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ORIGINAL ARTICLE

Relationship between NR1I2 polymorphisms and inflammatory bowel disease risk: A systematic review and meta-analysis

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Summary
Background and objective: Inconsistent results regarding an association between polymorphisms within the Homo sapiens nuclear receptor subfamily 1 group I member 2 (NR1I2) gene and susceptibility to inflammatory bowel disease (IBD) have been reported. A systematic review and meta-analysis was thus undertaken to determine whether NR1I2 gene polymorphisms are associated with an increased risk of IBD.
Methods: Article retrieval was performed using on-line databases, such as PubMed, Embase, CENTRAL, and WOS. After extracting eligible data, Mantel-Haenszel statistics were applied to calculate the odds radio (OR), 95% confidence interval (95% CI) and *P* value under a random or fixed-effects model.
Results: A total of seven articles with 4410 IBD subjects and 4028 controls were included. Compared with the control group, no significant increase in IBD susceptibility was observed for the −25385C/T (OR = 0.92, 95% CI = 0.78∼1.07, *P* = 0.259), −24381A/C (OR = 0.96, 95% CI = 0.87∼1.06, *P* = 0.378), +8055C/T (OR = 1.06, 95% CI = 0.97∼1.15, *P* = 0.186), or +7635A/G (OR = 0.96, 95% CI = 0.87∼1.05, *P* = 0.348) polymorphisms within the NR1I2 gene under the allele model.

Abbreviations: NR1I2, Homo sapiens nuclear receptor subfamily 1 group I member 2; IBD, inflammatory bowel diseases; UC, Ulcerative Colitis; CD, Crohn's Disease; OR, odd radio; CI, confidence interval; PPARα, peroxisome proliferator-activated receptor alpha; FXR, farnesoid X receptor; NRAMP1, natural resistance-associated macrophage protein 1; PXR, pregnane X receptor; SNPs, single nucleotide polymorphisms; WOS, Web of Science; HWE, Hardy-Weinberg Equilibrium; LD, linkage disequilibrium; CYP3A4, cytochrome P-450 monooxygenase 3A4; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.

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Conclusions: Our meta-analysis failed to demonstrate an association between −25385C/T, −24381A/C, +8055C/T, or +7635A/G polymorphisms within the NR1I2 gene and overall IBD risk. A larger sample size is needed to validate our conclusion.

Introduction

Inflammatory bowel disease (IBD), chronic inflammation within the gastrointestinal tract, is characterized by abdominal pain, malnutrition, and recurring diarrhea or rectal bleeding [1—3]. Ulcerative colitis (UC) and Crohn's disease (CD) are the main types of IBD [2]. The exact etiology of IBD remains unknown, but it may be linked to complicated environmental and genetic factors [4—7]. Accumulating evidence indicates that polymorphic variants of specific genes, such as peroxisome proliferation-activated receptor alpha (PPARα) [8], farnesoid X receptor (FXR) [9], natural resistance-associated macrophage protein 1 (NRAMP1) [10], and nuclear receptor subfamily 1 group I member 2 (NR1I2) [11], contribute to the pathogenesis or modulation of the inflammatory response in IBD. In the current study, we determined a potential association between human NR1I2 gene polymorphisms and risk of IBD by performing a meta-analysis, an efficient method used to assess genetic effects [12].

The human NR1I2 gene, also called the pregnane X receptor (PXR), is located on chromosome 13q12-q13.3, which encodes the NR1I2 protein, a member of the nuclear receptor superfamily [13—15]. The NR1I2 protein maintains intestinal integrity, regulates the inflammatory response and is involved in drug transport, gene transcription, energy metabolism, and the detoxification of steroids and xenobiotics [16—23]. Several single nucleotide polymorphisms (SNPs) that have been identified within the NR1I2 gene are reportedly linked to the risks of certain diseases in different populations [24—29]. For example, the rs3814058C/T SNP within the NR1I2 gene is associated with a susceptibility to colorectal cancer among the Chinese population [26]. However, the role of NR1I2 polymorphisms in the development of IBD remains controversial.

To our knowledge, no meta-analysis has assessed the potential association between NR1I2 polymorphisms and genetic susceptibility to IBD. Therefore, the relationship between NR1I2 polymorphisms and the incidence of IBD was evaluated through a systematic review and meta-analysis of previously published articles. Our findings show no evidence of an association between rs3814055 (−25385C/T), rs1523127 (−24381A/C), rs2276707 (+8055C/T), or rs6785049 (+7635A/G) polymorphisms within the NR1I2 gene and the overall risk of IBD under the allele model.

Methods

Systematic literature search

Relevant articles published before July 7th, 2016 were retrieved from nine electronic databases, including PubMed, Embase, CENTRAL, Web of Science (WOS), Scopus, Ovid, Wiley, EBSCO, and ScienceDirect, without any language restrictions. The following search terms were applied: ''NR1I2'' or ''PXR'' or ''walrycin A'' or ''pregnane X receptor/PXR activator'' or ''4-methoxy-1-naphthol'' or ''Nuclear Receptor Subfamily 1, Group I, Member 2''; ''inflammatory bowel diseases'' or ''Bowel Diseases, Inflammatory'' or ''Crohn Disease'' or ''Crohn's Enteritis'' or ''Inflammatory Bowel Disease 1'' or ''Enteritis, Granulomatous'' or ''Granulomatous Enteritis'' or ''Enteritis, Regional'' or ''Ileocolitis'' or ''Colitis, Granulomatous'' or ''Terminal Ileitis or Ileitis, Regional'' or ''Regional Ileitides or Regional Ileitis'' or ''Colitis, Ulcerative'' or ''Idiopathic Proctocolitis'' or ''Ulcerative Colitis'' or ''Colitis Gravis'' or ''Inflammatory Bowel Disease, Ulcerative Colitis Type''; ''Polymorphism, Genetic'' or ''Polymorphisms, Genetic'' or ''Genetic Polymorphism'' or ''Polymorphism (Genetics)'' or ''Genetic Polymorphisms''.

Selection criteria

Eligible articles were required to fulfill the following inclusion criteria:

- to provide sufficient or usable data regarding an association between NR1I2 polymorphisms and IBD risk;
- the genotypic distribution within the control group should follow Hardy-Weinberg Equilibrium (HWE).

The exclusion criteria were as follows:

- duplicated articles;
- review, meeting abstract, book or poster;
- case, trial or non-SNP data;
- non-clinical data;
- other genes;
- other diseases.

Data extraction strategy

The authors and two anonymous reviewers independently extracted and recorded the following information: name of the first author, publication year, country, SNPs, sample sizes in case (UC/CD) and control groups, source of the control group, and genotyping methods of the SNPs. In instances of disagreement or conflicting evaluations, a thorough discussion was performed during a meeting to reach a consensus. A request for missing data was sent to the respective corresponding authors via electronic mail.

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