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Original Article

Meta-analysis of macrophage migration inhibitory factor (MIF) gene -173G/C polymorphism and inflammatory bowel disease (IBD) risk

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Abstract: Macrophage migration inhibitory factor (MIF) is a multi-functional cytokine associated with inflammation and inflammatory bowel disease (IBD). The association between MIF-173G/C polymorphism and IBD risk has been extensively investigated. However, the results were conflicted and inconclusive. Therefore, we performed this meta-analysis. Online electronic databases (PubMed and EMBASE) was searched. All statistical tests were performed with the software STATA version 11.0 (Stata Corporation, College station, TX, USA). A total of nine studies (ten cohorts) with 3436 cases and 2742 controls were included for this meta-analysis. MIF-173G/C polymorphism was associated with a significantly increased risk of IBD when compared with CG and GG genotypes (OR=1.43; 95% CI 1.08-1.90; I^2=0%). In the subgroup analysis according to ethnicity, significantly increased IBD risk was observed in Asians (OR=1.74; 95% CI 1.10-2.74; I^2=0%) but not in Caucasians (OR=1.27; 95% CI 0.89-1.82; I^2=0%). In the subgroup analysis according to IBD type, significantly increased UC risk was observed (OR=1.43; 95% CI 1.04-1.95; I^2=0%). In conclusion, this meta-analysis suggested that MIF-173G/C polymorphism was associated with increased IBD risk.

Keywords: Inflammatory bowel disease, macrophage migration inhibitory factor, meta-analysis

Introduction

Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC). Although it is suggested that environmental and immunologic factors are involved in the pathogenesis of IBD, the etiology of IBD is still not completely understood. Some suggest that a family history of IBD may be one of the most important risk factors [1]. A family history of IBD was shown to increase the risk of developing IBD 10- to 15-fold in unaffected first-degree relatives and three-fold among close relatives of IBD patients [A population-based case control study of potential risk factors for IBD.]. Thus, genetic factors are very important for IBD development.

Macrophage migration inhibitory factor (MIF) is a multi-functional cytokine associated with inflammation and tumorigenesis [2]. It promotes the production of inflammatory Th1 cytokines, including TNF-α, IFN-γ, IL-2, and IL-6 [3]. Moreover, MIF inhibits p53 dependent apoptosis [9], and participates in T cell proliferation and activation [4]. de Yong et al. demonstrated that the expression of MIF was increased in a model of experimental colitis induced by the transfer of CD45RB high, and that blockade of MIF with anti-MIF antibody reduced the severity of colitis [5]. Previous study reported that the MIF protein was significantly increased in the sera of patients with Crohn's disease and those with UC [6].

The association between MIF-173G/C polymorphism and IBD risk has been extensively investigated [7-15]. However, the the results were conflicted and inconclusive. Therefore, we performed this meta-analysis to precisely estimate the association between the MIF-173G/C polymorphism and IBD risk.

Table 1. Characteristics of the studies included in this meta-analysis

First author/Year	Ethnicity	IBD type	HWE	No. of Case	No. of Control	Case		Control	
						G	C	G	C
Nohara/2004	Asian	UC	Yes	221	438	346	710	96	166
Oliver 1/2007	Caucasian	Both	Yes	623	261	1024	631	222	91
Oliver 2/2007	Caucasian	Both	Yes	672	526	1133	919	211	133
Dambacher/2007	Caucasian	CD	Yes	198	159	337	261	59	57
Fei/2008	Asian	Both	Yes	99	142	136	213	62	71
Shiroeda/2010	Asian	UC	Yes	111	209	175	328	47	90
Przybylowska/2011	Caucasian	Both	Yes	99	123	163	221	35	25
Sivaram/2012	Asian	UC	No	139	176	224	295	54	57
Falvey/2013	Caucasian	Both	Yes	988	488	2392	516	799	177
Mrowicki/2014	Caucasian	Both	Yes	286	220	481	91	356	84

IBM, inflammatory bowel disease; HWE, Hardy-Weinberg equilibrium.

Materials and methods

Search for publications

Online electronic databases (PubMed and EMBASE) was searched using the search terms: (Macrophage migration inhibitory factor or MIF) and ("Inflammatory bowel disease" or "IBD"). Additional studies were identifed by a hand search from reference of original studies or review articles on this topic. There was no language restriction.

Inclusion and exclusion criteria

The major inclusion criteria were: (1) case-control studies or cohort studies; (2) investigating the association between MIF-173G/C polymorphism and IBD risk; (3) available genotype distribution information in cases and controls or odds ratios (ORs) with 95% confidence intervals (CIs). The major reasons for exclusion of studies were: (1) reviews and repeated literatures; (2) case-only studies; (3) studies without detail genotype frequencies.

Data extraction

The following data were recorded from each article: first author, year of publication, ethnicity of participants, numbers of cases and controls, Hardy-Weinberg equilibrium (HWE), and genotype frequency in cases and controls. The data were extracted by two of the authors independently. Discrepancies between these two authors were resolved by discussion.

Statistical analysis

The strength of association between the MIF-173G/C polymorphism and IBD risk was assessed by calculating OR with 95% CI. A statistical test for heterogeneity was performed based on the Q statistic. The $P>0.10$ of the Q-test indicated a lack of heterogeneity among studies. If heterogeneity was observed among the studies, the random-effects model was used to estimate the pooled OR (the DerSimonian and Laird method). Otherwise, the fixed-effects model was adopted (the Mantel-Haenszel method). Stratified analysis was performed by ethnicity and IBD type. Potential publication bias was examined visually in a funnel plot and Egger's test. All statistical tests were performed with the software STATA version 11.0 (Stata Corporation, College station, TX, USA). A P value <0.05 was considered statistically significant.

Results

Characteristics of studies

A total of nine studies (ten cohorts) with 3436 cases and 2742 controls on the association between MIF-173G/C polymorphism and IBD risk were included for this meta-analysis. There were 4 studies of Asian populations and 6 studies of Caucasian populations. The characteristics of each case-control study and the genotype in each study are presented in **Table 1**.

Results of meta-analysis

The CC genotype of MIF-173G/C polymorphism was associated with a significantly increased risk of IBD when compared with CG and GG genotypes (OR=1.43; 95% CI 1.08-1.90; I^2=0%; **Figure 1**). In the subgroup analysis according to ethnicity, significantly increased IBD risk was observed in Asians (OR=1.74; 95% CI 1.10-

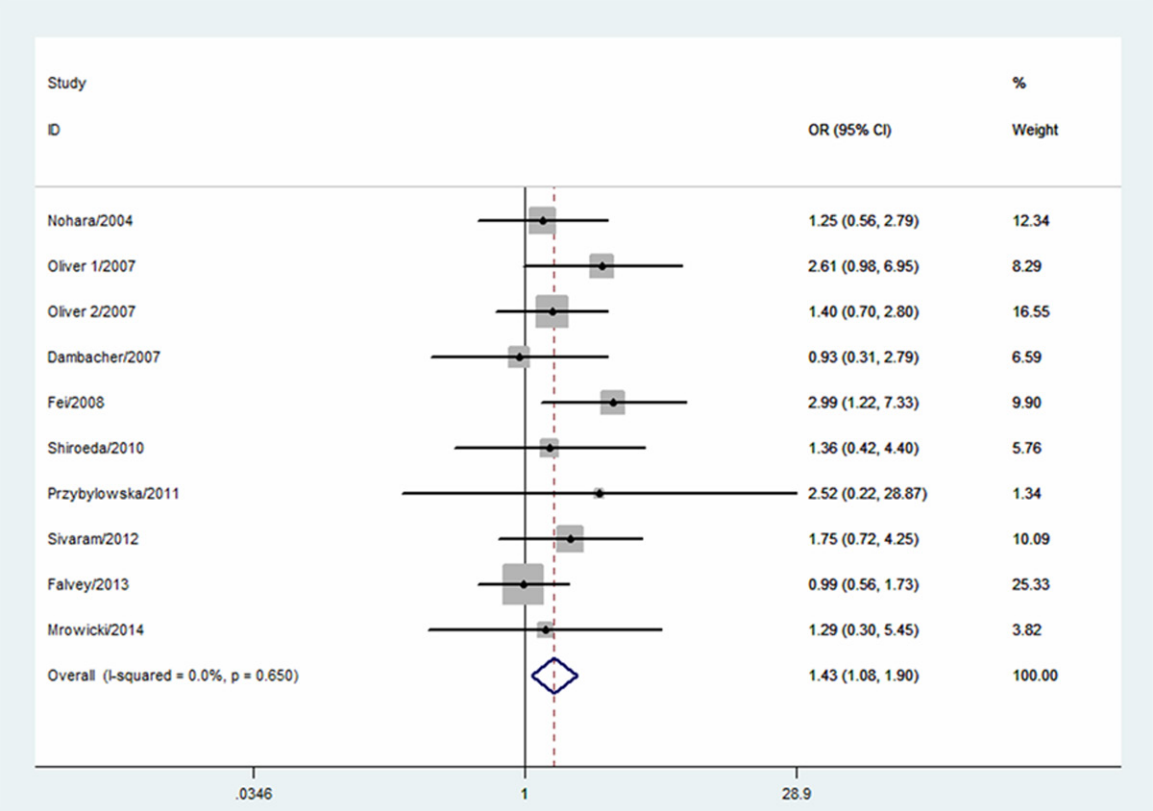

Figure 1. Meta-analysis for the association between MIF-173G/C polymorphism and IBD risk.

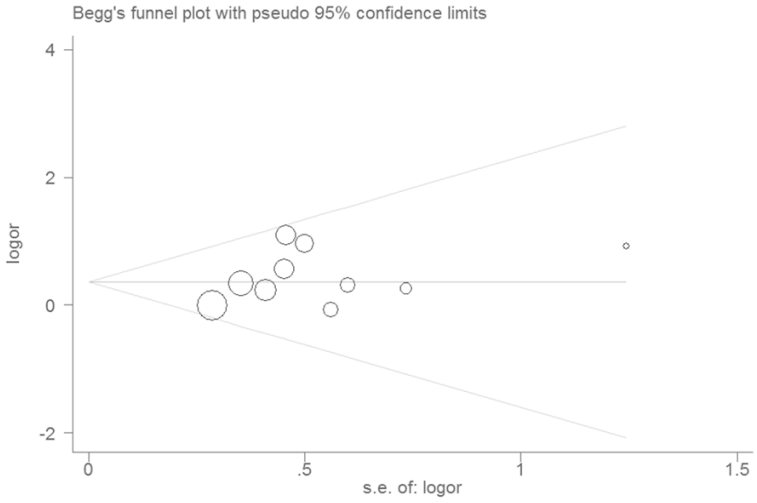

Figure 2. Funnel plot of associations between MIF-173G/C polymorphism and IBD.

2.74; I^2=0%) but not in Caucasians (OR=1.27; 95% CI 0.89-1.82; I^2=0%). In the subgroup analysis according to IBD type, significantly increased UC risk was observed (OR=1.43; 95% CI 1.04-1.95; I^2=0%).

The shape of the funnel plot did not reveal any evidence of obvious asymmetry (**Figure 2**). Egger's test did not find the evidence of publication bias (*P*=0.27).

Discussion

We performed a systematic search of the literature and combined the available results in this meta-analysis. MIF-173G/C polymorphism has been studied extensively about the relationship with IBD. Previous results of the studies on the relationship between MIF-173G/C polymorphism and IBD risk were contradictory. We thus performed a meta-analysis. We found that MIF-173G/C polymorphism was a risk factor for developing IBD. In the subgroup analysis by ethnicity, we noted that Asians carrying MIF-173G/C polymorphism had an increased IBD

risk, while Caucasians carrying MIF-173G/C polymorphism did not have an increased IBD risk. In the subgroup analysis by IBD type, MIF-173G/C polymorphism increased UC risk.

MIF was shown to markedly enhance the production of IL-8 in dendritic cells obtained from patients with UC compared with non-UC patients [16]. As for the G-to-C transition at position -173 of the MIF gene, this site became functionally active in the presence of C through the creation of an activator protein 4 transcription factor binding site [9]. The expression of MIF was increased in colon cancerous lesions [17]. Thus, an anti-MIF strategy for IBD treatment is advantageous not only for suppression of intestinal inflammation, but also for prevention of the colon cancer often seen at the late stage of IBD.

Some limitations should be addressed. First, more studies with large sample sizes are needed to further identify the association among different races. Second, because small negative studies are less likely to published, the possibility of publication bias cannot be ruled out completely. Third, a lack of original data from the eligible studies limited evaluation of the effects of the gene-gene and gene-environment interactions during IBD development.

In conclusion, this meta-analysis suggested that MIF-173G/C polymorphism was associated with increased IBD risk.

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Disclosure of conflict of interest

None.

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