ethnicity," the heterogeneity disappeared in all comparison models. However, meta-regression analyses revealed that sample size could explain 14.02% (allele model), 14.44% (dominant model), and 15.11% (recessive model) of the τ^2, and ethnicity could explain 9.02% (recessive model) of the τ^2. None of the other possible variables could explain the heterogeneity between studies by meta-regression analysis.

3.4. Sensitivity analysis

To assess the stability of the results, sensitivity analyses were performed to assess the influence of each individual study on the pooled OR. The omission of any study made no significant difference in each comparison in the polymorphisms of *IL-1β-31* and *IL-1β-511*, indicating that the results of this meta-analysis were statistically reliable (Fig. 2).

3.5. Publication bias

There was no publication bias in polymorphisms of *IL-1β-31* or *IL-1β-511* in the current study. The shape of either the Begg funnel plots or the Egger's plots did not reveal any evidence of obvious asymmetry in all comparison models (Fig. 3, Fig. 4).

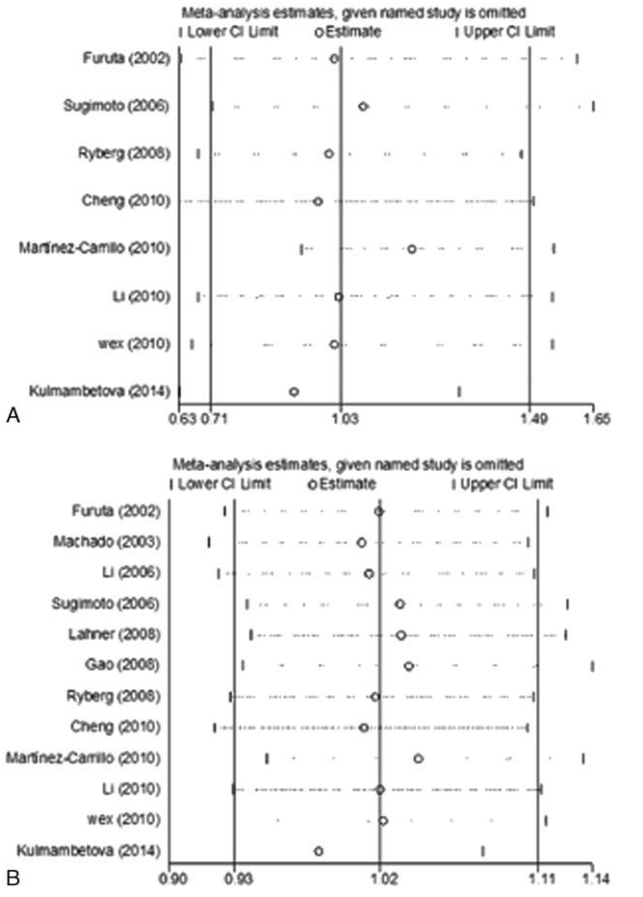

Figure 2. (A) Sensitivity analysis of the homozygous model in interleukin (IL)-1β-31 polymorphism. (B) Sensitivity analysis of the allele model in IL-1β-511 polymorphism.

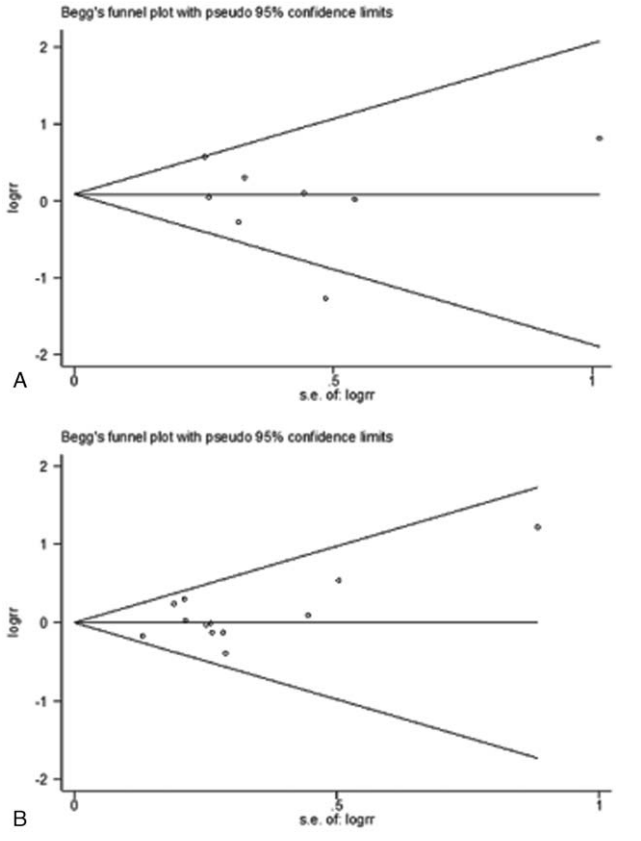

Figure 3. (A) Begg funnel plot for publication bias test under homozygous model in interleukin (IL)-1β-31 polymorphism. (B) Begg funnel plot for publication bias test under heterozygous model in IL-1β-511 polymorphism. Each point represents a separate study for the indicated association.

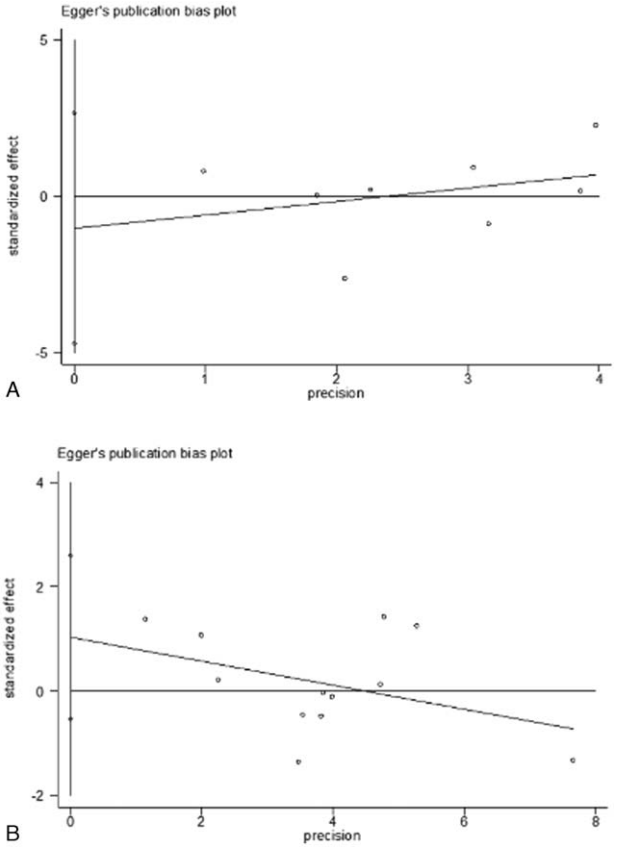

Figure 4. (A) Egger funnel plot for publication bias test under homozygous model in interleukin (IL)-1β-31 polymorphism. (B) Egger funnel plot for publication bias test under heterozygous model in IL-1β-511 polymorphism. Each point represents a separate study for the indicated association.

4. Discussion

In this study, we performed a systematic review of association between *IL-1β* promoter polymorphisms and gastritis risk based on 12 case–control studies. This review is also the 1st attempt to explore the individual association between the polymorphisms of *IL-1β-31* or *IL-1β-511* and gastritis risk. The results provided evidences that the *IL-1β-31* polymorphisms might be associated with the gastritis risk, especially the Caucasian population, while the *IL-1β-511* polymorphisms might not be.

IL-1β is involved in the host's immune response to many antigenic challenges, including *H pylori* infection.[30] Upon *H pylori* infection, a local increase of *IL-1β* was induced. *IL-1β* may work together with other inflammatory cytokines to recruit and activate neutrophils in the gastric mucosa, resulting in mucosal inflammation.[31]*IL-1β* could also inhibit the gastric acid secretion by modulating functions of several gastric epithelial cells.[32] As a consequence, the chronic superficial gastritis induced by *H pylori* infection could gradually develop into chronic atrophic gastritis and gastric carcinoma finally. However, this progression occurs in only some patients, implying that genetic characteristics and environmental factors may be involved in the process.[17] The association of *IL-1β* polymorphisms and gastric cancer has been implied by several studies,[4,33] whereas the association of *IL-1β* promoter polymorphisms and gastritis risk is still obscure.

Single nucleotide polymorphisms at positions -31 and -511 of the *IL-1β* gene were associated with increased expression of *IL-1β*. *IL-1β-31* got a TATA-box polymorphism that directly affects DNA-protein interactions.[4] The *IL-1β-511* polymorphism was in nearly complete linkage disequilibrium with *IL-1β-31*. El-Omar et al[4] proved *IL-1β-31T* was associated with increased *IL-1β* expression in Scottish and Polish populations. Hwang et al[34] showed the *IL-1β-511 TT* genotype was associated with increased *IL-1β* expression in the Japanese population. In the context of *H pylori* infected gastritis, the *IL-1β* gene is the prime candidate for studies of genetic factors involved in gastritis pathology. Many studies have been carried out to investigate the association between *IL-1β* promoter polymorphisms and gastritis risk; however, the results remained inconclusive. The *H pylori* infected patients carrying *IL-1β-511T/-31C* were found to have an increased risk of atrophic gastritis in the German population.[3] However, *IL-1β-511 CT/CC* genotypes have been found to be associated with the chronic gastritis in the Brazilian population,[15] as well as the Mexican population.[26] In the Japanese population, Furuta et al[18] failed to find any significant difference in *IL-1β-511* polymorphisms between gastritis patients and controls. Achyut et al[13] also failed to observe any significant association of *IL-1β-511* polymorphisms with gastritis in the Indian population. As far as *IL-1β-31* polymorphism was concerned, the study results remained contradictory. The T allele of *IL-1β-31* polymorphism was found to be associated with vulnerability to persistent *H pylori* infection in Hamajima study,[35] while *IL-1β-31 CC* may be associated with risk of development of relatively severe gastritis in South China.[36] The distribution of *IL-1β-31* polymorphism genotype

differed significantly between *H pylori* infected patients and the noninfected group, with frequency of TT genotype lower in the former group.[6]

In our meta-analysis, *IL-1β-31* C allele or CC genotype could increase the gastritis risk in the Caucasian population, while it could decrease the gastritis risk in the Mexican population. However, no association was found between *IL-1β-31* polymorphisms and gastritis risk in the background of *H pylori* infection. The contradictory results between the Caucasian population and the Mexican population may be due to the population constitutions and genotype distributions. In our study, the frequencies of *IL-1β-31* C allele and *IL-1β-511* T allele in the Mexican population varied largely from the frequencies in the other 2 populations. The Mexican population is a mixed population, and there is genomic diversity in different regions of Mexico. In our analysis, there had only been 1 study of a Mexican population, with it being the population of Guerrero constituting of dominant African ancestors and minor European ancestors. However, other studies based on the Mexican population proved the *IL-1β-31* CC genotype was associated with gastric cancer.[37,38] More studies of Mexican or African populations should be taken into the meta-analysis to further confirm our results.

Different population constitutions may also account for this inconsistency between the Asian and Caucasian populations. It is hypothesized that the lack of association between *IL-1β* polymorphisms and gastritis severity in the Indian population may be due to the comparatively lower level of cytokines secreted in the mucosa than the Caucasian population.[9] As the *IL-1β* polymorphisms lack association with gastritis risk in the Asian population entirely, the cytokines expression level may also influence the epidemiology study results of the whole Asian population.

However, in our study, the *IL-1β-511* polymorphism has no association with gastritis risk in overall comparison or subgroup analysis, which is not consistent with the linkage disequilibrium between *IL-1β-511* and *IL-1β-31* polymorphisms. One possible reason is that *IL-1β-31* locates in TATA box which could directly influence the expression of IL-1β, while *IL-1β-511* does not. Our results of *IL-1β-31* polymorphism were consistent with previous study,[3,8,9] and there seems to be no publication bias in both polymorphisms. However, the limited studies included in our study may also influence the analysis results. In the future, more studies should be included for reconfirmation.

Cam[39] showed a higher prevalence of familial history of gastric cancer in *H pylori* infected children, demonstrating the effect of genetic factors in the gastric pathological course of *H pylori* infected patients. However, neither of the polymorphism sites was proved to be able to affect the gastritis risk of *H pylori* infected patients in our study. The induction of gastritis by *H pylori* infection is a chronic process, during which multiple factors exert effects, including *IL-1β*, IL-8, tumor necrosis factor-alpha, etc., as well as environmental factors. The *IL-1β* protein may play a role in the development of gastritis, and the *IL-1β-31* polymorphism may affect gastritis risk as a genetic factor. However, the polymorphisms in *IL-1β* promoter may not contribute to the gastritis risk of *H pylori* infected patients, according to our study. We hypothesized that the influence of *IL-1β* on gastritis development in *H pylori* infected patients may not depend on the *IL-1β* promoter activity, implying clues for gastric pathological research. In addition, other *IL-1β* single nucleotide polymorphisms may affect gastritis risk in *H pylori* infected patients, such as +3954C>T polymorphism indicated by Hnatyszyn et al.[11] In any case, our results were inconsistent with Santos' study of the Brazilian population;[15] thus, more studies need to be carried out to confirm our results.

For a sound meta-analysis, 1 major concern is publication bias. No publication bias for the 2 polymorphisms was found by Begg funnel plot or Egger test. The shapes of the funnel plot were symmetrical in all the comparison models. Heterogeneity between studies is another major concern. In our study, there was no heterogeneity in *IL-1β-511* polymorphism by Q test. However, there is heterogeneity between studies in the allele model, homozygous model, and recessive model of *IL-1β-31* polymorphism. The heterogeneity disappeared in subgroup analysis by "ethnicity." The "sample size" and "ethnicity" could only explain part of the τ^2 by logistic meta-regression analyses. There may be other reasons accounting for the heterogeneity in *IL-1β-31* polymorphism. Nevertheless, sensitivity analysis proved that our meta-analysis results were statistically reliable.

Different ethnic groups, especially a mixed population such as the Mexican and the Brazilian, have their own migration history, genetic drift, allele-frequency-affecting mating status, lifestyle, and disease susceptibility. Therefore, in epidemiology investigation, ethnic differences may induce discrepancies in these studies. In our study, the ethnicity could induce heterogeneity and affect the meta-analysis results. In the future, the ethnicity should be paid more attention to when designing the study method and explaining study results in epidemiology investigation of *IL-1β* polymorphisms.

In conclusion, the current meta-analysis provides data to support the existence of association between *IL-1β-31* polymorphism and gastritis risk in the Caucasian population. It is necessary to conduct more studies with larger sample sizes and various ethnic populations to provide further evidence of the results. In addition, further studies evaluating the gene–-environment interaction effects may provide a more comprehensive explanation for the association between *IL-1β* promoter polymorphisms and gastritis risk.

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