Systematic Review/Meta-analysis

Protective association of TNFSF15 polymorphisms with Crohn's disease and ulcerative colitis: A meta-analysis

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Abstract

Background/Aims: Three extensively investigated polymorphisms (rs3810936, rs7848647, and rs6478108) in tumor necrosis factor super family member 15 (TNFSF15) gene have been implicated in risk for inflammatory bowel disease (IBD). We performed a quantitative synthesis of the evidence to clarify these associations of TNFSF15 polymorphisms with IBD.

Materials and Methods: Data were extracted from PubMed and EMBASE, up to March 15, 2018. Meta-analysis was performed by critically reviewing five studies for rs3810936 polymorphism (2251 cases and 2442 controls), four studies for rs7848647 polymorphism (1503 cases and 1816 controls), and four studies for rs6478108 polymorphism (1502 cases and 1817 controls).

Results: Our analysis suggested that rs3810936 polymorphism was significantly associated with decreased risk of Crohn's disease (CD) and ulcerative colitis (UC). For rs7848647 polymorphism, significantly protective association between this polymorphism and CD risk was also observed, but not in UC. For rs6478108 polymorphism, we also detected a significantly protective association with CD risk in all genetic model but not in UC.

Conclusions: This meta-analysis suggests that TNFSF15 polymorphisms may contribute to genetic susceptibility of IBD.

Keywords: Inflammatory bowel diseases, meta-analysis, polymorphism, TNFSF15

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INTRODUCTION

The inflammatory bowel diseases (IBD), including Crohn's diseases (CD) and ulcerative colitis (UC), are characterized by chronic progressive diseases of the gastrointestinal tract resulting from interactions between host genotypes and the microbiome.[1,2] Many environmental and lifestyle factors including diet, environmental carcinogens, and dwelling condition have been reported to be associated with an elevated IBD risk, but IBD are complex diseases in which the susceptibility depends on both genetic predisposition and environmental exposure. Intense and inappropriate mucosal immune responses to constituents of the intestinal microbiota contribute to the genesis of IBD, and these are determined by complex poorly understood genetic factors that confer vulnerability.[3,4] However, only a minority of

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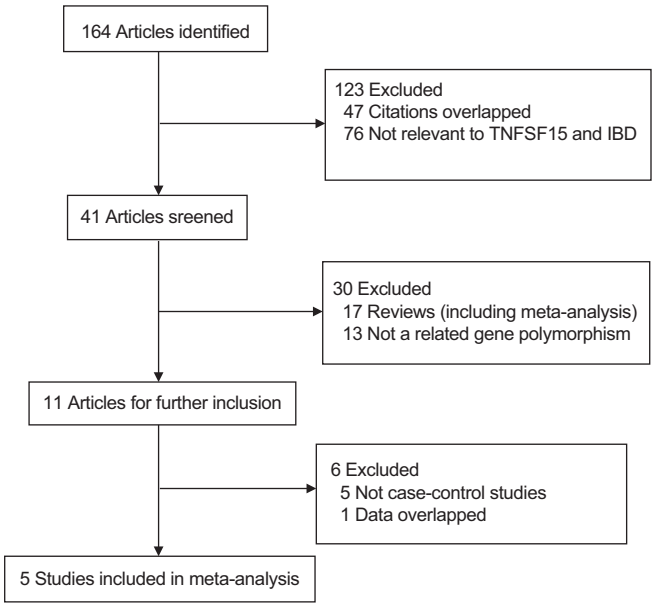

Figure 1: Flow of included studies

those exposed to changes in gut microbiota, that maintain homeostasis of the mucosal surface, eventually develop IBD, suggesting that genetic factors, such as single nucleotide polymorphisms (SNPs), may be crucial in modifying the risk for IBD.[5,6]

The tumor necrosis factor super family member 15 gene (TNFSF15) is a strong candidate IBD gene encoding a novel TNF-like factor. Previous immunological studies have demonstrated that increased TNFSF expression by macrophages, lymphocytes, and plasma cells in intestinal tissue from IBD patients compared to normal controls is further upregulated in inflamed intestine.[7] TNFSF15 binds to specific T-cell receptors and enhances in mucosal CD4+ T cells in synergy with interleukins 12 and 18 (IL12 and 18).[8]

To date, several epidemiologic studies have been performed to elucidate the effect of TNFSF15 polymorphism on IBD risk. TNFSF15 was the first CD-susceptibility gene identified through a genome-wide association screening (GWAS) of 72,738 SNPs in the Japanese population.[9] The association was well replicated in Korean and US populations.. The results of previous studies remain inconsistent across these studies due to limitations in individual studies to examine the association between TNFSF15 polymorphisms and the risk of IBD.

MATERIALS AND METHODS

Search strategy

All relevant studies on the association between TNFSF15 polymorphisms and IBD risk published up to March 15, 2018 were identified through literature searches using PubMed, EMBASE, Cochrane Library, and Web of Science, with the following terms and keywords: ("the tumor necrosis factor super family member 15" or "TNFSF15") and ("polymorphism" or "variation" or "mutation") and ("inflammatory bowel disease" OR "IBD" or "Crohn's diseases" or "CD" or "Ulcerative Colitis" or "UC"). The references cited in all studies were also reviewed to identify additional published articles, which were potentially not indexed by the above databases.

Inclusion criteria

Studies which met the following criteria were included in our meta-analysis: (1) A case–control study evaluating the TNFSF15 polymorphisms; (2) studies with full-text articles; (3) containing enough data for estimating the odds ratios (ORs) with the corresponding 95% confidence interval (CI); (4) no overlapping data.

Data extraction

Information was carefully extracted from all the eligible studies independently by two researchers according to the inclusion criteria listed above and a consensus reached on all the eligibility terms of reference. The following data were collected from each study: first author, publication year, total numbers of cases and controls, numbers of cases and controls for CD and UC, and result of the Hardy-Weinberg equilibrium (HWE) test. We did not define any minimum number of patients for inclusion in our meta-analysis.

Statistical analysis

Odds ratios with a corresponding 95% CI were used as the common measure of assessing the strength of association between TNFSF15 polymorphisms (rs3810936, rs7848647, and rs6478108) and IBD risk for each study. The pooled ORs were calculated in additive model (a allele vs. A allele, a was for the minor allele and A was for the major allele), dominant model (aa + Aa vs. AA), recessive model (aa vs. Aa + AA), and co-dominant model (aa vs. AA, Aa vs. AA).[10] The significance of the pooled ORs was determined by Z-test, and the level of statistical significance was established as $P < 0.05$. The heterogeneity among studies was checked by the Q-test.[11] The I^2 statistic, which is a quantitative measure of the proportion of the total variation across studies due to heterogeneity,[12] was also calculated. If the P value for the heterogeneity test was >0.05, the Mantel–Haenszel method-based fixed effects model was used to calculate the pooled OR.[13] Otherwise, the DerSimonian and Laird method-based random effects model was performed.[14] Potential publication bias was evaluated by visual inspection of the Begg funnel plots in which the standard error of log (OR) of each study was plotted against its log (OR). We

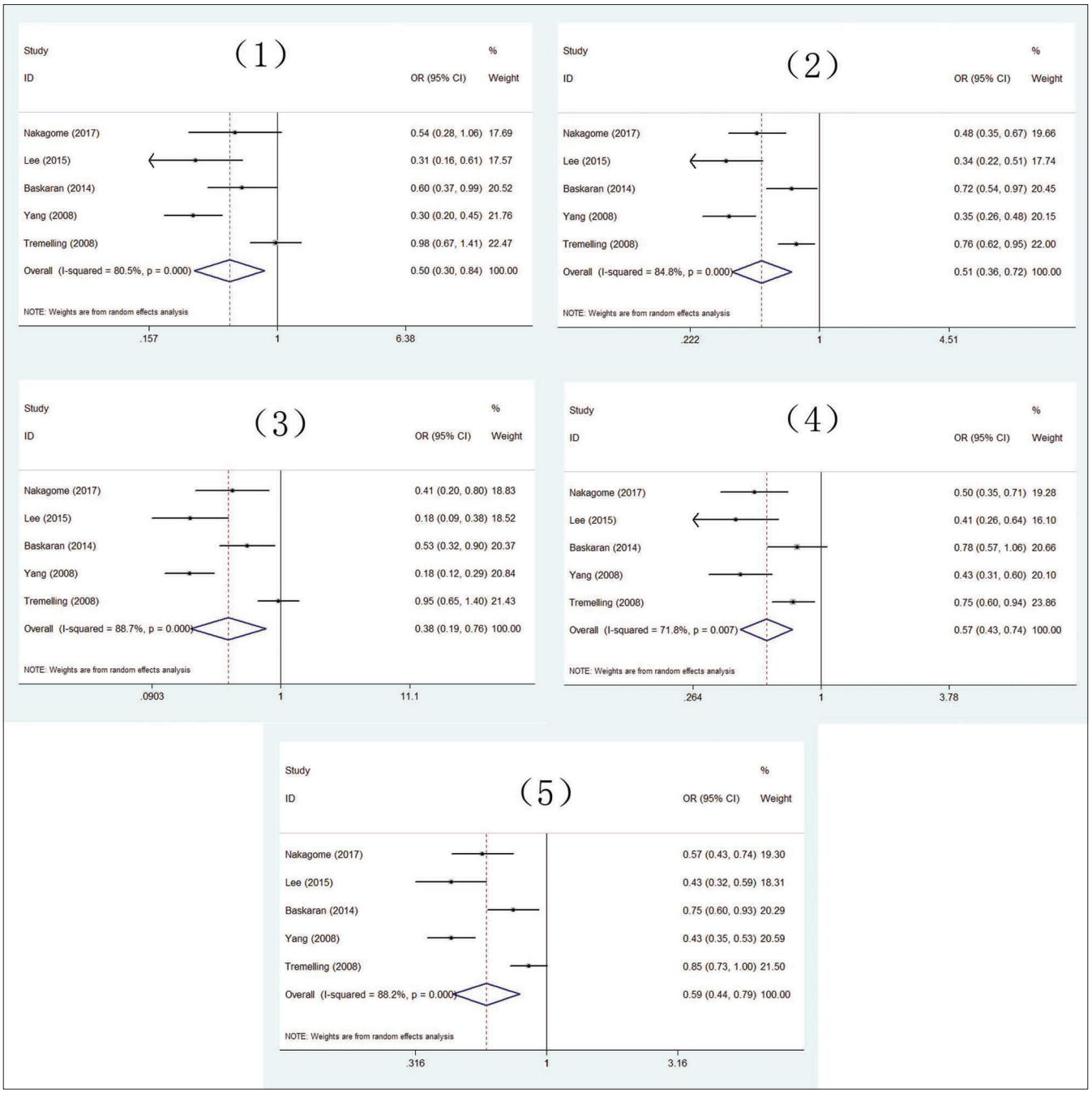

Figure 2: Forest plots of ORs with 95% CI for TNFSF15 rs3810936 polymorphism and the risk of CD (random effects). The center of each square represents the OR, the area of the square is the number of sample and thus the weight used in the meta-analysis, and the horizontal line indicates the 95% CI. (1) Recessive model. (2) Dominant model. (3) T/T vs. C/C. (4) C/T vs. C/C. (5) Additive model

also performed Egger's linear regression test ($P < 0.05$ was considered a significant publication bias).[15] All statistical analyses were performed using software programs STATA version 12.0 (Stata, College Station, TX, USA).

RESULTS

Extraction process and study characteristics

According to our search criterion, 164 articles were retrieved. Among them, the majority were excluded after the first screening based on abstracts or titles, mainly because for reasons of overlapped citations, not relevant to the TNFSF15 polymorphisms and IBD risk, reviews, conference abstracts, or not a related gene polymorphism. Eventually, a total of five case–control studies were selected,[16-20] including five studies for rs3810936 polymorphism (2251 cases and 2442 controls), four studies for rs7848647 polymorphism (1503 cases and 1816 controls), and four studies for rs6478108

polymorphism (1502 cases and 1817 controls) [Figure 1]. The characteristics of these included studies and the genotype distribution and allele frequency of TNFSF15 polymorphisms in case- and control-studies are shown in Table 1.

Overall analyses of outcomes

The main results of the meta-analysis are shown in Table 2. Our results revealed that rs3810936 polymorphism was significantly associated with decreased risk of CD (T/T vs. C/C: OR = 0.38, 95% CI = 0.19–0.76, *P* = 0.000; C/T vs. C/C: OR = 0.57, 95% CI = 0.43–0.74, *P* = 0.003; recessive model: OR = 0.50, 95% CI = 0.30–0.84, *P* = 0.000; dominant model: OR = 0.51, 95% CI = 0.36–0.72, *P* = 0.000; additive model: OR = 0.59, 95% CI = 0.44–0.79, *P* = 0.000 [Figure 2 and Table 2]); and UC (T/T vs. C/C: OR = 0.53, 95% CI = 0.34–0.81, *P* = 0.000; C/T vs. C/C: OR = 0.64, 95% CI = 0.51–0.81, *P* = 0.003; recessive model: OR = 0.54, 95% CI = 0.36–0.83, *P* = 0.000; additive model: OR = 0.82, 95% CI = 0.69–0.97, *P* = 0.000 [Figure 3 and Table 2]). For rs7848647 polymorphism, significantly protective association between this polymorphism and CD risk was also observed (T/T vs. C/C: OR = 0.27, 95% CI = 0.15–0.47, *P* = 0.000; C/T vs. C/C: OR = 0.50, 95% CI = 0.28–0.89, *P* = 0.003; recessive model: OR = 0.36, 95% CI = 0.27–0.49, *P* = 0.000; dominant model: OR = 0.44, 95% CI = 0.25–0.80, *P* = 0.000; additive model: OR = 0.52, 95% CI = 0.36–0.76, *P* = 0.000 [Figure 4 and Table 2]), but not in UC. For rs6478108 polymorphisms, we also detected significantly protective association with CD risk (C/C vs. T/T: OR = 0.27, 95% CI = 0.15–0.47, *P* = 0.000; T/C vs. T/T: OR = 0.52, 95% CI = 0.28–0.97, *P* = 0.003; recessive model: OR = 0.36, 95% CI = 0.27–0.48, *P* = 0.000; dominant model: OR = 0.46, 95% CI = 0.24–0.86, *P* = 0.000; additive model: OR = 0.53, 95% CI = 0.36–0.80, *P* = 0.000 [Figure 5 and Table 2]) in all genetic models but not in UC.

Heterogeneity and sensitivity analyses

The results of heterogeneity test indicated that there was no significant heterogeneity for all polymorphisms of UC across studies [Table 2]. However, we found heterogeneity for CD [Table 2]. Although one study deviated from HWE for the rs3810936 polymorphism, one study deviated from HWE for the rs7848647 polymorphism and two studies deviated from HWE for the rs6478108 polymorphism, the corresponding pooled ORs were not altered by including or not including these studies [Table 2]. Additionally, we also evaluated the influence of each individual study on the pooled ORs by sequential omission of individual studies. The results showed that the pooled ORs of these three polymorphisms were not materially altered by the contribution of any individual study, suggesting that the results of this meta-analysis are credible (data also not shown).

Publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias of literature. All these three genetic polymorphisms showed consistent results, indicating no evidence of publication bias in the meta-analysis. If we take rs3810936 polymorphism as an example, the shapes of the funnel plot did not indicate any evidence of obvious asymmetry in these five models [Figure 6], and the Egger's test suggested the absence of publication bias (*P* = 0.354 for T/T vs. C/C, *P* = 0.128 for C/T vs. C/C, *P* = 0.496 for recessive model, *P* = 0.107 for dominant model, and *P* = 0.216 for additive model).

DISCUSSION

TNFSF15, a member of the tumor necrosis factor super family, plays an important role in activation and proliferation of T cells. An increased expression level of TNFSF15 in intestinal lamina propria cells correlated with the degree of intestinal inflammation in CD and

Table 1: Characteristics of studies included in the meta-analysis and their genotype distributions of TNFSF15 polymorphisms

Polymorphism	First author	Year	Case (CD/UC)	Control	CD			UC			Control			MAF
					AA	Aa	aa	AA	Aa	aa	AA	Aa	aa	
rs3810936	Nakagome	2017	223/164	412	139	72	12	74	80	10	183	190	39	0.324
	Lee	2015	108/-	599	52	46	10	–	–	–	143	307	149	0.505
	Baskaran	2014	302/325	430	152	125	25	156	146	23	182	192	56	0.353
	Yang	2008	380/-	378	181	164	35	–	–	–	91	191	96	0.507
	Tremelling	2008	749/-	623	371	311	67	–	–	–	267	299	57	0.331
rs7848647	Nakagome	2017	223/164	412	153	60	10	78	78	8	200	185	27	0.290
	Lee	2015	108/-	595	54	46	8	–	–	–	146	313	136	0.492
	Baskaran	2014	304/324	431	176	117	11	194	112	18	246	149	36	0.246
	Yang	2008	380/-	378	208	141	31	–	–	–	96	199	83	0.483
rs6478108	Nakagome	2017	223/164	412	146	67	10	76	80	8	189	194	29	0.306
	Lee	2015	108/-	599	54	46	8	–	–	–	144	315	140	0.497
	Baskaran	2014	303/324	429	166	125	12	186	115	23	241	150	38	0.263
	Yang	2008	380/-	377	205	143	32	–	–	–	95	197	85	0.486

MAF: Minor allele frequency; A: the major allele; a: the minor

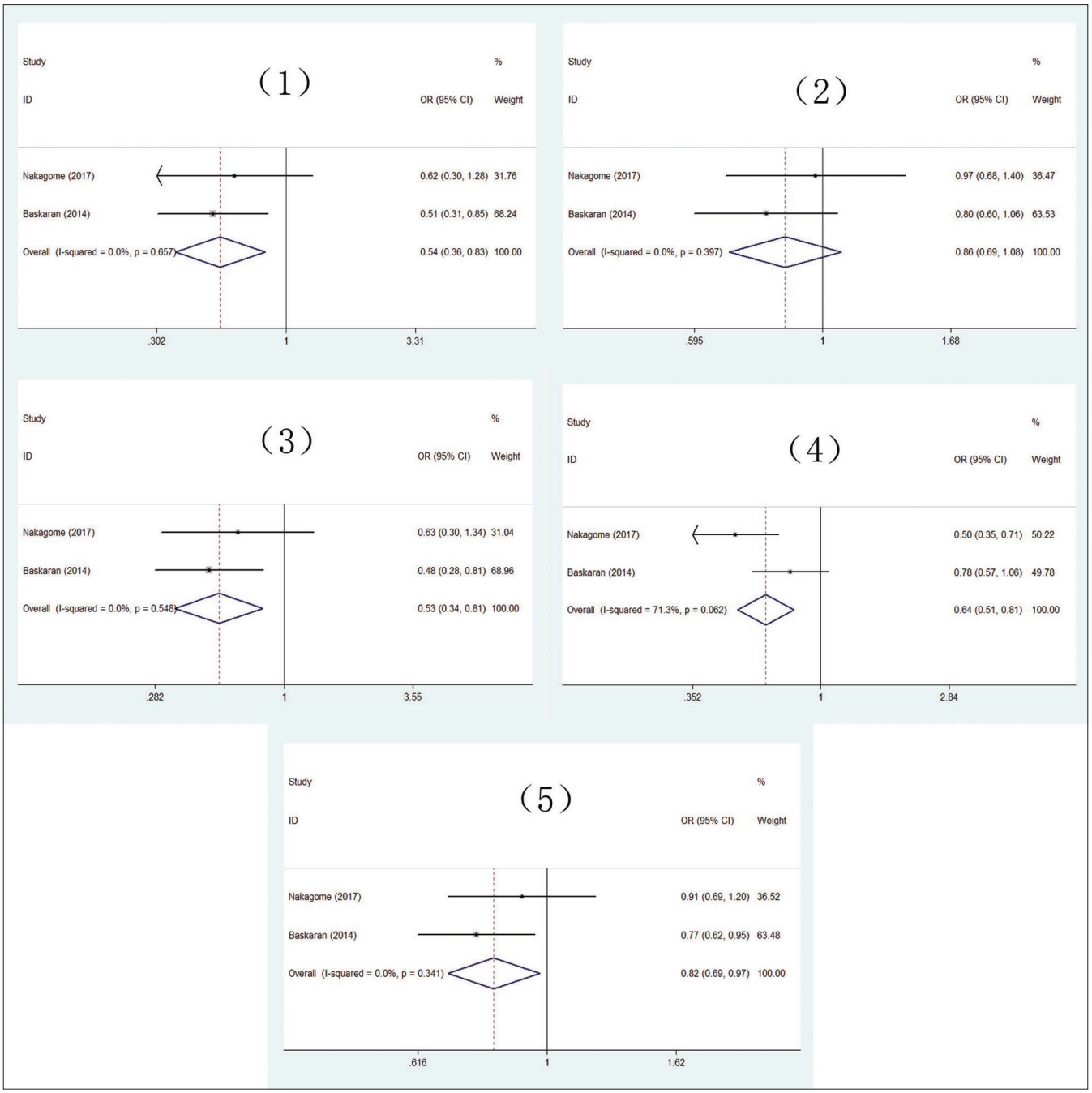

Figure 3: Forest plots of ORs with 95% CI for TNFSF15 rs3810936 polymorphism and the risk of UC (fixed effects). The center of each square represents the OR, the area of the square is the number of sample and thus the weight used in the meta-analysis, and the horizontal line indicates the 95% CI. (1) Recessive model. (2) Dominant model. (3) T/T vs. C/C. (4) C/T vs. C/C. (5) Additive model

UC patients. This was accompanied by cytokine-induced interferon-gamma production by CCR9+ mucosal and gut-homing T cells, resulting in generation of enhanced Th1 responses and mucosal inflammation. TNFSF15 encodes a ligand for the receptor of TNFRSF25 and a decoy receptor of TNFRSF21/DR6 and has been shown to respond to a bacterial infection and to activate the nuclear factor-κB pathway. Although epidemiological studies investigate the association of TNFSF15 polymorphisms with CD and UC risk, the individual studies might have been underpowered to detect the overall effect of polymorphisms on the susceptibility to CD and UC, and our meta-analysis enhances the statistical power.

To the best of authors' knowledge, this is the first meta-analysis undertaken so far of the largest and most comprehensive assessment of the relationship

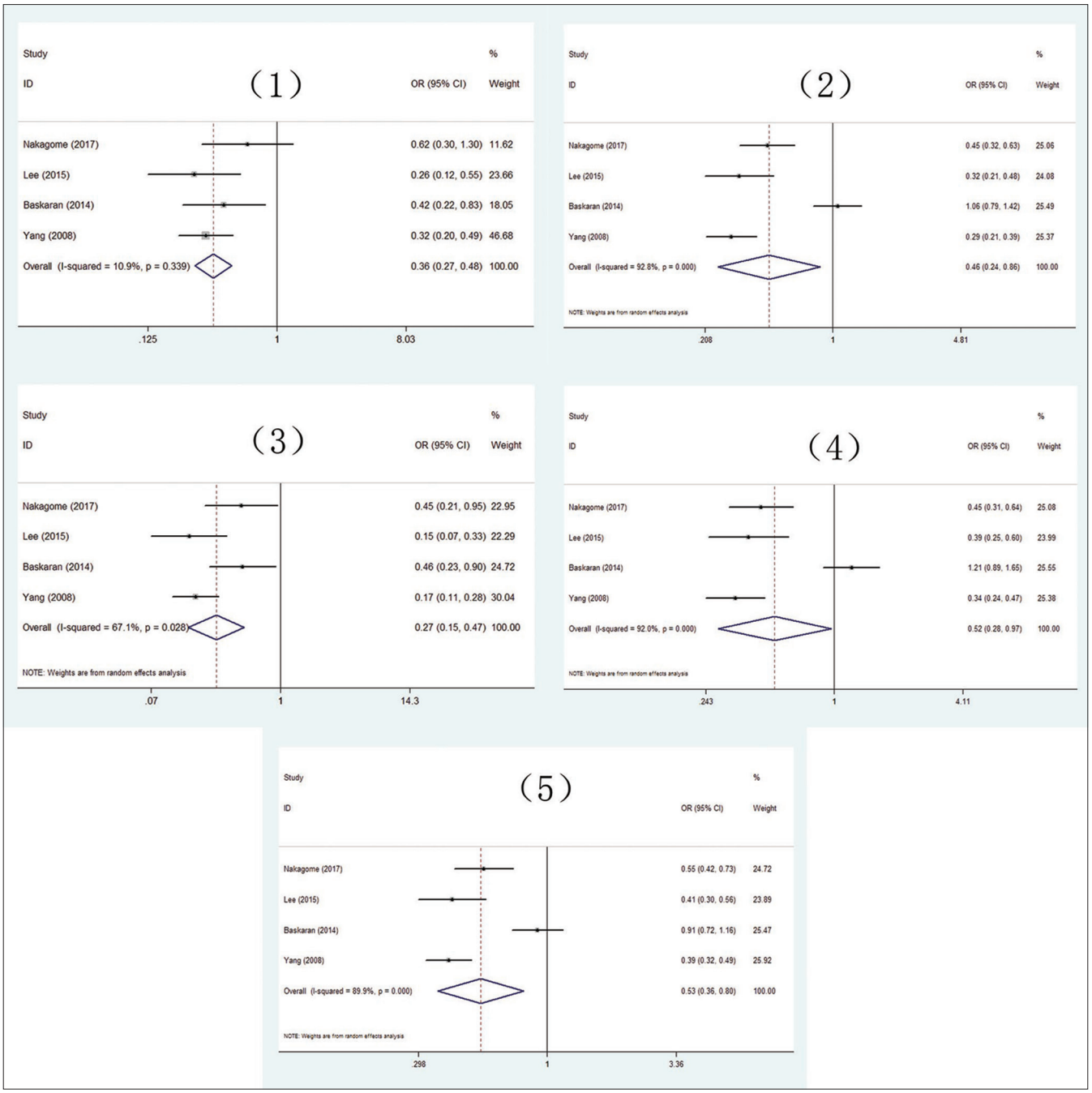

Figure 4: Forest plots of ORs with 95% CI for TNFSF15 rs7848647 polymorphism and the risk of CD (random effects). The center of each square represents the OR, the area of the square is the number of sample and thus the weight used in the meta-analysis, and the horizontal line indicates the 95% CI. (1) Recessive model. (2) Dominant model. (3) T/T vs. C/C. (4) C/T vs. C/C. (5) Additive model

between the TNFSF15 polymorphisms and the risk of CD and UC. Overall, our results suggest that rs3810936, rs7848647, and rs6478108 polymorphisms in TNFSF15 gene were associated with decreased risk of CD in all genetic models, which was consistent with the conclusion of individual studies involving these three polymorphisms. However we detected that only rs3810936 polymorphism might have a protective association of UC.

There was considerable heterogeneity for all polymorphisms of CD across studies but not in UC. The source of heterogeneity might have come from different genetic backgrounds, population stratification, and selection bias. The GWAS studies on SNP in IBD are highly specialized and may likely never go beyond the design of case–control studies. The number of published studies was not sufficiently large for stratified analysis in different ethnicities. In this meta-analysis, we performed sensitivity

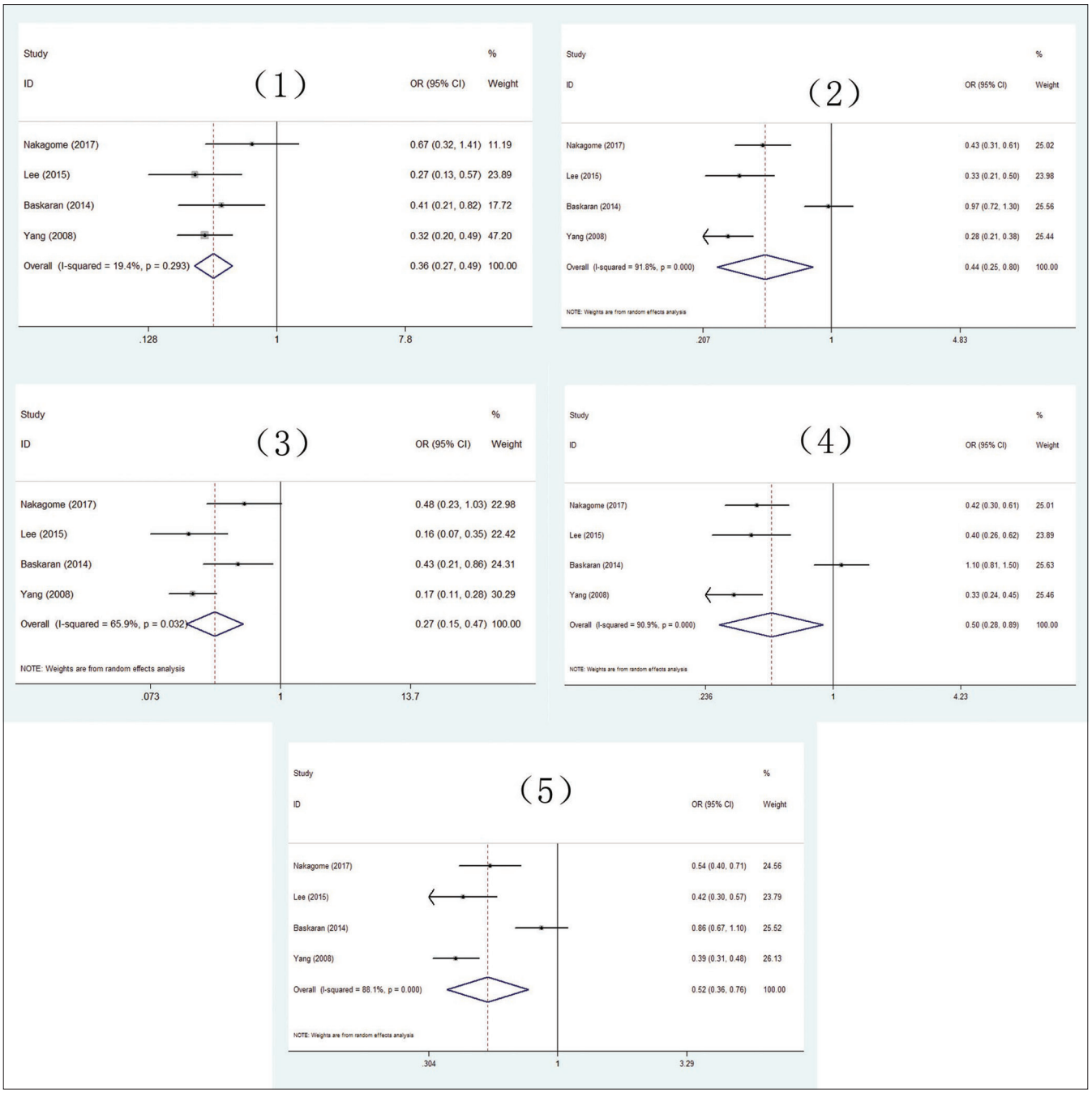

Figure 5: Forest plots of ORs with 95% CI for TNFSF15 rs6478108 polymorphism and the risk of CD (random effects). The center of each square represents the OR, the area of the square is the number of sample and thus the weight used in the meta-analysis, and the horizontal line indicates the 95% CI. (1) Recessive model. (2) Dominant model. (3) T/T vs. C/C. (4) C/T vs. C/C. (5) Additive model

analyses to check the robustness of our conclusion and the corresponding pooled ORs were not changed. In addition, we comprehensively assessed the publication bias using several means including the Begg's and Egger's tests as well as funnel plot tests, indicating no publication bias for these three genetic polymorphisms. In view of this, we are strongly convinced that the methods are appropriate and well described and the results or data of our meta-analysis, in essence, are sound and reliable.

When interpreting the results of the current study, some limitations should be addressed. First, the number of subjects and studies included in the meta-analysis were small to reveal the associations with IBD and lack the original data for the included studies, thus limiting further evaluation of the association between IBD risk and other risk factors, such as age, gender, environment factors, and other variables, which might have caused serious confounding bias. Second, we did

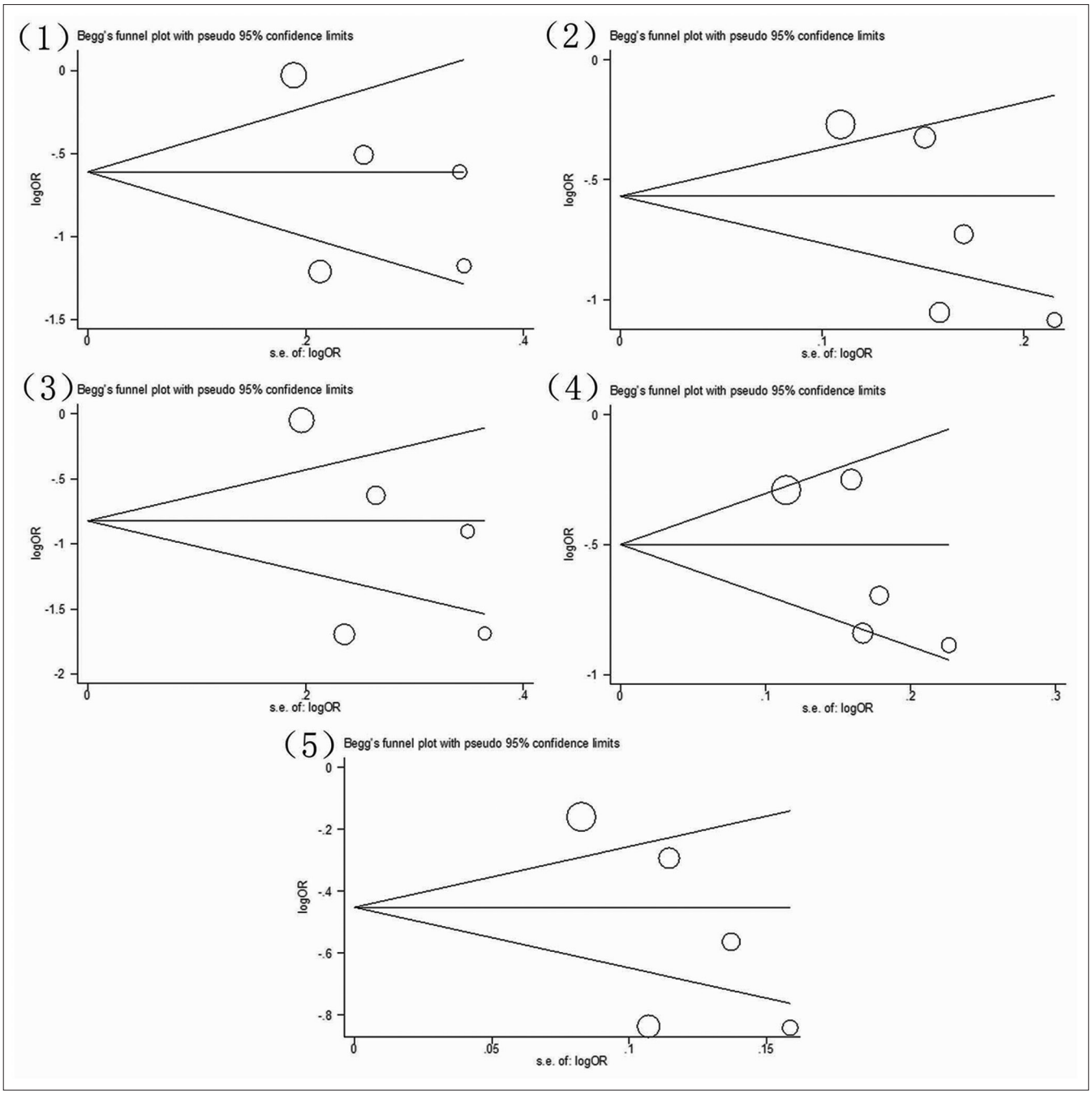

Figure 6: Begg's funnel plots of TNFSF15 rs3810936 polymorphism and the risk of CD for publication bias test. Each point represents a separate study for the indicated association. Log (OR), natural logarithm of OR. Horizontal line, mean effect size. (1) Recessive model. (2) Dominant model. (3) T/T vs. C/C. (4) C/T vs. C/C. (5) Additive model

not estimate the potential interactions among gene–gene, gene–environment, or even various polymorphisms loci of the same gene, which may alter the risk of IBD. Although the analysis of haplotype can increase the power to detect disease associations, our study was limited by analyzing a single SNP site owing to only one study focusing on TNFSF15 haplotype. Third, some inevitable publication bias might exist in the results because only published studies were retrieved, although the funnel plot and Egger's test indicated no remarkable publication bias.

CONCLUSION

In summary, this meta-analysis provides evidence that rs3810936, rs7848647, and rs6478108 polymorphisms may contribute to protective factor of CD. Nevertheless, large-scale, well-designed, and population-based studies are

Table 2: Results of meta-analysis for TNFSF15 polymorphisms and the risk of IBD

Genetic model		Recessive model			Dominant model			Homozygote			Heterozygote			Additive model		
rs3810936	n	T/T vs. C/T + C/C			T/T + C/T vs. C/C			T/T vs. C/C			C/T vs. C/C			T vs. C		
(C/T)		OR (95% CI)	P_h	I^2(%)	OR (95% CI)	P_h	I^2(%)	OR (95% CI)	P_h	I^2(%)	OR (95% CI)	P_h	I^2(%)	OR (95% CI)	P_h	I^2(%)
CD	5 (1762/2442)	0.50 (0.30–0.84)	0.000	80.5	0.51 (0.36–0.72)	0.000	84.4	0.38 (0.19–0.76)	0.000	88.7	0.57 (0.43–0.74)	0.007	71.8	0.59 (0.44-0.79)	0.000	88.2
UC	2 (489/842)	0.54 (0.36–0.83)	0.657	0.0	0.86 (0.69–1.08)	0.397	0.0	0.53 (0.34–0.81)	0.548	0.0	0.64 (0.51–0.81)	0.062	71.3	0.82 (0.69–0.97)	0.341	0.0
rs7848647	n	T/T vs. C/T + C/C			T/T + C/T vs. C/C			T/T vs. C/C			C/T vs. C/C			T vs. C		
(C/T)		OR (95% CI)	P_h	I^2(%)	OR (95% CI)	P_h	I^2(%)	OR (95% CI)	P_h	I^2(%)	OR (95% CI)	P_h	I^2(%)	OR (95% CI)	P_h	I^2(%)
CD	4 (1015/1816)	0.36 (0.27–0.49)	0.293	19.4	0.44 (0.25–0.80)	0.000	91.8	0.27 (0.15–0.47)	0.032	65.9	0.50 (0.28–0.89)	0.000	90.9	0.52 (0.36-0.76)	0.000	88.1
UC	2 (488/843)	0.67 (0.42–1.08)	0.807	0.0	0.95 (0.75–1.19)	0.515	0.0	0.67 (0.42–1.10)	0.729	0.0	1.00 (0.79–1.27)	0.610	0.0	0.91 (0.76-1.09)	0.472	0.0
rs6478108	N	C/C vs. T/C + T/T			C/C + T/C vs. T/T			C/C vs. T/T			T/C vs. T/T			C vs. T		
(T/C)		OR (95% CI)	P_h	I^2(%)	OR (95% CI)	P_h	I^2(%)	OR (95% CI)	P_h	I^2(%)	OR (95% CI)	P_h	I^2(%)	OR (95% CI)	P_h	I^2(%)
CD	4 (1014/1817)	0.36 (0.27–0.48)	0.339	10.9	0.46 (0.24–0.86)	0.000	92.8	0.27 (0.15–0.47)	0.028	67.1	0.52 (0.28–0.97)	0.000	92.0	0.53 (0.36-0.80)	0.000	89.9
UC	2 (488/841)	0.75 (0.48–1.17)	0.763	0.0	0.96 (0.77–1.21)	0.895	0.0	0.75 (0.48–1.19)	0.792	0.0	1.01 (0.79–1.28)	0.897	0.0	0.93 (0.78-1.11)	0.932	0.0

P_h: P values for heterogeneity from Q-test. Random effects model was used when P value for heterogeneity test <0.05; otherwise, fixed model was used

needed to investigate the combined effects of these variants within TNFSF gene and IBD, which may eventually lead to better comprehensive understanding of their possible roles in the pathogenesis of IBD.

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Conflicts of interest

There are no conflicts of interest.

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