

BMJ Open Macrophage migration inhibitory factor polymorphism and the risk of ulcerative colitis and Crohn's disease in Asian and European populations: a meta-analysis

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To cite: Hao N-B, He YF, Luo G, *et al.* Macrophage migration inhibitory factor polymorphism and the risk of ulcerative colitis and Crohn's disease in Asian and European populations: a meta-analysis. *BMJ Open* 2013;**3**:e003729. doi:10.1136/bmjopen-2013-003729

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2013-003729>).

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Received 7 August 2013
Revised 21 November 2013
Accepted 29 November 2013



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ABSTRACT

Objective: To determine whether macrophage migration inhibitory factor (MIF) gene polymorphism is associated with the risk of inflammatory bowel disease (IBD).

Design: System review and meta-analysis.

Methods: MEDLINE, EMBASE, Web of Science databases, Cochrane Library and the Chinese Biomedical Literature database (CBM) were searched for the case-control trails for MIF and IBD. All the studies included in this manuscript met the inclusion and exclusion criteria. An OR analysis using a 95% CI was employed to assess the association of the MIF-173 G/C polymorphism with IBD susceptibility.

Results: There was a significant association between the MIF-173 G/C gene polymorphism and IBD in the total population under the recessive model (CC vs GC +GG; OR=1.75, CI 1.04 to 2.95, p=0.04 for heterogeneity) and the codominant model (CC vs GG; OR=1.74, CI 1.02 to 2.97, p=0.04 for heterogeneity). In the stratified analysis by ethnicity, significantly increased risks were observed for Asians using the recessive (OR=1.75, CI 1.04 to 2.95, p=0.04 for heterogeneity) and codominant models (OR=1.74, CI 1.02 to 2.97, p=0.04 for heterogeneity). Within the subgroups of UC and CD, significant differences were observed regarding UC using the recessive (OR=1.60, CI 1.09 to 2.35, p=0.02 for heterogeneity) and codominant models (OR=1.64, CI 1.12 to 2.41, p=0.01 for heterogeneity). In the stratified analysis by ethnicity for UC, significant differences were observed regarding CC in Asians vs GC+GG (OR=1.73, CI 1.02 to 2.94, p=0.04 for heterogeneity).

Conclusions: The meta-analysis suggested that the MIF-173 G/C polymorphism contributed to the susceptibility of IBD. When considering the subgroups of ethnicity and UC and CD, the results suggested that the polymorphism is more significant for UC in Asians.

INTRODUCTION

Inflammatory bowel disease (IBD) currently represents one of the most common health problems worldwide. The highest incidence

Strengths and limitations of this study

- A large number of patients were concluded in this manuscript, which is important when examining the association between migration inhibitory factor (MIF) and inflammatory bowel disease (IBD).
- All the articles included in this manuscript must conform that all controls were in Hardy-Weinberg equilibrium.
- It still needs to demonstrate that MIF gene polymorphism was associated with IBD in other places such as Africa and South and North America.

rates and prevalence of ulcerative colitis (UC) and Crohn's disease (CD) have been reported in northern Europe, the UK and North America.¹ In addition, in low-incidence areas, such as Asia, southern Europe and most developing countries, rates also continue to rise.² However, the aetiology and pathogenesis are still unknown.

Our current understanding of IBD is a complex disease with a number of contributing factors, such as genetic predisposition, environmental factors, intestinal microbial flora and an aberrant immune response.¹ It has been demonstrated that many patients with IBD have a dysregulated intestinal mucosal T-cell-mediated immune response, specifically involving CD4 T helper type-1 (Th1) lymphocytes, which leads to the production of Th1-associated proinflammatory cytokines, such as interferon γ (IFN γ), interleukin (IL)-2 and tumour necrosis factor α (TNF α).³

In addition, another cytokine, macrophage migration inhibitory factor (MIF), is considered to play a critical role in immunity and inflammation. MIF is secreted by a series of immune cells, such as macrophages, dendritic cells, lymphocytes, neutrophils and pituitary cells.^{4,5} Once secreted, MIF regulates a broad range of immune and inflammatory activities, including the induction of inflammatory

cytokines, such as TNF α , IFN γ , IL-1 β , IL-12, IL-6 and CXCL8 (also known as IL-8), among others.⁶ However, if the MIF gene is mutated, it will disturb the immune balance in the microenvironment. It has been demonstrated that MIF gene mutation is associated with many autoimmune diseases, such as rheumatoid arthritis, glomerulonephritis and inflammatory bowel diseases.^{7–11} MIF genotyping studies have focused on the –794–CATT_(5–8) microsatellite and the MIF-173 G/C polymorphism.¹² Donn *et al*¹³ first reported that the MIF-173 polymorphism is a risk factor for juvenile idiopathic arthritis. Consequently, Baugh *et al*¹⁴ reported the association between the –794 CATT_(5–8) microsatellite and disease severity in patients with rheumatoid arthritis. In addition, it has also been reported that the MIF gene polymorphism is a risk factor for other immune diseases, such as atrophy, asthma and sarcoidosis in patients with erythema nodosum.¹² Therefore, it is important to explore whether MIF gene polymorphisms are associated with IBD. However, the research results are not in agreement. Thomas and colleagues found that there was no significant difference between patients with IBD and controls with the MIF gene type.¹⁵ In other articles, the MIF gene polymorphism has been reported to be a risk factor for IBD.^{16–17} Because most of the articles on MIF gene polymorphisms and IBD studied the MIF-173 G/C polymorphism, we performed a meta-analysis to determine whether the MIF-173 G/C polymorphism is a risk factor for IBD. Our analysis reveals that the MIF-173 G/C polymorphism is a risk factor for IBD, especially for UC in Asians.

MATERIALS AND METHODS

Search strategy

This meta-analysis followed the proposal of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group and was performed by searching PubMed, EMBASE, Web of Science databases, Cochrane Library and the Chinese Biomedical Literature database (CBM; last search updated in April 2013).¹⁸ The search strategy included the following terms: (macrophage migration inhibitory factor [MeSH] or MIF [TEXT WORD] and inflammatory bowel disease [MeSH] or ulcerative colitis [TEXT WORD] or Crohn's disease [TEXT WORD] or IBD [TEXT WORD] or UC [TEXT

WORD] or CD [TEXT WORD]). Searches also included scanning reference lists in relevant articles and conference proceedings as well as correspondence with authors when additional data were required. Two reviewers (N-BH and YFH) independently screened the titles and abstracts of each identified reference and categorised articles based on the full text to evaluate their eligibility for inclusion.

Inclusion and exclusion criteria

The inclusion criteria for primary studies were as follows: (1) the article evaluated MIF gene polymorphisms and IBD risk; (2) the article included case–control studies or a nested case–control study; (3) the article supplied the number of individual genotypes for the MIF polymorphisms in IBD cases and controls and (4) the article demonstrated that the distribution of genotypes among controls was in Hardy-Weinberg equilibrium (HWE). In addition, the following exclusion criteria were used. The studies were excluded when (1) it did not provide detailed data such as presented in abstracts, meeting reports and reviews; (2) the studies were repeated or that overlapped other publications; (3) the genotype frequency was not reported and (4) the controls do not meet the assumptions for HWE.

Data extraction

No article was included if it did not meet the four inclusion criteria. When the same study results appeared in several articles, only one study was used in this meta-analysis. Table 1 lists the characteristics of the extracted data, including the first author's name, publication date, region of study, ethnicity of the sample population, number of genotypes and the total number of cases and controls. The study regions included China, Japan, Spain, Germany and Poland. Data extraction was independently performed by two individuals (N-BH and YFH), and any disagreement was resolved by consensus or by consultation with additional reviewers (YZ and S-MY).

Qualitative assessment

Quality assessment was performed with the Newcastle-Ottawa quality assessment scale (NOS) for case-control studies. A 'star system' was used to judge data quality

Table 1 Characteristics of studies included in meta-analysis

First author	Years	Country	Ethnicity	Case number	Control number	Newcastle-Ottawa score	Genotyping
Griaga	2007	Germany	European	259	489	7/9	PCR-RFLP
Shiroeda	2010	Japan	Asian	111	209	6/9	PCR-SSCP
Fei	2008	China	Asian	99	142	9/9	PCR-RFLPtetra-primer ARMS
Oliver	2007	Spain	European	1295	887	8/9	PCR-RFLP
Przybyłowska	2011	Poland	European	99	123	6/9	PCR-RFLP
Nohara	2004	Japan	Asian	221	438	7/9	PCR-RFLPPCR-SSCP

ARMS, amplification refractory mutation system; PCR-RFLP, PCR-restriction fragment length polymorphism; PCR-SSCP, PCR-single-strand conformation polymorphism.

based on three broad perspectives: selection, comparability and outcome of interest for case-control studies. Star counts were totaled to compare the study quality in a quantitative fashion.¹⁹ Based on these criteria, the content validity was evaluated by N-BH and YFH, and any disagreement was resolved via discussions between N-BH and GL or with the other authors (YZ S-MY) for adjudication.

Statistical analysis

All statistical tests were performed using Revman V.5.0 software. Deviations from HWE were calculated for the control groups by χ^2 goodness-of-fit. The association between the MIF-173G/C gene polymorphism and IBD was compared by the OR and the corresponding 95% CI between the case and control groups. The statistical significance of the summary OR was determined with the Z test, and p value less than 0.05 was considered as statistically significant. The genetic models evaluated for the polymorphism were the dominant model (GC+CC vs GG), the recessive model (CC vs GC+GG), the allelic gene model (C vs G) and the codominant model (CC vs GG and GC vs GG).

The heterogeneity between studies was determined by the χ^2 -based Q test. A p value greater than 0.05 for the Q-test indicated a lack of heterogeneity among the studies. If there was a lack of heterogeneity, the pooled OR estimate of each study was calculated using a fixed-effects model (the Mantel-Haenszel method); otherwise, a random-effects model (the DerSimonian and Laird method) was used.^{20 21} In addition, subgroup analysis stratified by ethnicity and different disease types was also performed. The potential publication bias was estimated by a funnel plot. Egger's linear regression test on the natural logarithm scale of the OR was used to assess the funnel plot asymmetry; the significance was set at the $p < 0.05$ level.²²

RESULTS

Study characteristics

Figure 1 outlines our search process. First, a total of 123 articles were collected after the initial search with the key words listed previously. After reading the title and abstract, 12 reviews and 1 editorial were excluded. Next, 99 articles were excluded for no association with IBD and the MIF-173 G/C polymorphism. The remaining 11 articles were identified for full-text review and 4 articles were excluded because of repeated publications. In addition, 1 article was excluded because it deviated from HWE.²³ Finally, six articles met our inclusion criteria and were used for the meta-analysis with 2084 cases and 2288 controls.^{15–17 24–26} The basic characteristics of these articles are listed in table 1. Of the eligible studies, 3/6 articles researched the association of the MIF-173 gene polymorphism with UC and CD. The remaining 3/6 articles researched only the association of the MIF-173 G/C polymorphism with UC. In total, 3/6 studies were

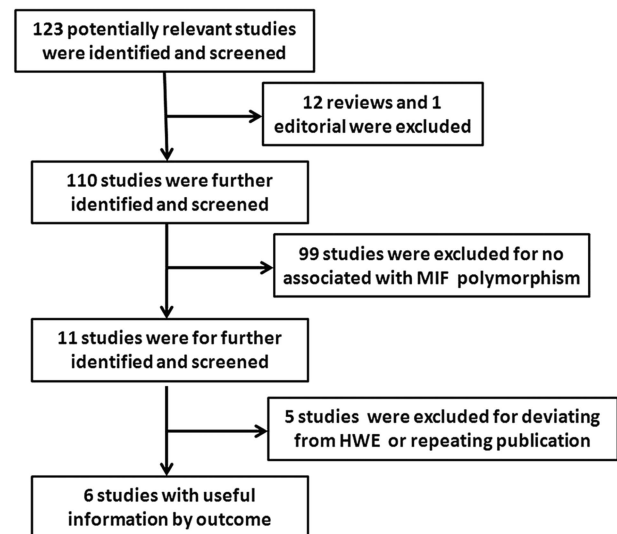


Figure 1 Flowchart of the study identification, inclusion and exclusion.

performed in Europeans and 3/6 studies were performed in Asians. All studies were cross-sectional case-control studies with sufficient data to calculate the possible relationship between the MIF-173 G/C polymorphism and IBD. All studies were published in English. The distribution of the MIF-173 gene type in IBD, UC and CD is listed in table 2.

Quantitative data synthesis

Table 3 lists the primary results. In the total population, we found a significant difference between the MIF-173 G/C gene polymorphism and the risk of IBD for two variants: CC vs GC+GG (OR=1.5, CI 1.07 to 2.14, $p=0.02$ for heterogeneity) and CC vs GG (OR=1.54, CI 1.09 to 2.24, $p=0.01$ for heterogeneity; figure 2A–D). No significant difference was observed for the variants of GC+CC vs GG, GC vs GG or the allele C vs G (table 3).

In the stratified analysis by ethnicity, a significantly increased risk was observed in Asians for CC vs GC+GG (OR=1.75, CI 1.04 to 2.95, $p=0.04$ for heterogeneity) and CC vs GG (OR=1.74, CI 1.02 to 2.97, $p=0.04$ for heterogeneity; figure 2A,B). However, no significant difference was observed in Europeans for CC vs GC+GG (OR=1.36, CI 0.86 to 2.15, $p=0.19$ for heterogeneity) or CC vs GG (OR=1.42, CI 0.89 to 2.24, $p=0.14$ for heterogeneity).

Because IBD includes UC and CD, we determined whether the role of the MIF-173 G/C gene polymorphism was different between the two diseases. Therefore, we analysed subgroups of UC and CD. Significant differences were observed in UC for CC vs GC+GG (OR=1.60, CI 1.09 to 2.35, $p=0.02$ for heterogeneity) and CC vs GG (OR=1.64, CI 1.12 to 2.41, $p=0.01$ for heterogeneity; figure 2C,D). However, no significant differences were found in CD for CC vs GC+GG (OR=1.41, CI 0.85 to

Table 2 Genotypes and allele frequencies of MIF-173G/C genes in patients and controls

Author	Year	Case					Control					Sample size	HWE (P)
		GG	GC	CC	G	C	GG	GC	CC	G	C		
IBD													
Fei	2008	52	32	15	136	62	79	55	8	213	71	99/142	0.70
Griaga	2007	188	67	4	443	75	318	156	15	792	186	259/489	0.43
Nohara	2004	135	76	10	346	96	288	134	16	710	166	221/438	0.93
Shiroeda	2010	69	37	5	175	47	126	76	7	328	90	111/209	0.27
Przybyłowska	2011	66	31	2	163	35	99	23	1	221	25	99/123	0.79
Oliver	2007	907	343	45	2157	433	681	188	18	1550	224	1295/887	0.24
UC													
Fei	2008	44	27	13	115	53	79	55	8	213	71	84/142	0.70
Griaga	2007	72	28	2	172	32	318	156	15	792	186	102/489	0.43
Nohara	2004	135	76	10	346	96	288	134	16	710	166	221/438	0.93
Oliver	2007	441	171	22	1053	215	681	188	18	1550	224	634/887	0.24
Przybyłowska	2011	38	19	1	95	21	99	23	1	221	25	58/123	0.79
Shiroeda	2010	69	37	5	175	47	126	76	7	328	90	111/209	0.27
CD													
Fei	2008	8	5	2	21	9	79	55	8	213	71	15/142	0.70
Griaga	2007	116	39	2	271	43	318	156	15	792	186	157/489	0.43
Oliver	2007	466	172	23	1104	218	681	188	18	1550	224	661/887	0.24
Przybyłowska	2011	28	12	1	68	14	99	23	1	221	25	41/123	0.79

CD, Crohn's disease; HWE, Hardy-Weinberg equilibrium; IBD, inflammatory bowel disease, MIF, migration inhibitory factor; UC, ulcerative colitis.

Table 3 Summary of different comparative results

Study	Sample size		Number of studies	Test of association			Model	Heterogeneity		
	Case	Control		OR (95% CI)	Z	p Value		χ^2	p Value	I ² (%)
GC+CC vs GG										
Overall	2084	2288	6	1.15 (0.87 to 1.52)	0.97	0.33	R	17.04	0.004	71.0
Asian	431	789	3	1.12 (0.88 to 1.44)	0.90	0.37	F	0.90	0.64	0.0
European	1653	1499	3	1.23 (0.70 to 2.14)	0.71	0.48	R	15.75	0.0004	87.0
UC	1210	2288	6	1.24 (1.06 to 1.44)	2.76	0.006	F	9.69	0.08	48.0
CD	874	1641	4	1.13 (0.69 to 1.87)	0.49	0.62	F	11.46	0.009	74.0
CC vs GC+GG										
Overall	2084	2282	6	1.51 (1.07 to 2.14)	2.34	0.02	F	6.72	0.24	26.0
Asian	431	789	3	1.75 (1.04 to 2.95)	2.10	0.04	F	2.21	0.33	9.0
European	1653	1499	3	1.36 (0.86 to 2.15)	1.31	0.19	F	4.16	0.12	52.0
UC	1210	2288	6	1.60 (1.09 to 2.35)	2.42	0.02	F	3.92	0.56	0.0
CD	874	1641	4	1.41 (0.85 to 2.36)	1.32	0.19	F	3.91	0.27	23.0
CC vs GG										
Overall	1498	1656	6	1.54 (1.09 to 2.24)	2.43	0.01	F	7.30	0.20	32.0
Asian	286	524	3	1.74 (1.02 to 2.97)	2.04	0.04	F	1.72	0.42	0.0
European	1212	1132	3	1.42 (0.89 to 2.24)	1.49	0.14	F	5.38	0.07	63.0
UC	852	1656	6	1.64 (1.12 to 2.41)	2.52	0.01	F	3.88	0.57	0.0
CD	646	1219	4	1.44 (0.86 to 2.40)	1.40	0.16	F	4.68	0.20	36.0
GC vs GG										
Overall	2003	1972	6	1.40 (1.00 to 1.95)	1.97	0.05	R	18.46	0.002	73.0
Asian	401	810	3	1.02 (0.79 to 1.31)	0.14	0.89	F	1.01	0.60	0.0
European	1602	1465	3	1.21 (0.72 to 2.03)	0.73	0.47	R	12.77	0.002	84.0
UC	1157	2223	6	1.20 (1.02 to 1.40)	2.20	0.03	F	9.64	0.09	48.0
CD	846	1599	4	1.09 (0.69 to 1.74)	0.39	0.70	R	9.13	0.03	67.0
C vs G										
Overall	4168	4576	6	1.17 (0.91 to 1.50)	1.25	0.21	R	18.47	0.002	73.0
Asian	862	1578	3	1.17 (0.96 to 1.43)	1.54	0.12	F	1.36	0.51	0.0
European	3306	2998	3	1.20 (0.72 to 2.01)	0.70	0.49	R	17.04	0.0002	88.0
UC	2420	4576	6	1.24 (1.09 to 1.41)	3.20	0.001	F	9.91	0.08	50.0
CD	1748	3282	4	1.16 (0.73 to 1.83)	0.63	0.53	R	12.78	0.005	77.0

CD, Crohn's disease; F, fixed-effects model; R, random-effects model; UC, ulcerative colitis.

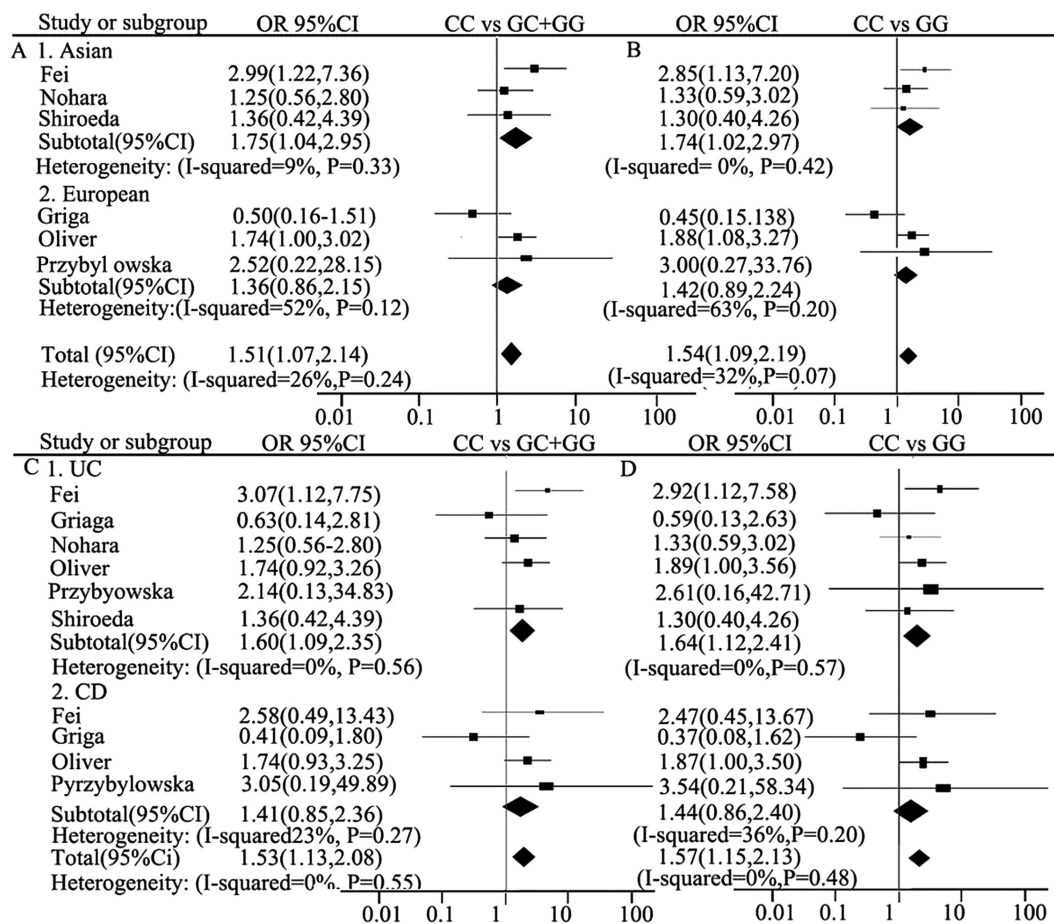


Figure 2 Forest plot of inflammatory bowel disease risk associated with migration inhibitory factor MIF-173 G/C polymorphism for different genetic model. (A) CC vs GG+GC and (B) CC vs GG for ethnicity; (C) CC vs GC+GG and (D) CC vs GG for ulcerative colitis (UC) and Crohn's disease (CD).

2.36, $p=0.19$ for heterogeneity) or CC vs GG (OR=1.44, CI 0.86 to 2.40, $p=0.16$ for heterogeneity).

Although IBD includes UC and CD, the cases of IBD in Asians included in our data were mainly UC, and only 15 cases were CD. This may influence the accuracy of the meta-analysis results in the subgroup of ethnicity. Therefore, we analysed the association of the MIF-173 G/C polymorphism with UC in the subgroup of ethnicity. As shown in figure 3A, a significant difference was observed in Asians for CC vs GC+GG (OR=1.73, CI 1.02 to 2.94, $p=0.04$ for heterogeneity). Similar to previous results, no significant difference was observed in Europeans for CC vs GC+GG (OR=1.47, CI 0.85 to 2.55, $p=0.17$ for heterogeneity).

Sensitivity analyses and publication bias

Sensitivity analyses were performed to assess the influence of each individual study on the pooled ORs by the systematic omission of the individual studies from the analyses. The corresponding pooled OR was not materially altered. Begg's funnel plot and the Egger's test were performed to assess the publication bias of the literature. As shown in figure 3B, the shape of the funnel plot did not reveal obvious asymmetry. The

Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not suggest any evidence of publication bias (data not shown).

DISCUSSION

The human MIF gene, which is located on chromosome 22q11.2, is short; it is composed of three exons of 205, 173 and 183 bp and two introns of 189 and 95 bp.^{12 27 28} Four polymorphisms of the human MIF gene have been reported, including a 5–8 CATT tetranucleotide repeat at position -794 CATT_(5–8) and 3 single-nucleotide polymorphisms at positions MIF-173 G/C, +254 T/C and +656 C/G.^{13 14 29} However, in IBD, studies on MIF gene polymorphisms have mainly focused on the MIF-173 G/C SNP. Therefore, in this meta-analysis, we mainly discussed the association of the MIF-173 G/C gene polymorphism with the susceptibility to IBD.

In the current meta-analysis of six studies consisting of 2084 cases and 2288 controls, we found that the MIF-173 G/C gene polymorphism is significantly associated with IBD susceptibility in the recessive model (OR 1.5) and codominant model (OR 1.54), while no significant associations were found in the dominant model or the

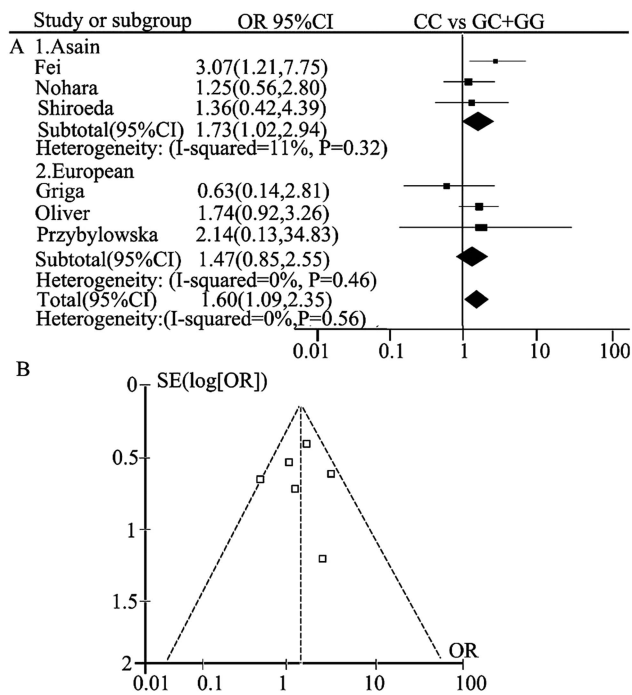


Figure 3 (A) Forest plot of ulcerative colitis (UC) risk associated with migration inhibitory factor (MIF)-173 G/C polymorphism for CC vs GG+GC in Asian and European; (B) Begg's funnel plot of the MIF-173 gene polymorphism and inflammatory bowel disease risk for combined CC vs GC+GG.

allelic model. The results indicated that the MIF-173 G/C polymorphism was a conspicuous high-risk factor for developing IBD in the overall study population.

The second finding of this meta-analysis is that in the subgroup of ethnicity, the MIF-173 G/C gene polymorphism was significantly different in Asians in the recessive (OR 1.75) and codominant (OR 1.74) models, while no significant differences were found in Europeans. This finding is consistent with previous results that a gene polymorphism does not have the same effect in different ethnicities. For example, the TNF- α 308A gene polymorphism plays an important role in Asian populations, while no conclusive data on this association exist in European patients.³⁰ In addition, the best studied genetic variant, a nucleotide oligomerisation domain 2 (NOD2) polymorphism, is present in up to 20% of patients with CD in White and Jewish populations, but major disease-associated variants have not been detected in individuals of Asian descent with CD.^{31 32}

The third finding of this meta-analysis is that in the subgroup of the two diseases, UC and CD, significant differences were found in the recessive (OR 1.60) and codominant (OR 1.64) model for UC, while no difference was found in the recessive or codominant model for CD. This result suggests that the MIF-173 G/C polymorphism seems to be a risk factor for UC but not for the CD. However, in another study, Zhang *et al*³³ confirmed that the peroxisome proliferator-activated receptor γ (PPAR γ) AlaAla genotype is a protective factor

against the development of CD, especially in the European Caucasian population, while no significant association was found in the development of UC. Both of these results indicated that the gene polymorphism has different effects in different diseases.

To further determine whether the MIF-173 gene polymorphism for UC was different in different ethnicities, we performed a meta-analysis of UC in the subgroup of ethnicity. A significant difference was found in the recessive model (OR 1.73) in Asians, while no significant difference was found in Europeans. Although only three studies were included in the subgroup analysis, they all have high quality. So the results in the subgroup analysis were credible.

In addition, two similar studies had been published. However, compared with the two studies,^{34 35} our study has the special strength. First, it has been claimed that the studies included in the meta-analysis should not be deviated from HWE. So in our study we did not include the study from India.²³ Second, in our study, we analysed MIF polymorphism and the risk of UC in Asian and European populations. Since the results of MIF polymorphism and the risk of IBD may be influenced by the bias because the number of CD in Asians was low. However, the present meta-analysis had several limitations that must be taken into consideration. First, the number of available studies that could be included in this meta-analysis was moderate. Therefore, the results could be influenced by factors such as random error. Therefore, next we will focus on research on the association between gene polymorphisms and IBD in our hospitals. Second, the overall outcomes were based on individual unadjusted ORs, while a more precise evaluation should be adjusted by other potentially suspected factors, including age, sex and environmental factors.

In summary, the current meta-analysis suggested that the MIF-173 G/C polymorphism contributed to the susceptibility of IBD. In the subgroups of ethnicity and UC and CD, the result suggested that this polymorphism was more significant for UC in Asians.

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Acknowledgements The authors would like to thank *American Journal of Experts* for providing help in the writing and polishing.

Contributors N-BH and YFH contributed to conception and design, acquisition of the data or analysis and interpretation of the data. N-BH and XY were involved in acquisition of the data. N-BH, YFH, GL and YZ were involved in analyses and interpretation of the data. N-BH and XY drafted the article.

Funding This work was funded by the Chongqing Science Fund for Distinguished Young Scholars (CSTC, 2009BA5045) and the National Natural Science Foundation of China (NSFC No. 81202220).

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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