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Association between *NCF4* rs4821544T/C polymorphism and inflammatory bowel disease risk in Caucasian: a meta-analysis

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Abstract
Objective Published studies on the association between *NCF4* rs4821544T/C polymorphism and inflammatory bowel disease (IBD) risk in Caucasian have yielded conflicting results. The present study aimed to provide more reliable conclusions by conducting a meta-analysis.
Methods All eligible studies were extracted from Wiley Online Library, Chinese National Knowledge Infrastructure and PubMed databases. Odds ratios (ORs) with 95 % confidence intervals (CIs) were used to assess the associations between rs4821544T/C polymorphism and IBD risk in Caucasian.
Results A total of 13 case–control studies comprising 7441 Crohn's disease (CD) patients, 2565 ulcerative colitis (UC) patients and 8315 controls were included in this meta-analysis. Significant associations were found between CD and the rs4821544T/C polymorphism in three genetic models (C vs T: OR = 1.11, 95 % CI: 1.06, 1.16, $P = 0.000$; CC vs TT: OR = 1.31, 95 % CI: 1.18, 1.45, $P = 0.000$; CC/TC vs TT: OR = 1.07, 95 % CI: 1.01, 1.13, $P = 0.014$; CC vs TC/TT: OR = 1.28, 95 % CI: 1.16, 1.42, $P = 0.000$). However, significant associations were not found in UC under any genetic models (C vs T: OR = 1.04, 95 % CI: 0.97, 1.11, $P = 0.264$; CC vs TT: OR = 1.10, 95 % CI: 0.93, 1.30, $P = 0.284$; TC vs TT: OR = 1.04, 95 % CI: 0.95, 1.13, $P = 0.429$; CC/TC vs TT: OR = 1.04, 95 % CI: 0.95, 1.13, $P = 0.390$; CC vs TC/TT: OR = 1.07, 95 % CI: 0.91, 1.26, $P = 0.409$).
Conclusion This meta-analysis suggested that the rs4821544T/C polymorphism was associated with CD, but not UC in Caucasian.

Keywords *NCF4* · Polymorphism · Inflammatory bowel disease · Meta-analysis

Introduction

Inflammatory bowel disease (IBD), a chronic non-specific gastrointestinal inflammatory disease, is typically classified into two clinical forms: Crohn's disease (CD) and ulcerative colitis (UC). Recently, the incidence of UC and CD has increased overall in Europe from 6.0/100,000 person-years in UC and 1.0 per 100,000 person-years in CD in 1962 to 9.8/100,000 person-years and 6.3 per 100,000 person-years in 2010, respectively [1]. Of note, there is wide geographic variability in the incidence and prevalence of IBD [1]. IBD seriously affects quality of life by causing abdominal pain, vomiting, diarrhea, and other extra-intestinal symptoms [2]. It has been established that IBD is associated with both an increased risk of colorectal cancer and cardiovascular disease [3, 4]. Therefore, patients with IBD carry a slightly higher risk of dying than the general population [3–5].

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Epidemiological data obtained from previous studies supports the underlying etiology of IBD is thought to be multifactorial [1]. Environmental factors including the composition of the gut microbiota, dietary fiber, saturated fats, depression and even impaired sleep act as an essential player in IBD [1]. Since CARD15 was initially identified as a candidate gene for CD in 2001 [6], people come to realize that IBD also arises as a result of a genetic predisposition [7]. Oxidative stress resulted from excessive reactive oxygen species (ROS) in the intestinal tract is also regarded as another major factor contributing to the pathogenesis and progression of gastrointestinal inflammation in IBD [8]. Nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) enzyme family often acts as catalyzer of the production ROS [8]. Genes encoding the NADPH complex consisted of *CYBB*, *CYBA*, *NCF4, NCF2* and *RAC2*. The *NCF4*, encoding for the p40-phox protein, located on chromosome 22 [9]. It has been found that genetic polymorphisms of NADPH oxidase including *NCF4* modulate subunit expression and enzyme activity [10]. Previous studies indicated that variation in *NCF4* was associated with colorectal cancer and rheumatoid arthritis risk [11, 12]. Therefore, variation in *NCF4* may influence susceptibility to IBD. Recently, a North American genome-wide association study identified variant in *NCF4* as being associated with CD [13]. Considerable efforts have been devoted to investigating the relationship between *NCF4* polymorphism and IBD risk in Caucasian [13–21]. However, results from previous studies have been inconsistent. Therefore, we designed a meta-analysis to better clarify the relationship between *NCF4* polymorphism and IBD risk in Caucasian.

Materials and methods

Search strategy

Genetic association studies regarding associations between rs4821544T/C polymorphism and IBD risk were searched in Wiley Online Library, PubMed and Chinese National Knowledge Infrastructure (CNKI) databases. Different combinations of the search terms were as follows: "Inflammatory bowel disease", "IBD", "Crohn's disease", "ulcerative colitis", ''CD'', ''UC'', and "*NCF4*", "rs4821544", and "polymorphism" or "variant" or "mutation". Search results were restricted to human populations and articles written in English or Chinese (up to May 20, 2015). Moreover, additional studies were identified by a full manual search from the reference of selected papers on this topic.

Criteria for inclusion and exclusion

The studies eligible should meet the following inclusion criteria: (1) case–control studies; (2) studies should be related to association between rs4821544T/C polymorphism and IBD; (3) studies that clearly describe IBD diagnoses and the sources of cases and controls; (4) enough information to calculate the odds ratio (OR) with 95 % confidence interval (CI); (5) studies in which the genotype distribution of the control population was in Hardy–Weinberg equilibrium (HWE); (6) subjects in all studies included must be Caucasians. Accordingly, the exclusion criteria were as follows: (1) duplicated studies; (2) not case–control study or family-based case–control study; (3) studies containing overlapping data; (4) investigations of the associations of other genes with IBD or the relationships between *NCF4* gene polymorphisms and other diseases; (5) subjects in all studies included are not Caucasians; (6) studies classified as review, case reports, animal or cell studies; (7) insufficient information to calculate OR and 95 % CI.

Data extraction

Two investigators independently extracted all the following data from the eligible studies: the name of first author, country of study, year of publication, the number of cases and controls, minor allele frequencies (MAF) in cases and controls.

Statistical analysis

To assess the association between rs4821544T/C polymorphism and IBD risk, ORs and its 95 % CI were calculated in four distinct genetic models: homozygote comparison, heterozygote comparison, dominant model and recessive model. Heterogeneity between studies was calculated by $\chi 2$-based Q test and I^2 test. If the data showed no heterogeneity ($P > 0.10$, $I^2 < 50$ %), Mantel–Haenszel fixed effect model was used [22], or else DerSimonian–Laird random effect model was used [22, 23]. The significance of the pooled OR was determined by the Z test. Publication bias was assessed by the shapes of the Begg's funnel plots and Egger's test [24]. The HWE in control group was assessed by $\chi 2$ goodness of fit. When heterogeneity between studies existed, subgroup analysis according to study characteristics should be performed [25]. All reported P values were two sided with $P < 0.05$ being considered as significant. STATA package version 11.0 (Stata Corporation, College Station, Texas) was used in our study.

Results

Main characteristics of eligible studies

Figure 1 shows the flowchart of study selection for this meta-analysis. In total, 24 relevant records were identified. After initial examination of titles and abstracts, 11 records were excluded because they were not related to *NCF4* ($N = 6$) or other unrelated disease ($N = 5$). After further screening full records, 4 records were excluded because they were not case–control studies ($N = 3$) or review ($N = 1$). Thus, a total of 9 records comprising 13 case–control studies were identified [13–21].

The studies were published from 2007 to 2013. 7441 CD patients, 2565 UC patients and 8315 controls were included in 9 and 4 case–control studies in 9 records. The characteristics of studies included in the meta-analysis are shown in Table 1. The genotype distribution of the control group in all studies was consistent with HWE (Table 1).

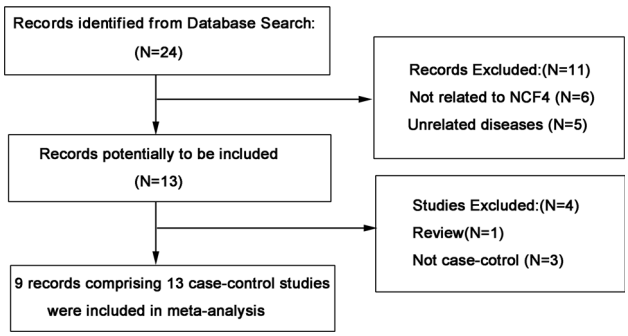

Fig. 1 The flowchart of study selection for this meta-analysis

Associations between rs4821544T/C and CD

For rs4821544T/C polymorphism, 9 case–control studies with 7441 cases and 8 315 controls were identified. Significant associations were found under three genetic models (C vs T: OR = 1.11, 95 % CI: 1.06, 1.16, $P = 0.000$; CC vs TT: OR = 1.31, 95 % CI: 1.18, 1.45, $P = 0.000$ (Fig. 2); CC/TC vs TT: OR = 1.07, 95 % CI: 1.01, 1.13, $P = 0.014$ (Fig. 3); CC vs TC/TT: OR = 1.28, 95 % CI: 1.16, 1.42, $P = 0.000$ (Fig. 4). However, no significant associations was found under the genetic model CC vs TT (OR = 1.05, 95 % CI: 0.95, 1.12, $P = 0.085$).

Associations between rs4821544T/C and UC

For rs4821544T/C polymorphism, 4 case–control studies with 2565 cases and 4624 controls were identified. No significant association was found in any of the genetic models (C vs T: OR = 1.04, 95 % CI: 0.97, 1.11, $P = 0.264$; CC vs TT: OR = 1.10, 95 % CI: 0.93, 1.30, $P = 0.284$; TC vs TT: OR = 1.04, 95 % CI: 0.95, 1.13, $P = 0.429$; CC/TC vs TT: OR = 1.04, 95 % CI: 0.95, 1.13, $P = 0.390$; CC vs TC/TT: OR = 1.07, 95 % CI: 0.91, 1.26, $P = 0.409$).

Publication bias

Begg's funnel plot and Egger's test were applied to assess the publication bias of the included studies. The results of Egger's test and the shapes of the funnel plots for all of the polymorphism indicated that there was no publication bias in the meta-analysis for the association between the *NCF4* polymorphism and CD (Fig. 5; Table 2).

Table 1 Characteristics of studies included in the meta-analysis

Study	Year	Disease	Country	Ethnicity	Sample size		MAF		HWE
					Case	Control	Case	Control	
Rioux JD	2007	CD	American	Caucasian	946	977	0.397	0.333	0.9748
Rioux JD	2007	CD	American	Caucasian	353	207	0.374	0.339	0.9973
Roberts RL	2008	CD	Zealand	Caucasian	496	525	0.303	0.275	0.1384
Franke A	2008	CD	Germany	Caucasian	1811	1747	0.333	0.309	0.6299
Glas J	2009	CD	European	Caucasian	854	1503	0.332	0.322	0.9867
Eglinton TW	2011	CD	Zealand	Caucasian	715	600	0.297	0.275	0.9712
Amre DK	2012	CD	Canada	Caucasian	392	416	0.350	0.350	0.9935
Jung C	2012	CD	France	Caucasian	798	960	0.380	0.330	0.9880
Muise AM	2012	CD	Canada	Caucasian	656	849	0.374	0.322	0.9867
Nasir BF	2013	CD	Australian	Caucasian	174	333	0.319	0.264	0.3391
Roberts RL	2008	UC	Zealand	Caucasian	471	525	0.301	0.275	0.1384
Franke A	2008	UC	Germany	Caucasian	1078	1747	0.328	0.309	0.6299
Glas J	2009	UC	European	Caucasian	756	1503	0.331	0.322	0.9867
Muise AM	2012	UC	Canada	Caucasian	544	849	0.314	0.322	0.9867

CD Crohn's disease, *UC* ulcerative colitis, *MAF* minor allele frequencies, *HWE* Hardy–Weinberg equilibrium

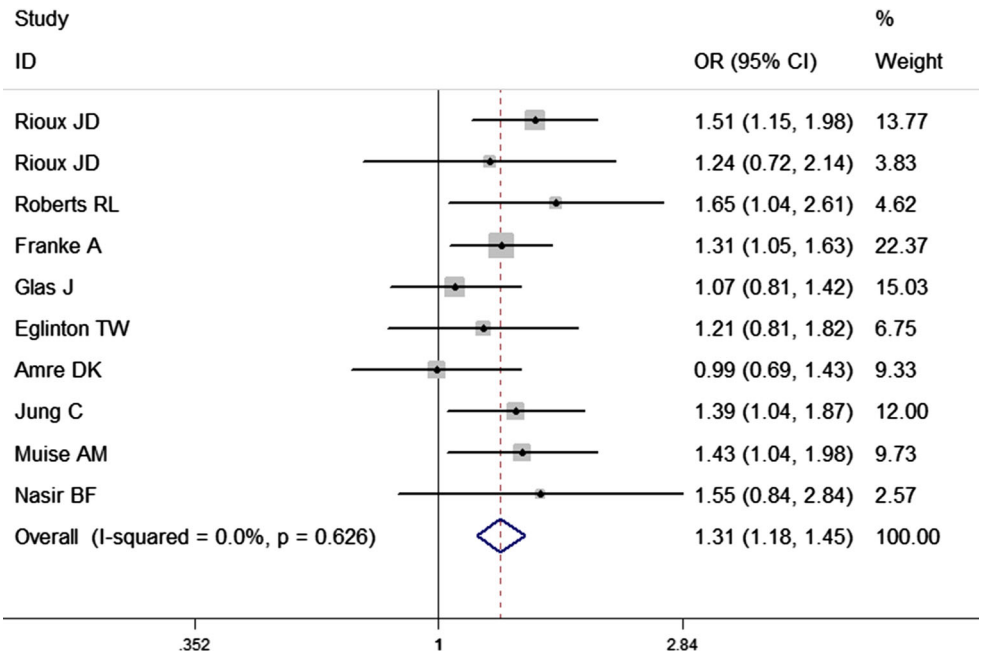

Fig. 2 Forest plots of rs4821544T/C and CD in CC vs TT

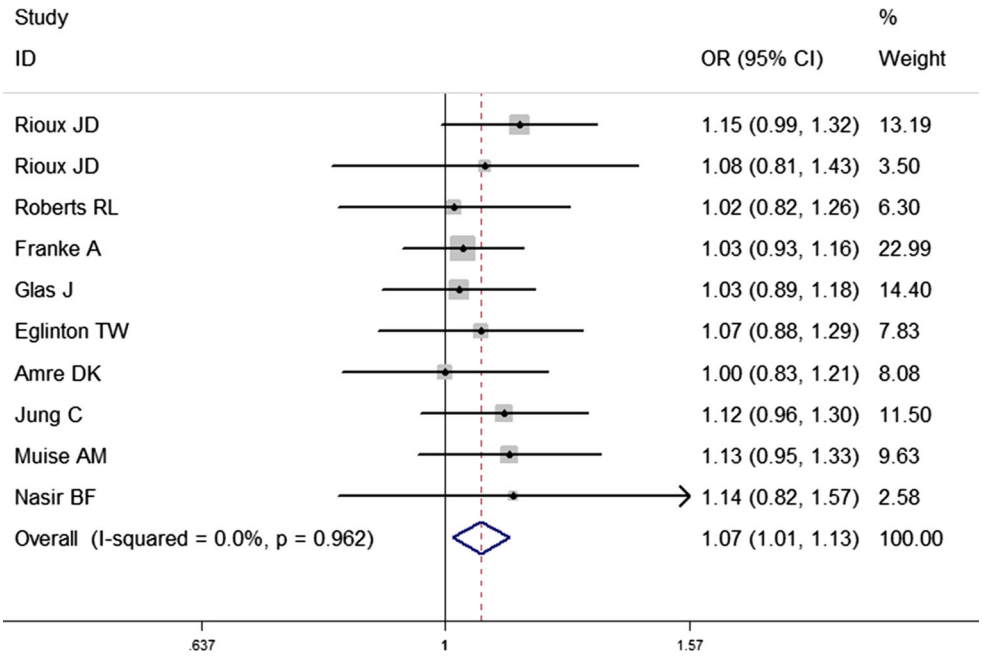

Fig. 3 Forest plots of rs4821544T/C and CD in CC/TC vs TT

Discussion

Although the pathogenesis of IBD was not fully elucidated, IBD is widely regarded to be product of interaction between intestinal microbial flora and genetic predisposition(s) [26]. As we know, phagocytic leukocytes (especially neutrophil) are critical for bacterial killing by ROS produced from NOX2 NADPH oxidase complex [27]. Interestingly, a very recent study indicates patients with chronic granulomatous disease, an inflammatory colitis indistinguishable from CD, have a mutated NADPH complex and are therefore deficient in ROS production [28]. NADPH complex was comprised with many subunits [28], of which p40-phox encoded by *NCF4* was widely studied [29, 30]. Neutrophils collected from a p40phox-/$^{-}$ mice exhibit severe defects in NADPH oxidase regulation and oxidant-dependent bacterial killing [27]. The studies mentioned above indicated p40(phox) may act as an essential player in IBD.

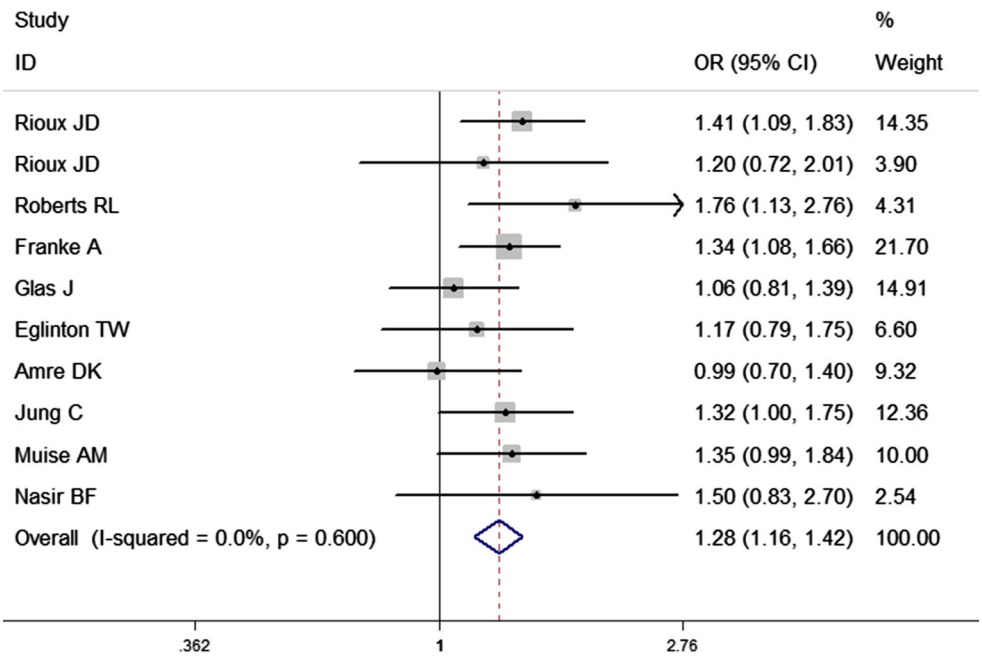

Fig. 4 Forest plots of rs4821544T/C and CD in CC vs TC/TT

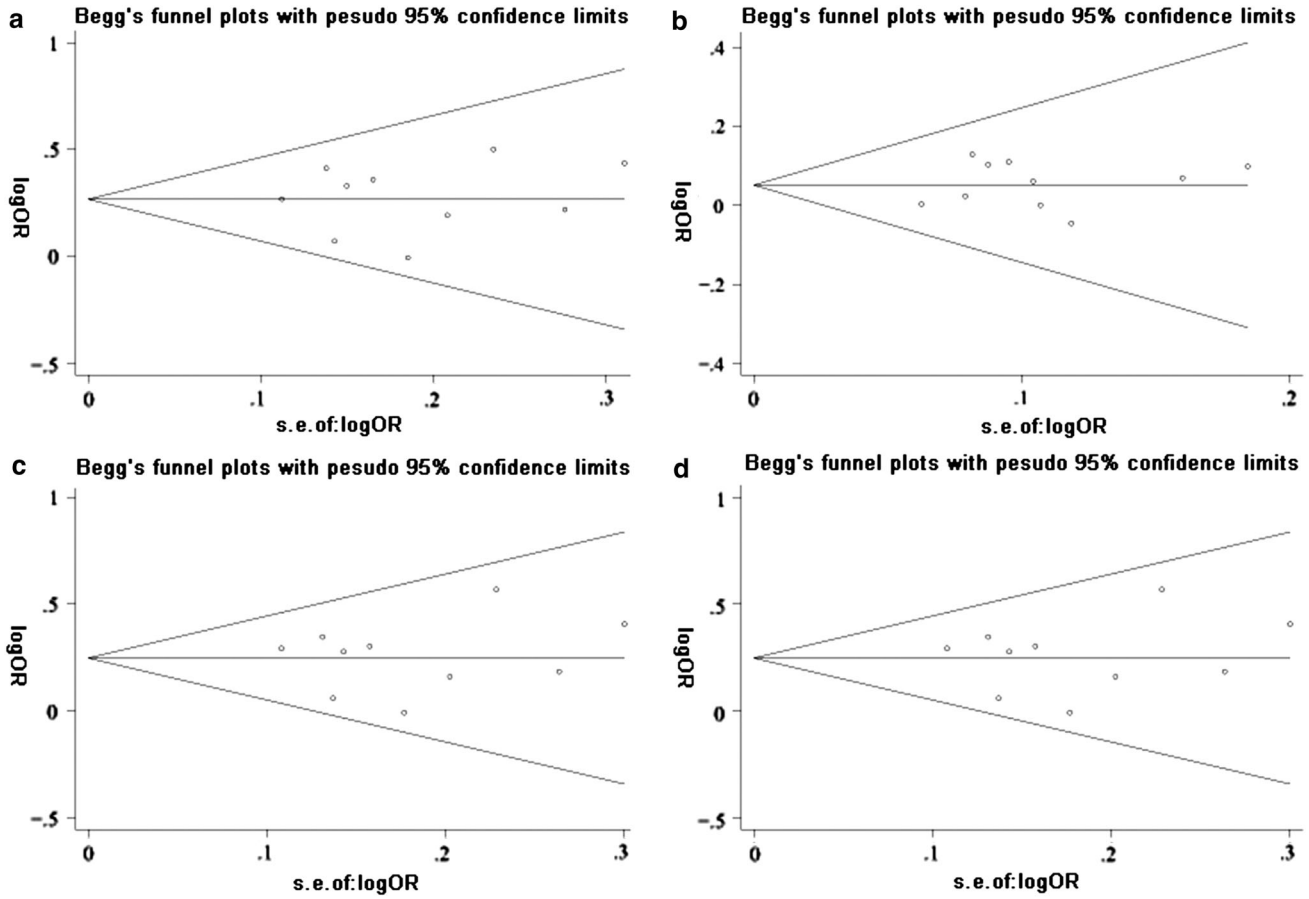

Fig. 5 Begg's funnel plot for rs4821544T/C and CD. **a** CC vs TT; **b** TC vs TT; **c** CC/TC vs TT; **d** CC vs TC/TT

Table 2 Pooled analysis for the associations between *NCF4* polymorphisms and risk of CD and UC

Disease	Comparison	Test of association		Test of heterogeneity			Egger's test (*P*)
		OR (95 % CI) *P*		$\chi 2$ I^2 (%) *P*			
CD	C vs T	1.11 (1.06, 1.16)	0.000	5.44	0.0	0.794	0.870
CD	CC vs TT	1.31 (1.18, 1.45)	0.000	7.11	0.0	0.626	0.816
CD	TC vs TT	1.05 (0.95, 1.12)	0.085	3.35	0.0	0.949	0.703
CD	TC/CC vs TT	1.07 (1.01, 1.13)	0.014	3.06	0.0	0.962	0.708
CD	CC vs TT/TC	1.28 (1.16, 1.42)	0.000	7.35	0.0	0.600	0.847
UC	C vs T	1.04 (0.97, 1.11)	0.264	1.10	0.0	0.775	0.936
UC	CC vs TT	1.10 (0.93, 1.30)	0.284	1.49	0.0	0.684	0.706
UC	TC vs TT	1.04 (0.95, 1.13)	0.429	0.56	0.0	0.906	0.344
UC	TC/CC vs TT	1.04 (0.95, 1.13)	0.390	0.62	0.0	0.891	0.556
UC	CC vs TT/TC	1.07 (0.91, 1.26)	0.409	1.30	0.0	0.729	0.501

From a genetic prospective, variant in *NCF4* may lead to functional alterations in granulocyte ROS production [31]. Recently, several reported genetic markers of *NCF4* have been suggested to have effects on rheumatoid arthritis identifies [12] whose genetic predisposition is partly similar to IBD [32]. To date, considerable efforts have been devoted to investigating the relationship between *NCF4* polymorphism and IBD risk. However, the results of existing studies are inconsistent. Given that subjects in all studies included are Caucasian, we designed a meta-analysis to better clarify the relationship between rs4821544T/C polymorphism and IBD risk in Caucasian.

To our knowledge, this is the first meta-analysis to comprehensively assess the associations between rs4821544T/C polymorphism and IBD risk in Caucasian. A total of 13 case–control studies comprising 7441 CD patients, 2565 UC patients and 8315 controls were included in this meta-analysis. Our results suggest that the rs4821544T/C polymorphism is associated with CD, but not UC in Caucasian. To date, there are limited data on how *NCF4* may functionally influence IBD susceptibility. A possible mechanism is that rs4821544 influences ROS production [14] and consequently impairs bacterial-killing capacity [27], which leads to alteration of intestinal flora.

Of note, there are several genome-wide association studies (GWASs) included in our meta-analysis [13, 17, 21]. GWASs, aimed at increasing g the power of studies by combining the results from different study populations, have led to the identification of novel associations that would not otherwise have been identified in individual studies with small sample. Most results of GWASs also were consistent with our meta-analysis.

Meta-analysis has been considered an effective tool to comprehensively estimate the effect of selected genetic polymorphism on disease risk [33, 34]. Publication bias, also known as the "file-drawer problem", can be considered a major drawback of meta-analyses by compromising their validity [35]. No significant publication bias was detected in all analyses. Heterogeneity, another important issue when performing a meta-analysis, was also not found in also analyses. Furthermore, sample size in each study is relatively larger. Based on the above analyses, our results are relatively scientific and reliable.

As in other systematic reviews and meta-analyses, some limitations require careful consideration. First, there was a lack data available, and we did not analyze the association between rs4821544T/C polymorphism and different histological subtypes, which requires further investigation. Second, only genetic factors were under consideration. A more precise analysis should be based on additional factors including smoking, drinking and other environmental factors. Last but not least, our studies only involved Caucasian. Therefore, representativeness bias of the study was unavoidable.

In conclusion, our meta-analysis suggested that the rs4821544T/C polymorphism was associated with CD, but not UC in Caucasian. Considering there were some limitations in our study, further well-designed case–control studies are necessary to validate the results of our present meta-analysis.

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