Interleukin-1 single-nucleotide polymorphisms as risk factors for susceptibility of inflammatory bowel disease: an Iraqi Arab population-based study

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ABSTRACT

Objectives: It is aimed to determine the association between four single-nucleotide polymorphisms (SNPs) of IL1 genes (rs1800587: IL1A−889 C/T, rs16944: IL1B−511 T/C, rs2234650: IL1R1post 1970 T/C and rs315952: IL1RAamp 11100 T/C) and the two types of IBD (UC and CD) in samples of Iraqi Arab patients.

Materials and Methods: Hundred Iraqi patients (66 UC and 34 CD) were genotyped for these SNPs by polymerase chain reaction-specific sequence primer (PCR-SSP) assay.

Results: A significant increased frequency of IL1A−889 C allele was observed in total IBD patients compared to controls (72.0 vs. 56.5%; Odds ratio = 1.98; Corrected p = 0.001). For IL1B−511 and IL1R1post 1970 SNPs, the T allele frequency was significantly increased in total patients (62.0 vs. 49.1%; Odds ratio = 1.65; Corrected p = 0.02 and 65.0 vs. 46.7%; Odds ratio = 2.12; Corrected p = 1 × 10^{-4}, respectively). Allele and genotype frequencies of IL1RAamp 11100 SNP showed no significant variation between total patients and controls. A similar profile of was observed in UC patients, but IL1RAamp 11100 T allele frequency was significantly increased in patients (72.7 vs. 60.2%; Odds ratio = 1.76; Corrected p = 0.05). Among CD patients, IL1A−889, IL1R1post 1970 and IL1RAamp 11100 SNP allele frequencies shared their distribution in total IBD patients. For IL1B−511 SNP, allele and genotype frequencies showed no significant difference between CD patients and controls.

Conclusion: These data suggests a significant role of IL1 SNPs in etiopathogenesis of IBD in Iraqi Arab population.

1. Introduction

Inflammatory bowel disease (IBD) is chronic inflammatory conditions that occur in the gastrointestinal tract. The major two clinical types of IBD are ulcerative colitis (UC) and Crohn’s disease (CD). UC is restricted to rectum and colon and invading epithelial lining of the gut, while CD can affect any part of the gastrointestinal tract and it causes transmural lesions [1]. The etiology of IBD is largely unknown, but recent investigations highlighted that host genetic susceptibility, external environment, intestinal microbiota and immune responses are functionally involved and integrated in IBD pathogenesis [2].

Studies comparing prevalence of IBD among different ethnic groups suggest a genetic tendency. IBD disease has been observed to occur two to four times greater in Jewish population compared to other ethnic groups. Further epidemiologic studies have shown higher rates in Whites and lower rates in African-Americans, while the lowest rates have been recorded in Asians [3]. The prevalence of IBD has also been reported to be increased in relatives of those who have CD and UC. Twin studies have further confirmed the genetic etiology of IBD. In CD, the concordance rate among monozygotic twins had a range of 20–50%, compared to approximately 10% in dizygotic twins; emphasizing a definite genetic component. In UC, a less concordance rate (16%) was reported in monozygotic twins, but it was still higher than that (4%) of dizygotic twins [4]. However, there have been great technological advances in the understanding of genetic factors that contribute to IBD etiology, which included DNA analysis and sequencing and the employment of multinational databases. These advances allowed for the achievement of genome-wide association studies (GWAS) that identified different single-nucleotide polymorphisms (SNPs) and defined their role in IBD. Based on these studies, the number of IBD-associated gene loci has been brought to163, which are distributed as 110 shared loci for both diseases, 30 loci as CD specific and 23 loci as UC associated. An understanding of gene loci that are shared by UC and CD may provide a pathway to elucidate the common pathogenesis involved in both forms of IBD [5].
Cytokine SNPs have also been suggested to be associated with IBD, especially if we consider that such polymorphisms in the cytokine gene regulatory regions have been correlated with cytokine secretion [6]. A wealth of data have indicated the importance of genetic background in regulating the cytokine network in IBD, and in fact, polymorphisms of cytokine/cytokine receptor genes have been shown to be associated with the development of IBD; implicating their role in determining the risk or protection from the disease expression [7,8].

Among these cytokines is interleukin-1 (IL-1). Four members of IL-1 have been recognized: IL-1α, IL-1β, IL-1 type I receptor (IL-1R) and IL-1 receptor antagonist (IL-1RA), which are controlled by four closely linked genes (IL1A, IL1B, IL1R1 and IL1RA, respectively) that are mapped to the long arm of chromosome 2 (2q14.2). The first two interleukins (IL-1α and IL-1β) are structurally related and recognize the same receptor (IL-1R), while IL-1RA binds IL-1R and blocks the activities of IL-1α and IL-1β [9]. IL-1 is mainly produced by activated monocytes and macrophages, and acts systemically and locally, while IL-1RA is produced by hepatocytes during the inflammatory acute-phase response, probably to control IL-1 effects [10]. An imbalance between IL-1 and IL-1RA production has been observed in mucosal biopsies obtained from inflamed colonic tissue of IBD patients, and an IL-1RA administration to rabbit model of dextran-induced colitis prevented mucosal inflammation and necrosis [11].

Several SNPs have been described for IL1 genes and among these are IL1A −889, IL1B −511, IL1R1pat1 1970 and IL1RAmspa1 11100 SNPs. Studies in CD and UC patients of different ethnicities have reported different correlations with the two forms of IBD, but some of them suggested that these polymorphisms may play a role in etiopathogenesis of IBD [12-20].

The present investigation is a part of a project that examined 22 SNPs belongs to 13 cytokines, and one of them was IL-1. It was aimed to determine the association between four SNPs of IL1 genes (rs1800587: IL1A −889 C/T, rs16944: IL1B −511 T/C, rs2234650: IL1R1pat1 1970 T/C and rs315952: IL1RAmspa1 11100 T/C) and the two types of IBD (UC and CD) in samples of Iraqi Arab patients. Such association study may help to understand the immunogenetic predisposition for the development of both types of IBD, as well as their protective effects can also be determined. Such determinations have not been reported in Iraqi IBD patients.

2. Materials and methods

2.1. Patients

The ethics committee at the Iraqi Ministry of Health approved the study, in which 100 Iraqi Arab IBD patients were enrolled. The patients attended the Gastrointestinal Tract Units at Al-Kindy Teaching Hospital, Al-Yarmouk Teaching Hospital and Al-Zuafirania General Hospital in Baghdad for diagnosis and treatment during the period August 2013–October 2014. The disease was clinically diagnosed by the consultant medical staff at the units. It was based on clinical, radiological, endoscopic and histopathological findings that are defined by the criteria of Lennard–Jones [21]. The patients were distributed into two clinical groups. The first included 66 UC patients (22 males and 42 females), and their age mean ± S.E. was 40.2 ± 8.1 years. In the second group, 34 CD patients (12 males and 22 females) were studied, and their age mean ± S.E. was 40.7 ± 3.9 years. In addition to patients, 224 Iraqi Arab control subjects (102 males and 122 females) were involved in the study. The control sample was previously genotyped for 22 cytokine SNPs, including the present study SNPs, and published by our group [22].

2.2. Methods

Genomic DNA was extracted from EDTA blood using Wizard Genomic DNA Purification Kit (Promega, USA). The SNPs (rs1800587: IL1A −889, rs16944: IL1B −511, rs2234650: IL1R1pat1 1970 and rs315952: IL1RAmspa1 11100) were detected by polymerase chain reaction-specific sequence primer (PCR-SSP) assay, followed by electrophoresis on 2% agarose-gel, by using the Cytokine CTS-PCR-SSP (Collaborative Transplant Study-PCR-SSP) Tray Kit (University Clinic, Heidelberg, Germany). As suggested by the kit’s supplier, the thermocycling conditions were optimized as the following: initial denaturation at 94°C for 2 min, followed by denaturation at 94°C for 15 s, and then 10 cycles of annealing and extension at 65°C for 60 s. This was followed by denaturation at 94°C for 15 s, and then 20 cycles of annealing at 61°C for 50 s and extension at 72°C for 30 s.

2.3. Statistical analysis

Allele frequency of IL1 SNPs was calculated by direct gene counting method, while a significant departure from Hardy–Weinberg equilibrium (HWE) was estimated by Pearson’s chi-square test using H–W calculator for two alleles. Alleles and genotypes of SNPs were given as percentage frequencies, and significant differences between their distributions in patients and controls were assessed by two-tailed Fisher’s exact probability (p), which was corrected (pc) for the number of comparison made at each locus (the p value was multiplied by 5). In addition, Odds ratio (OR) and its 95% confidence interval (CI) were also estimated to
define the association between an allele or a genotype and the disease. These estimations were calculated by using the WINPEPI computer programs for epidemiologists.

3. Results

The genotypes of all SNPs were in a good agreement with HWE with the exception of IL1A_{-889} (total IBD patients), IL1B_{-511} (total and UC patients), IL1R1_{psl 1970} (control) and IL1RA_{mspa 11100} (control).

The IL1A_{-889} C allele showed a significant increased frequency in total IBD patients compared to controls (72.0 vs. 56.5%; OR = 1.98; 95% CI = 1.38–2.84; pc = 0.001), while T allele frequency was significantly decreased (28.0 vs. 43.5%; OR = 0.50; 95% CI = 0.35–0.72; pc = 0.001). For IL1B_{-511} and IL1R1_{psl 1970} SNPs, the T allele frequency was significantly increased in patients compared to controls (62.0 vs. 49.1%; OR = 1.69; 95% CI = 1.20–2.37; pc = 0.02 and 65.0 vs. 46.7%; OR = 2.12; 95% CI = 1.51–3.00; pc = 1 × 10^{-4}, respectively), while C allele frequency was observed to have a significantly decreased frequency (38.0 vs. 50.9%; OR = 0.59; 95% CI = 0.42–0.83; pc = 0.02 and 35.0 vs. 53.3%; OR = 0.47; 95% CI = 0.33–0.66; pc = 1 × 10^{-4}, respectively). Allele and genotype frequencies of the fourth SNP (IL1RA_{mspa 11100}) showed no significant variation between patients and controls (Table 1).

A similar profile of allele frequency distribution was observed in UC patients, but IL1RA_{mspa 11100} was an exception. The T allele frequency of such SNP was significantly increased in patients compared to controls (72.7 vs. 60.2%; OR = 1.76; 95% CI = 1.15–2.70; pc = 0.05), while C allele frequency was significantly decreased (27.7 vs. 39.8%; OR = 0.57; 95% CI = 0.37–0.87; pc = 0.05) (Table 2).

Among CD patients, IL1A_{-889}, IL1R1_{psl 1970} and IL1RA_{mspa 11100} allele frequencies shared their distribution in total IBD patients. For IL1B_{-511}, SNP allele and genotype frequencies showed no significant difference between CD patients and controls (Table 3).

4. Discussion

The presented results were consistent with positive and negative associations between IL1A_{-889}, IL1B_{-511} and IL1R1_{psl 1970} SNP alleles and IBD, and such profile was also applicable for IL1RA_{mspa 11100} in UC patients. In the case of IL1A_{-889}, it is possible to consider C as a predisposing allele for IBD of both types (UC and CD), while T allele may have a protective effects against the development of disease. Reviewing the literature revealed that there was only one published study [19], in which IL1A_{-889} gene polymorphism was investigated in Spanish IBD patients (57 CD and 27 UC). No significant difference was reported between patients and controls in the

Table 1. Observed number and percentage frequencies of IL1 SNP alleles and genotypes in total inflammatory bowel disease patients and controls.

| IL1 SNP allele and genotype | Controls (no. = 224) | IBD patients (no. = 100) | OR  | 95% CI   | p-value | pc-value |
|----------------------------|----------------------|--------------------------|-----|----------|---------|----------|
| C                         | 253                  | 144                      | 1.98| 1.38–2.84| 2 × 10^{-4}| 0.001    |
| T                         | 195                  | 72                       | 0.50| 0.35–0.72| 2 × 10^{-4}| 0.001    |
| CC                        | 72                   | 56                       | 2.69| 1.66–4.35| 4 × 10^{-4}|          |
| CT                        | 109                  | 32                       | 0.50| 0.30–0.81| 3 × 10^{-4}|          |
| TT                        | 43                   | 12                       | 0.57| 0.29–1.14| 2 × 10^{-4}| 0.002    |
| HWE p-value               | < 0.04               |                          |     |          |         |          |
| IL1B_{-511} (rs16944)     | T                    | 220                      | 1.14| 0.87–1.50| 3 × 10^{-4}|          |
| CC                        | 122                  | 76                       | 0.59| 0.42–0.83| 4 × 10^{-4}| 0.002    |
| CT                        | 57                   | 32                       | 1.38| 0.82–2.31| 1 × 10^{-4}|          |
| TC                        | 106                  | 60                       | 1.67| 1.04–2.69| 1 × 10^{-4}|          |
| CC                        | 61                   | 8                        | 0.23| 0.11–0.51| 9 × 10^{-5}|          |
| HWE p-value               | < 0.01               |                          |     |          |         |          |
| IL1R1_{psl 1970} (rs2234650) | T                | 209                      | 2.12| 1.51–3.00| 2 × 10^{-5}| 1 × 10^{-4}|
| C                         | 239                  | 70                       | 0.47| 0.33–0.66| 2 × 10^{-5}| 1 × 10^{-4}|
| TT                        | 62                   | 42                       | 1.89| 1.16–3.09| 1 × 10^{-4}| 0.01      |
| TC                        | 85                   | 46                       | 1.39| 0.87–2.24| 1 × 10^{-4}|          |
| CC                        | 77                   | 12                       | 0.26| 0.13–0.50| 2 × 10^{-5}| 1 × 10^{-4}|
| HWE p-value               | < 0.01               |                          |     |          |         |          |
| IL1RA_{mspa 11100} (rs315952) | T              | 265                      | 136| 1.40| 0.99–2.00| 2 × 10^{-4}| 1 × 10^{-4}|
| C                         | 175                  | 64                       | 0.71| 0.50–1.01| 2 × 10^{-4}| 1 × 10^{-4}|
| TT                        | 95                   | 50                       | 1.32| 0.82–2.11| 1 × 10^{-4}| 0.01      |
| TC                        | 75                   | 36                       | 1.09| 0.66–1.78| 1 × 10^{-4}|          |
| CC                        | 50                   | 14                       | 0.55| 0.29–1.05| 2 × 10^{-4}| 1 × 10^{-4}|
| HWE p-value               | < 0.01               |                          |     |          |         |          |

IL1: interleukin 1; SNP: single-nucleotide polymorphism; IBD: inflammatory bowel disease; OR: odds ratio; CI: confidence interval; p: probability; pc: corrected p; NS: not significant; HWE: Hardy–Weinberg equilibrium; ■: number of controls: 220.
distribution of genotype and allele frequencies, but they were comparable to the corresponding frequencies in present study UC patients (C allele frequency: 71.2 vs. 72.2%) and CD (C allele frequency: 73.5 vs. 78.1%) patients. Whereas, a difference between the two controls was observed; the frequency of C allele in the present controls was lower than that of López-Hernández’s study (56.5 vs. 75.2%) [19]. Such observation suggests an ethnic variation between Iraqis and Spanish in the distribution of these frequencies. In this regard, it is well-documented that allele frequencies of cytokine SNPs show variations across populations of different ethnicities including Iraqi Arabs [22,23].
For ILB − 511, it is possible to consider T as a susceptibility allele in UC patients, while C allele may have a protective effect against the development of UC. Whereas, CD failed to show such association, and possibly ILB − 511 SNP is not related to the disease in Iraqi patients. Other investigated populations have shown contradictory results regarding ILB − 511 polymorphism in IBD of both types (CD and UC). Two earlier studies were carried out on north-east English and Turkish patients, and no significant differences in the distributions of IL1B genotypes were observed between IBD patients and controls [12,15]. A further study from China reported a significantly increased frequency of ILB−511 T allele in UC patients, but the authors suggested that combination polymorphisms between MCP-1 (monocyte chemoattractant protein-1) and ILB−511 can increase UC risk significantly [24]. A mutation in ILB−511 SNP has also been associated with a complex disease behavior in CD of Italian patients [16]. A contradictory result has also been found in Mexican UC patients, in whom the frequency of ILB−511 TC genotype was significantly decreased compared to healthy controls [17], while such genotype showed a non-significant increased frequency in total IBD patients, as well as, UC and CD patients. These inconsistencies could be related to race differences, and inter-population discrepancies in cytokine polymorphisms are often observed, and differences in allelic frequencies among ethnic groups have been reported [23].

The third SNP (IL1R1p1970) maintained a similar presentation in UC and CD patients, as well as, total IBD patients, and the OR of its T allele exceeded 2.0. The protein encoded by IL1R1 gene is a cytokine receptor belongs to IL-1 receptor family. It is an important mediator involved in many cytokine induced immune and inflammatory responses.[9] It has also been presented that a dysregulation in its expression may lead to activation of aberrant immune cells that may contribute to auto-inflammatory responses [25]. The obtained results favor such presentation in the ground of its genetic effects on both types of IBD, and the alleles of IL1R1p1970 SNP showed both types of associations (positive and negative) with CD and UC in the samples of Iraqi patients. Therefore, the functional role of such receptor may be subjected to the effects IL1R1p1970 SNP alleles and genotypes. Unfortunately, there has been no further investigation that can confirm these findings in IBD patients, but in Italian IBD patients, two further SNPs (rs13015714 and rs2058660) of IL1R1 were investigated. Significant associations were reported in CD patients with the two SNPs, and IL1R1 was suggested to have a role in increasing the risk of IBD in Italians [26].

The final SNP is IL1RAmspa 11100 and the results revealed no significant association between its alleles or genotypes and the disease in IBD or CD patients. However, among UC patients, the SNP T allele showed a significant increased frequency compared to control. Such difference scored OR value of 1.76. A previous investigation carried out a similar determination in Iranian IBD patients, and IL1RAmspa 11100 CC genotype was identified to have a positive association with CD, UC and IBD [18]. However, it is too early to reach a final conclusion about the role of IL1RAmspa 11100 SNP in pathogenesis of UC, and the observed association needs a confirmation.

5. Conclusion

The presented results highlighted the role of IL1 gene family in etiology of IBD, and such gene may harbor alleles that confer susceptibility to develop the disease, especially the SNP IL1RAmspa 11100 which has not been investigated in IBD. Also, it may be possible to make an etiological discrimination between UC and CD with regard to IL1RAmspa 11100 SNP, which was exclusively associated with UC.

Acknowledgments

The cooperation of the medical staff at Al-Kindy Teaching Hospital, Al-Yarmouk Teaching Hospital and Al-Zuafrania General Hospital is appreciated.

Disclosure statement

The authors declare that there is no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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