Human Immunology 77 (2016) 990–996

Contents lists available at ScienceDirect

journal homepage: www.elsevier.com/locate/humimm

A meta-analysis of the relationship between *MYO9B* gene polymorphisms and susceptibility to Crohn's disease and ulcerative colitis

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ARTICLE INFO

Article history:
Received 11 December 2014
Revised 20 June 2016
Accepted 15 July 2016
Available online 18 July 2016

Keywords:
Myosin IXB
Crohn's disease
Ulcerative colitis
Meta-analysis
Polymorphisms

ABSTRACT

Objective: Both Crohn's disease (CD) and ulcerative colitis (UC) have a complex etiology involving multiple genetic and environmental factors. Multiple UC and CD susceptibility genes have been identified through genome-wide association studies and subsequent meta-analyses. The aim of this meta-analysis was to clarify the impact of *MYO9B* gene polymorphisms on CD and UC risk.

Methods: The PubMed, Elsevier Science Direct and Embase databases were searched to identify eligible studies that were published before October 2014. Data were extracted and pooled crude odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated.

Results: A total of 11 studies, containing 3297 CD cases, 3903 UC cases and 8174 controls were included in this meta-analysis. Bonferroni correction results showed that rs1545620 A/C polymorphism of *MYO9B* gene was associated with both CD and UC susceptibility in Caucasians (OR = 0.88, 95% CI = 0.82 ~ 0.95, P = 0.001; OR = 0.82, 95% CI = 0.76 ~ 0.89, $P < 0.001$), but not in Chinese. rs1457092 G/T and rs2305764 C/T polymorphisms are associated with UC susceptibility (OR = 0.85, 95% CI = 0.79 ~ 0.91, $P < 0.001$; OR = 0.88, 95% CI = 0.83 ~ 0.93, $P < 0.001$), but not with CD susceptibility in Caucasians.

Conclusions: This meta-analysis suggested that rs1545620 is both CD and UC susceptible locus in Caucasians; rs1457092 and rs2305764 are UC susceptible loci, but are not CD susceptible loci in Caucasians. Further studies with more sample size are needed for a definitive conclusion.

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC), the two main types of inflammatory bowel disease (IBD), are idiopathic, chronic inflammatory disorders of the gastrointestinal tract [1]. When diagnosed, patients with UC or CD need lifelong medications. IBD currently represents a substantial economic burden affecting nearly 4 million people worldwide [2,3]. In the last three decades, we have witnessed an increasing trend of the prevalence of IBD especially of CD both in developed and developing regions [4]. Moreover, strictures, abscesses, fistulas, extra intestinal involvements and even carcinomas would complicate IBD and eventually affect the progression of IBD. Although the etiology of IBD have not been elucidated, an increasing number of clinical, epidemiological, and molecular studies support the hypothesis and point to a genetic predisposition that leads to a mucosal immune regulation cell defect, barrier leakage, and susceptibility to environmental triggers, including luminal bacteria and specific antigens [5,6].

Since the initial identification of *NOD2* as a CD susceptibility gene in 2001 [7,8], candidate gene approach and genome-wide

Abbreviations: MYO9B, myosin IXB; CD, Crohn's disease; UC, ulcerative colitis; OR, odds ratio; 95% CI, 95% confidence interval; IBD, inflammatory bowel disease; SNP, single nucleotide polymorphism; HWE, Hardy–Weinberg equilibrium; GWAS, genome wide association study.

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http://dx.doi.org/10.1016/j.humimm.2016.07.008
0198-8859/

association studies have shown that there are numerous genetic susceptibility factors for IBD [9–11]. Recently, several studies have reported Myosin IXB (*MYO9B*) gene might predispose to coeliac disease and another chronic inflammatory disorder of the gastrointestinal system, including CD and UC [12,13]. The *MYO9B* gene, encoding myosin IXB, was identified from the chromosome 19p13 CELIAC4 linkage locus by comprehensive screening of the region using 291 single-nucleotide polymorphisms (SNPs) across the peak 6-Mb linkage region in a cohort of Dutch celiac disease patients and controls [12]. MYO9B is expressed in intestinal epithelial cells and encodes a protein involved in actin remodeling in epithelial enterocytes and tight junction assembly [14,15]. Overexpression of the rat myosin IXB leads to actin filament–related morphologic changes in epithelial cells [16].

The *MYO9B* gene has recently been investigated in relation to IBD and produced inconsistent results. No association was observed in a Norwegian population [17], but shortly afterwards an international collaboration group performed a statistically powerful study on samples collected from the UK, Netherlands, Canada and Italy in which *MYO9B* was found to be associated with IBD, and with ulcerative colitis and Crohn's disease considered separately in some populations [18]. This inconsistency may be due to inadequate statistical power, racial and ethnic difference, and publication bias. So in the present study, we conducted a meta-analysis to overcome this shortcoming and explored whether the *MYO9B* (rs1545620, rs1457092, rs2305764) polymorphisms contributes to CD and UC susceptibility.

2. Materials and methods

2.1. Identification of eligible studies

We performed an exhaustive search on studies that examined the *MYO9B* gene polymorphisms in UC and CD. Data were collected from the following electronic databases: PubMed, Elsevier Science Direct and Embase with the last report up to October 2014, without restrictions on language. The following MeSH headings and keywords were used for searching: "MYO9B", "Myosin IXB", "MYOIXB" and "polymorphism" combined with "inflammatory bowel disease", "Crohn's disease" and "ulcerative colitis". The reference lists of eligible studies and review articles were also checked manually to identify other relevant publications.

A study was included in meta-analysis conform to following criteria: (1) it was a case–control study; (2) studied on *MYO9B* polymorphisms and CD or UC; (3) provided the allele frequency or genotype distribution data; (4) had enough information to estimate an odds ratio (OR) with 95% confidence interval (CI). Accordingly, the following exclusion criteria were also used: (1) abstracts and reviews; (2) repeated or overlapped publication.

2.2. Data extraction

For each publication, the data extraction was carried out by two investigators (Li and Yang) independently to ensure the accuracy of the data. The following information was recorded from each publication: first author, publishing year, population, studied polymorphisms, genotyping methods, number of case and control, Hardy–Weinberg equilibrium of controls. Discrepancies were resolved after discussion with our research team.

2.3. Statistical analysis

Pooled point estimate odds ratios (ORs) and its 95% CIs were evaluated the strength of association between the MYO9B variants and IBD susceptibility. We examined the contrast of allelic contrast, the recessive model and the dominant model.

The between-study heterogeneity was assessed using the Chi-square test–based Q-statistic [19]. A significant Q-statistic ($P < 0.10$) indicated heterogeneity across studies, and then the result of the DerSimonian and Laird method in the random effect model was selected [20]. Otherwise, the result of Mantel–Haenszel method in the fixed effect model was selected [21]. We also used the statistic of $I^2 = 100\%*(Q-df)/Q$ to efficiently test for the heterogeneity, with <25%, 25%–50%, and >50% to represent low, moderate, and high degree of heterogeneity, respectively [22].

As we performed multiple comparisons in this meta-analysis, the Bonferroni method, which controls false positive error rate, was used to adjust for multiple comparisons. We performed 9 times comparisons for rs1545620, 3 times comparisons for rs1457092 and 3 times comparisons for rs2305764 in CD and UC respectively, therefore, the *P* values that were less than 0.05/9 in rs1545620 and 0.05/3 in rs1457092 and rs2305764 showed significance after Bonferroni correction.

Sensitivity analysis was investigated to assess the stability of the results in this study. Publication bias was investigated with the funnel plot, in which the standard error of log OR of each study was plotted against its OR. Funnel plot asymmetry was further assessed by the method of Egger's linear regression test ($P < 0.05$ was considered representative of statistically significant publication bias) [23].

All the statistical analyses of meta-analysis were performed by STATA statistical software (version 11.0 STATA Corp LP, College Station, TX, USA).

2.4. Quality score assessment

Two authors (Li and Zhao) of this article independently assessed the qualities of included studies using the Newcastle–Ottawa scale (NOS). The NOS ranges between zero (worst) and nine stars (best). Studies with a score of seven stars or greater were considered to be of high quality [24]. Disagreement was settled by discussing with our research team.

3. Results

3.1. Studies included in the meta-analysis

The detailed study selecting process is shown in Fig. 1. Through literature searching, a total of 45 publications relevant to the searching keywords were screened. We excluded the repeated publications, the rest of 29 publications need to assessment in detail. Of these articles, five articles were not about *MYO9B* gene polymorphisms, seven articles studied *MYO9B* gene polymorphisms with other disease, and eight articles were reviews. Further reading the full-texts, we found two articles have no original data, then we excluded them [13,25]. Finally, seven articles without overlapping study populations were considered in current meta-analysis [17,18,26–30]. Of these seven articles, Prager et al. [26] and van Bodegraven et al. [18] contained three different groups and we analyzed these studies independently. Therefore, seven articles comprising eleven case-control studies were included in this meta-analysis. A total of 11 loci (rs1545620, rs1457092, rs2279003, rs2305764, rs2279002, rs962917, rs2305767, rs2279000, rs7259292, rs8107108, rs2305766) were reported in these studies. For these loci, eight loci (rs2279003, rs2279002, rs962917, rs2305767, rs2279000, rs2305766, rs2279003, rs7259292) are not suitable for meta-analysis because of limiting number of studies or the results without controversial, so we conducted a meta-analysis on the rest of three loci (rs1545620,