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Original Article

Lack of association between CD14-159 C/T polymorphism and acute pancreatitis: a meta-analysis

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Abstract: The CD14-159 C/T polymorphism has been implicated in susceptibility to acute pancreatitis (AP), but the results were inconclusive. The present meta-analysis aimed to explore the correlation between CD14-159 C/T polymorphism and AP risk. All eligible case-control studies published up to November 10th, 2014 were identified by searching PubMed, Web of Science, CNKI, and WanFang databases. Two reviewers independently identified the literature according to inclusion and exclusion criteria. Meta-analysis was performed using RevMan 5.2 and Stata 12.0 software. A total of five studies comprising 1211 cases and 932 controls were included. Overall, no significant association between CD14-159 C/T polymorphism and AP risk was found under all four genetic models [CT + TT vs CC: OR = 1.09, 95% CI (0.91, 1.31); TT vs CT + CC: OR = 1.04, 95% CI (0.83, 1.29); CT vs CC: OR = 1.08, 95% CI (0.89, 1.32); TT vs CC: OR = 1.15, 95% CI (0.88, 1.49)]; In stratification analysis by disease severity, we also failed to detect any association between CD14-159C/T polymorphism and the risk of mild AP (MAP) or severe AP (SAP); In subgroup analysis by ethnicity, similar results were observed in Asian and European populations. This meta-analysis suggested that the CD14-159C/T polymorphism is not associated with the susceptibility of acute pancreatitis.

Keywords: CD14, acute pancreatitis, polymorphism, meta-analysis

Introduction

Acute pancreatitis (AP) is a common disease that normally runs a benign course in the majority of patients. However, 25% to 30% of patients experience a severe attack with a high mortality rate [1]. Although gallstones, heavy alcohol consumption and overeating are generally considered the main risk factors for AP, the exact etiology underlying AP is still unclear. Recently, variants in several innate immunity genes have been identified as biologically plausible candidates for effects on AP, such as CD14.

CD14 is expressed on the surface of monocytes, macrophages, and neutrophils as membrane CD14 (mCD14) and in the serum as soluble CD14 (sCD14) and its expression may be partially regulated at the genetic level [2]. The CD14 gene is localized on chromosome 5q31.1, in a region shown to be linked to type 2 T lymphocyte (Th2) prevalent phenotypes, which encodes a receptor protein that binds to lipopolysaccharide (LPS), its primary ligand, and interacts with co-receptors toll-like receptor 4 (TLR4) and lymphocyte antigen 96 (LY96) [3, 4]. There are several polymorphism sites in the CD14 gene, and a well-studied common single nucleotide polymorphism (SNP) in the promoter region of CD14, -159C/T (rs2569190, also known as CD14-260C/T), has been associated with increased CD14 expression in vitro and in the serum of children [5].

Recently, the CD14-159C/T polymorphism is investigated extensively to the susceptibility of AP [6-11]. However, the results remain controversial. Therefore, we conduct a meta-analysis to evaluate the association between the CD14-159C/T polymorphism and AP risk.

Materials and methods

Search strategy

A literature research was conducted using PubMed, Web of Science, CNKI and WanFang databases up to November 10th, 2014 without language restrictions. Relevant studies were identified using the terms: [‘cluster of differen-

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

Study	Year	Country	Ethnicity	Genotype methods	Source of controls	Sample size (case/control)	Case			Control			HWE (*P* value)
							CC	CT	TT	CC	CT	TT	
Balog [6]	2005	Hungary	European	RT-PCR	PB	77/71	22	35	20	21	39	11	0.309
Chao [7]	2005	China	Asian	PCR-RFLP	HB	177/117	84	82	11	49	62	6	0.015
Masamune [8]	2010	Japan	Asian	PCR-RFLP	PB	346/319	71	172	103	69	143	107	0.106
Tukiainen [9]	2008	Finland	European	MALDI-TOF MS	PB	396/309	147	182	67	133	129	47	0.095
Zhang [10]	2005	China	Asian	PCR-RFLP	PB	215/116	128	59	28	71	32	13	0.004

RT-PCR: real-time polymerase chain reaction; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; MALDI-TOF MS: matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; PB: population-based; HB: hospital-based.

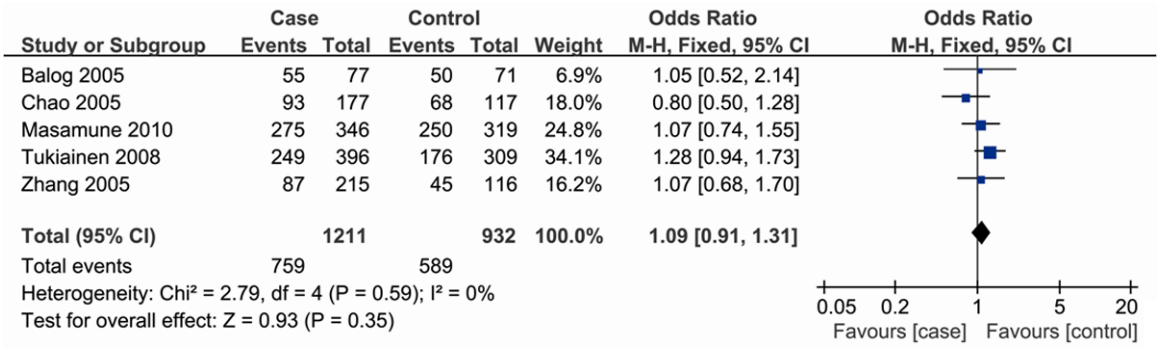

Figure 1. Meta-analysis of the association between CD14-159C/T polymorphism and susceptibility to AP (dominant model).

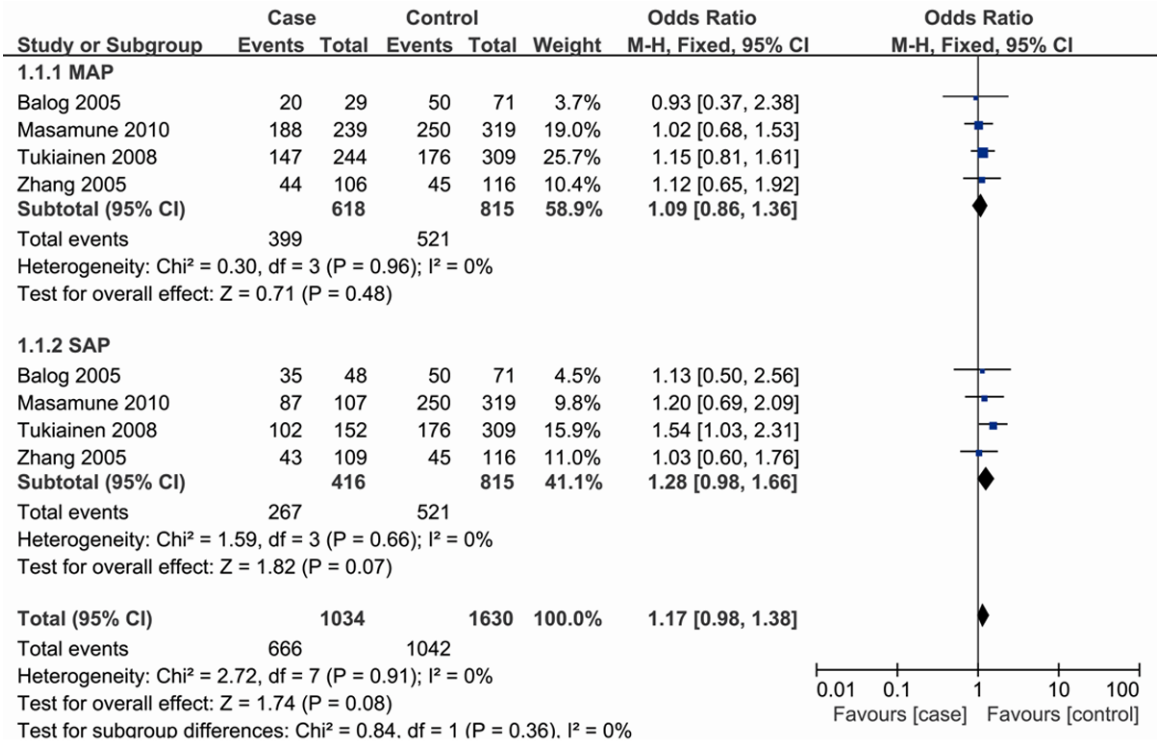

Figure 2. Subgroup analysis by severity of odds ratios for association between CD14-159C/T polymorphism and risk of AP (dominant model).

Table 2. Pooled analysis for the associations between the CD14-159C/T polymorphism and risk of AP

Models	Variables	N*	Test of association			Test of heterogeneity		Publication bias
			OR (95% CI)	Z	*P*	I^2	*P*	Egger's test (*P* value)
Dominant model	Total	5	1.09 (0.91, 1.31)	0.93	0.35	0	0.59	0.296
	Severity							
	MAP	4	1.09 (0.86, 1.36)	0.71	0.48	0	0.96	
	SAP	4	1.28 (0.98, 1.66)	1.82	0.07	0	0.66	
	Ethnicity							
	Asian	3	0.99 (0.77, 1.26)	0.10	0.92	0	0.58	
	European	2	1.24 (0.94, 1.64)	1.52	0.13	0	0.62	
Recessive model	Total	5	1.04 (0.83, 1.29)	0.31	0.76	4%	0.38	0.127
	Severity							
	MAP	4	0.94 (0.73, 1.22)	0.44	0.66	0	0.41	
	SAP	4	1.16 (0.86, 1.56)	0.96	0.34	10%	0.34	
	Ethnicity							
	Asian	3	0.92 (0.69, 1.22)	0.60	0.55	0	0.58	
	European	2	1.26 (0.88, 1.81)	1.25	0.21	20%	0.26	
CT *vs* CC	Total	5	1.08 (0.89, 1.32)	0.77	0.44	0	0.49	0.150
	Severity							
	MAP	4	1.10 (0.86, 1.41)	0.76	0.44	0	0.97	
	SAP	4	1.26 (0.95, 1.68)	1.61	0.11	0	0.40	
	Ethnicity							
	Asian	3	1.00 (0.77, 1.30)	0.03	0.98	0	0.43	
	European	2	1.20 (0.89, 1.61)	1.19	0.23	0	0.34	
TT *vs* CC	Total	5	1.15 (0.88, 1.49)	1.02	0.31	0	0.75	0.471
	Severity							
	MAP	4	1.05 (0.77, 1.42)	0.29	0.77	0	0.67	
	SAP	4	1.32 (0.92, 1.88)	1.51	0.13	0	0.77	
	Ethnicity							
	Asian	3	1.01 (0.71, 1.42)	0.03	0.97	0	0.84	
	European	2	1.36 (0.91, 2.03)	1.51	0.13	0	0.58	

*Number of comparison; MAP: mild acute pancreatitis; SAP: severe acute pancreatitis.

tiation 14 or CD14'] AND ['genetic polymorphism or polymorphisms or SNP'] AND ['acute pancreatitis or AP or mild acute pancreatitis or MAP or severe acute pancreatitis or SAP']. The search was restricted to humans. Additional studies were identified by a hand search of references of original or review articles on this topic.

Inclusion criteria and exclusion criteria

Studies were included if they met the following criteria: (1) studies that evaluated the association between the CD14-159C/T polymorphism and acute pancreatitis risk, (2) in a case-control study design, and (3) had detailed genotype frequency of cases and controls or could be calculated from the article text. Studies were excluded when they were: (1) not case-control study, (2) review, comment or editorial articles, (3) insufficient data, and (4) repetitive studies.

Data extraction

Two investigators independently extracted data and reached consensus on all of the items. If they generated different results, disagreements were discussed and resolved by a third investigator. Data extracted from the selected articles included: the first author's name, year of publication, country of origin, ethnicity of study population, genotyping methods, source of control, number of cases and controls and evidence of Hardy-Weinberg equilibrium (HWE) in controls.

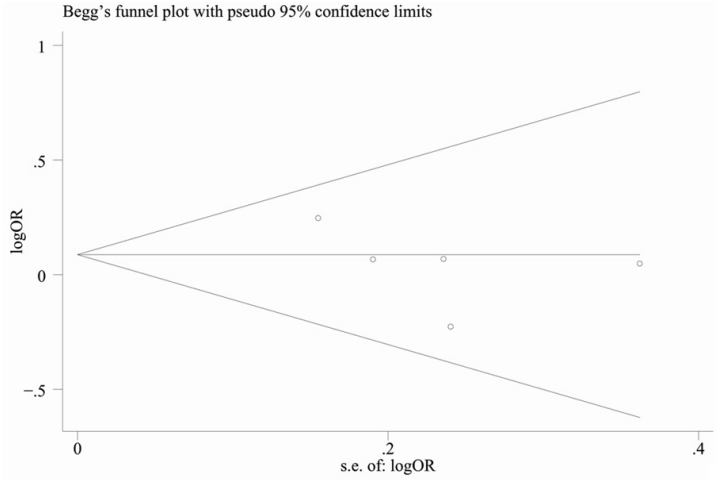

Figure 3. Begg's funnel plot for publication bias (dominant model).

Statistical analysis

The risk of AP associated with CD14-159C/T polymorphism was estimated for each study by odds ratio (OR) and 95% confidence interval (95% CI). Four different ORs were calculated: the dominant model (CT + TT *vs.* CC), the recessive model (TT *vs.* CT + CC), heterozygote comparison (CT *vs.* CC), and homozygote comparison (TT *vs.* CC). The χ^2-test-based Q statistic test and I^2 statistic were used to assess the between-study heterogeneity [12]. When a significant Q test ($P > 0.1$) or $I^2 < 50\%$ indicated homogeneity across studies, the fixed effects model was used [13], or else the random effects model was used [14]. HWE among controls for each study was examined by χ^2 test. We performed stratification analyses on ethnicity (Asian, European) and severity of AP (MAP, SAP). Analysis of sensitivity, after removing the studies deviating from HWE, was performed to evaluate the stability of the results. The potential publication bias was examined by Begg' funnel plot and Egger's regression test [15, 16]. $P < 0.05$ was regarded as statistically significant.

Statistical analyses were performed using the Cochrane Collaboration RevMan 5.2 and STATA package version 12.0 (Stata Corporation, College Station, Texas).

Results

Study characteristics

The search strategy retrieved 114 potentially relevant studies. According to the inclusion criteria, 6 studies [6-11] with full-text were included in this meta-analysis and 108 studies were excluded. Among those 6 publications, we excluded one study [11] because they did not present detailed genotyping information. Therefore, 5 eligible case-control studies, included 1211 cases and 932 controls, met the inclusion criteria. The characteristics of selected studies are summarized in **Table 1**. Of the 5 eligible studies, all were written in English. Two ethnicities were addressed: 3 studies [7, 8, 10] on Asian populations and 2 studies [6, 9] on Caucasians. The distribution of genotypes in the controls was consistent with the HWE for all selected studies, except for two studies [7, 10].

Quantitative data synthesis

There were no inter-study heterogeneity among overall studies of the CD14-159C/T polymorphism in all four genetic models (dominant model: $I^2 = 0\%$, P = 0.59; recessive model: $I^2 = 4\%$, P = 0.38; CT *vs.* CC: $I^2 = 0\%$, P = 0.49; TT *vs.* CC: $I^2 = 0\%$, P = 0.75). Therefore, we used the fixed-effects model that generated wider CIs. Overall, no significant associations between the CD14-159C/T polymorphism and AP risk were found [dominant model: OR = 1.09, 95% CI (0.91, 1.31); recessive model: OR = 1.04, 95% CI (0.83, 1.29); CT *vs.* CC: OR = 1.08, 95% CI (0.89, 1.32); TT *vs.* CC: OR = 1.15, 95% CI (0.88, 1.49)] (**Figure 1**).

In the subgroup analysis by severity, similar results were observed in either MAP or SAP (**Figure 2**; **Table 2**). Stratification based on ethnicity, we also failed to detect any association in both Asian and European populations (**Table 2**).

Sensitivity analyses

We examined the influence of these studies on the pooled OR by repeating the meta-analysis while excluding the study that was not in HWE. The estimated pooled ORs were not materially altered [dominant model: OR = 1.18, 95% CI (0.94, 1.47); recessive model: OR = 1.01, 95% CI (0.79, 1.29); CT *vs.* CC: OR = 1.19, 95% CI (0.94, 1.51); TT *vs.* CC: OR = 1.14, 95% CI

(0.85, 1.53)], indicating that our results were statistically robust.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the potential publication bias in the available literature. The shape of funnel plots did not reveal any evidence of funnel plot asymmetry (**Figure 3**). Egger's test also showed that there was no statistical significance for the evaluation of publication bias (dominant model: $P = 0.296$; recessive model: $P = 0.127$; CT *vs.* CC: $P = 0.150$; TT *vs.* CC: $P = 0.471$).

Discussion

AP is a common disorder that severely affects human health. Many candidate genes were reported to be associated to AP risk, such as TNF-α, IL, ACE, GSTs, TLRs and CD14, and there have been reported polymorphisms associated with AP risk in these candidate genes [17]. Yin YW [18] reported the TNF-α gene-308A/G polymorphism is not associated with AP risk. Later on, another meta-analysis [19] conducted by Yin YW suggested the IL-8-251 T/A polymorphism, but not the IL-1b, IL-6 and IL-10 polymorphisms, is associated with an increased risk of AP. As for CD14, it is a pattern-recognition receptor that plays a central role in innate immunity and directs the adaptive immune responses [20]. As a co-receptor of TLRs, CD14 acts primarily by transferring LPS and other bacterial ligands from circulating LPS-binding protein to the TLR4/MD-2 signaling complex [21].

The -159C/T polymorphism in CD14 gene has been investigated the association with many diseases, such as inflammatory bowel disease [22], cancer [23], alcoholic liver disease [24], allergic rhinitis [25]. To our knowledge, this is the first meta-analysis which comprehensively assessed the association between CD14-159C/T polymorphism and AP risk. The current meta-analysis including 5 case-control studies and 2143 subjects were conducted to explore the association of the CD14-159C/T polymorphism with AR. Overall, no evidence has indicated that the CD14-159C/T polymorphism was associated with the susceptibility to AP. That is to say, the CD14-159C/T genotype distribution between AP and control group was no significant difference. In the subgroup analysis by ethnicity and severity, similarly, we did not detect any association between CD14-159C/T polymorphism and AP risk in Asians, Europeans, MAP and SAP. The results may be caused by the following reasons: (1) the association between the -159C/T polymorphism of CD14 gene and AP is indeed unrelated; (2) interactions with other genetic variants are the possible reasons; and (3) gene-environmental factors (such as lifestyle) may also affect the results.

It would be hard to interpret results, if significant heterogeneity were present. In this study, we did not find any obvious heterogeneity across studies. In addition, studies have reported that deviation from HWE might reflect the presence of genotyping errors, population stratification and selection bias in the controls [26]. Therefore, individual studies not in HWE were excluded to assess the stability of our results. However, we also failed to detect any association between CD14-159 C/T polymorphism and AP risk after exclusion of two studies [7, 10], which further confirmed the results.

Some limitations of this meta-analysis should be addressed. First, because of incomplete raw data or publication limitations, some relevant studies could not be included in our analysis. Second, our results were based on unadjusted estimates, while lacking of the information for the date analysis may cause serious confounding bias. Third, the number of published studies was not large enough, especially in subgroup analysis (e.g. etiology). Thus, we may fail to explore the real association.

In conclusion, this meta-analysis suggested that the CD14-159C/T polymorphism is not associated with AP risk. However, considering the limitations in our study, large and well-designed studies are warranted to validate our findings.

Disclosure of conflict of interest

None.

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