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ORIGINAL ARTICLE

Interleukin-23 receptor single nucleotide polymorphisms in ulcerative colitis. A study in Iranian populations

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Summary
Background/objective: Genetic factors seem to play an important role in the pathogenesis of ulcerative colitis (UC). Genome wide association studies showed a highly significant association between interleukin 23 receptor (IL23R) single nucleotide polymorphisms (SNPs) and Crohn's disease; however, there are contrary results regarding the disease-modifying effects of IL23R variants in UC. This study was performed in a group of patients with UC to test the possible role of *IL23R* SNPs in conferring susceptibility or protection against the disease.
Methods: The study was performed on 67 Iranian adult patients with UC and 78 healthy controls. Eight IL23R SNPs were genotyped, using real-time polymerase chain reaction (RT-PCR). The frequencies of alleles and genotype at each position were determined and compared between two groups of patients and controls.

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Results: The frequency of the T allele at position *rs1343151* was significantly higher in the patient group, compared to the controls ($P = 0.018$). The TT genotype at the same position was also significantly overrepresented in the patient group ($P = 0.02$). There was no significant difference in alleles and genotype frequencies of other SNPs between patients and controls.
Conclusions: This study identified a new susceptibility locus associated with UC. Our findings provide further insight into the genetics of UC, which might be amenable to future therapeutic intervention.
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Introduction

Inflammatory bowel diseases (IBDs) are chronic, idiopathic, relapsing—remitting inflammatory disorders of gastrointestinal tract. Crohn's disease (CD) and ulcerative colitis (UC) are the two major distinct forms of IBD despite some similarities in the feature [1,2].

Over the past decade, considerable progress has been made in understanding the role of mucosal immunity and host genetics in the pathogenesis of CD and UC. Although exact causative factors in disease pathogenesis are not well understood, a complex interaction between genetic and environmental factors would trigger an exaggerated mucosal immune response to commensal bacterial flora in genetically susceptible individuals [3,4].

Genetic factors play an important role in the pathogenesis of IBD. A higher prevalence of the disease among Ashkenazi Jews population, family inheritance of the disorder, and higher disease concordance with monozygotic, than dizygotic, twins provide solid evidence for contribution of genetic factors in pathogenesis of the disease [5,6].

Besides, recent genome wide association and basic science studies corroborate the association of IBD with specific genetic variants, particularly NOD2/CARD15 polymorphisms on 16q12 chromosome and IBD5 haplotype on 5q31 chromosome, consisting of *SLC22A4* and *SLC22A5* genes, coding for the OCTN1 and 2 (novel organic cation transporter) proteins, respectively [7,8].

In addition, although the adaptive immune branch of mucosal immunity has attracted tremendous attention into the pathogenesis of IBD, it is now obvious that innate immune responses have an equally significant, or perhaps even principal role, in disease initiation [9].

So far, activation of macrophages and increased secretion of the proinflammatory cytokines, TNF- alpha, IL-1 and IL-6, has been reported in the etiology of both forms of IBD [10].

Regarding the adaptive immune responses, the role of T-helper (Th) 1-mediated cytokines in CD and Th2-mediated cytokines in UC has been postulated previously. Soon after, mounting studies suggested an additional Th subset contributing to IBD pathogenesis besides the conventionally dichotomous Th1/Th2 paradigm [9].

Although UC was known as a Th2 dominant disease, some recent evidence, by discovering the role of IL-23 receptor (IL-23R), IL-21B (encoding a common subunit of IL-12 and IL-23) and IL12 single nucleotide polymorphisms (SNPs) in UC, propounded Th17-mediated immune responses in the pathogenesis of UC [11—13].

Regardless of numerous studies concerning the characterization of the interleukin-23/Th17 axis in immunopathogenesis of CD, similar data regarding Th17 effector pathway in UC is sparse [14].

IL-23 is a pro-inflammatory cytokine produced by macrophages and dendritic cells. IL-23, in combination with IL-6 and TGF-β1, stimulates naive CD4+T cells and subverts Th1 and Th2 differentiation for the generation of Th17 [15].

Despite several genome wide association studies (GWAS) and compelling evidence, which confirm a highly significant association between IL23R SNPs and CD, there are few similar data with contrary results regarding the disease-modifying effects of IL23R variants in protection against, or increased susceptibility to, UC in diverse ethnicity [4,11,16].

Given the importance of genetic determinants of UC in understanding the pathogenic mechanism of the disease, this study was performed to investigate potential associations of UC with IL23R variants.

Patients and methods

The study population was compromised of 67 adult patients with UC who were referred to a referral general hospital, affiliated to Tehran University of Medical Sciences, Tehran, Iran. The patients were diagnosed according to established guidelines based on endoscopic, radiological, and histopathological criteria [17]. Seventy-eight healthy individuals from the hospital staff without history of any gastrointestinal disease any other inflammatory disorders were enrolled as controls. All the individuals were recruited from the same ethnicity in Iran.

Direct history taking and physical exam were performed for ruling out presence of such disorders.

Patients with history of CD or intermediate colitis were excluded from the study.

Data collection was done through questionnaire consisted of patient's demographic and clinical characteristics such as age, sex, age of disease diagnosis, disease duration, anatomic location of the disease, and the need for surgery or immunosuppressive therapy.

Informed consent was obtained from each individual before enrollment in the study. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences.

A total of 5 mL of venous blood was collected from each participant in an EDTA tube for DNA extraction. Genomic DNA was extracted from peripheral blood leukocyte by salting-out method and was stored at −20 °C [18].

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