Research Article

Association Between IL12A rs568408, IL12B rs3212227 and IL-12 Receptor rs383483 Polymorphisms and Risk of Pulmonary Tuberculosis

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Abstract

Background: Interleukine-12 (IL-12) induced interferon- γ (IFN- γ) production and development of T cells into Th1 cells, which has a critical role in immunity to intracellular pathogens.

Objectives: The current study aimed to evaluate the possible association between IL12A rs568408, IL12B rs3212227 as well as IL-12 receptor (IL-12R) rs383483 polymorphisms and pulmonary tuberculosis (PTB).

Methods: This case-control study was conducted on 174 confirmed PTB patients and 177 healthy subjects in a sample of southeast Iranian population. Genotyping was performed by the tetra amplification refractory mutation system- polymerase chain reaction (T-ARMS-PCR) method.

Results: The frequencies of GG, GA and AA genotypes of IL12A rs568408 variant in cases and controls were 58.9%, 38.5%, 1.7% and 61.6%, 37.3%, 1.1%, respectively. Regarding rs3212227 variant, the frequencies of AA, AC and CC genotypes in cases and controls were 47.1%, 54.4%, 7.5% and 50.8%, 43.5%, 5.7%, respectively. Concerning IL12R rs383483 polymorphism, the frequencies of AA, AG and GG in cases and controls were 39.1%, 31.4%, 29.5% and 40.2%, 25.3%, 34.5%, respectively. There was no significant difference in allele and genotype frequency of IL12A rs568408, IL12B rs3212227 and IL-12R rs383483 polymorphisms between patients with PTB and control groups (P > 0.05).

Conclusions: The findings of the current study show that neither IL12A rs568408 and IL12B rs3212227 nor IL-12R rs383483 polymorphisms are associated with the risk of PTB in our population. Further studies with larger sample sizes and various ethnicities are needed to certify our findings.

Keywords: IL-12, IL-12R, Polymorphism, Pulmonary Tuberculosis

1. Background

Pulmonary tuberculosis (TB) caused by Mycobacterium tuberculosis (MTB), is still a public health concern, and leading cause of morbidity and mortality throughout the world, especially in Africa and Asia (1). Based on the world health organization report, the incidence and mortality rates from tuberculosis were 9.6 million new cases and 1.5 million deaths in 2014 (1). Approximately one third of the world's population has been latently infected with TB, while 10% of the infected individuals developed active TB, which indicates that host genetic factors play a critical role in developing clinical symptom of TB (2-4). Several cytokines participate in control of MTB infection. Interleukine-12 (IL-12) is an important immunoregulatory cytokine that is naturally produced by phagocytic cells such as dendritic cells, macrophages and neutrophils in response to antigenic stimulation (5). It induced IFN-

 γ production from T cells and has an important role in macrophage activation for controlling mycobacterium infection (6). Interleukine-12 takes part in differentiation and development of T cells into Th1 cells and forms a link between innate and acquired immune responses (5). Interleukine-12 made of two subunit, p35 (light chain) and p40 (heavy chain), that is encodes by two separate genes IL-12A and IL-12B, respectively. The IL-12A gene is located on chromosome 3 (3p12), whereas IL12B gene is located on chromosome 5 (5q31) (7). IL-12R is a heterodimeric receptor expressed on NK cells and activated Th1 cells. It consists of IL-12R- β 1 and beta IL-12R- β 2 subunits. These subunits are responsible for signaling through the JAK/STAT pathway (8). Reduced expression of IL12R β can cause immunodeficiency of MTB patients (9). Several studies have shown the association among IL-12A, IL12-B and its receptor polymorphism with the risk of TB but the results were

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controversial (10-13). Therefore, the present case-control study was designed to investigate the possible association between IL12A rs568408, IL12B rs3212227 and IL-12R rs383483 polymorphisms and PTB in a sample of southeast Iranian population.

2. Methods

This case-control study was conducted on 174 patients with PTB (newly diagnosed PTB cases and underwent treatment subjects for PTB) who referred to university-affiliated hospital center for TB (Bou-Ali hospital, Zahedan, Iran) from February to October 2012. The study was approved by the local ethics committee of Zahedan University of Medical Sciences (Ir.zaums.Rec.1390.1240) and written informed consent was taken from all subjects participated in the study according to guidelines from the ethical committee. Pulmonary tuberculosis was confirmed by clinical symptoms, radiological evidence and positive sputum smear for acid-fast bacilli (14-16). The control group consisted of 177 healthy subjects with no history of TB or pulmonary disease and had no inflammatory disease or a history of the chronic infectious disease. All patients with PTB and healthy individuals were from the same geographical origin (Zahedan, southeast Iran). Blood samples were collected in tubes containing EDTA and genomic DNA was extracted from whole blood using the salting out method as described previously (17). Genotyping of polymorphisms was performed by the tetra amplification refractory mutation system-polymerase chain reaction (T-ARMS-PCR) method, which is a simple and reliable method for recognition of single nucleotide polymorphism (SNP) (18, 19). For detection of each polymorphism four primers, two external primers (forward outer, reverse outer) and two allele-specific internal primers were used. The primers were used for T-ARMS-PCR are shown in Table 1. For genotyping of each variant we used two external primers (forward outer and reverse outer) and two inner primers (forward inner and reverse inner). The amplification was performed using commercially available PCR premix (AccuPower PCR PreMix, BIONEER, Daejeon, South Korea). Polymerase chain reactions (PCRs) were performed in 0.2 mL PCR tube AccuPower PCR PreMix containing 1 μ L template DNA (~ 100 ng/ μ L), 1 μ L of each primer (10 μ M) and 15 μ L DNase-free water. The amplification program was as follows: 94°C for 5 minutes, 30 cycles of 94°C for 30 seconds. 64°C for 30 seconds and 72°C for 30 seconds, with a final 5-min extension at 72°C. The PCR products were monitored by electrophoresis on a 2% agarose gel containing 0.5 μ g/mL ethidium bromide.

2.1. Statistical Analysis

Data were analyzed using the statistical package SPSS 20 software (SPSS for Windows, SPSS Inc., Illinois, USA) and the level of significance was set to a P value of < 0.05. Differences between genotype distribution and allele frequency were analyzed using the Fisher's exact test and association between polymorphisms and risk of tuberculosis was estimated by calculation of odds ratio (OR) and 95% confidence intervals (95% CI) from logistic regression analysis.

3. Results

The study groups consisted of 174 PTB patients (58 males and 98 females) and 177 control subjects (67 males and 87 females). Mean age of the PTB patients and control group were 50.17 \pm 20.17 and 46.88 \pm 15.45, respectively. There was no significant difference between the PTB patient and healthy individuals regarding sex and age (P > 0.050). The frequency distribution of IL12A rs568408 genotypes in PTB patients and normal subjects is shown in Table 2. There was no significant difference between the case and control groups regarding IL12A rs568408 polymorphism $(\chi^2 = 0.299, P = 0.861)$. The IL12A rs568408 variant was not a risk factor for susceptibility to PTB in codominant, dominant and recessive tested inheritance models (Table 2). Moreover, the allele frequency of IL12A rs568408 was not different between the two groups (OR = 1.07, 95% CI = 0.74 -1.55, P = 0.70). As shown in Table 3, there was no significant difference between the case and control groups regarding IL12B rs3212227 ($\chi^2 = 0.763$, P = 0.682). The IL12B rs3212227 polymorphism was not associated with PTB in any inheritance models tested (codominant, dominant and recessive). In addition, the rs3212227 C allele was not associated with PTB (OR = 1.14, 95% CI = 0.82 - 1.58, P = 0.453).

The analysis of the PTB patients and healthy controls revealed no statistically significant difference between the groups concerning the IL-12R rs383483 polymorphism (χ^2 = 1.627, P = 0.443). The results of the current study showed that the IL-12R rs383483 polymorphism was not a risk factor for PTB in codominant, dominant and recessive tested inheritance models (Table 4).

4. Discussion

Interleukine-12 is an immunoregulatory cytokine, which linked innate and acquired immune responses to mycobacterium through induction of IFN- γ production. In the current study, we investigated the impact of IL12A rs568408, IL12B rs3212227 and IL-12R rs383483 polymorphisms on PTB risk in a sample of Iranian population who were living in southeast of Iran. We found no association

Primer	Sequence (5'-> 3')	Ampelicon Size, bp		
IL12A rs568408		566		
Forward outer	AATTTTGGAATACCATGTAAGTCATGCT			
Reverse outer	AGTTAGCTCAGATGCTTTCATGATTACC			
Forward inner (Aallele)	GAAGGATGGGACTATTACATCCACCTA	271		
Reverse inner (G allele)	AAATGTCAAAAATACTTGATCAGAGGTCTC	352		
IL12B rs3212227		304		
Forward outer	ATTAAGCAAAATGTTTAAAGACACAACG			
Reverse outer	GATGGATCAGGTCATAAGAGTATGAAAAC			
Forward inner (C allele)	AATGATATCTTTGCTGTATTTGTATAGCTC	217		
Reverse inner (A allele)	GATGGATCAGGTCATAAGAGTATGAAAAC	143		
IL-12Receptor rs383483		245		
Forward outer	ATGGGAAGGGGTATGGAGCACT			
Reverse outer	AGCTCCTCTCACTGGTCCCCTT			
Forward inner (A allele)	AATGCGTAACCCTTGTCCATCG	117		
Reverse inner (G allele)	TCCAAGTCTTTTTATTGGGTGCAAAT	175		

Table 1. Primer Sequence for Detection of IL12A G/A rs568408, IL12B A/C rs3212227 and IL-12 Receptor A/G rs383483 Gene Polymorphisms

Table 2. The Genotypes and Allele Distribution of the IL12A G/A rs568408 Polymorphism in Pulmonary Tuberculosis Patients and Control Groups^a

Polymorphis	m Patients	Normal	OR (95% CI)	P Value	OR (95% CI)	P Value
Codominant						
GG	104 (59.8)	109 (61.6)	1.00		1.00	
GA	67 (38.5)	66 (37.3)	1.06 (0.69 - 1.64)	0.78	1.08 (0.70 - 1.69)	0.72
AA	3 (1.7)	2 (1.1)	1.57 (0.26 - 9.60)	0.62	1.48 (0.24 - 9.17)	0.67
Dominant						0.68
GG	104 (59.8)	109 (61.6)	1.00		1.00	
GA+	+ AA 70 (40.2)	68 (38.4)	1.08 (0.70 - 1.66)	0.73	1.09 (0.71 - 1.70)	
Recessive						0.70
GG -	+ GA 171 (98.3)	175 (65.5)	1.00		1.00	
AA	3 (1.7)	2 (1.1)	1.53 (0.25 - 9.30)	0.64	1.43 (0.23 - 8.81)	
Alleles						
G	275 (79)	284 (80.2)	1.00			
А	73 (21)	70 (19.8)	1.07 (0.74 - 1.55)	0.70		

^a Values are expressed as No. (%).

between the IL12A rs568408, IL12B rs3212227 as well as IL-12R rs383483 polymorphisms and the risk of PTB in our population. In contrast to our findings, Morris et al. (20) revealed an association between IL12B rs3212227 and PTB risk in Guinea-Bissau and African-Americans population. Morahan et al. (21) showed that the distribution of 3' UTR genotype of IL12B gene was different between the TB patients and control groups, besides they demonstrated a positive correlation between the expression of IL-12 and this polymorphism. They suggested that this polymorphism can cause increased IL-12 expression. Wang et al.

(22) detected that genetic polymorphism of rs2243115 in IL12A was associated with a significantly decreased risk of TB in a population of China while they found no association between two other SNPs rs568408 and rs3212227 of IL12 and the risk of TB. In agreement with our study, Selvaraj et al. (23) showed no significant difference in IL-12B 1188 A/C (rs3212227) between the PTB patients and normal healthy subjects. However, they found that the expression of IL-12B varies with different genotypes in both cases and controls. They demonstrated that IL-12B levels decreased in normal subjects with AA genotype,

Polymorphism	Patients	Normal	OR (95% CI)	P Value	OR (95% CI)	P Value
Codominant						
AA	82 (47.1)	90 (50.8)	1.00		1.00	
AC	79 (45.4)	77 (43.5)	1.13 (0.73 - 1.73)	0.592	0.94 (0.58 - 1.53)	0.816
CC	13 (7.5)	10 (5.7)	1.43 (0.59 - 3.43)	0.427	1.35 (0.55 - 3.26)	0.511
Dominant						0.99
AA	82 (47.1)	90 (50.8)	1.00		1.00	
AC + CC	92 (52.9)	87(49.2)	1.16 (0.76 - 1.76)	0.486	1.00 (0.63 - 1.58)	
Recessive						0.467
AA + AC	161 (92.5)	167 (94.3)	1.00		1.00	
CC	13 (7.5)	10 (5.7)	1.34 (0.57 - 3.16)	0.492	1.38 (0.58 - 3.26)	
Alleles						
А	243 (69.8)	257 (72.6)	1.00			
C	105 (30.2)	97 (27.4)	1.14 (0.82 - 1.58)	0.453		
3						

Table 3. The Genotypes and Allele Distribution of the IL12B A/C rs3212227 Polymorphism in Pulmonary Tuberculosis Patients and Control Groups^a

^a Values are expressed as No. (%).

Table 4. The Genotypes and Allele Distribution of the IL-12 Receptor rs383483 Polymorphism in Pulmonary Tuberculosis Patients and Control Groups^a

Polymorphism	Patients	Normal	OR (95% CI)	P Value	OR (95% CI)	P Value
Codominant						
AA	61 (39.1)	62 (40.2)	1.00		1.00	
AG	49 (31.4)	39 (25.3)	1.27 (0.73 - 2.21)	0.383	1.27 (0.73 - 2.20)	0.391
GG	46 (29.5)	53 (34.5)	0.88 (0.52 - 1.50)	0.643	0.91 (0.53 - 1.54)	0.722
Dominant						0.79
AA	61 (39.1)	62(40.2)	1.00		1.00	
AG + GG	95 (60.9)	92 (59.8)	1.05 (0.66 - 1.65)	0.83	1.06 (0.67 - 1.68)	
Recessive						0.42
AA + AG	158 (70.5)	157 (65.5)	1.00		1.00	
GG	46 (29.5)	53 (34.5)	0.80 (0.49 - 1.29)	0.35	0.82 (0.51 - 1.33)	
Alleles						
А	171 (54.8)	163 (52.9)	1.00			
G	141 (45.2)	145 (47.1)	1.07 (0.79 - 1.48)	0.687		

^aValues are expressed as No. (%).

whereas in the PTB patients with the CC genotype the IL-12B levels are increased compared to other genotypes. They deducted that this polymorphism of IL-12B gene may regulate IL-12B production and has a key role on controlling mycobacterium infection and acquired immunity to tuberculosis (23). Sahiratmadja et al. (11) in a study on Indonesian population compared 6 polymorphisms of IL-12B and IL12RB in PTB patients and controls. They reported no significant association between alleles or genotypes and susceptibility to Prabhu Anand et al. (24) and Ma et al. (25) found that allelic as well as genotypic frequencies of IL-12B 1188 A/C (rs3212227) did not differ significantly between the patients and normal subjects. Lee et al. (12) in a study on Korean population found no significant association between PTB and the IL-12R polymorphism while, Remus et al. (13) showed a positive correlation between IL-12R polymorphism and susceptibility to TB and pointed out that the polymorphism in IL12-R may affect the risk of PTB development. Interleukine-12 influence on macrophage to controlling MTB (26) and polymorphism in IL-12 and its receptors may affect its production.

One of the limitations of the current study is the relatively small sample size. In addition, we did not determine the gene environmental interactions. There is no clear reason for controversial findings among various studies. The discrepancies may be related to genetic and environmental differences between the populations investigated.

In conclusion, the findings of the present study showed that IL12A rs568408, IL12B rs3212227 and IL-12R rs383483 polymorphisms were not major genetic factors for resistance or susceptibility to PTB in a sample of southeast Iranian population. The discrepancies observed among various populations may be due to sample size and different ethnic groups. A large-scale association study with different ethnicity and functional analysis is necessary to validate our findings.

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Footnotes

Authors' Contribution: Mohsen Taheri and Mohammad Naderi and Mohammad Hashemi designed the study concepts, analyzed data and prepared the manuscript. Marzieh Abiri and Maryam Sarabandi were involved in sample and data collection, conducted experimental studies and approval of the final manuscript.

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