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Association of Promoter Polymorphisms of Interleukin-10 and Interferon-Gamma Genes with Tuberculosis in Azeri Population of Iran

Mohammad Asgharzadeh[1], Sajjad Ghorghanlu[2], Jalil Rashedi[1], Behroz Mahdavi Poor[1], Fatemeh Khaki-Khatibi[3], Seyyed Reza Moaddab[4], Hossein Samadi-Kafil[4], and Mahya Pourostadi[5]

[1] Department of Laboratory Sciences, Faculty of Paramedical, Tabriz University of Medical Sciences, Tabriz, Iran
[2] Biotechnology Research Center, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran
[3] Department of Clinical Biochemistry, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[4] Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[5] Infectious Disease and Tropical Medicine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

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ABSTRACT

Promoter polymorphism of cytokine genes may lead to inter-individual differences in cytokine levels, therefore, polymorphisms may associate with susceptibility to infectious diseases. In this study, we investigated a possible association between interleukin-10 (IL-10) -1082A/G (rs1800896) and interferon (IFN)-gamma +874T/A (rs2430561) promoter polymorphisms and tuberculosis (TB) in the Azeri population of Iran.

IL-10 -1082G/A and IFN-gamma +874T/A single nucleotide polymorphisms (SNPs) were genotyped by amplification refractory mutation system (ARMS)-PCR in 200 healthy controls and 124 tuberculosis patients.

IL-10 -1082 A allele was more frequent in the control group than in the patient group (p=0.001, odds ratio [OR]=2.183). On the other hand, the AA genotype was significantly more frequent in the control group (p=0.0001). The frequency of IFN-gamma +874 T allele was significantly higher in the controls (p=0.013, OR=1.56). There was no significant association between IFN-gamma +874 T/A genotypes and susceptibility to tuberculosis (p=0.078), but TT genotype was more frequent in the control group.

Our findings suggest that interleukin-10 -1082G/A polymorphism may play an important role in susceptibility to tuberculosis in our population. On the other hand, the +874T allele, which has been suggested to be associated with high IFN-gamma levels, was significantly higher in the controls and TT genotype was also more frequent in the control group. Thus, +874 T allele may be associated with resistance to tuberculosis in this Azeri population of Iran.

Keywords*:* Association; Interferon-gamma; Interleukin-10; Polymorphism; Susceptibility; Tuberculosis

Corresponding Author: Sajjad Ghorghanlu, MSc;
Mailing address: Biotechnology Research Center, Faculty of Advanced Medical Sciences, University of Medical Sciences, Tabriz, Iran. Tel: (+98 41) 3335 7126, Fax: (+98 41) 3337 1971, E-mail: Ghorghanlu@yahoo.com

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INTRODUCTION

Tuberculosis (TB) is considered one of the important causes of mortality and morbidity in humans. According to World Health Organization (WHO) reports in 2012, it is estimated that tuberculosis is responsible for 1.5 million deaths per year.[1] Approximately one-third of the world's population is infected with *Mycobacterium tuberculosis*, but only 10% of infected individuals develop active clinical TB.[2] Furthermore, several twin studies have indicated a significantly higher concordance rate among monozygotic twins (identical genetically) than dizygotic twins for the development of tuberculosis.[3,4] Therefore, all these findings indicate that host genetic factors, in addition to environmental factors, play an important role in the development of TB disease.

IL-10 is an anti-inflammatory and immune-regulatory cytokine, which induces T cell anergy by down-regulation of co-stimulatory molecule B7-1/B7-2 expression, major histocompatibility (MHC) class II expression and proinflammatory cytokines like interferon-gamma (IFN-γ), Tumor necrosis factor (TNF)-alpha, and interleukin (IL)-12 and chemokine in activated macrophages.[5,6] One of the most important SNPs in the promoter region of IL-10 gene is -1082A⁄G (rs1800896) polymorphism that may have an effect on the transcriptional binding site; thus, this SNP may alter the rate of gene expression.[7] Indeed, the presence of G allele at position -1082 correlates with higher IL-10 protein production in vitro[8] and in the pleural fluid of active TB patient.[9] These studies suggest that -1082 G allele carrier individuals are likely to have a high risk for the progression of latent TB to active TB because the -1082 G allele may suppress the immune response by increasing the expression of IL-10.

IFN-gamma is an important T helper type-1 (Th1) cytokine that is secreted by natural killer (NK) cells and T cells; its production plays a critical role in macrophage activation for controlling *Mycobacterium tuberculosis* infection.[10,11] IL-12 promotes IFN-gamma production by NK cells and enhances antigen specific Th1 cells.[12] The IL-12/IFN-gamma axis influences macrophage activation by T cells, generation of T-helper cells type 1 lymphocytes, and further bacterial clearance.[13] There is a single nucleotide polymorphism at the +874T/A (rs2430561) position in the first intron of human IFN-gamma gene. The +874 T allele is absolutely linked to the 12-CA-repeat microsatellite while the +874 A allele is adjacent to a non-12 CA repeats.[14] IFN-gamma +874T/A SNP is located within a binding site for NFκB (the transcription factor that can induce the expression of interferon-gamma) and NFκB specifically binds to the DNA sequence containing T allele.[15] Indeed, it has been shown that the T and A alleles most likely correlate with high and low expression of IFN-gamma, respectively.[16]

Therefore, for revealing the biological significance of these SNPs in susceptibility to tuberculosis, further studies are needed to be conducted in different populations. In this study, we investigated a possible association between IL-10 -1082A⁄G and IFN-gamma +874T/A promoter polymorphisms and tuberculosis (TB) in the Azeri population of Iran.

MATERIALS AND METHODS

Study Population

124 tuberculosis patients (71 males and 53 females) who were confirmed by conventional bacteriological methods (smear/culture positive) and 200 healthy subjects (183 males and 17 females) as controls participated in this study. The control subjects were selected from Azeri population; all the TB patients were recruited for this study from Sina Hospital, Tuberculosis and Lung Disease Research Center and Imam Reza Hospital from 2011 to 2014. The inclusion criteria for the control group were the absence of pulmonary disease, autoimmune diseases and family history of TB disease and, for the patients were the absence of HIV infection and a history of immunosuppressive conditions. All the patients and healthy individuals belong to the same geographical area (East Azerbaijan Province, Iran) and ethnic background. Written informed consents were obtained from all individuals. The study was approved by the Ethical Committee of the Tabriz University of Medical Sciences, Iran (project number 9253).

Preparation of Genomic DNA from Peripheral Blood Samples

Preparation of genomic DNA described by Asgharzadeh et al.[17] About 300 µl of buffy-coat was suspended in 150 µl of TE buffer (10 mM Tris-HCL, 1 mM EDTA, pH 8.0) by shaking. Then 60 µl of 10% sodium dodecyl sulfate (SDS) and 10 µl of 20 mg/mL proteinase K were added. The solution was mixed thoroughly and incubated overnight at 60 °C. Thereafter 100 µl of 5 M NaCl was added and vortexed thoroughly. Next, 80 µl of the warmed (65°C)

CTAB/NaCl (10%CTAB+0.7M NaCl) solution was added and vigorously mixed and incubated for 10 min at 65°C. Afterwards, about 700 µl of chloroform/ isoamyl alcohol (24:1) was added, mixed thoroughly for 20 s, and centrifuged at 11,000×g for 8 min. The supernatant was transferred to a fresh microtube and 0.6 volume of 2-propanol was added and incubated for 30 min at -20 °C. Then the suspension was centrifuged at 12,000 × g for 15 min. For washing the DNA pellet, 1 mL of cold 70% ethanol was added, gently vortexed and centrifuged at 12,000×g for 5 min. The supernatant was discarded and the microtube was placed at room temperature for approximately 15 min for drying of the DNA pellet. Finally, the DNA pellet was resuspended in 50 µl of distilled water and stored at -20 °C.

Cytokine Genotyping

IL-10 -1082G/A and IFN-gamma +874T/A promoter polymorphisms were genotyped using ARMS-PCR method as previously described.[15,18] The primer sequences used in the present study were: IL-10 -1082 G/A SNP, (common primer, antisense) 5′-CAGTGCCAACTGAGAATTTGG-3′, (primer G, allele1, sense) 5′-CTACTAAGGCTTCTTTGGGAG-3′, (primer A, allele2, sense) 5′-ACTACTAAGGCTTCTTTGGGAA-3′; IFN-gamma +874T/A SNP, 5′-TCA ACA AAG CTG ATA CTC CA-3′ (generic primer, antisense), 5′-TTC TTA CAA CAC AAA ATC AAA TCT-3′ (primer T, allele1, sense), and 5′-TTC TTA CAA CAC AAA ATC AAA TCA-3′ (primer A, allele2, sense). The PCR reactions were performed using a Mastercycler gradient thermal cycler (Eppendorf-Germany).

Purified DNA (about 50 ng) was added to the PCR reaction mixture (20µl) containing 100µM of each dNTP, 1.5 mM MgCl2, 50mM KCl, 20 mM Tris-HCl (PH=8.4), 0.5µM of each primer, and 1.25 units of recombinant Taq DNA polymerase (CinnaGen, Iran). The PCR condition was as follows: initial denaturation at 94°C for 7 min and 35 cycles at 94°C for 45s, at 59°C for 45s, at 72°C for 50s, and a final extension at 72°C for 7 min. The PCR products were electrophoresed in 1.2% agarose gel and, then, stained with 0.5µg/ml ethidium bromide and visualized under ultraviolet. The amplicon size was determined by comparison with 100bp DNA ladder plus size marker (Fermentas, Lithuania). PCR product size was 259bp for IL-10 and 264 bp for IFN-gamma.

Statistical Analysis

Statistical analysis was performed using SPSS software for Windows, version 22. Mann–Whitney test was conducted to calculate the statistically significant difference of age between the study populations and Chi-square test was used for gender and smoking status differences between the patients and controls. The allele frequencies in both patient and control groups were calculated by direct counting then, the expected genotypes were obtained. The expected genotype and observed genotype in the patient and control groups were tested for Hardy-Weinberg equilibrium by Chi-square test. For the analysis of the association between genotype and tuberculosis and for the calculation of ORs and 95% confidence intervals (CIs), logistic regression analysis was used to adjust for confounding factors (age, sex, and smoking status). The allele distribution of IFN-gamma and IL-10 polymorphisms were compared between the patients and controls by Pearson Chi-Square probability. The *p*-value which remained less than 0.05 after correction for the number of variables (P corrected=Number of variables×*p*-value) was considered statistically significant (Bonferroni correction).

RESULTS

IL-10 -1082 Genotype and Allele Frequencies

The demographic characteristics of the TB patients and controls are shown in Table 1. IL-10 -1082 A allele frequency was more frequent in the control group than in the patient group (p=0.001, OR=2.183) and -1082 G allele was also significantly higher in the patient group (55.7% vs. 36.5%). Moreover, the G allele was associated with 2.183-fold increased risk of tuberculosis (Table 2). The AA genotype was significantly more frequent in the control group (p=0.000). Therefore, AA genotype is considered as a protective factor against tuberculosis. On the other hand, the AG genotype was more frequent in the patient group than in the control group (75.8% vs. 43%). Moreover, the distribution of the GG genotype was not significantly different between the control and patient groups (controls=15%, patients=17.7%) (Table 2).

The genotype frequencies of IL-10 -1082G/A polymorphism was in Hardy–Weinberg equilibrium in the control group (p=0.785, p>0.05), but was not in the patient group (p=0.015).

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Table 1. Demographic Characteristics of the study population

Demographic features	Healthy controls n (%)	TB Patients n (%)	*p*
Total subjects	200	124	
Male	183(91.5)	71(57.3)	0.000[a]
Female	17(8.5)	53(42.7)	
Age (years)			
Mean (SD), y	32.12(7.19)	34.34(12.69)	0.374[b]
TB types			
Pulmonary	-	116(93.5)	
Extrapulmonary	-	8(6.5)	
Smoking			
Smoking	31(15.5)	17(13.7)	0.659[a]
Nonsmoking	169(84.5)	107(86.3)	
Family history of TB	-	19(15.3)	

[a] chi-square test. [b] Mann-Whitney test.

Table 2. Genotype and allele frequencies of the IL-10 -1082G/A and IFN-γ +874T/A polymorphisms in TB patients and controls.

Gene	Genotype	Controls N (%)	TB Patients N (%)	OR	95%CI	*p*-value	Pc
IL-10	AA	84 (42%)	8 (6.5%)	7.804	2.923-20.834	**0.000**	**0.000**
	AG	86 (43%)	94 (75.8%)	0.656	0.331-1.300	0.227	NS
	GG (referent)	30 (15%)	22 (17.7%)	1	referent	-	-
	AA[b]	84 (42%)	8 (6.5%)	0.093	0.041-0.214	**0.000**	**0.000**
	AG+GG	116 (58%)	116 (93.5%)				
IFN-γ	AA	91 (45.5%)	72 (58%)	0.462	0.195–1.092	0.078	NS
	AT	81 (40.5%)	42 (33.87%)	0.703	0.289–1.714	0.439	NS
	TT (referent)	28 (14%)	10 (8.07%)	1	referent	-	-
	AA	91 (45.5%)	72 (58%)	1.649	1.002-2.714	0.049	NS
	AT+TT	109 (54.5%)	52 (41.9%)				
	Total	200	124				
	Allele						
IL-10	A	254 (63.5%)	110 (44.3%)	2.183	1.58-3.014	0.001	0.002
	G	146 (36.5%)	138 (55.7%)				
IFN-γ	A	263 (65.75%)	186 (75%)	1.56	1.096–2.23	0.013	0.026
	T	137 (34.25%)	62 (25%)				
	Total	400	248				

N: number of subjects; OR: odds ratio; CI: confidence intervals; Pc: corrected *p*-values (*p*-value × number of genotypes/alleles); NS: non-significant

Genotype frequencies difference in TB patients versus controls were calculated by logistic regression analysis and adjusted by age, gender and smoking status of the study population. Alleles frequencies in TB patients versus controls were calculated by Chi- square test (2×2 comparison).

IFN-gamma +874 Genotype and Allele Frequencies

The frequency of +874 T allele was significantly higher in the controls than in the patients (p=0.013, OR=1.56). Frequencies of +874 A and T alleles were higher (75%) and lower (25%) among the TB patients, respectively. Also, the A allele was associated with 1.56-fold increased susceptibility to TB (Table 2). On the other hand, although the TT genotype was more frequent in the control group than in the patient group and the AA genotype was overrepresented in the

control subjects, there was no statistically significant difference in the frequency of IFN-gamma +874T/A genotypes between the controls and TB patients (p=0.078).

The genotype frequencies of IFN-gamma +874A/T polymorphism were in Hardy–Weinberg equilibrium in both patient and control groups (p=0.768, p=0.576 respectively>0.05).

DISCUSSION

Genetic factors can influence the efficacy of drugs, vaccine responses, and outcomes of infectious disease. Therefore, research on genetic factors leads to new strategies for control and prevention of infectious diseases.[19]

The present study showed a significant association between IL-10 -1082 G allele (p=0.001, OR=2.183) and susceptibility to tuberculosis. Moreover, IL-10 -1082 AA genotype was significantly more frequent in the control group than in the patient group (p=0.000). It was found that -1082 A allele leads to an increase resistance to tuberculosis. Liang et al. showed that the AA genotype of IL-10 -1082G/A polymorphism, compared with AG/GG genotypes, was associated with low levels of IL-10 in pleural fluid.[9] Yılmaz et al. indicated that, when -1082 A allele carriers were stimulated with Staphylococcus aureus Cowan strain I (SAC) or purified protein derivative (PPD), they produced low-levels of IL-10 compared with non-A allele carriers.[20] It was also shown that IL-10 concentrations were significantly higher in the pleural fluid than in serum and plays an important role in down-regulation of the local immune response.[21] Thus, the AA genotype may participate in resistance to *Mycobacterium tuberculosis* infection by down regulation of IL-10. IL-10 -1082 G/A polymorphism may also influence the Th1/Th2 balance and, thus, increases the risk of tuberculosis.[22] Our result was consistent with the result of previous studies in the Turkish,[22] Pakistani[23] and Indian populations.[7] On the other hand, no significant association has been found between IL-10 -1082 promoter polymorphism and susceptibility to TB in the Korean population[24] and in another ethnic group of Iran.[25] Moreover, a recent meta-analysis showed that IL-10 -1082G/A polymorphism was significantly associated with risk of tuberculosis in Europeans and Americans, but no association was found in Asians and Africans.[26] The frequency of the high-risk -1082GG genotype in our healthy population (15%) was significantly different from the populations of Pakistan (3.03%),[23] Korea (1.1%),[24] and another ethnic group of Iran (5.7%).[25] On the other hand, our result was similar to that of the Indian population (16%).[7]

In this study, we indicated that the frequency of +874 A allele was significantly higher in TB patients than in the healthy individuals (p=0.013, OR=1.56). Our results indicate that having an A allele at the +874 position of the IFN- gamma gene could increase 1.56-fold risk of developing active TB, whereas T allele was associated with resistance to TB. Indeed, +874 A allele is associated with low expression of IFN-gamma gene; since IFN-gamma is essential for macrophage activation,[27] therefore, low levels of IFN-gamma resulted in impaired activation of macrophages that may be the cause of TB development. We did not find significant association between IFN-gamma+874 genotype and susceptibility to tuberculosis (p=0.078). There was a contradiction in our results between the association of the allele and genotype with TB: the alleles were associated with susceptibility to TB, but genotypes were not associated, which may occur due to the small sample size.

Our genotype analysis results were not consistent with those of studies that have shown an association between IFN-gamma +874T/A polymorphism and susceptibility to tuberculosis.[18,28-30] However, our result was consistent with some previous studies.[31,32] The allele analysis result of this study was consistent with some previous studies,[14,29,30] but was not in agreement with several others.[31,32] In a recent meta-analysis, Tian et al.[33] represented that IFN-gamma +874A allele carriers may be associated with susceptibility to tuberculosis in Asians, but not in Caucasians.

The frequency of the low producer +874 A/A genotype[27] in our healthy population (45.5%) was similar to that of Hong Kong (45.7%)[14] and Brazilian populations (41%),[28] but was significantly different from that of Egyptian (5.1%) (18), Tunisian (28%),[29] and other Iranian ethnic group (13.2%).[30]

These conflicting results in the association of IL-10 -1082G/A and IFN-gamma +874T/A polymorphisms with TB in different studies may be related to ethnic-specific genetic variations, study selection criteria, study sample size, distal promoter elements and existing linkage disequilibrium with other genes in different populations.

In summary, the present data suggest the possible role of interleukin-10 -1082 polymorphism in TB susceptibility in our population. Indeed, the AA genotype may have a protective role against tuberculosis. On the other hand, the +874T allele, which has been suggested to be associated with high IFN-gamma levels, was significantly higher in the controls and TT genotype was also more frequent in the controls. Thus, the +874T allele may be associated with resistance to tuberculosis in a sample of Azeri population of Iran. Further investigations on these SNPs with large sample size are needed to clarify the roles of these cytokines in the progression of tuberculosis.

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