Immunologic Research (2019) 67:142–150
https://doi.org/10.1007/s12026-018-9061-0

ORIGINAL ARTICLE

Correlations between *TLR* polymorphisms and inflammatory bowel disease: a meta-analysis of 49 case-control studies

Huijuan Wang[1] · Shuhong Zhou[1] · Jiahong Zhang[1] · Shangwen Lei[1] · Jing Zhou[1]

Published online: 8 January 2019

Abstract

Recently, the roles of toll-like receptor (*TLR*) polymorphisms in inflammatory bowel disease (IBD) were intensively explored, with conflicting results. Therefore, we performed this study to better assess the relationship between *TLR* polymorphisms and the risk of IBD. Eligible studies were searched in PubMed, Medline, Embase, and Web of Science. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to estimate associations between *TLR* polymorphisms and IBD. Significant associations with the risk of IBD were detected for the *TLR1* rs5743611, TLR4 rs4986790, TLR4 rs4986791, and TLR6 rs5743810 polymorphisms in overall analyses. Further subgroup analyses according to ethnicity of participants revealed that the *TLR1* rs5743611, *TLR4* rs4986790, *TLR4* rs4986791, *TLR6* rs5743810, and *TLR9* rs352140 polymorphisms were significantly associated with the risk of IBD in Caucasians. Moreover, the *TLR4* rs4986790 polymorphism was significantly correlated with the risk of IBD in West Asians, while the *TLR9* rs352140 polymorphism was significantly associated with the risk of IBD in Africans. When we stratified available data according to type of disease, we found similar positive results for *TLR1* rs5743611, *TLR4* rs4986790, *TLR4* rs4986791, and *TLR6* rs5743810 polymorphisms. Our findings indicate that *TLR1* rs5743611, *TLR4* rs4986790, *TLR4* rs4986791, *TLR6* rs5743810, and *TLR9* rs352140 polymorphisms may serve as genetic biomarkers of IBD in certain ethnicities. However, further well-designed studies are still warranted to confirm our findings.

Keywords Toll-like receptor (*TLR*) · Gene polymorphisms · Inflammatory bowel disease (IBD) · Crohn's disease (CD) · Ulcerative colitis (UC) · Meta-analysis

Introduction

Inflammatory bowel disease (IBD) refers to a chronic and recurrent inflammatory condition that occurs in the intestinal tract, and it usually manifests as Crohn's disease (CD) or ulcerative colitis (UC) [1]. To date, the exact underlying pathogenic mechanism of IBD is still not fully elucidated. Nevertheless, there is abundant evidence to support that immune dysfunction plays a central role in its pathogenesis. First, previous experimental studies have found that serum levels of pro-inflammatory cytokines are elevated whereas serum levels of anti-inflammatory cytokines are reduced in IBD patients [2, 3]. Second, various auto-antibodies have been identified in serum of IBD patients [4]. Third, anti-inflammatory and immune-suppressive therapies have been shown to be associated with symptomatic improvement and even disease regression in IBD patients [5, 6]. Overall, these findings jointly indicate that immune dysfunction is an important pathogenic factor of IBD.

Toll-like receptors (TLRs) are a group of type 1 transmembrane proteins expressed on a variety of immune cells which recognize stimuli from exogenous pathogens or endogenous cell damage [7]. The binding of TLRs with their corresponding ligands leads to recruitment of adaptor proteins, activation of downstream signal transduction pathways, upregulation of cytokine and chemokine production, and ultimately the development of immune responses [8]. Consequently, it is biologically plausible that functional *TLR* polymorphisms may lead to immune dysfunction and contribute to the development of IBD.

To date, numerous studies have been conducted to investigate the possible correlations of *TLR* polymorphisms with the risk of IBD. But the results of these studies were conflicting and the sample size of individual studies was inadequate to

✉ Huijuan Wang
huijuanwang898@aliyun.com

[1] Department of Immunology and Rheumatology, Gansu Provincial Hospital, No. 204 Donggang West Road, Lanzhou 730000, Gansu, China

draw a definite conclusion [9–12]. Therefore, we performed the present meta-analysis to better elucidate the roles of *TLR* polymorphisms in IBD.

Materials and methods

Literature search and inclusion criteria

The current meta-analysis was performed according to the checklist of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [13]. Potentially relevant articles were searched in PubMed, Medline, Embase, and Web of Science using the following keywords: "Toll like receptor," "TLR," "polymorphism," "variant," "mutation," "genotype," "allele," "Inflammatory bowel disease," "Ulcerative colitis," "Crohn's disease," "IBD," "UC," and "CD." The initial literature search was conducted in November 2017 and the latest update was finished in June 2018. In addition, the reference lists of all retrieved articles were also screened to identify other potentially related literatures.

Included studies should meet all the following criteria: (1) case-control study on associations of *TLR* gene polymorphisms with risk of IBD, (2) provide sufficient data to calculate odds ratios (ORs) with 95% confidence intervals (CIs), and (3) full text in English or Chinese available. For duplicate reports, only the most recent and complete one was included. Abstracts, pedigree studies, case reports, case series, reviews, comments, letters, and conference presentations were intentionally excluded.

Data extraction and quality assessment

The following data were extracted from all included studies: (1) name of first author, (2) year of publication, (3) country and ethnicity of study subjects, (4) type of disease, (5) sample size, and (6) the genotypic distribution of *TLR* gene polymorphisms in cases and controls. Additionally, the probability value (*P* value) of Hardy-Weinberg equilibrium (HWE) test was also calculated on the basis of the genotypic frequencies of certain *TLR* gene polymorphisms in the control group.

The Newcastle-Ottawa scale (NOS) was used to assess the quality of eligible studies from three aspects: (1) selection of cases and controls, (2) comparability between cases and controls, and (3) exposure in cases and controls [14]. The NOS has a score range of zero to nine, and studies with a score of more than seven were considered to be of high quality.

Two reviewers (Wang and Zhou) conducted the data extraction and quality assessment independently. When necessary, the reviewers wrote to the corresponding authors for extra information or raw data. Any discordance between two reviewers was settled by discussion with the third reviewer (Zhang) until a consensus was reached.

Statistical analysis

All statistical analyses in the present study were performed using Review Manager Version 5.3.3 (The Cochrane Collaboration, Software Update, Oxford, UK). ORs and 95% CIs were used to estimate potential associations of *TLR* gene polymorphisms with the risk of IBD in the dominant, recessive, additive, and allele models, and a *P* value of 0.05 or less was considered as statistically significant. Between-study heterogeneity was evaluated on the basis of *Q* test and I^2 statistic. If *P* value of *Q* test was less than 0.1 or I^2 was greater than 50%, the random-effect model (REM) would be adopted for analyses due to the existence of obvious heterogeneity. Otherwise, the fixed-effect model (FEM) would be employed for analyses. Subgroup analyses by ethnicity of study population and type of disease were subsequently conducted to obtain more specific results. Sensitivity analyses were carried out to test the stability of the results. Funnel plots were applied to assess possible publication bias.

Availability of data and material The current study was based on results of relevant published studies.

Results

Characteristics of included studies

The literature search identified 867 potentially relevant articles. After exclusion of irrelevant or duplicate articles by reading titles and abstracts, 81 articles were retrieved for further evaluation. Another 32 articles were subsequently excluded after reading the full text, and a total of 49 studies that met the inclusion criteria of this meta-analysis were finally included (see Fig. 1). All eligible studies were published between 2002 and 2016. The NOS score of eligible articles ranged from 7 to 9, which indicated that all included studies were of relatively high quality. Characteristics of the included studies were summarized in Table 1.

Overall analyses

Significant associations with the risk of IBD were detected for the *TLR1* rs5743611 polymorphism in the recessive ($P = 0.03$, OR = 2.46, 95%CI 1.09–5.53) model, for the *TLR4* rs4986790 polymorphism in the dominant ($P < 0.0001$, OR = 0.70, 95%CI 0.64–0.77), recessive ($P < 0.0001$, OR = 2.21, 95%CI 1.52–3.23), additive ($P < 0.0001$, OR = 1.36, 95%CI 1.24–1.50), and allele ($P < 0.0001$, OR = 0.76, 95%CI 0.67–0.86) models, for the *TLR4* rs4986791 polymorphism in the dominant ($P < 0.0001$, OR = 0.71, 95%CI 0.62–0.81), recessive ($P = 0.009$, OR = 2.30, 95%CI 1.23–4.29), additive ($P =$

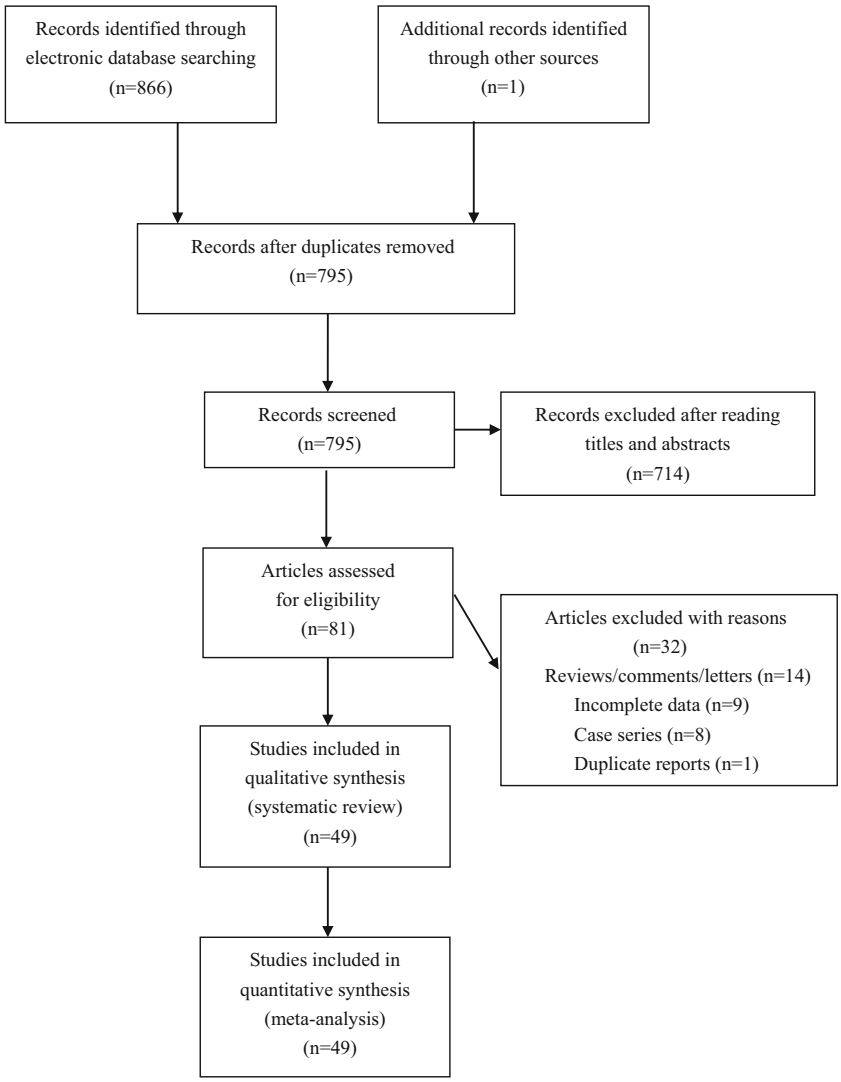

Fig. 1 Flowchart of study selection for the present study

0.0002, OR = 1.52, 95%CI 1.22–1.90), and allele ($P < 0.0001$, OR = 0.76, 95%CI 0.68–0.85) models, for the *TLR6* rs5743810 polymorphism in the dominant ($P = 0.01$, OR = 1.29, 95%CI 1.06–1.57) and additive ($P = 0.004$, OR = 0.78, 95%CI 0.65–0.92) models in overall analyses (see Table 2).

Subgroup analyses

Subgroup analyses according to ethnicity of participants revealed that the *TLR1* rs5743611 (recessive model: $P = 0.03$, OR = 2.46, 95%CI 1.09–5.53), *TLR4* rs4986790 (dominant model: $P < 0.0001$, OR = 0.67, 95%CI 0.61–0.74; recessive model: $P = 0.002$, OR = 1.95, 95%CI 1.27–2.98; additive model: $P < 0.0001$, OR = 1.45, 95%CI 1.31–1.61; allele model: $P < 0.0001$, OR = 0.73, 95%CI 0.64–0.84), *TLR4* rs4986791 (dominant model: $P < 0.0001$, OR = 0.71, 95%CI 0.61–0.82; additive model: $P = 0.0002$, OR = 1.63, 95%CI 1.26–2.10; allele model: $P < 0.0001$, OR = 0.77, 95%CI 0.69–0.87), *TLR6* rs5743810 (dominant model: $P = 0.007$, OR = 1.31, 95%CI 1.07–1.59; additive model: $P = 0.003$, OR = 0.77, 95%CI 0.64–0.91), and *TLR9* rs352140 (recessive model: $P = 0.03$, OR = 1.26, 95%CI 1.03–1.55) polymorphisms were significantly associated with the risk of IBD in Caucasians. In addition, the *TLR4* rs4986790 polymorphism (recessive model: $P = 0.001$, OR = 7.17, 95%CI 2.15–23.91) was significantly correlated with the risk of IBD in West Asians, while the *TLR9* rs352140 (recessive model: $P = 0.008$, OR = 0.58, 95%CI 0.39–0.87; additive model: $P = 0.0006$, OR = 1.73, 95%CI 1.27–2.37) polymorphism was significantly associated with the risk of IBD in Africans.

When we stratified available data according to type of disease, we found that the *TLR4* rs4986790 (dominant model: $P < 0.0001$, OR = 0.70, 95%CI 0.61–0.79; recessive model: $P = 0.01$, OR = 1.92, 95%CI 1.16–3.16; additive model: $P < 0.0001$, OR = 1.39, 95%CI 1.23–1.58; allele model:

Table 1 The characteristics of included studies for TLR gene polymorphisms and IBD

First author, year	Country	Ethnicity	Type of disease	Sample size	Genotype distribution		*P* value for HWE	NOS score
					Cases	controls		
TLR1 rs5743611					GG/GC/CC			
Henckaerts 2007	Belgium	Caucasian	CD	830/289	669/145/16	236/50/3	0.847	7
Henckaerts 2007	Belgium	Caucasian	UC	242/289	207/29/6	236/50/3	0.847	7
Kim 2012	Korea	East Asian	CD	45/178	45/0/0	178/0/0	NA	7
Kim 2012	Korea	East Asian	UC	99/178	99/0/0	178/0/0	NA	7
Meena 2015	India	West Asian	UC	328/350	328/0/0	350/0/0	NA	9
Pierik 2006	Belgium	Caucasian	CD	179/191	142/33/4	155/35/1	0.512	7
Pierik 2006	Belgium	Caucasian	UC	106/191	91/13/2	155/35/1	0.512	7
TLR2 rs5743708					GG/GA/AA			
Chen 2012	China	East Asian	IBD	146/164	146/0/0	164/0/0	NA	8
Henckaerts 2007	Belgium	Caucasian	CD	829/277	797/30/2	263/14/0	0.666	7
Henckaerts 2007	Belgium	Caucasian	UC	246/277	234/12/0	263/14/0	0.666	7
Hong 2007	New Zealand	Caucasian	CD	182/188	176/6/0	177/11/0	0.679	7
Kim 2012	Korea	East Asian	CD	45/178	45/0/0	178/0/0	NA	7
Kim 2012	Korea	East Asian	UC	99/178	99/0/0	178/0/0	NA	7
Meena 2015	India	West Asian	UC	328/350	327/1/0	350/0/0	NA	9
Pierik 2006	Belgium	Caucasian	CD	179/191	171/8/0	182/9/0	0.739	7
Pierik 2006	Belgium	Caucasian	UC	106/191	100/6/0	182/9/0	0.739	7
Queiroz 2009	Brazil	African	CD	43/541	43/0/0	530/11/0	0.811	7
Queiroz 2009	Brazil	African	UC	42/541	41/1/0	530/11/0	0.811	7
Shen 2010	China	East Asian	CD	30/120	30/0/0	120/0/0	NA	7
Shen 2010	China	East Asian	UC	83/120	83/0/0	120/0/0	NA	7
Török 2017	Germany	Caucasian	CD	837/784	784/50/3	735/48/1	0.815	7
Török 2017	Germany	Caucasian	UC	401/784	370/31/0	735/48/1	0.815	7
TLR2 rs121917864					CC/CT/TT			
Chen 2012	China	East Asian	IBD	146/164	146/0/0	164/0/0	NA	8
Kim 2012	Korea	East Asian	CD	45/178	45/0/0	178/0/0	NA	7
Kim 2012	Korea	East Asian	UC	99/178	99/0/0	178/0/0	NA	7
Queiroz 2009	Brazil	African	CD	43/541	43/0/0	530/11/0	0.811	7
Queiroz 2009	Brazil	African	UC	42/541	41/1/0	530/11/0	0.811	7
Shen 2010	China	East Asian	CD	30/120	30/0/0	120/0/0	NA	7
Shen 2010	China	East Asian	UC	83/120	83/0/0	120/0/0	NA	7
TLR4 rs4986790					AA/AG/GG			
Arnott 2004	UK	Caucasian	CD	234/189	186/46/2	157/31/1	0.688	7
Arnott 2004	UK	Caucasian	UC	246/189	212/32/2	158/31/1	0.688	7
Baumgart 2007	Germany	Caucasian	CD	241/403	215/24/2	356/45/2	0.656	7
Baumgart 2007	Germany	Caucasian	UC	145/403	122/22/1	356/45/2	0.656	7
Braat 2005	The Netherlands	Caucasian	CD	411/137	349/56/6	124/13/0	0.560	7
Braat 2005	The Netherlands	Caucasian	UC	226/137	201/24/1	124/13/0	0.560	7
Brand 2005	Germany	Caucasian	CD	204/199	175/29/0	184/15/0	0.581	7
Browning 2007	New Zealand	Caucasian	CD	386/402	337/48/1	359/43/0	0.257	7
Browning 2007	New Zealand	Caucasian	UC	405/402	356/47/2	359/43/0	0.257	7
Bueno 2009	Belgium	Caucasian	CD	80/79	66/11/3	71/8/0	0.635	7
Bueno 2009	Belgium	Caucasian	UC	15/79	15/0/0	71/8/0	0.635	7
Chen 2012	China	East Asian	IBD	146/164	146/0/0	164/0/0	NA	8
de Ridder 2007	The Netherlands	Caucasian	CD	450/244	382/62/6	224/20/0	0.504	7
de Ridder 2007	The Netherlands	Caucasian	UC	257/244	222/33/2	224/20/0	0.504	7

Table 1 (continued)

First author, year	Country	Ethnicity	Type of disease	Sample size	Genotype distribution		*P* value for HWE	NOS score
					Cases controls			
Figueroa 2006	Chile	Caucasian	CD	22/20	21/1/0	20/0/0	NA	7
Figueroa 2006	Chile	Caucasian	UC	22/20	21/1/0	20/0/0	NA	7
Franchimont 2004	Belgium	Caucasian	CD	447/139	353/89/5	126/12/1	0.251	7
Franchimont 2004	Belgium	Caucasian	UC	163/139	133/28/2	126/12/1	0.251	7
Fries 2005	Italy	Caucasian	CD	23/59	21/2/0	57/2/0	0.895	7
Gazouli 2005	Greece	Caucasian	CD	120/100	103/15/2	95/4/1	0.002	7
Gazouli 2005	Greece	Caucasian	UC	85/100	79/6/0	95/4/1	0.002	7
Guo 2005	China	East Asian	UC	114/160	114/0/0	160/0/0	NA	7
Henckaerts 2007	Belgium	Caucasian	CD	856/293	717/128/11	264/27/2	0.169	7
Henckaerts 2007	Belgium	Caucasian	UC	250/293	209/38/3	264/27/2	0.169	7
Hong 2007	New Zealand	Caucasian	CD	182/188	156/26/0	158/28/2	0.550	7
Hume 2008	Australia	Caucasian	CD	619/360	NA	NA	NA	7
Kim 2012	Korea	East Asian	CD	45/178	45/0/0	178/0/0	NA	7
Kim 2012	Korea	East Asian	UC	99/178	99/0/0	178/0/0	NA	7
Lakatos 2005	Hungary	Caucasian	CD	527/200	475/50/2	176/23/1	0.792	7
Lappalainen 2008	Finland	Caucasian	CD	240/190	NA	NA	NA	7
Lappalainen 2008	Finland	Caucasian	UC	459/190	NA	NA	NA	7
Manolakis 2013	Greece	Caucasian	CD	163/274	144/19/0	242/31/1	0.995	7
Manolakis 2013	Greece	Caucasian	UC	187/274	146/41/0	242/31/1	0.995	7
Martinez-Chamorro 2016	Spain	Caucasian	CD	371/636	NA	NA	NA	7
Meena 2013	India	West Asian	CD	46/201	38/6/2	154/46/1	0.211	8
Meena 2013	India	West Asian	UC	199/201	151/37/11	154/46/1	0.211	8
Mohammadi 2013	Iran	West Asian	UC	85/256	75/10/0	216/39/1	0.586	7
Okayama 2002	Japan	East Asian	UC	86/107	86/0/0	107/0/0	NA	7
Oostenbrug 2005	The Netherlands	Caucasian	CD	393/296	343/47/3	269/27/0	0.411	7
Oostenbrug 2005	The Netherlands	Caucasian	UC	179/296	159/19/1	269/27/0	0.411	7
Ouburg 2005	The Netherlands	Caucasian	CD	112/170	91/19/2	153/16/1	0.423	7
Pierik 2006	Belgium	Caucasian	CD	179/191	142/35/2	174/16/1	0.353	7
Pierik 2006	Belgium	Caucasian	UC	106/191	89/15/2	174/16/1	0.353	7
Queiroz 2009	Brazil	African	CD	43/539	41/2/0	489/50/0	0.259	7
Queiroz 2009	Brazil	African	UC	42/539	38/3/1	489/50/0	0.259	7
Rigoli 2008	Italy	Caucasian	CD	133/103	123/10/0	95/8/0	0.682	7
Rigoli 2008	Italy	Caucasian	UC	45/103	42/3/0	95/8/0	0.682	7
Riis 2007	Denmark	Caucasian	CD	211/618	NA	NA	NA	7
Riis 2007	Denmark	Caucasian	UC	404/618	NA	NA	NA	7
Senhaji 2014	Morocco	Caucasian	CD	83/112	74/9/0	103/8/1	0.085	8
Senhaji 2014	Morocco	Caucasian	UC	34/112	28/6/0	103/8/1	0.085	8
Shen 2010	China	East Asian	CD	30/120	30/0/0	120/0/0	NA	7
Shen 2010	China	East Asian	UC	83/120	83/0/0	120/0/0	NA	7
Sivaram 2012	India	West Asian	UC	139/176	107/30/2	153/23/0	0.354	7
Stankovic 2015	Serbia	Caucasian	CD	72/101	60/11/1	94/7/0	0.718	8
Stankovic 2015	Serbia	Caucasian	UC	95/101	80/15/0	94/7/0	0.718	8
Tolentino 2016	Brazil	African	CD	67/78	58/8/1	70/7/1	0.123	7
Tolentino 2016	Brazil	African	UC	61/78	59/2/0	70/7/1	0.123	7
Török 2004	Germany	Caucasian	CD	102/145	87/15/0	132/13/0	0.572	7
Török 2004	Germany	Caucasian	UC	98/145	81/16/1	132/13/0	0.572	7
Wagner 2010	Australia	Caucasian	CD	72/98	59/11/2	84/12/2	0.070	7

Table 1 (continued)

First author, year	Country	Ethnicity	Type of disease	Sample size	Genotype distribution		*P* value for HWE	NOS score
					Cases controls			
Ye 2009	Korea	East Asian	CD	360/337	360/0/0	336/1/0	0.978	7
Zouiten-Mekki 2009	Tunisia	Caucasian	CD	90/80	78/12/0	71/9/0	0.594	7
TLR4 rs4986791					CC/CT/TT			
Azzam 2012	Saudi Arabia	West Asian	CD	46/50	24/18/4	32/14/4	0.193	7
Brand 2005	Germany	Caucasian	CD	204/199	174/30/0	180/19/0	0.479	7
Browning 2007	New Zealand	Caucasian	CD	385/393	339/45/1	347/46/0	0.218	7
Browning 2007	New Zealand	Caucasian	UC	405/393	348/55/2	347/46/0	0.218	7
Chen 2012	China	East Asian	IBD	146/164	NA	NA	NA	8
de Ridder 2007	The Netherlands	Caucasian	CD	430/248	361/66/3	215/32/1	0.869	7
Gazouli 2005	Greece	Caucasian	CD	120/100	119/1/0	98/2/0	0.920	7
Gazouli 2005	Greece	Caucasian	UC	85/100	82/3/0	98/2/0	0.920	7
Hong 2007	New Zealand	Caucasian	CD	182/188	152/30/0	158/28/2	0.583	7
Kim 2012	Korea	East Asian	CD	45/178	45/0/0	178/0/0	NA	7
Kim 2012	Korea	East Asian	UC	99/178	99/0/0	178/0/0	NA	7
Lappalainen 2008	Finland	Caucasian	CD	240/190	NA	NA	NA	7
Lappalainen 2008	Finland	Caucasian	UC	459/190	NA	NA	NA	7
Manolakis 2013	Greece	Caucasian	CD	163/274	144/19/0	242/31/1	0.995	7
Manolakis 2013	Greece	Caucasian	UC	187/274	146/41/0	242/31/1	0.995	7
Martinez-Chamorro 2016	Spain	Caucasian	CD	371/636	NA	NA	NA	7
Meena 2013	India	West Asian	CD	46/201	41/5/0	183/18/0	0.506	8
Meena 2013	India	West Asian	UC	199/201	157/35/7	183/18/0	0.506	8
Mohammadi 2013	Iran	West Asian	UC	85/256	74/11/0	212/43/1	0.446	7
Oostenbrug 2005	The Netherlands	Caucasian	CD	464/299	400/59/5	270/29/0	0.378	7
Oostenbrug 2005	The Netherlands	Caucasian	UC	217/299	194/22/1	270/29/0	0.378	7
Rigoli 2008	Italy	Caucasian	CD	133/103	125/8/0	97/6/0	0.761	7
Rigoli 2008	Italy	Caucasian	UC	45/103	42/3/0	97/6/0	0.761	7
Senhaji 2014	Morocco	Caucasian	CD	83/112	76/7/0	109/3/0	0.886	8
Senhaji 2014	Morocco	Caucasian	UC	34/112	32/1/1	109/3/0	0.886	8
Shen 2010	China	East Asian	CD	30/120	30/0/0	120/0/0	NA	7
Shen 2010	China	East Asian	UC	83/120	83/0/0	120/0/0	NA	7
Stankovic 2015	Serbia	Caucasian	CD	72/101	61/10/1	91/10/0	0.601	8
Stankovic 2015	Serbia	Caucasian	UC	95/101	79/16/0	91/10/0	0.601	8
Tolentino 2016	Brazil	African	CD	67/83	61/6/0	77/6/0	0.733	7
Tolentino 2016	Brazil	African	UC	61/83	59/2/0	77/6/0	0.733	7
Török 2004	Germany	Caucasian	CD	102/145	86/16/0	139/6/0	0.799	7
Török 2004	Germany	Caucasian	UC	98/145	78/19/1	139/6/0	0.799	7
Ye 2009	Korea	East Asian	CD	360/337	360/0/0	336/1/0	0.978	7
Zouiten-Mekki 2009	Tunisia	Caucasian	CD	90/80	77/13/0	72/8/0	0.638	7
Zouiten-Mekki 2009	Tunisia	Caucasian	UC	30/80	28/2/0	72/8/0	0.638	7
TLR6 rs5743810					GG/GA/AA			
Abad 2011	Spain	Caucasian	CD	508/576	NA	NA	NA	7
Henckaerts 2007	Belgium	Caucasian	CD	818/291	258/391/169	72/157/62	0.171	7
Henckaerts 2007	Belgium	Caucasian	UC	244/291	80/104/60	72/157/62	0.171	7
Kim 2012	Korea	East Asian	CD	45/178	45/0/0	178/0/0	NA	7
Kim 2012	Korea	East Asian	UC	99/178	99/0/0	178/0/0	NA	7
Meena 2015	India	West Asian	UC	328/350	326/2/0	350/0/0	NA	9
Pierik 2006	Belgium	Caucasian	CD	179/191	46/94/39	49/103/39	0.260	7

Table 1 (continued)

First author, year	Country	Ethnicity	Type of disease	Sample size	Genotype distribution		*P* value for HWE	NOS score
					Cases controls			
Pierik 2006	Belgium	Caucasian	UC	106/191	30/51/25	49/103/39	0.260	7
TLR9 rs352140					GG/GA/AA			
Fuse 2010	Japan	East Asian	UC	48/47	19/24/5	9/25/13	0.624	8
Török 2004	Germany	Caucasian	CD	606/792	184/292/130	262/395/135	0.503	7
Török 2004	Germany	Caucasian	UC	350/792	111/171/68	262/395/135	0.503	7
Valverde-Villegas 2014	Brazil	African	CD	134/239	30/86/18	72/109/58	0.190	7
Valverde-Villegas 2014	Brazil	African	UC	110/239	31/59/20	72/109/58	0.190	7
TLR9 rs5743836					TT/TC/CC			
Hong 2007	New Zealand	Caucasian	CD	182/188	152/30/0	158/28/2	0.550	7
Hotte 2012	Canada	Caucasian	CD	15/21	11/4/0	15/5/1	0.513	7
Hotte 2012	Canada	Caucasian	UC	14/21	10/2/2	15/5/1	0.513	7
Petermann 2009	New Zealand	Caucasian	CD	387/412	282/94/11	291/112/9	0.642	7
Petermann 2009	New Zealand	Caucasian	UC	406/412	290/106/10	291/112/9	0.642	7
Shen 2010	China	East Asian	CD	30/120	29/1/0	119/1/0	0.963	7
Shen 2010	China	East Asian	UC	83/120	81/2/0	119/1/0	0.963	7
Török 2004	Germany	Caucasian	CD	605/792	435/159/11	593/189/10	0.240	7
Török 2004	Germany	Caucasian	UC	348/792	256/86/6	593/189/10	0.240	7
Valverde-Villegas 2014	Brazil	African	CD	132/239	86/39/7	171/62/6	0.893	7
Valverde-Villegas 2014	Brazil	African	UC	107/239	73/30/4	171/62/6	0.893	7
Ye 2009	Korea	East Asian	CD	366/351	366/0/0	350/1/0	0.979	7

TLR, toll-like receptor; *IBD*, inflammatory bowel disease; *CD*, Crohn's disease; *UC*, ulcerative colitis; *HWE*, Hardy-Weinberg equilibrium; *NOS*, Newcastle-Ottawa scale; *NA*, not available

$P < 0.0001$, OR = 0.76, 95%CI 0.69–0.84) and *TLR4* rs4986791 (dominant model: $P = 0.002$, OR = 0.76, 95%CI 0.64–0.90; additive model: $P = 0.004$, OR = 1.30, 95%CI 1.09–1.55; allele model: $P = 0.002$, OR = 0.80, 95%CI 0.70–0.93) polymorphisms were significantly correlated with the risk of CD, whereas *TLR1* rs5743611 (additive model: $P = 0.03$, OR = 0.64, 95%CI 0.43–0.96), *TLR4* rs4986790 (dominant model: $P < 0.0001$, OR = 0.73, 95%CI 0.63–0.85; recessive model: $P = 0.002$, OR = 2.58, 95%CI 1.44–4.64; additive model: $P < 0.0001$, OR = 1.30, 95%CI 1.11–1.51; allele model: $P = 0.04$, OR = 0.80, 95%CI 0.64–0.99), *TLR4* rs4986791 (dominant model: $P = 0.02$, OR = 0.65, 95%CI 0.45–0.92; recessive model: $P = 0.0005$, OR = 4.29, 95%CI 1.54–11.95; additive model: $P = 0.01$, OR = 1.82, 95%CI 1.15–2.89; allele model: $P = 0.02$, OR = 0.68, 95%CI 0.49–0.95), and *TLR6* rs5743810 (additive model: $P = 0.01$, OR = 0.70, 95%CI 0.53–0.93) polymorphisms were significantly correlated with the risk of UC (see Table 2).

Sensitivity analyses

Sensitivity analyses were performed to examine the stability of meta-analysis results by eliminating studies that deviated from HWE. No changes of results were detected for investigated *TLR* gene polymorphisms in any comparisons, which suggested that our findings were statistically reliable.

Publication bias

Potential publication bias in the present study was assessed with funnel plots. No obvious asymmetry of funnel plots was observed in any comparisons, which indicated that no severe publication bias existed in our meta-analysis.

Discussion

The inflammatory nature of IBD has long been recognized. Firstly, pro-inflammatory cytokines such as tumor necrosis factor-alpha, interferon-gamma, interleukin-1, interleukin-6, and interleukin-17 were found to promote the development and progression of the disease, while anti-inflammatory cytokines such as transforming growth factor-beta and interleukin-10 could lead to disease regression [2, 3]. Secondly, several pilot studies also demonstrated that anti-inflammatory therapy is a rational and effective treatment option for IBD patients [5, 6, 15]. Therefore, it is biologically plausible that functional

Table 2 Overall and subgroup analyses for TLR gene polymorphisms and IBD

Polymorphisms	Population	Sample size	Dominant comparison *P* value OR (95%CI)	Recessive comparison *P* value OR (95%CI)	Additive comparison *P* value OR (95%CI)	Allele comparison *P* value OR (95%CI)
TLR1 rs5743611	Overall	1829/1666	0.61 1.06 (0.85–1.33)	*0.03 2.46 (1.09–5.53)*	0.20 0.86 (0.68–1.08)	0.84 0.98 (0.80–1.20)
	Caucasian	1357/960	0.61 1.06 (0.85–1.33)	*0.03 2.46 (1.09–5.53)*	0.20 0.86 (0.68–1.08)	0.84 0.98 (0.80–1.20)
	CD	1054/658	0.57 0.92 (0.69–1.22)	0.13 2.31 (0.78–6.83)	0.94 1.01 (0.75–1.36)	0.33 0.88 (0.67–1.14)
	UC	775/1008	0.12 1.36 (0.93–1.98)	0.11 2.68 (0.80–8.98)	*0.03 0.64 (0.43–0.96)*	0.34 1.18 (0.84–1.67)
TLR2 rs5743708	Overall	3596/4884	0.99 1.00 (0.79–1.27)	0.47 1.72 (0.39–7.63)	0.88 0.98 (0.77–1.25)	0.91 0.99 (0.78–1.24)
	Caucasian	2780/2692	0.96 1.01 (0.79–1.28)	0.47 1.72 (0.39–7.63)	0.86 0.98 (0.77–1.24)	0.93 0.99 (0.78–1.25)
	African	85/1082	0.83 1.19 (0.23–6.33)	NA NA	0.83 0.84 (0.16–4.43)	0.84 1.19 (0.23–6.24)
	CD	2145/2279	0.42 1.13 (0.84–1.53)	0.36 2.34 (0.38–14.51)	0.30 0.85 (0.62–1.16)	0.58 1.09 (0.81–1.46)
	UC	1305/2441	0.34 0.84 (0.58–1.21)	0.79 0.65 (0.03–16.00)	0.31 1.21 (0.84–1.75)	0.38 0.85 (0.59–1.22)
TLR2 rs121917864	Overall	488/1842	0.83 1.19 (0.23–6.33)	NA NA	0.83 0.84 (0.16–4.43)	0.84 1.19 (0.23–6.24)
	African	85/1082	0.83 1.19 (0.23–6.33)	NA NA	0.83 0.84 (0.16–4.43)	0.84 1.19 (0.23–6.24)
	CD	118/839	0.66 1.89 (0.11–32.55)	NA NA	0.66 0.53 (0.03–9.15)	0.67 1.86 (0.11–31.78)
	UC	224/839	0.88 0.85 (0.11–6.75)	NA NA	0.88 1.18 (0.15–9.33)	0.88 0.85 (0.11–6.68)
TLR4 rs4986790	Overall	12,089/13494	*< 0.0001 0.70 (0.64–0.77)*	*< 0.0001 2.21 (1.52–3.23)*	*< 0.0001 1.36 (1.24–1.50)*	*< 0.0001 0.76 (0.67–0.86)*
	Caucasian	10,444/10062	*< 0.0001 0.67 (0.61–0.74)*	*0.002 1.95 (1.27–2.98)*	*< 0.0001 1.45 (1.31–1.61)*	*< 0.0001 0.73 (0.64–0.84)*
	West Asian	469/834	0.81 0.94 (0.59–1.50)	*0.001 7.17 (2.15–23.91)*	0.68 0.90 (0.53–1.52)	0.12 0.81 (0.62–1.06)
	African	213/1234	0.40 1.29 (0.72–2.31)	0.48 1.28 (0.19–35.19)	0.30 0.72 (0.39–1.34)	0.52 1.20 (0.69–2.06)
	CD	7614/7479	*< 0.0001 0.70 (0.61–0.79)*	*0.01 1.92 (1.16–3.16)*	*< 0.0001 1.39 (1.23–1.58)*	*< 0.0001 0.76 (0.69–0.84)*
	UC	4190/5675	*< 0.0001 0.73 (0.63–0.85)*	*0.002 2.58 (1.44–4.64)*	*< 0.0001 1.30 (1.11–1.51)*	*0.04 0.80 (0.64–0.99)*
TLR4 rs4986791	Overall	5961/6836	*< 0.0001 0.71 (0.62–0.81)*	*0.009 2.30 (1.23–4.29)*	*0.0002 1.52 (1.22–1.90)*	*< 0.0001 0.76 (0.68–0.85)*
	Caucasian	4694/4865	*< 0.0001 0.71 (0.61–0.82)*	0.05 2.17 (1.00–4.72)	*0.0002 1.63 (1.26–2.10)*	*< 0.0001 0.77 (0.69–0.87)*
	West Asian	376/708	0.26 0.69 (0.37–1.31)	0.08 2.56 (0.90–7.25)	0.07 1.40 (0.97–2.02)	0.29 0.70 (0.36–1.36)
	African	128/166	0.73 1.18 (0.47–2.99)	NA NA	0.73 0.85 (0.33–2.14)	0.73 1.17 (0.47–2.92)
	CD	3633/4037	*0.002 0.76 (0.64–0.90)*	0.33 1.50 (0.67–3.36)	*0.004 1.30 (1.09–1.55)*	*0.002 0.80 (0.70–0.93)*
	UC	2182/2635	*0.02 0.65 (0.45–0.92)*	*0.0005 4.29 (1.54–11.95)*	*0.01 1.82 (1.15–2.89)*	*0.02 0.68 (0.49–0.95)*
TLR6 rs5743810	Overall	2327/2246	*0.01 1.29 (1.06–1.57)*	0.49 1.08 (0.87–1.33)	*0.004 0.78 (0.65–0.92)*	0.08 1.09 (0.99–1.21)
	Caucasian	1855/1540	*0.007 1.31 (1.07–1.59)*	0.49 1.08 (0.87–1.33)	*0.003 0.77 (0.64–0.91)*	0.07 1.10 (0.99–1.21)
	CD	1550/1236	0.06 1.27 (0.99–1.64)	0.99 1.00 (0.76–1.31)	0.10 0.83 (0.66–1.04)	0.08 1.11 (0.99–1.25)
	UC	777/1010	0.07 1.32 (0.97–1.79)	0.27 1.20 (0.87–1.67)	*0.01 0.70 (0.53–0.93)*	0.62 1.05 (0.86–1.28)
TLR9 rs352140	Overall	1248/2109	0.22 0.91 (0.78–1.06)	0.34 0.81 (0.52–1.25)	0.29 1.18 (0.87–1.58)	0.80 1.02 (0.85–1.23)
	Caucasian	956/1584	0.26 0.91 (0.76–1.08)	*0.03 1.26 (1.03–1.55)*	0.49 0.95 (0.80–1.11)	0.05 0.89 (0.79–1.00)
	African	244/478	0.16 0.78 (0.55–1.10)	*0.008 0.58 (0.39–0.87)*	*0.0006 1.73 (1.27–2.37)*	0.52 1.07 (0.86–1.34)
	CD	740/1031	0.10 0.84 (0.68–1.03)	0.71 0.83 (0.31–2.23)	0.43 1.38 (0.62–3.10)	0.13 0.90 (0.79–1.03)
	UC	508/1078	0.63 1.12 (0.71–1.78)	0.37 0.75 (0.39–1.41)	0.76 1.03 (0.84–1.28)	0.38 1.18 (0.81–1.71)
TLR9 rs5743836	Overall	2675/3707	0.30 0.94 (0.83–1.06)	0.13 1.35 (0.92–1.99)	0.57 1.04 (0.91–1.18)	0.17 0.93 (0.83–1.03)
	Caucasian	1957/2638	0.60 0.96 (0.84–1.10)	0.33 1.24 (0.80–1.92)	0.82 1.02 (0.89–1.17)	0.46 0.96 (0.85–1.08)
	East Asian	479/591	0.52 0.61 (0.14–2.67)	NA NA	0.52 1.63 (0.37–7.09)	0.52 0.62 (0.14–2.67)
	African	239/478	0.17 0.79 (0.57–1.11)	0.15 1.86 (0.81–4.30)	0.41 1.16 (0.82–1.64)	0.09 0.78 (0.59–1.04)
	CD	1717/2123	0.33 0.92 (0.78–1.09)	0.26 1.35 (0.80–2.25)	0.52 1.06 (0.89–1.25)	0.24 0.91 (0.79–1.06)
	UC	958/1584	0.64 0.96 (0.79–1.16)	0.30 1.36 (0.76–2.43)	0.89 1.01 (0.83–1.23)	0.48 0.90 (0.80–1.11)

The values in italic represent there is statistically significant differences between cases and controls

OR, odds ratio; *CI*, confidence interval; *NA*, not available; *TLR*, toll-like receptor; *IBD*, inflammatory bowel disease; *CD*, Crohn's disease; *UC*, ulcerative colitis; *HWE*, Hardy-Weinberg equilibrium; *NOS*, Newcastle-Ottawa scale

polymorphisms in immune-related genes may be implicated in the pathogenesis of IBD.

TLRs are a group of pattern recognition receptors (PRRs) for structural conserved exogenous pathogen-associated molecules (PAMs) and endogenous damage-associated molecules (DAMs), which play prominent roles in evoking immune reactions in response to both infectious and non-infectious stimuli [7]. The interaction of TLRs with their corresponding ligands activates the TLR signaling pathway, which leads to pro-inflammatory cytokine production and leukocyte infiltration [8]. Given the crucial roles of TLRs in regulating immune responses, the potential correlations of certain *TLR* gene polymorphisms with the risk of inflammatory diseases like IBD were extensively studied, but the results of these studies were contradictory. Hence, we performed the present meta-analysis of all published literatures on relationship between *TLR* gene polymorphisms and IBD to obtain a more conclusive result.

Significant associations with the risk of IBD were detected for the *TLR1* rs5743611 polymorphism in the recessive model, for the *TLR4* rs4986790 polymorphism in the dominant, recessive, additive, and allele models, for the *TLR4* rs4986791 polymorphism in the dominant, recessive, additive, and allele models, for the *TLR6* rs5743810 polymorphism in the dominant and additive models in overall analyses. Further subgroup analyses according to ethnicity of participants revealed that the *TLR1* rs5743611, *TLR4* rs4986790, *TLR4* rs4986791, *TLR6* rs5743810, and *TLR9* rs352140 polymorphisms were significantly associated with the risk of IBD in Caucasians. In addition, the *TLR4* rs4986790 polymorphism was significantly correlated with the risk of IBD in West Asians, while the *TLR9* rs352140 polymorphism was significantly associated with the risk of IBD in Africans. When we stratified available data according to the type of disease, we found that the *TLR4* rs4986790 and *TLR4* rs4986791 polymorphisms were significantly correlated with the risk of CD, whereas *TLR1* rs5743611, *TLR4* rs4986790, *TLR4* rs4986791, and *TLR6* rs5743810 polymorphisms were significantly correlated with the risk of UC. No any other significant associations were detected in overall and subgroup analyses. The stability of the results was subsequently tested in sensitivity analyses, and no statistically significant alterations were observed in any comparisons, which indicated that our synthetic results were quite reliable. As for the evaluation of the heterogeneity, only trivial between-study heterogeneity was detected and nearly all comparisons were performed with the fixed-effect model.

There is no denying that this meta-analysis has some limitations. First, our results were based on unadjusted estimations due to lack of original data, and failure to perform further stratified analyses according to age, gender, and co-morbidity conditions may influence the precision of our findings. Second, the pathogenic mechanism of IBD is extremely complex, and thus it is unlikely that a single genetic polymorphism can significantly contribute to the occurrence and development of this disease. Third, associations between *TLR* gene polymorphisms and IBD may also be modified by gene-gene and gene-environmental interactions. However, most studies did not consider these potential interactions, which impeded us to conduct relevant analyses accordingly. Taken these limitations into consideration, the results of the current study should be interpreted with caution.

In conclusion, the present meta-analysis indicated that *TLR1* rs5743611, *TLR4* rs4986790, *TLR4* rs4986791, *TLR6* rs5743810, and *TLR9* rs352140 polymorphisms may serve as genetic biomarkers of IBD in certain ethnicities. However, further well-designed studies are still warranted to confirm our findings, and future investigations also need to explore the potential roles of other *TLR* gene loci in IBD.

Authors' contributions Huijuan Wang and Shuhong Zhou conceived of the study and participated in its design. Huijuan Wang and Shuhong Zhou conducted the systematic literature review. Jiahong Zhang, Shangwen Lei, and Jing Zhou performed data analyses. Huijuan Wang and Shuhong Zhou drafted the manuscript. All authors have read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Informed consent For this type of study formal consent is not required.

References

1. Burisch J, Munkholm P. The epidemiology of inflammatory bowel disease. Scand J Gastroenterol. 2015;50:942–51.
2. Bouguen G, Chevaux JB, Peyrin-Biroulet L. Recent advances in cytokines: therapeutic implications for inflammatory bowel diseases. World J Gastroenterol. 2011;17:547–56.
3. Neurath MF. Cytokines in inflammatory bowel disease. Nat Rev Immunol. 2014;14:329–42.
4. Mitsuyama K, Niwa M, Takedatsu H, Yamasaki H, Kuwaki K, Yoshioka S, et al. Antibody markers in the diagnosis of inflammatory bowel disease. World J Gastroenterol. 2016;22:1304–10.
5. Ko JK, Auyeung KK. Inflammatory bowel disease: etiology, pathogenesis and current therapy. Curr Pharm Des. 2014;20:1082–96.
6. Altwegg R, Vincent T. TNF blocking therapies and immunomonitoring in patients with inflammatory bowel disease. Mediat Inflamm. 2014;2014:172821.
7. West AP, Koblansky AA, Ghosh S. Recognition and signaling by toll-like receptors. Annu Rev Cell Dev Biol. 2006;22:409–37.
8. De Nardo D. Toll-like receptors: activation, signalling and transcriptional modulation. Cytokine. 2015;74:181–9.
9. Kim EJ, Chung WC, Lee KM, Paik CN, Jung SH, Lee BI, et al. Association between toll-like receptors/CD14 gene polymorphisms and inflammatory bowel disease in Korean population. J Korean Med Sci. 2012;27:72–7.
10. Chen L, Lin MJ, Zhan LL, Lv XP. Analysis of TLR4 and TLR2 polymorphisms in inflammatory bowel disease in a Guangxi Zhuang population. World J Gastroenterol. 2012;18:6856–60.
11. Pierik M, Joossens S, Van Steen K, Van Schuerbeek N, Vlietinck R, Rutgeerts P, et al. Toll-like receptor-1, -2, and -6 polymorphisms influence disease extension in inflammatory bowel diseases. Inflamm Bowel Dis. 2006;12:1–8.
12. Abad C, González-Escribano MF, Diaz-Gallo LM, Lucena-Soto JM, Márquez JL, Leo E, et al. Association of Toll-like receptor 10 and susceptibility to Crohn's disease independent of NOD2. Genes Immun. 2011;12:635–42.
13. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151:264–9.
14. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25:603–5.
15. Bernstein CN. Treatment of IBD: where we are and where we are going. Am J Gastroenterol. 2015;110:114–26.