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Interleukin-10 gene rs1800896 polymorphism increases risk of acute pancreatitis

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Abstract

Background: The association between interleukin-10 (IL-10) gene rs1800896 polymorphism and susceptibility to acute pancreatitis (AP) has been investigated in several studies, but with contradictory findings. Therefore, a comprehensive meta-analysis is needed to assess the strength of such association.

Methods: Literatures on PubMed, EMBASE, and CNKI were searched to identify relevant studies. The strength of association between IL-10 gene rs1800896 polymorphism and AP risk was assessed using pooled odds ratios and 95% confidence intervals.

Results: Totally 7 case–control studies involving 1527 cases and 1511 controls were identified. Analyses proved that IL-10 gene rs1800896 polymorphism was significantly associated with an increased risk of AP. Stratification analysis of ethnicity found such significant association only among Asians, but not Caucasians.

Conclusion: IL-10 gene rs1800896 polymorphism increases the risk of AP.

Abbreviations: AP = acute pancreatitis, CI = confidence interval, HWE = Hardy–Weinberg equilibrium, IL-10 = interleukin-10, NOS = Newcastle–Ottawa Scale, OR = odds ratio, SNP = single-nucleotide polymorphism.

Keywords: acute pancreatitis, interleukin-10, meta-analysis, polymorphism

1. Introduction

Acute pancreatitis (AP) is a common lethal disease with a mortality rate of 10% to 25%.[1] AP is divided by the disease severity into mild AP and severe AP. The main recognized risk factors of AP are gallstones, overeating, and heavy alcohol consumption.[2] Though many studies prove that inflammation is significantly associated with its pathogenesis,[3,4] the etiology of AP is still poorly understood.

Cytokines are pivotal in AP development by causing an inflammatory response that can trigger the recruitment and activation of inflammatory cells and induce pancreatic necrosis.[5] Inflammatory cells in AP patients produce some proinflammatory cytokines[6–8] that could lead to tissue damage and organ dysfunction or failure in AP patients.[3] One such cytokine is interleukin (IL)-10, located on chromosome 1 (1q31–1q32).

The association between IL-10 gene rs1800896 polymorphism and AP susceptibility has been investigated extensively,[9–15] but

with conflicting findings. Individual studies with small sample sizes have insufficient statistical power to detect positive associations. On the contrary, meta-analysis integrates the findings of individual studies and thereby increases the statistical power and resolution. Therefore, this meta-analysis was performed to confirm whether IL-10 gene rs1800896 polymorphism was associated with AP susceptibility.

2. Materials and methods

2.1. Selection of published studies

PubMed, Elsevier, Embase, and CNKI were systematically searched to identify studies through January 26, 2017. The following key words were used: "acute pancreatitis" or "AP"; "interleukin10", "interleukin-10", "IL-10" or "IL10"; "polymorphism" or "polymorphisms". The references of identified studies were also hand-screened.

2.2. Inclusion and exclusion criteria

Inclusion criteria were: evaluation of association between IL-10 gene rs1800896 polymorphism and AP risk, provision of sufficient data to calculate the odds ratios (ORs), 95% confidence intervals (CIs), and P value, and case–control study. Exclusion criteria were: duplication; review, meta-analysis or other non-original studies; and lack of detailed genotype data.

2.3. Data extraction and quality assessment

From each eligible study, 2 investigators carefully extracted and reviewed the following information: name of first author, year of publication, source of controls, country of origin, ethnicity, and genotype numbers of cases and controls. Two investigators independently assessed the study quality based on the Newcastle–Ottawa Scale (NOS).[16,17] Any potential conflict was resolved by discussion.
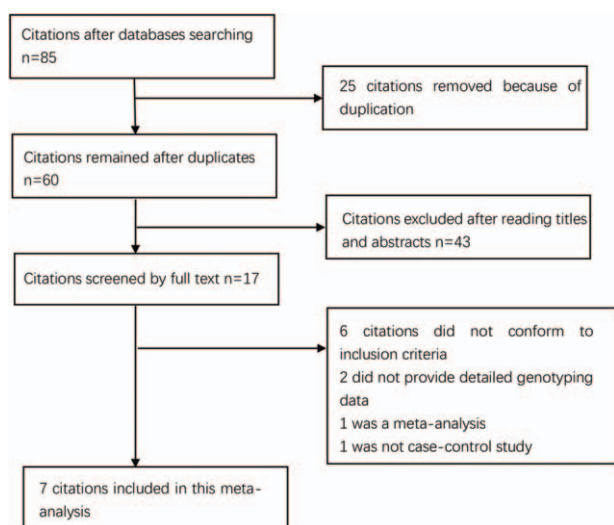
Figure 1. Selection for eligible studies in this meta-analysis.

2.4. Statistical analysis

Our meta-analysis was conducted according to *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) checklists and guidelines.[18] The strength of association between IL-10 gene rs1800896 polymorphism and AP risk was assessed using ORs and 95% CIs. The study-specific ORs were pooled using a fixed-effect or random-effect model depending on the heterogeneity. When a Q test indicated $P < .1$ or $I^2 > 50\%$, a random-effect model was used; otherwise, a fixed-effect model was applied.[19] Pooled ORs were calculated for allele model, homozygous model, heterozygous model, dominant model, and recessive model separately. Stratification analyses based on ethnicity, source of controls (SOC), and Hardy–Weinberg equilibrium (HWE) status were also performed. The stability of overall results was evaluated through sensitivity analysis by omitting each study sequentially. The departure from HWE in the controls was assessed using Pearson's χ^2 test. Publication bias was estimated using the Begger and Egger linear regression test.[20] All statistical analyses were conducted on Stata V.11.0 (StataCorp, College Station, TX). $P < .05$ was considered as significant. All analyses of this meta-analysis were based on previous published studies, and this meta-analysis did not have original data. Thus, no ethical approval and patient consent are required.

3. Results

3.1. Characteristics of the included studies

A detailed flow diagram of the searching process is presented in Figure 1. The initial search returned a total of 85 citations, from which 25 duplicates were removed. After the titles and abstracts were screened, 43 citations were deleted. Then 10 of the remaining 17 citations were removed after full text review. Finally 7 studies were included,[9–15] which targeted at either Asians[9–13,15] or Caucasians.[14] The characteristics of the included studies are summarized in Table 1.

3.2. Quantitative data synthesis

Meta-analysis demonstrated a significant association between IL-10 gene rs1800896 polymorphism and AP risk (G vs A: OR, 1.27; 95% CI, 1.14–1.42, $P < .001$, Fig. 2, Table 2). Stratification analysis of ethnicity found a significant association between rs1800896 polymorphism and the increased risk of AP only among Asians (GG+AG vs AA: OR, 1.29; 95% CI, 1.11–1.50, $P < .001$, Fig. 3), but not Caucasians. The stratification analyses of HWE status and SOC both uncovered an association between positive HWE status and hospital-based controls (Table 3). Sensitivity analysis suggested the data of this meta-analysis were stable and trustworthy for this single-nucleotide polymorphism (SNP; GG+AG vs AA, Fig. 4). Neither Begger nor Egger test showed any evidence of publication bias in this meta-analysis.

4. Discussion

This meta-analysis showed that the IL-10 gene rs1800896 polymorphism increased the risk of AP. Stratification analysis by ethnicity found that rs1800896 polymorphism increased the risk of AP among Asians, but not Caucasians. Subgroup analysis of HWE status revealed an association between AP risk and positive HWE.

A Chinese study involving 215 cases and 116 controls was the first in this area, but did not find any association between IL-10 gene rs1800896 polymorphism and AP risk.[15] Subsequent studies also failed to detect any association among Chinese subjects.[9,13] A study from the UK also could not demonstrate any association between rs1800896 polymorphism and AP risk among Caucasian populations.[14] Nevertheless, other studies from China revealed that IL-10 rs1800896 polymorphism increased the risk of AP.[10–12] Obviously, the findings of the included studies were conflicting, which may be attributed to the clinical heterogeneity, different ethnic populations and small sample sizes.

Table 1

Characteristics of included studies.

Author and year	SOC	Country	Ethnicity	Case			Control			HWE	NOS
				AA	AG	GG	AA	AG	GG		
Jiang et al (2016)	HB	China	Asian	69	85	28	130	112	20	Y	6
Li et al (2015)	HB	China	Asian	84	67	25	91	65	20	Y	5
Jia et al (2015)	HB	China	Asian	106	114	35	128	108	19	Y	6
Cai et al (2015)	HB	China	Asian	92	113	35	116	105	19	Y	5
Bao et al (2015)	HB	China	Asian	163	123	49	176	118	41	N	6
Zhang et al (2015)	PB	China	Asian	156	59	0	79	37	0	N	6
Sargen et al (2000)	PB	UK	Caucasian	24	61	39	28	63	36	Y	6

HB = hospital-based controls, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle–Ottawa Scale, PB = population-based controls, SOC = source of controls.
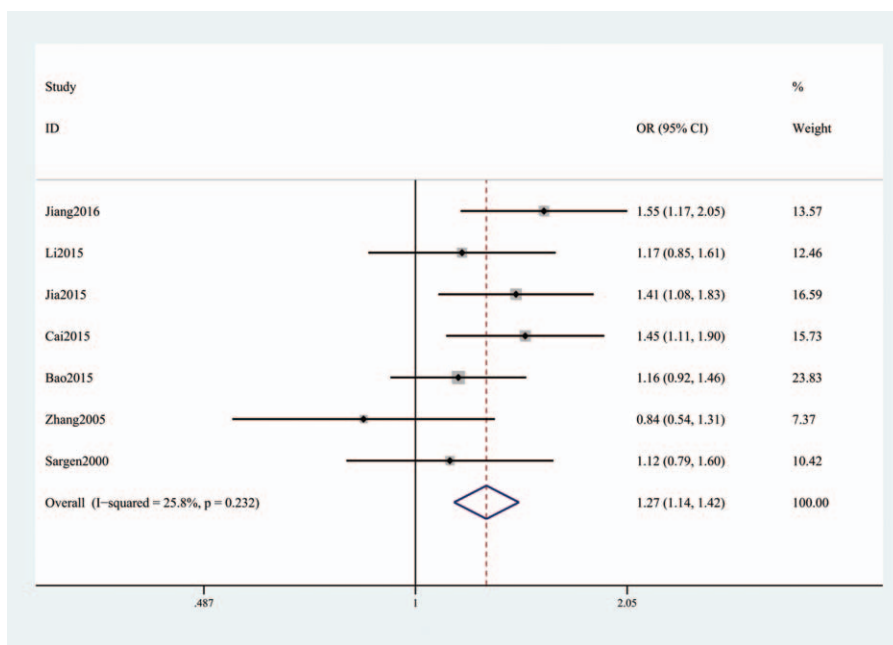
Figure 2. Forest plot showing OR for the association between IL-10 gene rs1800896 polymorphism and AP risk (G vs A). AP=acute pancreas, IL=ilnterleukin, OR=odds ratio.

Table 2

Meta-analysis of association between IL-10 rs1800896 polymorphism and the risk of acute pancreatitis.

Comparison	OR (95% CI)	P-value	P for heterogeneity	I^2 (%)	Model
G vs A	**1.27 (1.14,1.42)**	<.001	.232	25.8	Fixed
GG+AG vs AA	**1.28 (1.10,1.48)**	.001	.377	6.6	Fixed
GG vs AG +AA	**1.53 (1.22,1.92)**	<.001	.406	1.3	Fixed
GG vs AA	**1.72 (1.35,2.20)**	<.001	.311	16.0	Fixed
AG vs AA	**1.19 (1.02,1.39)**	.029	.681	0.0	Fixed

CI=confidence interval, OR=odds ratio.
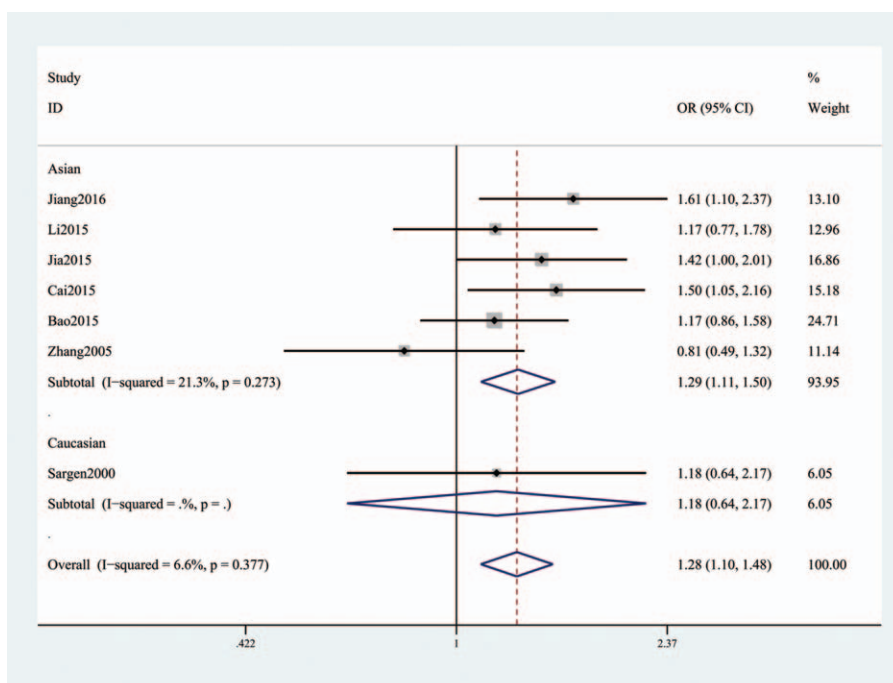[*]Bold values are statistically significant (P<.05).

Figure 3. Stratification analysis of ethnicity showing OR for the association between IL-10 gene rs1800896 polymorphism and AP risk (GG+AG vs AA). AP=acute pancreas, IL=ilnterleukin, OR=odds ratio.

Table 3

Summary of the subgroup analyses in this meta-analysis.

Comparison	Category	Category	Studies	OR (95% CI)	P-value	P for heterogeneity
G vs A	Ethnicity	Asian	6	**1.29 (1.15,1.45)**	<.001	.183
		Caucasian	1	1.12 (0.79,1.60)	.514	N/A
	SOC	HB	5	**1.33 (1.18,1.50)**	<.001	.448
		PB	2	1.01 (0.76,1.33)	.968	.311
	HWE	Yes	5	**1.36 (1.19,1.55)**	<.001	.547
		No	2	1.08 (0.88,1.33)	.455	.209
GG+AG vs AA	Ethnicity	Asian	6	**1.29 (1.11,1.50)**	.001	.273
		Caucasian	1	1.18 (0.64,2.17)	.599	N/A
	SOC	HB	5	**1.35 (1.15,1.59)**	<.001	.636
		PB	2	0.94 (0.64,1.38)	.744	.345
	HWE	Yes	5	**1.41 (1.17,1.68)**	<.001	.796
		No	2	1.06 (0.82,1.37)	.679	.211
GG vs AG+AA	Ethnicity	Asian	5	**1.62 (1.27,2.08)**	<.001	.427
		Caucasian	1	1.16 (0.68,1.99)	.591	N/A
	SOC	HB	5	**1.62 (1.27,2.08)**	<.001	.427
		PB	1	1.16 (0.68,1.99)	.591	N/A
	HWE	Yes	5	**1.65 (1.27,2.15)**	<.001	.432
		No	1	1.23 (0.79,1.92)	.365	N/A
GG vs AA	Ethnicity	Asian	5	**1.80 (1.38,2.33)**	<.001	.274
		Caucasian	1	1.26 (0.62,2.57)	.517	N/A
	SOC	HB	5	**1.80 (1.38,2.33)**	<.001	.274
		PB	1	1.26 (0.62,2.57)	.517	N/A
	HWE	Yes	5	**1.92 (1.44,2.56)**	<.001	.415
		No	1	1.29 (0.81,2.06)	.284	N/A
AG vs AA	Ethnicity	Asian	6	**1.19 (1.02,1.40)**	.031	.557
		Caucasian	1	1.13 (0.59,2.16)	.713	N/A
	SOC	HB	5	**1.25 (1.05,1.48)**	.010	.872
		PB	2	0.91 (0.62,1.35)	.653	.419
	HWE	Yes	5	**1.28 (1.06,1.55)**	.010	.929
		No	2	1.02 (0.77,1.34)	.910	.272

CI = confidence interval, HB = hospital-based controls; OR = odds ratio, PB = population-based controls; SOC = source of controls.
Bold values are statistically significant (P < .05).

To resolve inconsistencies, Yin et al[21] performed a meta-analysis, but did not find any significant association between IL-10 gene rs1800896 polymorphism and AP risk.[21] However, this meta-analysis only included 2 studies with small sample sizes (339 cases and 243 controls).[14,15] Given the small number of participants, their findings should be interpreted with caution. Moreover, they only conducted the allelic model in their meta-analysis[21] and we thought other genetic models were needed to investigate this SNP. After this meta-analysis,[21] several studies were reported in recent years.[9–13] Thus, a new meta-analysis involving these updated data was needed to determine whether IL-10 gene SNP was associated with susceptibility to AP. In our meta-analysis, quantitative synthesis showed that rs1800896 polymorphism was associated with the risk of AP. Stratification analyses of ethnicity, SOC, and HWE status showed that this SNP increased the risk of AP among Asians, hospital-based control groups, and positive HWE groups, respectively, which was not found in the previous meta-analysis.

Our meta-analysis has several potential limitations. First, no further stratification analyses of other potential factors (e.g. age and sex) could be conducted. Second, our results were based on unadjusted estimates of confounding factors, which might affect the final conclusions. Third, the sample size of Caucasians in stratification analyses was small.

In conclusion, this meta-analysis provides evidence that IL-10 gene rs1800896 polymorphism is associated with the risk of AP. Nevertheless, larger case–control studies in different ethnicities are needed to validate the association.

Figure 4. Sensitivity analysis for the association between IL-10 gene rs1800896 polymorphism and AP risk (GG+AG vs. AA). AP = acute pancreas, IL = iInterleukin.

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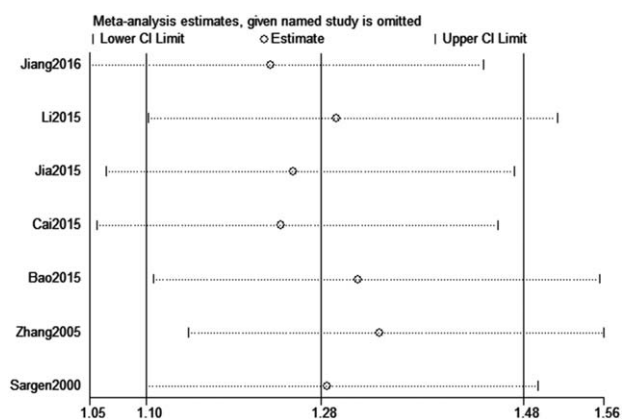
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