Immunome Research
ISSN: 1745-7580

Guha, et al. Immunome Res 2014, 10:2
DOI: 10.4172/1745-7580.1000082

Review Article Open Access

Intracellular Adhesion Molecule-1 K469E Gene Polymorphism and the Risk of Inflammatory Bowel Disease: A Meta-Analysis

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Abstract

Background and objective: Several studies have evaluated the association of the K469E (rs5498, A/G) gene polymorphism in Intracellular Adhesion Molecule-1 (ICAM-1) with Inflammatory Bowel Disease (IBD), including Crohn's Disease (CD) and Ulcerative Colitis (UC), in different populations. However, the results of these individual studies have been inconsistent. Therefore, a meta-analysis was performed.

Methods: The current meta-analysis, which involved 3260 subjects from nine separate studies, was conducted to explore the relationship between the ICAM-1 K469E gene polymorphism and IBD. The pooled odds ratios (OR) and 95% Confidence Intervals (CI) were assessed using the random effect model. Data were analyzed using STATA software.

Results: Overall, we observed no significant association between the ICAM-1 K469E gene polymorphism and IBD, CD, or UC. Stratification of cases by ethnicity revealed that the ICAM-1 K469E gene polymorphism was significantly associated with IBD only in the East Asian population (KK+KE vs. EE: OR=2.586, 95% CI=1.411-4.742; KK vs. KE+EE: OR=1.828, 95% CI=1.081-3.092; K vs. E: OR=1.739, 95% CI=1.240-2.439; EE vs. KK: OR=0.305, 95% CI=0.151-0.615).

Conclusions: This meta-analysis suggested that the K469E polymorphism in ICAM-1 likely does not represent a major factor affecting susceptibility to IBD. However, additional large case-control studies should be performed to clarify the possible role of ICAM-1 in IBD, especially studies examining potential ethnic differences and/or genotype-phenotype interactions.

Keywords: Inflammatory bowel disease; Intracellular adhesion molecule-1; Polymorphism; Meta-analysis

Abbreviations: IBD: Inflammatory Bowel Disease; CD: Crohn's Disease; UC: Ulcerative Colitis; ICAM-1: Intercellular Adhesion Molecule-1; HWE: Hardy-Weinberg Equilibrium; LFA-1: Lymphocyte Function–associated Antigen-1; CR3: Complement Receptor 3; OR: Odds Ratio

Introduction

Inflammatory bowel disease (IBD), which includes Crohn's Disease (CD) and Ulcerative Colitis (UC), has long been considered a disease that predominantly affects Western populations. However, recent data have revealed an increased incidence and prevalence of IBD in Asia [1]. Although the etiology of IBD remains unknown, it is widely accepted that interactions between genetic, environmental, and immunological factors contribute to the onset of IBD [2]. Recent genome-wide association studies have revealed genetic associations between IBD and genes that are known to be important in the host defense against infection, thus highlighting the importance of the host immune response in IBD [3].

Intercellular adhesion molecule-1 (ICAM-1) is a widely expressed member of the large immunoglobulin superfamily that plays a key role in the influx of neutrophil granulocytes into the colonic mucosa, which is a critical event in IBD pathogenesis [4]. Multiple lines of evidence have suggested that changes in ICAM-1 expression and function might be involved in the pathogenesis of UC and CD [5,6]. In addition, clinical trials of Alicaforsen, an antisense oligonucleotide that inhibits the synthesis of ICAM-1, have shown positive results in the treatment of patients with UC [7]. A common genetic polymorphism (rs5498) at position 1548 in the 6th exon of the *ICAM-1* gene results in a glutamate (E) residue being replaced by a lysine (K) at the 469th amino acid in ICAM-1's Ig domain 5 sequence. This gene polymorphism has been reported to influence the serum levels and activity of ICAM-1 [8]. Several published meta-analyses have demonstrated that the K469E gene polymorphism is associated with susceptibility to certain inflammatory diseases, including coronary artery disease, psoriasis, and multiple sclerosis [8-11].

In 2004, Matsuzawa et al. reported that the frequency of the K469 allele of *ICAM-1* is associated with both CD and UC in a Japanese population [12]. Interestingly, other studies have reported that the homozygous genotype E/E469 occurs more frequently in Caucasian IBD patients than in controls [4,13]. However, both Yang et al. and Ozen et al. reported no significant differences between patients with UC, patients with CD, and controls with respect to the *ICAM-1* K469E polymorphism [14,15].

Despite the extensive studies investigating the association between the *ICAM-1* K469E gene polymorphism and IBD, this relationship remains controversial. Therefore, it is necessary to perform a meta-analysis to evaluate the association of the *ICAM-1* K469E gene polymorphism with IBD risk by pooling the results from these

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Received October 02, 2014; **Accepted** December 02, 2014; **Published** December 04, 2014

Citation: Qiu Y, Liu Q, Chen G, Xu C, Peng K, et al. (2014) Intracellular Adhesion Molecule-1 K469E Gene Polymorphism and the Risk of Inflammatory Bowel Disease: A Meta-Analysis. Immunome Res 10: 082. doi: 10.4172/17457580.1000082

published studies. The present meta-analysis, which included nine eligible published case–control studies, was performed to obtain a reliable conclusion regarding the relationship between the *ICAM-1* K469E gene polymorphism and IBD.

Materials and Methods

Search strategy for the identification of studies

We searched the PubMed, EMBASE, and Web of Science databases for studies published before Aug 20, 2014, using "inflammatory bowel disease", "IBD", "Crohn's disease", "CD", "ulcerative colitis", and "UC" in combination with "intracellular adhesion molecule-1", "intracellular adhesion molecule 1", "ICAM-1", and "ICAM 1" as search terms. These computer searches were limited to human studies and English-language articles, and they did not include any unpublished dissertations or abstracts. In addition, the reference lists of all retrieved articles were examined for other eligible reports that might not have been identified using the aforementioned database search. When the same patient population was included in several publications, only the results from the most recent or most complete study were used in the present meta-analysis.

Inclusion criteria

The following inclusion criteria were used for the present meta-analysis: (1) each study had to examine the *ICAM-1*-K469E polymorphism in IBD; (2) only published case-control studies were included; (3) the full text article had to be available; (4) the study had to contain sufficient information and numbers of individuals of each genotype in both the IBD and control groups for estimating an odds ratio (OR) with a 95% confidence interval (CI), and (5) the study did not contain republished data.

Data extraction

Two of this study's authors (Y. Qiu and Q.X. Liu) independently extracted the data from all eligible studies. If these two authors could not reach a consensus, disagreements were discussed and resolved by a third author (G.Q. Chen). The following data were collected from each study: (1) the first author's last name; (2) the year of publication; (3) the country of the first author; (4) the ethnicity of the population examined; (5) the subtype of IBD; (6) case and control inclusion criteria; (7) the total number of cases and controls; and (8) the Hardy-Weinberg Equilibrium (HWE).

Statistical Analysis

In this meta-analysis, we assessed the association between the *ICAM-1* gene K469E polymorphism and IBD risk under recessive, dominant, allelic, and co-dominant models. Crude OR and 95% CI were calculated to compare and contrast the distribution of alleles and genotypes between patients and controls.

Deviations from Hardy-Weinberg equilibrium were assessed using Pearson χ^2 test [16]. A random effect model using the DerSimonian and Laird method was employed to control for between-study heterogeneity in the individual effect size estimates [17]. Heterogeneity was evaluated using the I^2 statistic, which was documented as the percentage of the observed between-study variability that was due to heterogeneity rather than chance. The values for this statistic ranged from 0 to 100% [I^2= 0-25%, no heterogeneity; I^2=25-50%, moderate heterogeneity; I^2=50-75%, large heterogeneity; I^2=75-100%, extreme heterogeneity] [18]. When between-study heterogeneity was observed, we examined potential study characteristics that would allow for the stratification of studies into subgroups with homogeneous effects. Subgroup analyses were conducted after stratifying studies based on the ethnic populations examined or based on the different disease subtypes under investigation.

Finally, evidence for publication bias was assessed using Egger's tests and visual funnel plot inspections. Egger's tests detect funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the standardized effect estimates against their precision [19].

The significance threshold was set at p=0.05 for all tests except the I^2 statistic and publication tests, for which a significance level p=0.1 was chosen. Statistical analyses were performed using STATA version 12.0 for Windows (StataCorp LP, College Station, Texas, USA).

Results

Search results

Figure 1 outlines the study selection process. Briefly, an initial search identified a total of 85 articles. Upon reading the abstracts, we removed 69 articles that did not pertain to the relevant *ICAM-1* polymorphism and IBD susceptibility. After the full texts of the remaining 16 articles were examined, seven additional articles were excluded. Ultimately, a total of nine case-control studies examining 1944 IBD patients and 1316 controls were determined to meet our inclusion criteria [4,12-15, 20-23].

Study characteristics

A list of details of all studies included in the meta-analysis is provided in Table 1. Among the nine included studies, only one study focused exclusively on UC [21]; the other eight studies analyzed both UC and CD. One study was conducted in the USA, one in Germany, one in Japan, one in Britain, one in Italy, one in Turkey, one in New Zealand, one in the Czech Republic, and one in Tunisia. Eight studies involved Caucasian participants, and one study involved East Asian participants. Most cases were diagnosed based on clinical, radiological, endoscopic, and histological parameters. Controls consisted primarily of healthy individuals who were matched with cases for gender, age, ethnicity, and residential area (Table 2). The distribution of genotypes in the control group deviated from HWE in three of the included studies [4,13,15].

Overall effects

The association between the *ICAM-1* K469E polymorphism and IBD was investigated in nine studies with 1944 IBD cases and

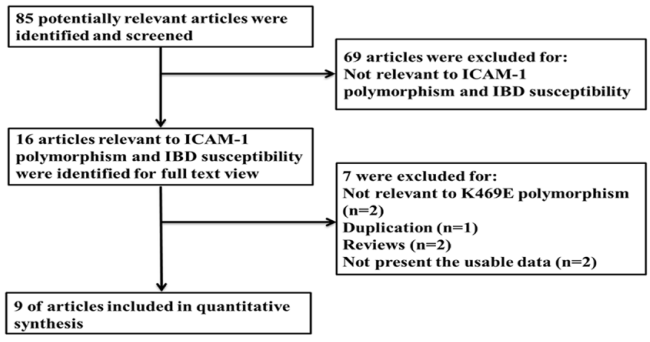

Figure 1: The flowchart of study selection based on the inclusion and exclusion criteria.

First author (Reference)	Year	Country	Ethnicity	Type of disease	Case/Control	Genotyping method	HWE Y/N (p)
Yang [14]	1995	USA	Caucasian	CD,UC	248/77	Probe	Y(0.83292)
Braun [4]	2001	Germany	Caucasian	CD,UC	217/116	Probe	N(0.00314)
Matsuzawa [12]	2003	Japan	Asian	CD,UC	207/103	PCR-RFLP	Y(0.76825)
Low [20]	2004	UK	Caucasian	CD,UC	471/286	Probe	Y(0.20645)
Papa [13]	2004	Italy	Caucasian	CD,UC	165/187	PCR-RFLP	N(0.02592)
Ozen [15]	2006	Turkey	Caucasian	CD,UC	190/106	PCR-RFLP	N(0.00004)
Hong [21]	2007	New Zealand	Caucasian	CD	182/188	PCR-RFLP	Y(0.92341)
Hosek [22]	2008	Czech	Caucasian	CD,UC	67/59	PCR-RFLP	Y(0.61323)
Khazen [23]	2009	Tunisia	Caucasian	CD,UC	197/194	PCR-RFLP	Y(0.37271)

HWE: Hardy–Weinberg Equilibrium; Y: Yes; N: No; IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis; CD: Crohn's Disease; PCR: Polymerase Chain Reaction; RFLP: Restriction Fragment Length Polymorphism

Table 1: Characteristics of individual studies included in the meta-analysis

First Author (Reference)	Case and control selection
Yang [14]	Case: diagnosis was established using endoscopic, histological, and clinical criteria
	Control: matched for age, sex, and ethnicity (without IBD, MS, SLE, and AID)
Braun [4]	Case: not mentioned
	Control: matched for age and sex
Matsuzawa [12]	Case: diagnosis was established using endoscopic, histological, and clinical criteria
	Control: healthy volunteers (without MS, SLE, and AID)
Low [20]	Case: clinical, radiological, endoscopic, and histological criteria
	Control: blood samples collected from health screening clinics
Papa [1]	Case: clinical, radiological, endoscopic, and histological criteria
	Control: matched for age and sex (without neoplastic, metabolic, or inflammatory disease)
Ozen [15]	Case: diagnosis and classification of IBD was made according to international criteria
	Control: matched for age and sex (without bowel disease)
Hong [21]	Case: clinical, radiological, endoscopic, and histological criteria
	Control: matched for age, sex, and ethnicity
Hosek [22]	Case: diagnosis was made according to standard examination methods
	Control: healthy volunteers (without IBD and with negative familiar case history)
Khazen [23]	Case: radiological, endoscopic, and histological criteria
	Control: matched for age and ethnicity (without AID and DM)

IBD: Inflammatory Bowel Disease; MS: Multiple Sclerosis; SLE: Systemic Lupus Erythematosus; AID: Autoimmune Disease; DM: Diabetes Mellitus.

Table 2: The criteria for selection of patients and controls in included studies

1316 controls. We first analyzed the heterogeneity of the five genetic models to choose the most suitable calculation model. The Q-test of heterogeneity (I^2>50%) was significant, and we conducted analyses using random effect models. No significant associations between the *ICAM-1* K469E polymorphism and IBD were observed (KK+KE vs. EE: OR=0.785, 95% CI=0.492-1.251, P=0.308, Figure 2; KK vs. KE+EE: OR=0.903, 95% CI=0.664-1.228, P=0.516; K vs. E: OR=0.892, 95% CI=0.701-1.135, P=0.352; EE vs. KK: OR=1.295, 95% CI=0.765-2.192, P=0.335; KE vs. KK: OR=1.052, 95% CI=0.789-1.402, P=0.729). Although three studies were shown to deviate from HWE, the corresponding pooled odds ratios (ORs) were not significantly altered by the exclusion of these three studies in all comparisons.

Analysis of the CD population

The association between the *ICAM-1* K469E polymorphism and CD was investigated in nine studies with 1029 CD cases and 1316 controls. There was strong evidence of between-study heterogeneity (I^2>50%), and we conducted our analyses using random effect models. No significant associations were observed in any of the five genetic models employed (KK+KE vs. EE: OR=0.754, 95% CI=0.438-1.298, P=0.308, Figure 3; KK vs. KE+EE: OR=0.895, 95% CI=0.623-1.287, P=0.55; K vs. E: OR=0.882, 95% CI=0.660-1.179, P=0.396; EE vs. KK: OR=1.371, 95% CI=0.730-2.577, P=0.327; KE vs. KK: OR=1.059, 95% CI=0.767-1.464, P=0.727). In addition, the pooled OR did not change in the meta-analysis by excluding the three studies that significantly deviated from HWE.

Analysis of UC population

The association between the *ICAM-1* K469E polymorphism and UC was investigated in eight studies with 915 UC cases and 1316 controls. Between-study heterogeneity was not detected in the comparisons of KK vs. KE+EE and KE vs. KK. Thus, we chose the fixed effect model to synthesize the data in these two models. Our meta-analysis reveals no evidence of a significant association between K469E polymorphism and UC susceptibility using any of the genetic models employed in the overall analysis (KK+KE vs. EE: OR=0.831, 95% CI=0.516-1.338, P=0.447, Fig. 4; KK vs. KE+EE: OR=1.013, 95% CI=0.772-1.328, P=0.926; K vs. E: OR=0.953, 95% CI=0.771-1.177, P=0.652; EE vs. KK: OR=1.119, 95% CI=0.690-1.816, P=0.648; KE vs. KK: OR=0.945, 95% CI=0.712-1.253, P=0.693) or in the analysis excluding the three studies that deviated from HWE.

Analyses in the caucasian population

The association between the *ICAM-1* K469E polymorphism and IBD in the Caucasian population was investigated in eight studies with 1737 IBD cases and 1213 controls. There was strong evidence of between-study heterogeneity (I^2>50%), and we conducted our analyses using random effect models. No significant associations were observed between this polymorphism and IBD in the Caucasian population (Figure 2). In the allelic model, the pooled OR was 0.827 (95% CI: 0.661-1.036), and the associated Z value was 1.34 (p=0.181). These results suggested the possibility that K allele carriers have a lower risk

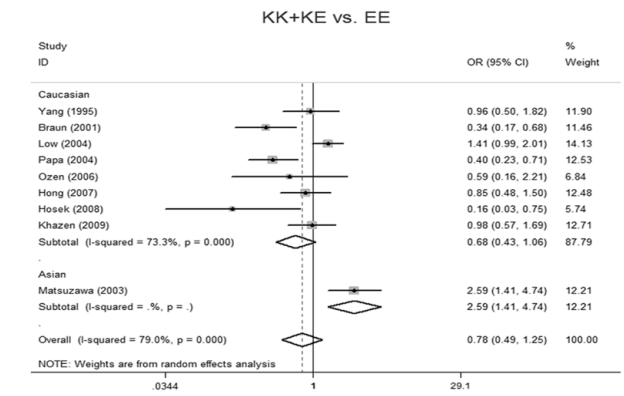

Figure 2: Meta-analysis for the association between *ICAM-1* K469E gene polymorphism and IBD susceptibility in the recessive model (KK + KE vs. EE), stratified by different ethnicity.

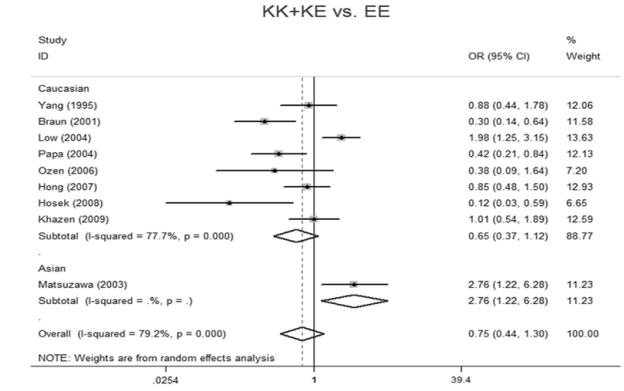

Figure 3: Meta-analysis for the association between *ICAM-1* K469E gene polymorphism and CD susceptibility in the recessive model (KK + KE vs. EE), stratified by different ethnicity.

of IBD than carriers of the E allele, but these results did not achieve statistical significance.

In the subgroup analysis stratified by CD and UC, no significant associations between the *ICAM-1* K469E polymorphism and CD or UC were observed in the Caucasian population.

Analyses in the East Asian population

The association between the *ICAM-1* K469E polymorphism and IBD was investigated in the East Asian population in one study with 128 UC cases, 79 CD cases, and 103 controls. A significant association between the K469E polymorphism and IBD was observed in the East Asian population when examining the comparisons of KK+KE vs. EE (OR=2.586, 95% CI=1.411-4.742, Figure 2), KK vs. KE+EE (OR=1.828, 95% CI=1.081-3.092), K vs. E (OR=1.739, 95% CI=1.240-2.439), EE vs. KK (OR=0.305, 95% CI=0.151-0.615).

In the subgroup analysis stratified by CD and UC, the results for the CD subgroup were similar to those of the overall study (for KK+KE vs. EE: OR=2.763, 95% CI=1.215-6.282, P=0.015, Figure 3; KK vs. KE+EE: OR=2.125, 95% CI=1.131-3.991, P=0.019; K vs. E: OR=1.909, 95% CI=1.247-2.924, P=0.003; EE vs. KK: OR=0.263, 95% CI=0.105-0.654, P=0.004). Moreover, we found a significant association between the K469E polymorphism and UC risk (for KK+KE vs. EE: OR=2.487, 95% CI=1.255-4.926, P=0.009, Figure 4; K vs. E: OR=1.644, 95% CI=1.134-2.384, P=0.009; EE vs. KK: OR=0.335, 95% CI=0.153-0.733, P=0.006).

Sensitivity analysis

Sensitivity analyses were conducted by omitting individual studies sequentially. For the *ICAM-1* K469E polymorphism and IBD (i.e., both CD and UC) susceptibility, the results did not change under any genetic models, and in some conditions, the indicators for heterogeneity were reduced. Sensitivity analyses suggested that the results for the *ICAM-1* K469E polymorphism and IBD susceptibility were stable and statistically robust (Figure 5). However, we found that the results would become statistically significant in both the recessive genetic model (KK+KE vs. EE) and the allelic model (K vs. E) for the *ICAM-1* K469E polymorphism and IBD (CD and UC) susceptibility in the Caucasian population if the study by Low *et al* was removed (Figure 6) [20].

Publication bias

Begg's funnel plot and Egger's tests were performed to assess publication bias within the literature. No obvious asymmetry was observed in any genetic model according to visual assessments of the funnel plots (Figure 7). Similarly, Egger's tests did not provide any evidence of publication bias (p=0.143 for KK+KE vs. EE, p=0.163 for KK vs. KE+EE).

Discussion

To the best of our knowledge, the present study involving 3260 subjects represents the first meta-analysis investigating the relationship between the *ICAM-1* K469E Gene Polymorphism and the risk for IBD. Our results suggest that there is no significant association between the K469E polymorphism and IBD susceptibility in the Caucasian population or in the overall analysis, regardless of the genetic model used. However, a significant association was observed between K469 and IBD in the East Asian population. Because this meta-analysis included only one study performed in an East Asian population, we cannot completely exclude the possibility of a false positive association between the *ICAM-1* K469E polymorphism and IBD in this population. Nonetheless, the relatively large samples examined and the low probability of publication bias, which is reflected in the funnel plots and the results from Egger's tests, indicated the robustness of our results.

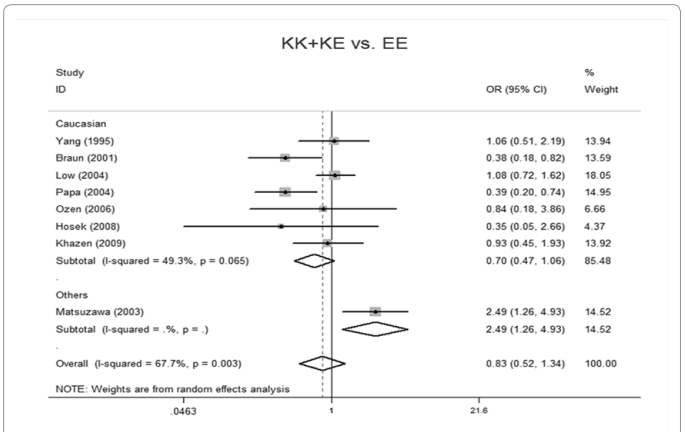

Figure 4: Meta-analysis for the association between *ICAM-1* K469E gene polymorphism and UC susceptibility in the recessive model (KK + KE vs. EE), stratified by different ethnicity.

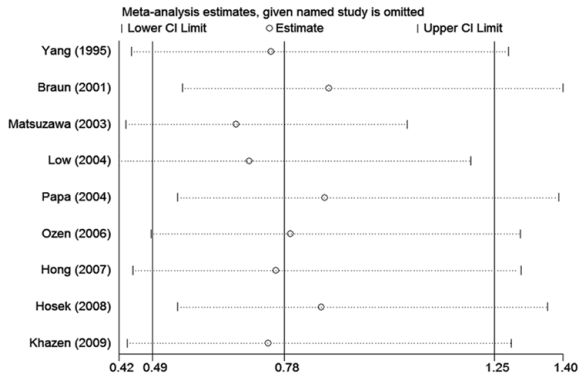

Figure 5: Sensitivity analysis of the summary odds ratio coefficients on the association between *ICAM-1* K469E polymorphism and IBD risk (KK + KE vs. EE). Results were computed by omitting each study in turn. Meta-analysis random-effect estimates (exponential form) were used. The two ends of the dotted lines represent the 95% CI.

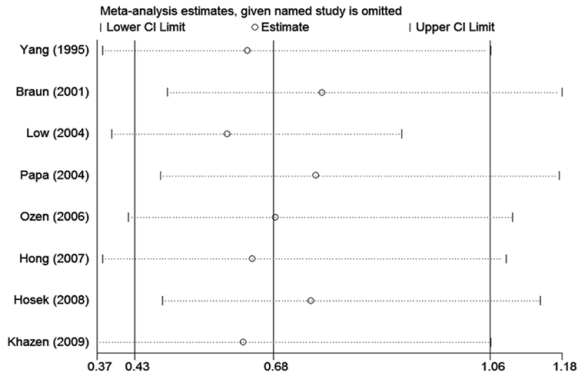

Figure 6: Sensitivity analysis of the summary odds ratio coefficients on the association between *ICAM-1* K469E polymorphism and IBD risk in Caucasian (KK + KE vs. EE). Results were computed by omitting each study in turn. Meta-analysis random-effect estimates (exponential form) were used. The two ends of the dotted lines represent the 95% CI.

Evidence implicating ICAM-1 in the pathogenesis of UC and CD comes from both human and animal studies [24]. The K allele of the *ICAM-1* K469E gene polymorphism could alter the structure and function of the ICAM-1 D5 functional region. This region has been implicated in the dimerization of ICAM-1 and is thought to play an important role in its adhesion function. Mutations in this region may also affect the binding of ICAM-1 to ligands such as the lymphocyte function–associated antigen-1 (LFA-1) and the complement receptor 3 (CR3) [25,26]. These alterations in ICAM-1-ligand combinations have been reported to enhance the adhesion of leukocytes to vascular endothelial cells and facilitate their infiltration into mucosa [5,27]. ICAM-1 has been widely studied in recent years, and several recent studies have suggested that the *ICAM-1* K469E gene polymorphism is associated with IBD susceptibility. However, the reported associations have been variable, with only a subset of studies finding this association to be significant. Because of these conflicting results, a comprehensive meta-analysis was required to assess the importance of the *ICAM-1* K469E gene polymorphism in the pathogenesis of IBD.

In general, the nine studies included in our meta-analysis were of high quality. Most of the studies clearly stated their total sample size, the inclusion criteria for study subjects, the characteristics of participants, and the methods used for genotyping. Cases and controls were matched in age and gender, but the control groups from three of the studies deviated from HWE [4,13,15].

Of the nine datasets regarding the K469E polymorphism and IBD susceptibility, eight consisted entirely of data from Caucasian subjects [4,13-15,20-23], and one dataset was obtained from East Asian subjects [12]. The studies by Braun et al., Papa et al., and Hozek et al. suggested that E carriers are more susceptible to IBD, whereas the studies by Low et al. and Matsuzawa et al. reported that E carriers are associated with a lower incidence of IBD. The other four studies reported no significant associations between the K469E polymorphism and IBD, including CD and UC. The results from our meta-analysis demonstrate that there is no significant association between the K469E polymorphism and IBD susceptibility using any of the genetic models employed in our overall analysis or in Caucasian populations. Interestingly, in our ethnicity-stratified analyses, the finding was not always stable. For example, when the study by Low et al., was removed, significant associations were observed between the *ICAM-1* K469E gene polymorphism and IBD (KK+KE vs. EE: OR=0.597, 95% CI=0.395-0.902; K vs. E: OR=0.776, 95% CI=0.653-0.921), CD (KK+KE vs. EE: OR=0.555, 95% CI=0.351-0.877; K vs. E: OR=0.745, 95% CI=0.611-0.907), and UC (KK+KE vs. EE: OR=0.611, 95% CI=0.396-0.941; K vs. E: OR=0.836, 95% CI=0.708-0.987) in the Caucasian population (Figure 6). Notably, the study by Low et al. had the largest sample size of any of the studies examined. Thus, the results related to the Caucasian population should be interpreted with caution. In addition, the significant association we observed in the East Asian population in the present study should be evaluated in future studies because of the possibility of false positive results given the relatively small number of Asian populations used in the current analysis (i.e., only one study by Matsuzawa et al.).

Because the publication of findings often depends on the expectations of researchers, false negative results can be suppressed or false positive results can be magnified [28]. Although the results of the current study did not reveal significant publication bias, the number of studies included in this meta-analysis was small and large inter-study heterogeneity was observed. Significant heterogeneity existed in the overall comparisons from each genetic model. The observed heterogeneity could be attributed to differences in several factors, such as the IBD subtype, anti-neutrophil cytoplasmic antibodies status, ethnic variations, environmental factors, and methodological factors in the design and conduct of the different studies [29]. The differing genetic backgrounds of various racial or ethnic populations with different allele frequencies may affect IBD susceptibilities and could influence the genetic heterogeneity observed between different ethnicities [30,31].

Several limitations of this study should also be discussed. First, heterogeneity is a potential problem when interpreting any results obtained through meta-analyses. We minimized the likelihood of this problem by performing a careful search for published studies, using explicit criteria for study inclusion, precise data extraction techniques, and strict data analysis, such as excluding studies that significantly departed from HWE. However, some pooled ORs were obtained from heterogeneous studies. Second, most of the original studies included in the current analysis examined Caucasian populations. Only one study was conducted among Asian subjects. Additional studies in Asians and in individuals of other ethnicities are required to generalize these findings. Finally, the current meta-analysis only included published studies, not abstracts from meetings or conferences. Thus, publication bias may have occurred even though the employed statistical tests did

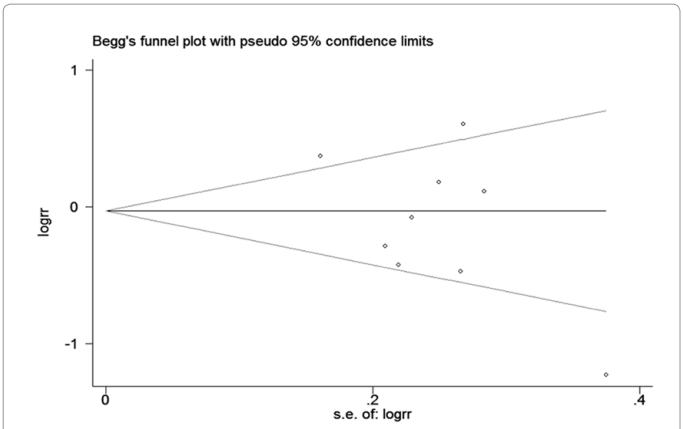

Figure 7: Begg's funnel plot analysis to detect publication bias for KK + KE vs. EE genotype. Each point represents a separate study for the indicated association.

not reveal it.

In summary, our meta-analysis of nine independent studies identified no significant associations between the *ICAM-1* K469E gene polymorphism and IBD risk. However, given the small number of studies examined in this meta-analysis (and the overall small sample size), larger, multi-center investigations, especially in Asia, are warranted for further confirmation of our results.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgement

This work was supported by funding from the National Natural Science Foundation of China (NSFC 81330013 and NSFC 81272078 to H.Y., NSFC 81270451 to W.D.X.) and the Program for Chang Jiang Scholars and Innovative Research Team in University ((2013) 59 to H.Y.).

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