Meta-Analysis

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(10) 1–13

DOI: 10.1177/0300060520961675
journals.sagepub.com/home/imr
SAGE

Polymorphism rs6478109 in the *TNFSF15* gene contributes to the susceptibility to Crohn's disease but not ulcerative colitis: a meta-analysis

Yuan Zhou*, Yi Zhu*, HongGang Jiang, ZhiHeng Chen, BoHao Lu, Jin Li and Xuning Shen

Abstract

Objective: Polymorphisms in the tumor necrosis factor superfamily 15 (*TNFSF15*) gene contribute to susceptibility to inflammatory bowel disease (IBD). However, associations between *TNFSF15* rs6478109, rs7869487, and rs7865494 polymorphisms and IBD remain unclear.

Methods: Eligible articles were retrieved from the PubMed, EMBASE, Web of Science, and CNKI databases through 20 March 2020. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the relationships of *TNFSF15* polymorphisms with IBD susceptibility.

Results: Under the recessive model, *TNFSF15* rs6478109 was associated with IBD risk (OR = 0.56; 95% CI: 0.35, 0.92). Stratification analyses based on the type of disease—Crohn's disease (CD) or ulcerative colitis (UC)—revealed a significant association under the allelic and recessive models between *TNFSF15* rs6478109 and CD (allelic model: OR = 0.84, 95% CI: 0.71, 0.99; recessive model: OR = 0.44, 95% CI: 0.22, 0.87) but not UC. Stratification by ethnicity indicated a significantly decreased risk of IBD in Asian populations with *TNFSF15* rs6478109 under the recessive model (OR = 0.56, 95% CI: 0.35, 0.92).

Conclusions: Our meta-analysis suggested that under the allelic and recessive models, the *TNFSF15* rs6478109 polymorphism was likely protective for CD but not UC in the Asian population.

Department of Gastrointestinal Surgery, The Affiliated Hospital of Jiaxing University, Jiaxing, Zhejiang, China

*These authors contributed equally to this work.

Corresponding author:
Yi Zhu, Department of Gastrointestinal Surgery, The Affiliated Hospital of Jiaxing University, No. 1882, Centre South Road, Jiaxing, Zhejiang 314001, China.
Email: zhuanwen456@163.com

Keywords
Tumor necrosis factor superfamily 15, polymorphism, inflammatory bowel disease, genetic association, meta-analysis, Crohn's disease, ulcerative colitis

Date received: 27 May 2020; accepted: 4 September 2020

Introduction

Inflammatory bowel disease (IBD) is a type of chronic, nonspecific intestinal inflammation.[1,2] Crohn's disease (CD) and ulcerative colitis (UC) are two subtypes of IBD.[2] The etiology and pathogenesis of IBD are still unclear, but may be related to the combined effects of three aspects: intestinal flora, abnormal immune-mediated tissue damage, and genetic susceptibility.[3,4] Genetic factors are also considered to play an important role in the development of IBD. Research has shown that the coincidence of monozygotic twins in patients with IBD is 20% to 50%.[5] In recent years, a number of genes, including nucleotide binding oligomerization domain containing 2 (*NOD2*),[6] vitamin D receptor (*VDR*),[7] intercellular adhesion molecule-1 (*ICAM1*),[8] human lymphocyte antigen (*HLA*),[9] *N*-acetyltransferase (*NAT2*),[10] toll-like receptors (*TLR*),[11] and tumor necrosis factor superfamily 15 (*TNFSF15*),[12] have been shown to be closely related to the incidence of CD or UC.

The *TNFSF15* gene is located on chromosome 9 (9q32) and encodes the tumor necrosis factor-like ligand 1A (*TL1A*).[13,14] TL1A not only inhibits tumor cell growth and induces cell apoptosis, but it can also bind to death receptor 3 (DR3) and activate nuclear factor kappa B (NF-κB), and then promote the secretion of inflammatory factors, which is a key process in immune regulation and the pathogenesis of inflammatory diseases.[15,16] The *TNFSF15* gene has been reported to be susceptibility factor in a number of immunogenic diseases such as leprosy,[17] tumors,[18,19] irritable bowel syndrome,[20] and rheumatoid arthritis.[21]

An increasing number of studies have revealed that polymorphisms in *TNFSF15* are associated with susceptibility to IBD.[12,22,23] A meta-analysis suggested that the *TNFSF15* rs3810936 polymorphism was significantly correlated with a decreased risk of CD and UC. The rs7848647 and rs6478108 polymorphisms in *TNFSF15* were shown to have a significantly protective association with CD but not with UC.[24] Apart from these polymorphisms, other single nucleotide polymorphisms (SNPs) in *TNFSF15*, such as rs6478109, rs7869487, and rs7865494, have been widely studied. Baskaran et al.[25] identified that *TNFSF15* rs6478109 was significantly associated with CD but not with UC. However, no associations were detected in studies conducted by Guo et al.,[26] Lee et al.,[27] and Wang et al.[28] No relationship was found between *TNFSF15* rs7865494 and IBD risk.

Considering the limited sample sizes in individual studies, we performed a meta-analysis by including eligible published studies to evaluate the relationship of the *TNFSF15* rs6478109, rs7869487, and rs7865494 polymorphisms and susceptibility to IBD.

Materials and methods

Publication search

A comprehensive systematic search was performed for all related publications up

to 20 March 2020, using the following search terms: "tumor necrosis factor super family member 15 gene" or "TNFSF15", and "polymorphism" or "single nucleotide polymorphism" or "SNP" or "variant" and "inflammatory bowel disease" or "IBD" or "Crohn's disease" or "CD" or "ulcerative colitis" or "UC" through PubMed, EMBASE, Web of Science, and China National Knowledge Infrastructure (CNKI) databases. All procedures were conducted in accordance with Cochrane definitions and PRISMA 2009 guidelines for meta-analysis and systematic reviews. No limitations concerning language and publication year were set. Additionally, references from the relevant literature were manually screened. Ethical approval was considered unnecessary for this meta-analysis.

Inclusion and exclusion criteria

The criteria for inclusion were (1) case-control studies; (2) studies that documented the genetic association of *TNFSF15* rs6478109, rs7869487, and rs7865494 polymorphisms with IBD; (3) studies that had available genotype frequencies; and (4) studies in which distributions of the genotypes in control group were in Hardy–Weinberg equilibrium (HWE). The criteria for exclusion were (1) duplicate studies; (2) short or non-specific publications, such as abstracts, letters, short communications, reviews, and case reports; (3) data unavailable in the case or control group; or (4) distributions of the genotypes in the control group were not in HWE.

Data extraction and quality assessment

The following data were reviewed and collected: the first author's name, year of publication, ethnicity, mean ages, percentage of males, numbers of cases and controls, and genotype and allele frequencies. Two authors (J.H.G. and C.Z.H.) carried out the data extraction independently. Discrepancies were resolved by discussion. The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of an individual study. The NOS scores ranged from 0 to 8. Studies were enrolled in the present meta-analysis if a NOS score ≥ 6 was obtained.

Statistical analysis

Pooled odd ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the relationship of the *TNFSF15* rs6478109, rs7869487, and rs7865494 polymorphisms with IBD susceptibility. The significance of the pooled ORs was assessed by Z test. The heterogeneity assumption was tested by the chi-square-based Q-test. A random-effects model was applied if significant between-study heterogeneity was obtained ($I^2 > 50\%$). Otherwise, they were pooled applying a fixed model. Subgroup analysis was conducted on the basis of ethnicity and type of disease (CD or UC). Sensitivity analysis was carried out by sequentially excluding a single study each time to evaluate the influence of individual study. Publication bias was determined with the use of Begg's and Egger's linear regression test. $P < 0.05$ was considered to indicate significant publication bias. STATA 12.0 software (StataCorp LLC, College Station, TX, USA) and Revman 5 (Cochrane, London, UK) were used to calculate all the statistical tests.

Results

Characteristics of eligible studies

As shown in Figure 1, 679 studies were initially found after the initial search. After screening the titles, abstracts, and full text, 672 irrelevant studies were excluded and seven studies were enrolled in this meta-analysis.[25–31] Table 1 summarizes the main

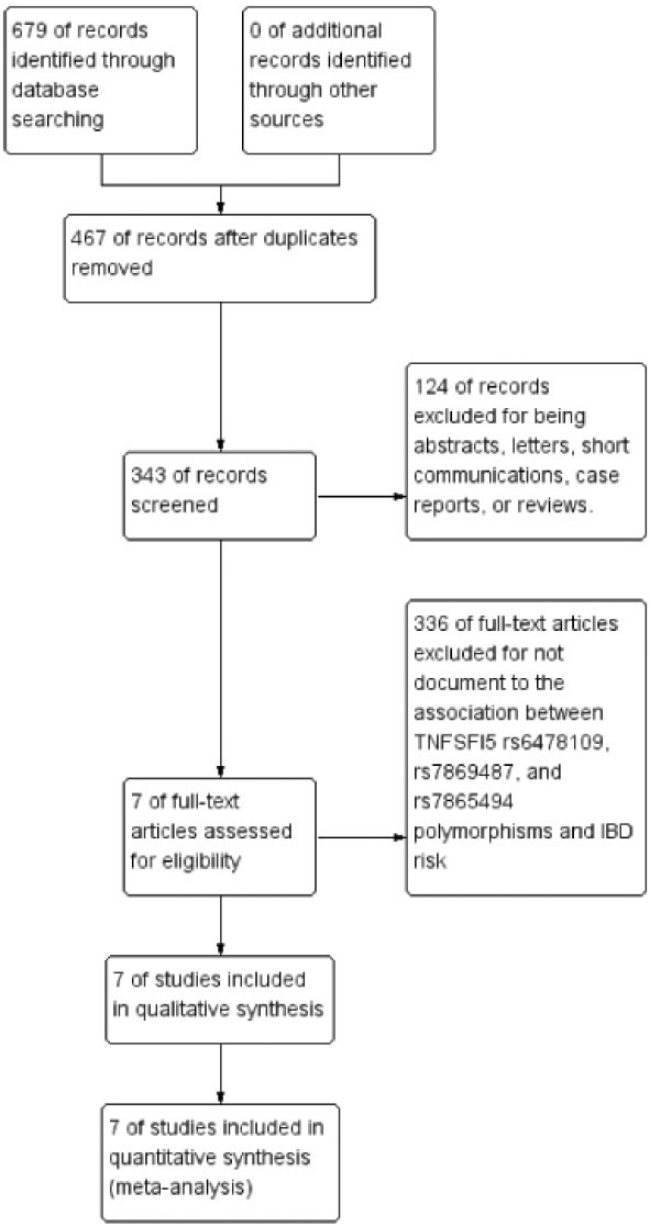

Figure 1. PRISMA flowchart showing inclusion and exclusion of studies

characteristics of these eligible studies. One study was in a Caucasian population[29] and six were in Asian populations.[25–28,30,31] Five articles were on CD[25,27–30] and two were on UC.[26,31] One study was conducted on both CD and UC.[25] The studies in control groups were consistent with HWE. All of the eligible studies achieved NOS scores >6, indicating that they were of high methodological quality (Table 1).

Table 1. Characteristics of included studies.

Study	Ethnicity	Male % (case/control)	Age, years (mean ± SD)	Disease	Case (n)	Control (n)	HWE	NOS
Baskaran et al., 2014; study 1[25]	Indian			CD	309	437	>0.05	7
Baskaran et al., 2014; study 2[25]	Indian			UC	330	437	>0.05	7
Guo et al., 2016[26]	Chinese	55.3/49.5	42.8±6.5/43.1±6.8	UC	103	103	>0.05	6
Lee et al., 2015[27]	Korean			CD	108	599	>0.05	6
Wang et al., 2013[28]	Chinese	61.9/59.1		CD	42	49	>0.05	6
Tremelling et al., 2008[29]	Caucasian	35.7/43.4		CD	756	636	>0.05	7
Yang et al., 2008[30]	Koreans	62.6/56.3	23.5 ± 7.3/36.6±13.8	CD	380	380	>0.05	7
Yang et al., 2011[31]	Koreans	52.1/51.6	40.8±13.3/27.4±8.1	UC	654	601	>0.05	8

SD, standard deviation; CD, Crohn's disease; UC, ulcerative colitis; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa Scale.

Combined outcomes

A significant association was found between *TNFSF15* rs6478109 and IBD risk in the recessive model (OR = 0.56, 95% CI: 0.35, 0.92; $P = 0.02$), but not in the allelic (OR = 0.74, 95% CI: 0.56, 0.99) or dominant (OR = 0.71, 95% CI: 0.48, 1.05) models (Figure 2, Table 2). No association was detected between the *TNFSF15* rs7869487 and rs7865494 polymorphisms and susceptibility to IBD in any of the genetic models (Figures 3 and 4; Tables 3 and 4).

We performed a stratification analysis on the basis of ethnicity. Individuals in the Asian population carrying the *TNFSF15* rs6478109 polymorphism had a significantly decreased risk of IBD under the recessive model (OR = 0.56, 95% CI: 0.35, 0.92; $P = 0.02$) (Table 2). Because of a lack of data, the genetic association between the *TNFSF15* rs6478109 polymorphism and IBD risk under the recessive model could not be calculated in Caucasians. Additionally, in a subgroup analyses based on the type of disease (CD or UC), we detected a significantly decreased risk of CD associated with the *TNFSF15* rs6478109 polymorphism in the allelic (OR = 0.84, 95% CI: 0.71, 0.99; $P = 0.04$) and recessive (OR = 0.44, 95% CI: 0.22, 0.87; $P = 0.02$) models (Table 2). No associations were found between the *TNFSF15* rs7869487 and rs7865494 polymorphisms and the susceptibility to IBD in subgroup analysis stratified by ethnicity or type of disease (Tables 3 and 4).

Heterogeneity and sensitivity analyses

Significant heterogeneity was found in all genetic models for the *TNFSF15* rs6478109 and rs7865494 polymorphisms in both the overall and subgroup analyses (Tables 2 and 4). This significant heterogeneity across studies was mainly due to the study conducted by Baskaran et al.[25] An $I^2 = 0\%$ ($P = 0.89$) was obtained after excluding this study. The results of sensitivity analysis revealed that the ORs were not significantly altered by omitting individual studies, indicating that our data were stable and reliable (Figure 5).

Publication bias

The funnel plots were symmetrical and the results of Egger's test indicated no evidence of publication bias for *TNFSF15* rs6478109 ($P_{Egger} = 0.866$), rs7869487 ($P_{Egger} = 0.781$),

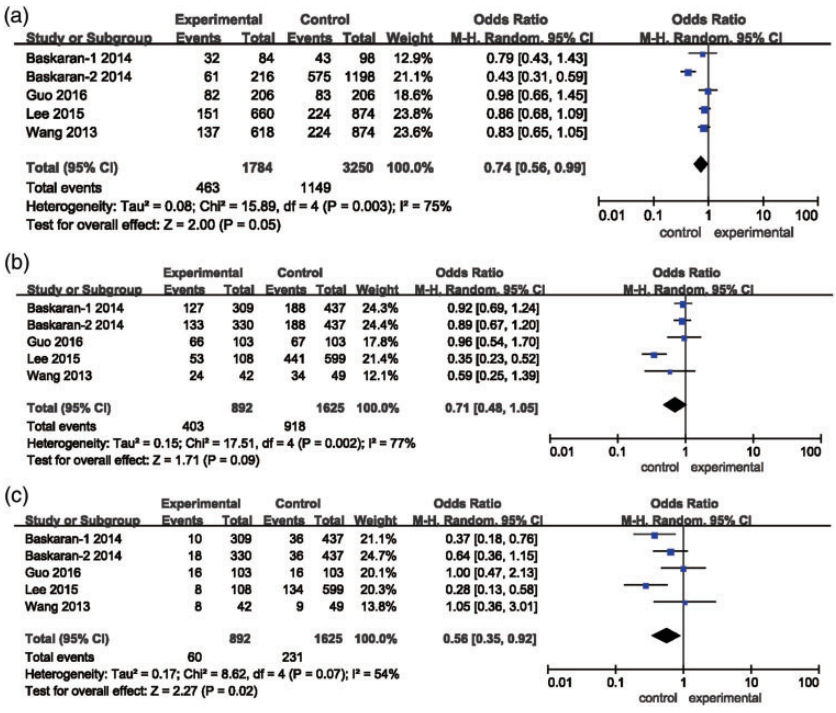

Figure 2. Forest plots of odds ratios (and 95% confidence intervals, CI) for the association between *TNFSF15* polymorphism rs6478109 and inflammatory bowel disease: (a) allelic model; (b) dominant model; (c) recessive model.

Table 2. Association between *TNFSF15* rs6478109 polymorphism and IBD risk.

Genetic model	Subgroup	Studies, n	Test of association				Test of heterogeneity	
			OR	95% CI	*P*-value	Model	*P*-value	I^2 (%)
Allelic	Total	5	0.74	[0.56, 0.99]	0.05	R	0.003	75
	CD	3	0.84	[0.71, 0.99]	0.04	F	0.95	0
	UC	2	0.58	[0.46, 0.74]	0.29	R	0.001	90
	Asian	5	0.74	[0.56, 0.99]	0.05	R	0.003	75
	Caucasian	–	–	–	–	–	–	–
Dominant	Total	5	0.71	[0.48, 1.05]	0.09	R	0.002	77
	CD	3	0.58	[0.28, 1.19]	0.14	R	0.0008	86
	UC	2	0.91	[0.70, 1.17]	0.46	F	0.83	0
	Asian	5	0.71	[0.48, 1.05]	0.09	R	0.002	77
	Caucasian	–	–	–	–	–	–	–
Recessive	Total	5	0.56	[0.35, 0.92]	0.02	R	0.07	54
	CD	3	0.44	[0.22, 0.87]	0.02	R	0.12	52
	UC	2	0.76	[0.48, 1.19]	0.23	F	0.36	0
	Asian	5	0.56	[0.35, 0.92]	0.02	R	0.07	54
	Caucasian	–	–	–	–	–	–	–

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; OR, odds ratio; CI, confidence interval; F, fixed model; R, random model.

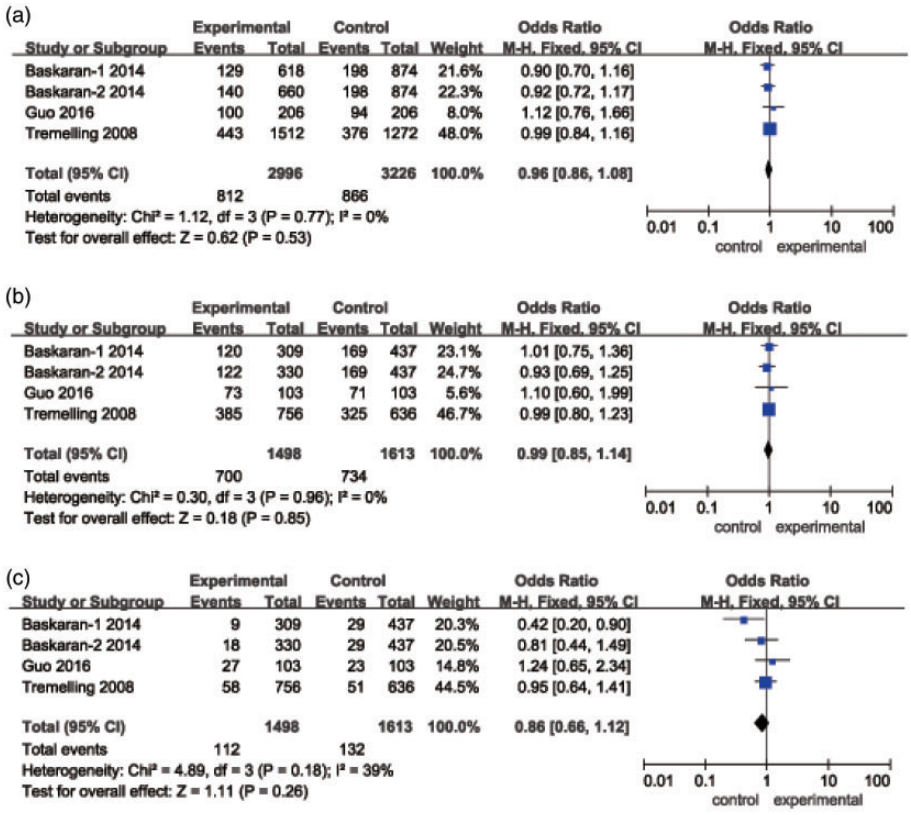

Figure 3. Forest plots of odds ratios (and 95% confidence intervals, CI) for the association between *TNFSF15* polymorphism rs7869487 and inflammatory bowel disease: (a) allelic model; (b) dominant model; (c) recessive model.

and rs7865494 ($P_{\text{Egger}} = 0.271$) polymorphisms (Figure 6).

Discussion

According to the differences in secreted cytokines and mediated immune functions, $CD4^+$ T cells can be divided into T helper (Th)1 and Th2 cells.[32] Th1 cells mainly secrete interleukin (IL)-12 and interferon (IFN)-γ, whereas Th2 cells mainly secrete IL-4, IL-13, and IL-10.[33] The Th1/Th2 imbalance has always been considered part of the pathogenesis of IBD. CD is mainly considered a type of Th1 disease, with secretion of IFN-γ, tumor necrosis factor (TNF)-α, IL-2, and IL-18 from intestinal mucosal cells,[34] whereas UC is a Th2 disease.

TNF-like ligand 1A (TL1A) is locally expressed in $CD4^+$, $CD8^+$ T lymphocytes and plasma cells of patients with UC. The amount of TL1A protein and the number of TL1A-positive cells are positively correlated with the severity of inflammation.[35] TL1A can bind to DR3 (TNFRSF25), activate NF-κB, and regulate DR3-mediated apoptosis. It also promotes the release of proinflammatory cytokines by immune cells.[21] Kamada et al. showed that TL1A not only induced differentiation of naïve $CD4^+$ T cells to Th1 and Th17 in the

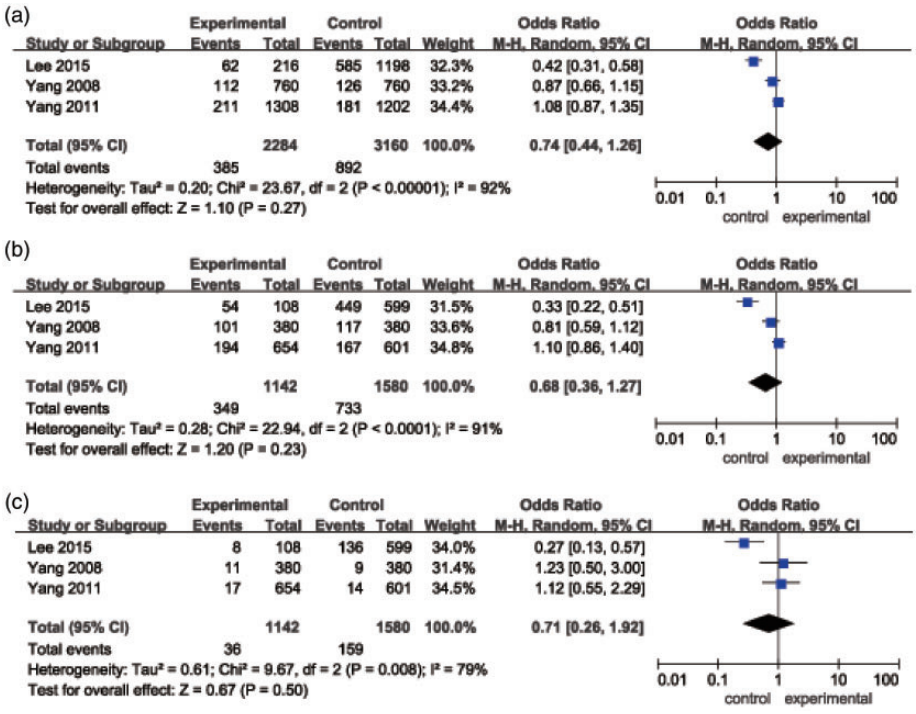

Figure 4. Forest plots of odds ratios (and 95% confidence intervals, CI) for the association between *TNFSF15* polymorphism rs7865494 and inflammatory bowel disease: (a) allelic model; (b) dominant model; (c) recessive model.

Table 3. Association between *TNFSF15* rs7869487 polymorphism and IBD risk.

Genetic models	Subgroups	Studies, n	Test of association				Test of heterogeneity	
			OR	95% CI	*P*-value	Model	*P*-value	I^2 (%)
Allelic	Total	4	0.96	[0.86, 1.08]	0.53	F	0.77	0
	CD	2	0.96	[0.84, 1.10]	0.56	F	0.55	0
	UC	2	0.97	[0.79, 1.20]	0.80	F	0.39	0
	Asian	3	0.94	[0.80, 1.11]	0.47	F	0.60	0
	Caucasian	1	0.99	[0.84, 1.16]	0.88	–	–	–
Dominant	Total	4	0.99	[0.85, 1.14]	0.85	F	0.96	0
	CD	2	1.00	[0.84, 1.19]	0.98	F	0.94	0
	UC	2	0.96	[0.74, 1.25]	0.77	F	0.63	0
	Asian	3	0.98	[0.80, 1.20]	0.85	F	0.87	0
	Caucasian	1	0.99	[0.80, 1.23]	0.95	–	–	–
Recessive	Total	4	0.86	[0.66, 1.12]	0.26	F	0.18	39
	CD	2	0.68	[0.31, 1.49]	0.34	R	0.06	71
	UC	2	0.99	[0.64, 1.54]	0.97	F	0.35	0
	Asian	3	0.78	[0.44, 1.38]	0.39	R	0.11	56
	Caucasian	1	0.95	[0.64, 1.41]	0.84	–	–	–

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; OR, odds ratio; CI, confidence interval; F, fixed model; R, random model.

Table 4. The association between TNFSF15 rs7865494 polymorphism and IBD risk.

Genetic models	Subgroups	Studies, n	Test of association			Model	Test of heterogeneity	
			OR	95% CI	*P*-value		*P*-value	I^2 (%)
Allelic	Total	3	0.74	[0.44, 1.26]	0.27	R	<0.00001	92
	CD	2	0.61	[0.30, 1.24]	0.17	R	0.0007	91
	UC	1	1.08	[0.87, 1.35]	0.46	–	–	–
	Asian	3	0.74	[0.44, 1.26]	0.27	R	<0.00001	92
	Caucasian	0	–	–	–	–	–	–
Dominant	Total	3	0.68	[0.36, 1.27]	0.23	R	<0.0001	91
	CD	2	0.53	[0.22, 1.26]	0.15	R	0.0009	91
	UC	1	1.10	[0.86, 1.40]	0.46	–	–	–
	Asian	3	0.68	[0.36, 1.27]	0.23	R	<0.0001	91
	Caucasian	0	–	–	–	–	–	–
Recessive	Total	3	0.71	[0.26, 1.92]	0.50	R	0.008	79
	CD	2	0.57	[0.13, 2.53]	0.46	R	0.01	85
	UC	1	1.12	[0.55, 2.29]	0.76	–	–	–
	Asian	3	0.71	[0.26, 1.92]	0.50	R	0.008	79
	Caucasian	0	–	–	–	–	–	–

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; OR, odds ratio; CI, confidence interval; R, random model.

intestinal mucosa lamina propria, but also promoted the secretion of IFN-γ and IL-17 in coordination with IL-23.[36] Thus, TL1A plays an important role in the occurrence and pathogenesis of intestinal mucosal inflammatory response in IBD.

The *TNFSF15* gene, as one of the susceptibility genes for IBD, has ethnic and regional differences. In a case-control study of 482 patients with CD, a number of *TNFSF15* polymorphisms were shown to be susceptibility factors for CD in a Japanese population.[12] A potential correlation with UC in a Caucasian population was also observed.[12] The genetic association between six SNPs (rs3810936, rs6478108, rs6478109, rs7848647, rs7865494, and rs4979642) in the *TNFSF15* gene and IBD risk is widely known; of these, only rs3810936 is in the coding region (exon 4) of the gene. These six polymorphisms were further investigated in other Japanese populations,[37,38] confirming that the *TNFSF15* rs3810936 allele was significantly correlated with CD but not with UC. Additionally, Yang et al. confirmed that *TNFSF15* rs3810936, rs6478108, and rs7848647 were significantly correlated with CD in a Korean population.[30] However, the association between *TNFSF15* polymorphisms and CD was less significant in a European population.[29] Furthermore, a protective effect of *TNFSF15* rs3810936, rs6478108, rs6478109, rs7848647, and rs7869487 was found in patients with CD and UC in a non-Jewish population, but not in a Jewish population.[39]

In this meta-analysis, we found that *TNFSF15* rs6478109 was a protective factor for IBD under the recessive model. Subgroup analysis on the basis of type of disease indicated that *TNFSF15* rs6478109 under both the allelic and recessive genetic models was associated with a decreased risk for CD but not for UC. To our knowledge, this is the first study to demonstrate a significant genetic association between

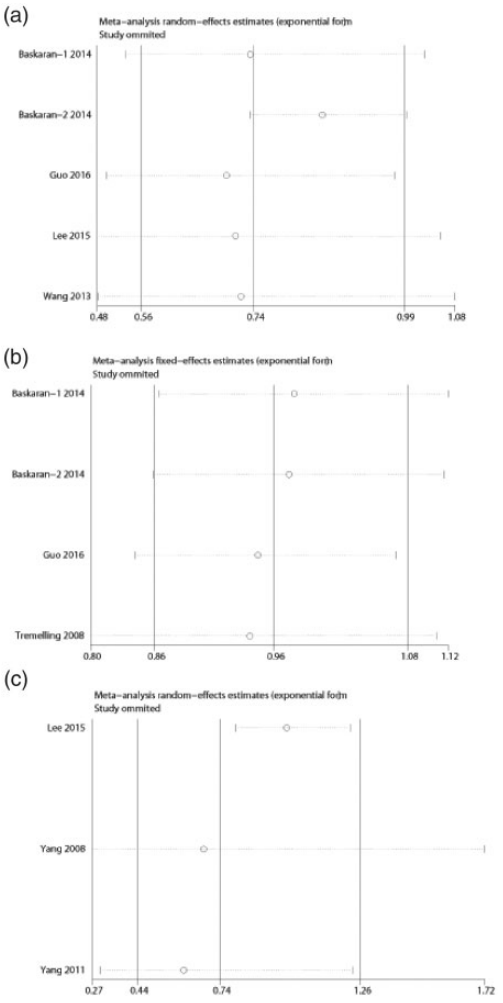

Figure 5. Sensitivity analyses between *TNFSF15* rs6478109, rs7869487, and rs7865494 and inflammatory bowel disease: (a) rs6478109; (b) rs7869487; (c) rs7865494.

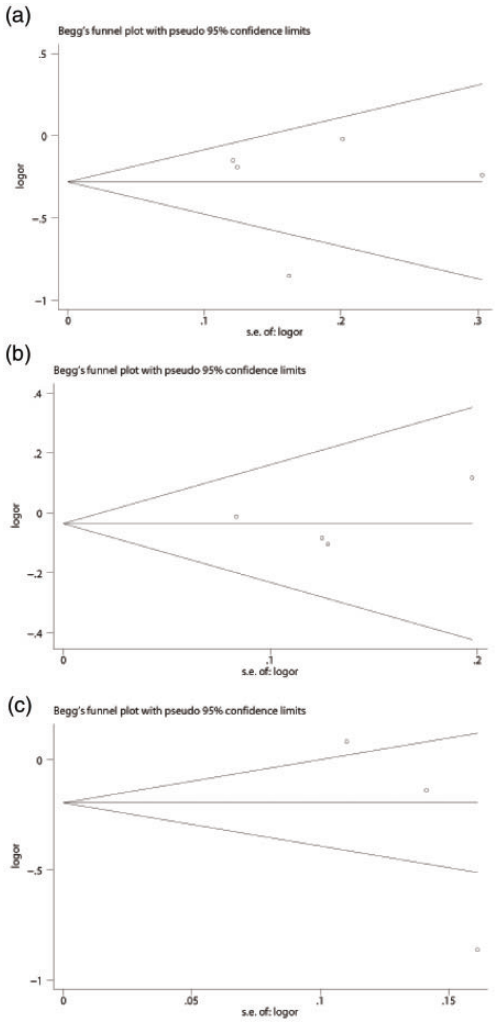

Figure 6. Publication bias of literatures for allelic model of *TNFSF15* rs6478109, rs7869487, and rs7865494 was tested by Begg's funnel plot. (a) rs6478109; (b) rs7869487; (c) rs786549 Logor, log of the odds ratio; s.e., standard error.

rs6478109 and CD risk detected by meta-analysis. The rs6478109 polymorphism is located in the 5′-untranslated region (UTR) of the *TNFSF15* gene and thus may influence expression of *TNFSF15*. This polymorphism has been shown to be a genetic risk factor for psoriasis,[13] liver cancer,[40] and gastric adenocarcinoma.[41] A study revealed that *TNFSF15* rs6478109 was in tight linkage disequilibrium with rs3810936, rs6478108, rs7848647, and rs7869487,[25] indicating that this polymorphism might regulate expression of the *TNFSF15* gene and play a role in the pathogenesis of CD. We cannot be completely sure that *TNFSF15* rs6478109 was not related to UC because of the small sample

size in the present analysis. We also found that *TNFSF15* rs6478109 was associated with IBD in an Asian population but not in a Caucasian population. Again, this might be due to insufficient data in the Caucasian population. Thus, larger case-control studies are needed to fully elucidate the association between *TNFSF15* rs6478109 and IBD risk, especially in Caucasians.

The current meta-analysis has a number of limitations. First, although seven studies with 2682 cases and 3242 controls were included, the sample size of the subgroup analyses, particularly for the Caucasian subgroup, was insufficient, which may affect the correlations. Second, both genetic and environmental factors can affect the process of IBD development. However, we failed to assess the effect of these factors in IBD. Third, the studies included in the present study were conducted in Asian and Caucasian populations; no studies with participants of other ethnicities were included.

Conclusions

Our meta-analysis suggested that under the allelic and recessive models, the *TNFSF15* rs6478109 polymorphism was likely protective for CD but not UC in an Asian population. Larger sample sizes and a greater number of well-designed case-control studies are needed to demonstrate a genetic association between the rs6478109 polymorphism in *TNFSF15* and CD risk.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This work was supported by the Medical and Health Science and Technology Project of Zhejiang Province, China (2019KY214, 2019KY692); the Jiaxing Key Discipline of Medicine-Oncology (Supporting Subject) 2019-zc-11; the Basic Public Welfare Research Program of Zhejiang Province, China (LGF18H160033); and the project of Public Welfare research of Jiaxing (2019AD32257).

ORCID iD

Yi Zhu https://orcid.org/0000-0002-5089-8635

References

1. Fischbach MA and Segre JA. Signaling in host-associated microbial communities. *Cell* 2016; 164: 1288–1300.
2. Wlodarska M, Kostic AD and Xavier RJ. An integrative view of microbiome-host interactions in inflammatory bowel diseases. *Cell Host Microbe* 2015; 17: 577–591.
3. Xavier RJ and Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 2007; 448: 427–434.
4. Fiocchi C. Inflammatory bowel disease: etiology and pathogenesis. *Gastroenterology* 1998; 115: 182–205.
5. Halfvarson J, Bodin L, Tysk C, et al. Inflammatory bowel disease in a Swedish twin cohort: a long-term follow-up of concordance and clinical characteristics. *Gastroenterology* 2003; 124: 1767–1773.
6. Lesage S, Zouali H, Cézard JP, et al. CARD15/NOD2 mutational analysis and genotype-phenotype correlation in 612 patients with inflammatory bowel disease. *Am J Hum Genet* 2002; 70: 845–857.
7. Stuchlíková M, Hlavatý T, Ďuriš F, et al. The relationship between selected VDR gene polymorphisms and susceptibility to inflammatory bowel disease in Slovak population. *Biologia* 2019; 74: 573–581.
8. Low JH, Williams FA, Yang X, et al. Inflammatory bowel disease is linked to 19p13 and associated with ICAM-1. *Inflamm Bowel Dis* 2004; 10: 173–181.
9. Milia AF, Manetti M, Generini S, et al. TNFα blockade prevents the development of inflammatory bowel disease in HLA-B27 transgenic rats. *J Cel Mol Med* 2009; 13: 164–176.

10. Chen M, Xia B, Chen B, et al. *N*-Acetyltransferase 2 slow acetylator genotype associated with adverse effects of sulphasalazine in the treatment of inflammatory bowel disease. *Can J Gastroenterol* 2007; 21: 155–158.
11. Yang C, Yun Z, Xiuping H, et al. Association between TLR2 and TLR4 gene polymorphisms and the susceptibility to inflammatory bowel disease: a meta-analysis. *PLoS One* 2015; 10: e0126803.
12. Keiko Y, Dermot M, Jiannis R, et al. Single nucleotide polymorphisms in TNFSF15 confer susceptibility to Crohn's disease. *Hum Mol Genet* 2005; 14: 3499–3506.
13. Képíró L, Széll M, Kovács L, et al. Genetic risk and protective factors of TNFSF15 gene variants detected using single nucleotide polymorphisms in Hungarians with psoriasis and psoriatic arthritis. *Hum Immunol* 2014; 75: 159–162.
14. Migone TS, Zhang J, Luo X, et al. TL1A is a TNF-like ligand for DR3 and TR6/DcR3 and functions as a T cell costimulator. *Immunity* 2002; 16: 479–492.
15. Ma ZJ, Wang B, Wang MM, et al. TL1A increased IL-6 production on fibroblast-like synoviocytes by preferentially activating TNF receptor 2 in rheumatoid arthritis. *Cytokine* 2016; 83: 92–98.
16. Siakavellas SI and Bamias G. Tumor necrosis factor-like cytokine TL1A and its receptors DR3 and DcR3: important new factors in mucosal homeostasis and inflammation. *Inflamm Bowel Dis* 2015; 21: 2441–2452.
17. Fava VM, Carolinne SM, Alexandre A, et al. Age-dependent association of TNFSF15/TNFSF8 variants and leprosy type 1 reaction. *Front Immunol* 2017; 8: 155.
18. Hou W, Medynski D, Wu S, et al. VEGI-192, a new isoform of TNFSF15, specifically eliminates tumor vascular endothelial cells and suppresses tumor growth. *Clin Cancer Res* 2005; 11: 5595–5602.
19. Zhou J, Yang Z, Tsuji T, et al. LITAF and TNFSF15, two downstream targets of AMPK, exert inhibitory effects on tumor growth. *Oncogene* 2011; 30: 1892–1900.
20. Sachdev AH and Pimentel M. Identifying and testing candidate genetic polymorphisms in irritable bowel syndrome: association with TNFSF15 and tumor necrosis factor-α. *Ann Gastroenterol* 2013; 26: 87–88.
21. Siakavellas SI, Sfikakis PP and Bamias G. The TL1A/DR3/DcR3 pathway in autoimmune rheumatic diseases. *Semin Arthritis Rheum* 2015; 45: 1–8.
22. Kakuta Y. Association study of TNFSF15 polymorphisms in Japanese patients with inflammatory bowel disease. *Gut* 2006; 55: 1527–1528.
23. Yang DH, Yang SK, Song K, et al. TNFSF15 is an independent predictor for the development of Crohn's disease-related complications in Koreans. *J Crohns Colitis* 2014; 8: 1315–1326.
24. He L, Chen J, Sun J, et al. Protective association of TNFSF15 polymorphisms with Crohn's disease and ulcerative colitis: A meta-analysis. *Saudi J Gastroenterol* 2018; 24: 201–210.
25. Baskaran K, Pugazhendhi S and Ramakrishna BS. Protective association of tumor necrosis factor superfamily 15 (TNFSF15) polymorphic haplotype with ulcerative colitis and Crohn's disease in an Indian population. *PLoS One* 2014; 9: e114665.
26. Guo GY, Huang ZC, Ye YC, et al. Tumor necrosis factor superfamily member 15 research of the relativity with ulcerative colitis. *China & Foreign Medical Treatment* 2016; 33: 21–24.
27. Lee YJ, Kim KM, Jang JY, et al. Association of TNFSF15 gene polymorphisms in Korean children with Crohn's disease. *Pediatr Int* 2015; 57: 1149–1153.
28. Wang Q, Wen ZZ, Liu J, et al. Association of TNFSF15 with Crohn's disease of Han nationality in Zhejiang Province of China. *New Medicine* 2013; 44: 622–625.
29. Tremelling M, Berzuini C, Massey D, et al. Contribution of TNFSF15 gene variants to Crohn's disease susceptibility confirmed in UK population. *Inflamm Bowel Dis* 2008; 14: 733–737.
30. Yang SK, Lim J, Chang HS, et al. Association of TNFSF15 with Crohn's disease in Koreans. *Am J Gastroenterol* 2008; 103: 1437–1442.

31. Yang SK, Jung Y, Hong M, et al. No association between TNFSF15 and IL23R with ulcerative colitis in Koreans. *J Hum Genet* 2011; 56: 200–204.
32. Zenewicz LA, Antov A and Flavell RA. CD4 T-cell differentiation and inflammatory bowel disease. *Trends Mol Med* 2009; 15: 199–207.
33. Noma T. Helper T cell paradigm: Th17 and regulatory T cells involved in autoimmune inflammatory disorders, pathogen defense and allergic diseases. *Nihon Rinsho Meneki Gakkai Kaishi* 2010; 33: 262–271.
34. Xia SL, Xue ZX, Cai ZZ, et al. Imbalance among Th1, Th2 and Th17 cells and Crohn's disease. *Chinese Journal of Gastroenterology* 2017; 22: 331–336.
35. Bamias G, Martin C, Marini M, et al. Expression, localization, and functional activity of TL1A, a novel Th1-polarizing cytokine in inflammatory bowel disease. *J Immunol* 2003; 171: 4868–4874.
36. Kamada N, Hisamatsu T, Honda H, et a1. TLl A produced by lamina propria macrophages induces Th l and Th 17 immune responses in cooperation with IL-23 in patients with Crohn's disease. *Inflamm Bowel Dis*. 2010; 16: 568–575.
37. Atsushi H, Keiko Y, Junji U, et al. Association study of 71 European Crohn's disease susceptibility loci in a Japanese population. *Inflamm Bowel Dis*. 2013; 19: 526–533.
38. Nakagome S, Takeyama Y, Mano S, et al. Population-specific susceptibility to Crohn's disease and ulcerative colitis; dominant and recessive relative risks in the Japanese population. *Ann Hum Genet*. 2010; 74: 126–136.
39. Picornell Y, Mei L, Taylor K, et al. TNFSF15 is an ethnic-specific IBD gene. *Inflamm Bowel Dis*. 2007; 13: 1333–1338.
40. Gao H, Xu HJ, Xie YN, et al. Study on the correlation between TNFSF15 promoter region -358 T>C genetic variation and the risk of liver cancer. *The Chinese Journal of Clinical Pharmacology*. 2019; (16): 1731–1734.
41. Zhang Z, Yu D, Lu J, et al. Functional genetic variants of TNFSF15 and their association with gastric adenocarcinoma: a case-control study. *PLOS ONE*. 2014; 9: e108321.