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Association between IL-10 rs1800872 Polymorphism in the Promoter Region of Human *IL-10* Gene and Susceptibility to Rheumatoid Arthritis in the Patients in Southwest of Iran

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ABSTRACT

Aims Interleukin-10 is an important immunoregulatory cytokine that has an inhibitory effect on the initiation and progression of inflammatory responses in different situations such as autoimmune diseases including rheumatoid arthritis. Polymorphism in IL-10 promoter region affects the expression of this gene. It therefore seems reasonable that these polymorphisms may contribute to rheumatoid arthritis susceptibility in special populations. the aim of this study was to investigate the association between *IL-10* rs1800872 polymorphism in the promoter region of human IL-10 gene and susceptibility to rheumatoid arthritis in the patients in southwest of Iran.

Materials & Methods The present study is a case-control study conducted among patients with and without rheumatoid arthritis referred to the Mofateh clinic in Yasuj, Iran. Both case (n=64) and control (n=65) groups were selected using purposive sampling and were matched in terms of age, gender and ethnicity. Peripheral blood samples were collected from subjects and rs1800872 genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism method. SPSS 26.0 software was used for statistical analysis of data

Findings The association between the frequency of TT genotypes and the incidence of rheumatoid arthritis was significant (OR=6.45; 95% CI= 1.30-32.00; p=0.023). On the other hand, the distribution of the T allele showed a significant relationship with rheumatoid arthritis (OR= 2.23; 95% CI= 1.26–3.97; p=0.006).

Conclusion TT genotype of rs1800872 polymorphism is associated with rheumatoid arthritis susceptibility in southwestern Iranian population and can be considered as a risk factor for rheumatism.

Keywords Rheumatoid Arthritis; Polymorphism; Single nucleotide polymorphism

CITATION LINKS

[1] Pathogenetic insights from the treatment ... [2] Epidemiology and treatment patterns ... [3] Epidemiology of, risk factors for... [4] Sex differences in rheumatoid ... [5] Gender differences in autoimmune ... [6] Three functional variants in ... [7] Genetics of rheumatoid arthritis ... [8] Genetic and environmental risk factors ... [9] Genetics of rheumatoid ... [10] Genome-wide association study ... [11] Immune modulation by curcumin ... [12] Anti-arthritogenic property of interleukin ... [13] Comparison of single nucleotide polymorphisms ... [14] IL-10 gene Rs1800871, Rs1800872, and ... [15] Rheumatoid arthritis susceptibility and ... [16] Association of polymorphisms in the ... [17] Common genetic variants account for differences ... [18] Ethnic background and genetic variation ... [19] 2010 Rheumatoid arthritis classification ... [20] Genetics of Rheumatoid arthritis contributes ... [21] Gene, environment, microbiome and ... [22] Association of environmental and genetic factors and ... [23] Genetic polymorphisms in Spanish Rheumatoid ... [24] Role of interleukin 10 transcriptional regulation ... [25] IL-10 gene polymorphisms in infectious ... [26] Polymorphisms in STAT-4, IL-10, PSORS1C1, PTPN2 and ... [27] Influence of interleukin 10 promoter ... [28] Are differences in interleukin 10 production ...

Introduction

Rheumatoid Arthritis (RA) is the most common inflammatory arthropathy worldwide. It is a long-standing disorder, complex, and heterogeneous Autoimmune Disease (AD). It is characterized by the presence of chronic inflammation of the diarthrodial joints resulting in symmetric polyarthritis and synovial membrane hypertrophy with advancing joint destruction, bone and cartilage damage as well as irregularity. The autoimmune compromise is systemic, leading to Extra-Articular Manifestations (EAM) bone [1]. The prevalence of this disease is about 0.5 to 1% and increases with age. The incidence of RA increases between the ages of 25 and 55, after which it plateaus until the age of 75 and then decreases. Symptoms of RA are typically caused by inflammation of the joints, tendons, and bursa. Patients often complain of early morning joint stiffness that lasts for more than 1 hour and is relieved by physical activity [2, 3]. The prevalence of rheumatoid arthritis, like most autoimmune diseases, is not balanced between the two sexes (the ratio of women to men is about 3:1) [4, 5].

RA has a multifactorial etiology, suggesting that the interaction of various genetic and environmental factors is associated with an increased risk of developing the disease [6]. Numerous evidences reveal that hereditary determinants are seriously involved in the incidence of RA. Two studies showed that 50-60% of the onset of RA can be attributed to genetic factors [7, 8].

Hence, several autoimmune disorders such as diabetes mellitus, systemic sclerosis, autoimmune hepatitis, vitiligo and myasthenia gravis are affected by the hereditary variability of the autoimmune regulatory gene. The heritability of RA is 53-60%, on the other hand the relative risk for siblings of RA patients is between 7 and 12. These epidemiologic genetic data show that genetic factors play a role in disease susceptibility. Several genes have been revealed in association with RA, among which the leucocyte antigen *HLA-DRB1* gene has a major contribution to RA susceptibility. Some other genes have been proved to be associated with disease susceptibility and may influence a specific disease pattern [9].

In RA, CD4+ T- lymphocytes stimulate monocytes, macrophages, and synovial fibroblasts, leading them to secrete a large number of cytokines. Interleukin-10 (IL-10) as a cytokine has both immunoregulatory and anti-inflammatory impacts in RA by inhibiting the synthesis of proinflammatory cytokines [10]. In an animal model of RA, an exotic IL-10 has been shown to have an inhibitory effect on the onset and potency of RA [11, 12]. Some studies proposed that expression of *IL-10* gene is controlled by transcriptional regulatory region in the promoter of *IL-10* gene [9]. −1087G > A (rs1800896), −824C > T (rs1800871), and −597C > A (rs1800872) are such important Single-Nucleotide Polymorphisms in IL-10 promoter [13]. The Rs1800872 SNP is located in the STAT3 binding site, which probably alters STAT3 binding that subsequently affects IL-10 expression [14].

The association of SNPs in the promoter region of the human *IL-10* gene and RA susceptibility has been controversial. In their study, McKay *et al*. concluded that there was no association between interleukin 10 alleles and RA [15]. While the results of Ying *et al*.'s study in 2011 showed that there is an association between IL-10-592 polymorphism and RA, and IL-10-592 is associated with susceptibility of RA [16]. Genetic variants in certain ethnic groups may overproduce or underproduce IL-10 and have potential effects on disease [17, 18].

Our research question was whether rs1800872 in the promoter region of the human *IL-10* gene might affect susceptibility to RA. Therefore, the aim of this study was to investigate the association between IL-10 rs1800872 polymorphism in the promoter region of human *IL-10* gene and susceptibility to rheumatoid arthritis in the patients in southwest of Iran.

Materials and Methods

The present study is a case-control study that was conducted in 2019 among patients with and without rheumatoid arthritis referred to the Mofateh clinic in Yasuj, from southwest of Iran. Based on polymorphism frequency and statistical indexes including population size and approximate number of RA patients in the studied population, the sample size was estimated to be 129 participants. Both case and control groups were selected using purposive sampling and were matched in terms of age, gender and ethnicity. Inclusion criteria were at least 18 years of age and being naive for biological treatment. All RA patients met the diagnostic criteria established by the American College of Rheumatology (ACR; revised 2010) [19]. The presence of bone erosion in hand and foot radiographs was assessed by the simple erosion narrowing score method by an experienced reader, who was blinded to clinical, biological and genetic data. Participants who had autoimmune diseases beside RA were excluded from the study. Volunteers with negative RA test results and no symptoms or personal and family history of RA or other immune and autoimmune disorders were selected as the control group. Therefore, 64 RA patients as case group and 65 healthy subjects as control group participated in the study.

The participants of both groups were then tested for the IL-10 rs1800872 polymorphism to determine whether this polymorphism could be a risk factor for rheumatic disease in patients or whether there is an association between rs1800872 in the promoter region of the human *IL-10* gene and susceptibility to RA.

Demographic information was collected using a

form including age, gender, locality, tribe, family history and duration of RA.

DNA extraction: Approximately 5 ml of venous blood was collected into ethylenediaminetetraacetic acid (EDTA) anticoagulant tubes from each participant. The samples were stored at 20°C for DNA isolation. Genomic DNA was extracted from 200 µL of peripheral blood samples using kit (Genet Bio; South Korea) according to the instruction manual. The purity and concentration of all genomic DNA samples were assessed by agarose gel electrophoresis and spectroscopy at wavelengths of 260 and 280 nm, respectively, and then DNA was stored at -20°C.

Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP): The promoter region of the human *IL-10* gene containing the –597C > A was amplified PCR using forward 5-TGTGGGTTCTCATTCGCGTGT-3 and reverse 5-GAGACGGTAGGGGTCATGGTG -3 primers. PCR was performed using commercially available PCR premix (GenAll PCR PreMix, GenAll; Seoul, South Korea) according to the manufacturer's recommended protocol. Into a 0.2 ml PCR tube containing the PCR PreMix, 1 µl template DNA (about 50 ng/µl), 3 µl of each primer (1 pmol/µl) and 13 µl DNase-free water were added. The total volume for the PCR was 20 µl. PCR was performed using the following cycling conditions: 30 cycles at 95°C for 30 s, 58°C for 30 s and 72°C for 1 min. The purified PCR product was then digested with Rsa I restriction enzymes (Jena Bioscience; Seoul, South Korea) according to the manufacturer's instruction.

Statistical analysis: SPSS 26.0 software (IBM, Armonk, NY: IBM Corp) was used for statistical analysis of data. The Hardy–Weinberg equilibrium was verified for all SNPs by the chi-square test. Odds Ratios (ORs) with 95% Confidence Interval (CI) were calculated. Two-tailed P-values less than 0.05 were considered statistically significant.

Findings

A total of 129 people were studied in both case and control groups. 64 patients (54 women and 10 men) were in the case group and 65 healthy people (40 women and 25 men) were in the control group. The mean age of disease onset in the case group was 41.54±12.91 years. There was no significant difference between the case and control groups in terms of age and gender (Table 1). Also, there was a significant difference in disease distribution between men and women (p<0.001). The RFLP patterns obtained following the PCR-RFLP analysis are shown in Figure 1.

Table1) Comparison of demographic variables between case group (n=64) and control group (n=65)

Demographic variables	Control group	Case group	P-value
Gender, No.			
Male	20	10	0.067*
Female	45	54	
Age (years)			
Mean±SD	59.37±3.20	49.52±3.78	0.562**

*Chi-square test; **Student t-test

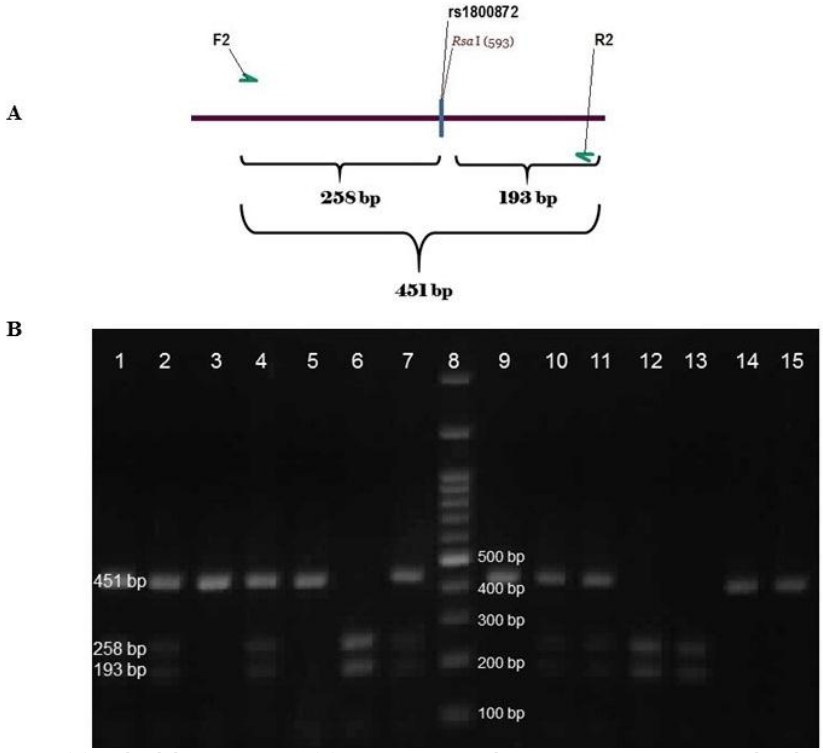

Figure 1) Schematic (A) and gel documentation (B) represent typical Restriction Fragment Length Polymorphism (RFLP) patterns following digestion with the Rsa I restriction enzyme.

(A) Amplification of the promoter region by primers results in a 451 bp band. (B) Lane 3, 5, 14 and 15 represents undigested homozygous genotype (GG), Lane 1, 2, 4, 7, 10 and 11 represents heterozygous genotype (GT), Lane 6, 12 and 13 represents homozygous genotype (TT) . Lane 8 represents the 100 bp DNA ladder.

Distribution of genotypes and alleles under different legacy models (codominant, dominant, recessive and over dominant) was evaluated in RA patients and healthy participants and Hardy– Weinberg equilibrium (HWE) was verified. The frequency of GG, GT and TT genotypes in the RA group was 46.9%, 39.1% and 14.1%, respectively, versus 66.2%, 30.8% and 3.1% in the control group. The relationship between the frequency of TT genotypes and the incidence of RA was significant (OR=6.45; 95% CI= 1.30-32.00; p=0.023), and the distribution of the T allele showed a significant relationship with RA (33.6% in patients versus 18.5% in controls; p=0.006). In other words, people with TT genotype of rs1800872 polymorphism were 6.45 times more likely to suffer from rheumatism than people without the polymorphism. Also, the probability of rheumatism in people with T allele of rs1800872 polymorphism was 3.97 times higher than people without polymorphism (Table 2).

Table2) Distribution of genotypes and alleles of rs1800872 in case group (n=64) and control group (n=65), and their relationship with the incidence of RA

Variables	Case group, No. (%)	Control group, No. (%)	OR (95% CI)	P-value*
Genotypes				
GG	30 (46.9)	43 (66.2)	1.00 (Reference)	-
GT	25 (39.1)	20 (30.8)	1.7917 (0.846 - 3.7946)	0.128
TT	9 (14.1)	2 (3.1)	6.45(1.30 - 32.00)	0.023
Alleles				
G	85 (66.4)	106 (81.5)	1.00 (Reference)	-
T	43 (33.6)	24(18.5)	2.23 (1.26 - 3.97)	0.006

*Logistic regression test

Discussion

This study is the first research in the southwestern population of Iran that reveals IL-10 rs1800872 polymorphism in rheumatoid arthritis patients. Rheumatoid Arthritis (RA) is an important progressive autoimmune disease with multifactorial etiology. Genetic and environmental factors can be considered in the etiology and pathogenesis of RA [20, 21].

Considering the disagreements in the results of studies in this regard in different areas and ethnic groups and the absence of dependable studies in Iran, We tried to investigate the association of genetic variants of IL-10 rs1800872 with susceptibility to rheumatoid arthritis compared to healthy individuals in southwestern Iranian population. In this study, we showed that SNP rs1800872 with minor T allele increases the risk of rheumatoid arthritis in the population of southwestern Iran (OR= 2.23; 95% CI= 1.26–3.97; p=0.006).

Some studies reported the association between polymorphism in this gene and various autoimmune diseases. Some risk alleles have been highlighted in a number of genetic loci. RA susceptibility genes include genetic changes in immunoregulatory cytokines [22].

One of these polymorphisms is rs2075876, which is an intronic modification. Bioinformatics evaluations reveal that a large number of nucleotide sequences around this polymorphism show high protective.

Hee *et al*. showed the association of *IL-10* gene promoter SNPs with RA in a Malaysian population and displayed a significant relationship between -1082 (G/A) alleles and genotypes with increased disease risk [13]. Also, Martínez *et al*. showed a significant correlation between -1082 (G/A) genetic variants and RA susceptibility in Spain [23]. Due to the lack of study on the relationship between IL-10 rs1800872 polymorphism and susceptibility to rheumatoid arthritis patients, comparison with other studies is not possible, but the result of our study was similar to another study that evaluated the association between -1082 (G/A) alleles and genotypes with increased disease risk. An additional report showed that SNP rs878081 in the autoimmunity regulatory gene was significantly associated with the risk of RA in the Caucasian population [23].

It has been shown that low level of IL-10 play a pivotal role in the formation and progression of autoimmune disease [24]. On the other hand, Opdal showed that genetic factors account for 50 to 75% of IL-10 production, respectively [25]. Since our study showed that the TT genotype of the rs1800872 polymorphism is associated with RA susceptibility, SNPs in the promoter region of IL-10 may be considered as genetic factors in RA susceptibility. However, the contribution of this polymorphism to RA susceptibility has been controversial so far. The same discrepancy was also observed between IL-10 promoter SNPs and its production [13, 20, 26].

In their study, Alvarez-Rodriguez *et al*. reported that there was no association between IL-10 variants and susceptibility or clinical Phenotype of Polymyalgia Rheumatica (PMR) in Spanish patients [27]. Some researchers reported that IL-10 production was significantly lower in the ATA/ATA genotype in Lipopolysaccharide (LPS)-stimulated cultures [28].

In the present study, there was a significant difference in disease distribution between men and women (p<0.001). The healthy control group was similar to RA patients in terms of gender (p=0.067) and age (p=0.562). Different populations have different profile of genetic variation, thus a specific SNP might be an important genetic susceptibility factor for a specific multifactorial disease in one population but not in another.

Cicacci *et al*. investigated the association of rs1800872 and RA in 192 RA patients compared with 278 HC in an Italian population. Their findings indicated that the rs1800872 polymorphism has a protective effect on RA [26]. In the study by Hee *et al*.,

the T allele of rs1800872 was associated with RA in a Malaysian population, however none of the genotypes of this polymorphism were associated with RA [13].

Altogether, research on the effect of rs1800872 polymorphism on RA has shown that this polymorphism probably influences RA susceptibility in Asian population; however, our literature search did not reveal any studies in Middle Eastern populations. We observed a significant association between 1800872 and RA susceptibility in Yasuj population of Iran. TT genotype and T alleles of this SNP were significantly associated with RA.

Identifying the TT genotype of the rs1800872 polymorphism in people, especially relatives of patients with rheumatoid arthritis, can help predict the occurrence of the disease, and by teaching preventive principles and knowing the predisposing factors in the occurrence of rheumatism, it is possible to help prevent the occurrence of rheumatism in these people. Also, if the results are confirmed in larger studies, the screening of this gene can be considered necessary in public health programs. There are probably some possible limitations in the statistical validity of our results, such as the small sample size. Additional studies with a larger sample size or with a prospective method are recommended.

Although current research provides evidence of genetic susceptibility to RA, many clinical trials and genetic studies are needed to reveal the role of rs1800872 polymorphism in RA pathogenesis.

Conclusion

TT genotype of rs1800872 polymorphism is associated with rheumatoid arthritis susceptibility in southwestern Iranian population and can be considered as a risk factor for rheumatism.

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Ethical Permission: The study protocol was approved by the local ethics committee of the Yasuj University of Medical Science (IR.YUMS.REC.1397.112). Written informed consent was obtained from the patients.

Conflict of Interests: We declare that we have no conflict of interest.

Authors' Contribution: Hassanzadeh S. (First author), Introduction author/Original researcher (35%); Hedayati F. (Second author), Assistant researcher/ Discussion author (10%); Hosseini E. (Third author), Assistant researcher/ Discussion author (15%); Malekzadeh J.M. (Fourth author), Assistant researcher/ Statistical analyst(15%); Masnavi E. (Fifth author), Assistant Researcher (10%); Keshtkari A. (Sixth author), Methodologist (15%)

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