Association between PTGER4 polymorphisms and inflammatory bowel disease risk in Caucasian
A meta-analysis

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Abstract

Background: The results from previous studies on association between prostaglandin E receptor 4 (PTGER4) polymorphisms and inflammatory bowel disease (IBD) risk in Caucasian were conflict. The present study aimed to investigate the genetic association by conducting a meta-analysis.

Methods: Systematic literature search was conducted through Wiley Online Library, Chinese National Knowledge Infrastructure (CNKI), and PubMed databases. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to investigate the associations between rs4613763T/C, 17234657T/G polymorphisms, and IBD risk in Caucasian.

Results: Twenty case-control studies consisting of 18,495 Crohn disease (CD) patients and 4203 ulcerative colitis (UC) patients, as well as 26,063 controls were included in this meta-analysis. The rs4613763T/C polymorphism had obvious influence on CD, UC risk in Caucasian. However, rs17234657T/G polymorphism had obvious influence on CD but not UC in Caucasian.

Conclusion: This meta-analysis suggested that both the rs4613763T/C, rs17234657T/G polymorphisms had obvious influence on risk of CD in Caucasian. In addition, rs4613763T/C, polymorphism had obvious influence on risk of UC in Caucasian.

Abbreviations: CD = Crohn disease, CI = confidence interval, CNKI = Chinese National Knowledge Infrastructure, IBD = inflammatory bowel disease, OR = odds ratio, PTGER4 = prostaglandin E receptor 4, UC = ulcerative colitis.

Keywords: inflammatory bowel disease, meta-analysis, polymorphism, PTGER4

1. Introduction

Inflammatory bowel disease (IBD), a complex chronic inflammatory disorder, is typically classified into 2 clinical syndromes: Crohn disease (CD) and ulcerative colitis (UC). Recently, the incidence rate IBD has been gradually increasing in Europe. Of note, geographic variability in the incidence and prevalence of IBD was found around the world.[1] The majority of IBD patients abdominal pain, vomiting, diarrhea, and other extra-intestinal symptoms, which seriously affects their quality of life.[2] In addition it has been widely accepted that IBD may increase gastrointestinal cancer and cardiovascular disease risk.[3,4] Therefore, IBD patients were at a slightly higher risk of dying from the general population.[3-5]

It was well established the underlying etiology of IBD is multifactorial.[1] Environmental, genetic immune, microbial, and even emotional factors acted as essential players in IBD.[1] Since the first gene CARD15 was demonstrated to be associated with CD in 2001,[6] people gradually realized that genetic predisposition had considerable influence on IBD risk.[7] As we known, disturbed epithelial barrier integrity acts a crucial role in the progression of IBD.[8] Of note, the prostaglandin receptor EP4, encoded by PTGER4, has been believed to be essential for maintenance of epithelial barrier integrity.[9] It had been reported that PTGER4 polymorphisms were associated with ankylosing spondylitis,[10] asthma,[11] rheumatoid arthritis[12] whose genetic predisposition some degree of overlaps with IBD. In 2007, a genome-wide association study (GWAS) identified PTGER4 contributing to CD susceptibility.[13] Recently, a series of studies investigated the relationship between PTGER4 polymorphisms and IBD risk in Caucasian, but their results were conflict.[12-28] Therefore, we performed a meta-analysis to strengthen the associations between PTGER4 polymorphisms and IBD risk in Caucasian.

2. Materials and methods

2.1. Search strategy

Wiley Online Library, PubMed, and Chinese National Knowledge Infrastructure (CNKI) databases were searched up to
January 20, 2019 for studies regarding associations between PTGER4 polymorphism and IBD risk. Both medical subject heading terms and text words in search strategy were as follows: (“Inflammatory bowel disease” or “IBD” or “Crohn’s disease” or “ulcerative colitis” or “CD” or “UC”) and (“PTGER4” or “prostaglandin receptor EP4”) and (“SNP” or “polymorphism” or “variant” or “mutation”). Moreover, additional studies were identified by a full manual search from the reference of selected papers on this topic. Ethical approval was obtained from the Renmin Hospital of Wuhan University Ethics Committee Board.

2.2. Criteria for inclusion and exclusion

The studies eligible should meet following inclusion criteria: case-control studies; studies documented association between PTGER4 polymorphisms and IBD risk; IBD was clearly diagnosed; the odds ratio (OR) with 95% confidence interval (CI) can be calculated according to information in study; control population was in Hardy-Weinberg equilibrium (HWE); subjects were restricted to Caucasian populations. Accordingly, the exclusion criteria were as follows: duplication of previous publications; not original articles; incomplete genotype data; study on associations between PTGER4 polymorphisms and other diseases; subjects in studies included are not Caucasians; no control population.

2.3. Data extraction

The author name, region, publication year, number of subjects, minor allele frequencies (MAF), or frequencies of genotypic distributions in cases and controls and other information about the eligible studies was extracted by 2 authors. Any dispute was resolved by a final decision after discussion.

2.4. Statistical analysis

Meta-analysis was performed by STATA, version 11.0 (Stata Corporation, College Station, TX). Pooled ORs and 95% CI were used to estimate potential associations of PTGER4 gene polymorphisms with IBD risk under distinct genetic models. Chi-square-based Q test and I² test was used to access heterogeneity between included studies. If P > .10 and I² < 50% showed significant heterogeneity, Mantel–Haenszel fixed effect model was executed, otherwise DerSimonian–Laird random effect model was executed. Z test was applied to access significance of OR. Egger test was also used in the occurrence of Publication bias.

3. Results

3.1. Main characteristics of eligible studies

Forty three records were identified in initial search. After reading titles and abstracts, 7 articles in all records, 21 records were not satisfied inclusion criteria because they were duplicate records (N = 18) or other uncorrelated disease (N = 3). After careful screening, another 8 records were further excluded because they were not case-control studies (N = 4) or not target SNPs (N = 4). Finally, 14 eligible records consisting of 20 case-control studies were identified in this meta-analysis [12–25]. Twenty case-control studies consisting of 18,495 CD patients and 4203 UC patients, as well as 26,063 controls were included in this meta-analysis. The characteristics of all studies included in the meta-analysis is summarized in Table 1.

3.2. Associations between rs4613763 T/C and CD

For rs4613763 T/C polymorphism, 8 case-control studies with 10,193 cases and 10,394 controls were identified. There was significant association found under all genetic models (C vs T: OR = 1.19, 95% CI: 1.05, 1.36, P = .01; CC vs TT: OR = 1.30, 95% CI: 1.05, 1.62, P = .02; TC vs TT: OR = 1.16, 95% CI: 1.03, 1.30).

Table 1

| Study          | Year | Disease | Country | SNP            | Sample size | MAF   | HWE   |
|----------------|------|---------|---------|----------------|-------------|-------|-------|
| Libioulle C    | 2007 | CD      | Belgium | rs4613763      | 547          | 0.191 | 0.931 |
| Laukens D      | 2010 | CD      | Belgium | rs4613763      | 1069         | 0.179 | 0.103 |
| Danoy P        | 2010 | CD      | Australia| rs4613763     | 2773         | 0.130 | 0.952 |
| Latino A       | 2011 | CD      | Italy   | rs4613763      | 657          | 0.107 | 0.337 |
| Latino A       | 2011 | UC      | Italy   | rs4613763      | 692          | 0.114 | 0.337 |
| Peter I        | 2011 | CD      | USA     | rs4613763      | 360          | 0.080 | 0.796 |
| Barrett JC     | 2008 | CD      | UK      | rs4613763      | 3230         | 0.125 | 0.993 |
| Amre DK        | 2010 | CD      | Canada  | rs4613763      | 406          | 0.160 | 0.991 |
| Silverberg MS  | 2009 | UC      | Canada  | rs4613763      | 1,052        | 0.140 | 0.982 |
| Waterman M     | 2011 | CD      | Canada  | rs4613763      | 1,144        | 0.133 | 0.964 |
| Waterman M     | 2011 | UC      | Canada  | rs4613763      | 1,230        | 0.144 | 0.964 |
| WTCCC          | 2007 | CD      | UK      | rs17234657     | 2000         | 0.181 | 0.980 |
| Parkes M       | 2007 | CD      | UK      | rs17234657     | 1,747        | 0.182 | 0.556 |
| Parkes M       | 2007 | CD      | UK      | rs17234657     | 1,116        | 0.151 | 0.081 |
| Jung C         | 2012 | CD      | France  | rs17234657     | 708          | 0.150 | 0.074 |
| van der Heide F| 2010 | CD      | Netherlands| rs17234657 | 310          | 0.180 | 0.911 |
| Weersma RK     | 2009 | CD      | Netherlands| rs17234657 | 1,621        | 0.170 | 0.034 |
| Perdigones N   | 2010 | CD      | Spain   | rs17234657     | 709          | 0.136 | 0.657 |
| Perdigones N   | 2010 | UC      | Spain   | rs17234657     | 662          | 0.125 | 0.657 |
| Wang MH        | 2014 | UC      | USA     | rs174257      | 566          | 0.370 | 0.980 |

CD = Crohn disease; UC = ulcerative colitis.
1.30, \( P = .01 \); CC/TC vs TT: OR = 1.17, 95% CI: 1.04, 1.32, \( P = .01 \); CC vs TC/TT: OR = 1.26, 95% CI: 1.01, 1.57, \( P = .04 \) (Table 2).

3.3. Associations between rs4613763 T/C and UC

For rs4613763T/C polymorphism, 3 case-control studies consisting of 2978 cases and 3853 controls were identified. There was significant association found in following genetic models (C vs T: OR = 1.24, 95% CI: 1.12, 1.38, \( P = .00 \); CC vs TT: OR = 1.54, 95% CI: 1.04, 2.29, \( P = .03 \); TC vs TT: OR = 1.22, 95% CI: 1.09, 1.37, \( P = .00 \); CC/TC vs TT: OR = 1.23, 95% CI: 1.10, 1.37, \( P = .00 \)) However, no significant association was found in CC versus TC/TT: OR = 1.47, 95% CI: 0.99, 2.17, \( P = .06 \) (Table 2).

3.4. Associations between rs17234657T/G and CD

For rs17234657T/G polymorphism, 7 case-control studies consisting of 8302 cases and 12,169 controls were identified. There was significant association found under all genetic models (G vs T: OR = 1.33, 95% CI: 1.26, 1.41, \( P = .00 \); GG vs TT: OR = 1.97, 95% CI: 1.63, 2.39, \( P = .00 \); TG vs TT: OR = 1.27, 95% CI: 1.20, 1.36, \( P = .00 \); GG/TG vs TT: OR = 1.30, 95% CI: 1.22, 1.38, \( P = .00 \); GG vs TG/TT: OR = 1.83, 95% CI: 1.52, 2.21, \( P = .00 \)) (Table 3).

3.5. Associations between rs17234657T/G and UC

For rs17234657T/G polymorphism, 2 case-control studies consisting of 1228 cases and 1797 controls were included. There was no significant association found under all genetic models (G vs T: OR = 1.01, 95% CI: 0.90, 1.26, \( P = .91 \); GG vs TT: 0.98, 95% CI: 0.75, 1.30, \( P = .91 \); TG vs TT: OR = 1.01, 95% CI: 0.88, 1.61, \( P = .00 \); GG/TG vs TT: OR = 1.01, 95% CI: 0.88, 1.15, \( P = .06 \); GG vs TG/TT: OR = 0.99, 95% CI: 0.76, 1.28, \( P = .92 \) (Table 3).

3.6. Publication bias

Egger test was applied to evaluate the publication bias of our meta-analysis. The results of Egger test revealed that there was no publication bias in all analysis (Tables 2 and 3).

4. Discussion

Although the exact of IBD etiology was remains unclear, disturbed intestinal homeostasis was major factor contributing to the pathogenesis and progression of intestinal inflammation in IBD.\(^{[33]}\) Prostaglandins are arachidonic acid metabolites produced by the action of the enzymes cyclooxygenase-1 and -2 which have been identified to play a crucial role in maintenance of intestinal homeostasis.\(^{[34,35]}\) Moreover, a haplotype of prostaglandin synthase 2/cyclooxygenase 2 has been shown to have a
strong association with IBD[36] and microsomal prostaglandin E synthase-1 is altered in IBD.[37] Recently, it was reported that Ptger4-/- mice more easily developed severe colitis induced by dextran sodium sulphate while treatment with EP4-selective agonists exerted protective effects against colitis through enhancement of epithelium survival and regeneration.[38–40] EP4 may act a driver of the differentiation of Th1 cells and proliferation of Th17 cells,[41] which play an important role in the pathogenesis of CD.[42]

Genetically, variant in PTGER4 may lead to functional alterations in its production.[11] Recently, numerous studies have indicated that genetic markers of PTGER4 had effects on inflammatory and autoimmune disease including ankylosing spondylitis,[10] asthma,[11] rheumatoid arthritis[12] whose genetic predisposition overlaps with IBD.[20] Up to now, scientists spent considerable efforts to investigate the relationship between PTGER4 polymorphism and IBD risk. However, the results of all existing studies are conflict. Considering that subjects in included studies are all Caucasian population, we conducted a meta-analysis to investigate the genetic association.

To our knowledge, this meta-analysis systematically investigated the associations between PTGER4 polymorphisms and IBD risk in Caucasian population. Twenty case-control studies consisting of 18,495 CD and 4203 UC patients as well as 26,063 controls were included in this meta-analysis. Our synthetic results suggested that the both rs4613763T/C, rs17234657T/G polymorphisms had obvious influence on risk of CD in Caucasian. Moreover, rs4613763T/C, polymorphism had obvious influence on risk of UC in Caucasian. Up to now, there is few data about how PTGER4 involving in influencing IBD susceptibility. A possible mechanism is that NF-κB and XBP1 binds to some gene loci in PTGER4[43] and then modulates PTGER4 expression,[44] which finally leads to altering IBD susceptibility.

It is worth to note that several genome-wide association studies (GWASs) were included in current meta-analysis,[16–18,24–26,28] GWASs, aimed at increasing the reliability of results by comprehensively analyzing different study from different regions, have led to the identification of novel associations that would not otherwise have been identified in individual studies with small sample. The results of our meta-analysis also were consistent with most of GWASs.

It was widely accepted that meta-analysis was a powerful tool to systematically evaluate genetic effect of polymorphism on disease susceptibility.[45,46] Publication bias, also regarded as a “file-drawer problem,” was often a major drawback of meta-analyses by compromising their validity.[47] There was no significant publication bias in current analyses. Heterogeneity, known as another important issue in meta-analysis, did not exist. In addition, the sample size is relatively larger. Therefore, our synthetic results are comparatively persuasive and reliable.

Undoubtedly, some limitations in our study still need be careful considered. First, because there was no enough available data, we did not conducted subgroup analysis according to study characteristics, which requires further investigation. Second, the underlying etiology of IBD is extremely complex, but only genetic factors were under our consideration. Last but not least, our studies did not consider potential interaction between gene–gene and gene–environmental interactions had obvious influence on associations between PTGER4 polymorphisms and IBD risk. Therefore, representativeness bias of the result should be fully valued.

In conclusion, our meta-analysis revealed that both the rs4613763T/C, rs17234657T/G polymorphisms had obvious influence on risk of CD in Caucasian. In addition, rs4613763T/C polymorphism had obvious influence on risk of UC in Caucasian. Given that some limitations exist in our study, further well-designed case-control studies are still warranted to confirm the results of our present meta-analysis.

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