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

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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.

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

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 (\(NF-\kappa B\)), 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.\textsuperscript{25–31} Table 1 summarizes the main
characteristics of these eligible studies. One study was in a Caucasian population and six were in Asian populations. Five articles were on CD and two were on UC. One study was conducted on both CD and UC. 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).
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. 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 \( \text{TNFSF15} \) polymorphism rs6478109 and inflammatory bowel disease: (a) allelic model; (b) dominant model; (c) recessive model.

Table 2. Association between \( \text{TNFSF15} \) 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| –          | –                   | –                     | –         | –     | –       | –         |
|               | Total    | 5          | 0.71                | [0.60, 1.19]          | 0.09      | R     | 0.002   | 77        |
|               | CD       | 3          | 0.58                | [0.28, 1.19]          | 0.14      | R     | 0.0008  | 86        |
|               | UC       | 2          | 0.71                | [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| –          | –                   | –                     | –         | –     | –       | –         |
|               | 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     | 0.07    | 54        |
|               | 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.
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)-$\gamma$, 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-$\gamma$, tumor necrosis factor (TNF)-$\alpha$, 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-$\kappa$B, 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 | OR    | 95% CI   | P-value | Test of association | Model | P-value | Test of heterogeneity | I² (%) |
|----------------|-----------|------------|--------|----------|---------|----------------------|-------|---------|-----------------------|--------|
| 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.
intestinal mucosa lamina propria, but also promoted the secretion of IFN-\(\gamma\) 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

| Genetic models | Subgroups | Studies, n | Test of association | Test of heterogeneity |
|----------------|-----------|------------|---------------------|----------------------|
|                |           |            | OR  | 95% CI | P-value | Model | 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.
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, liver cancer, and gastric adenocarcinoma. A study revealed that TNFSF15 rs6478109 was in tight linkage disequilibrium with rs3810936, rs6478108, rs7848647, and rs7869487, 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.

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.
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.

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