Monocyte chemoattractant protein-1 (-2581 A/G) and interferon gamma (+874 T/A) polymorphisms in an Iranian population with pulmonary tuberculosis

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Abstract

Background: Genetic polymorphisms are predictors of the immune response and susceptibility to certain infectious diseases, including pulmonary tuberculosis (TB). We evaluated the association of monocyte chemoattractant protein-1 (MCP1) (-2581 A/G) and interferon-gamma (IFNγ) (+874 T/A) polymorphisms with susceptibility to pulmonary TB in an Iranian population.

Methods: A total of 124 patients with pulmonary tuberculosis and 244 healthy subjects (121 related normal controls and 123 unrelated subjects) were included. The MCP1 polymorphic region (-2518 A/G) was genotyped by PCR-RFLP, while ARMS-PCR was used to amplify and detect IFNγ (+874 T/A). SNPStats and SPSS v. 20 were used for the statistical analysis of the data.

Results: The comparison of MCP1 (-2518 A/G) alleles and genotypes in TB patients and healthy subjects showed no significant association in all the constructed heredity models. No association was observed between TB patients and normal subjects in all the constructed inheritance models for IFNγ (+874 T/A) alleles and genotypes.

Conclusion: Due to the lack of association between MCP1 (-2518 A/G) and IFNγ (874 T/A) polymorphisms and susceptibility to PT in our study and the conflicting results of some previous studies, further clinical and molecular research is needed to clarify the role of the studied polymorphisms in the pathogenesis of tuberculosis.

Highlights

- MCP1 (-2518 A/G) allele frequency analysis showed that allele A was more frequent in normal subjects, and no association between MCP1 (-2518 A/G) genotypes and tuberculosis was observed in our population.

- Allele frequency analysis in IFNγ (+874 T/A) showed that the T allele was more frequent in normal subjects, and no association between IFNγ (+874 T/A) genotypes and tuberculosis was observed in our population.

Introduction

Tuberculosis (TB) is a heterogeneous disease to which humans are highly susceptible and continues to be a major cause of mortality and morbidity and a public health burden in developing countries (1, 2). Despite enormous efforts to eradicate TB, it remains a leading cause of mortality and morbidity worldwide (3). It is estimated that TB causes approximately 1.4 million deaths and 8.7 million new cases each year (4). *Mycobacterium tuberculosis* (MTB) is a slow-growing facultative pathogen and the microbial agent of TB development (5). The TB situation is worsening worldwide due to the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of MTB and the increasing incidence of human immunodeficiency virus (HIV) in TB patients (6). Although almost one-third of the world's population is infected with MTB, the number of clinical TB cases does not exceed 10%, which highlights the role of genetic and individual factors, such as the personal immune status of the patients (7-9). Therefore, we need to understand the genetic factors, including the genetic variants that predispose or alter the susceptibility of healthy individuals to TB development. Case-control and genome-wide association studies (GWAS) have shown that host genetic factors play an important role in determining inter-individual differences in susceptibility or resistance to TB (10, 11). However, the mechanisms that limit disease progression in latent infection or lead to severe active disease remain largely unknown. Several genetic loci within the immune system have been suggested as pulmonary TB predisposing genetic factors, such as polymorphisms in toll-like receptor (TLR) genes, vitamin D receptor (VDR), TNF, IL10, IL6, IL1β, and other cytokines (12). Still, little is known about the association of monocyte chemoattractant protein-1 (MCP1) (-2581 A/G) and

interferon-gamma (IFNγ) (+874 T/A) polymorphisms with the susceptibility to pulmonary tuberculosis (PT) in Iranian populations. The MCP1 is a CC chemokine located on chromosome 17q11.2, which protein interacts with chemokine C-C motif receptor 2 (CCR2) to activate and recruit monocytes and macrophages (13). It should be produced to provoke and efficient innate immune response against *M. tuberculosis*. The MCP1 (-2518 A/G) single-nucleotide polymorphism (SNP) in the promoter region of its gene is associated with the altered expression of MCP1 and has been addressed in several studies (14-16). The IFNγ is a T-helper 1 (Th1) pro-inflammatory cytokine that is located on chromosome 12q24 and is composed of four exons with many known SNPs, including IFNγ (+874 T/A) rs2430561(17). The association of IFNγ (+874 T/A) SNP has been assessed in various infectious diseases, including TB (18-20). Limited association studies have been conducted by Hashemi et al. on both polymorphic loci (21, 22) and Beiranvand et al. on IFNγ (+874 T/A) SNP (23), and their results are controversial. Therefore, we evaluated the association between IFNγ (+874 T/A) rs2430561 and MCP1 (-2518 A/G) rs1024611 polymorphisms and the susceptibility to pulmonary TB in an Iranian population.

Methods

2.1. Patients and controls

A total of 124 pulmonary TB patients were enrolled in the present case-control study from public health centers and teaching hospitals affiliated with Golestan University of Medical Sciences (Iran). A specialist who was an expert in infectious diseases confirmed the primary diagnosis and clinical features. Patients with pregnancy and chronic inflammatory disorders, including diabetes, autoimmune diseases, cancer, and heart failure, were not included. We also divided normal subjects (244 individuals) into 2 subgroups and recruited 121 related normal controls and 123 nonrelatives. This study was conducted in accordance with the Declaration of Helsinki (24) and all participants signed a written informed consent. The clinical characteristics and laboratory findings of all patients and normal subjects are listed in Table 1.

Then, 2 mL of whole blood was taken from all the individuals and transferred to the laboratory. Genomic deoxyribonucleic acid (DNA) was extracted from whole blood samples using a modified nonenzymatic salting out method (25) and immediately stored at -20 ºC until use.

2.2. Genotyping

Polymerase chain reaction (PCR), followed by the restriction fragment length polymorphism (RFLP) technique, was used to detect the MCP1 (-2518 A/G) rs1024611 polymorphism. The PCR was performed in a final volume of 25 mL

of the reaction mixture containing 50 ng of the template DNA, 2X PCR buffer (GENET BIO, Korea), 0.4 μM forward primer (5´-GCTCCGGGCCCAGTATCT-3´), 0.4 μM reverse primers (5´-ACAGGGAAGGTGAAGGGTATGA -3´), and 1.5 U of Taq polymerase (GENET BIO, Korea) as follows: initial denaturation at 95 ºC for 3 min, 35 cycles of 95 °C for 15 s, 64 °C for 20 s, 72 °C for 20 s, and final extension at 72 °C for 7 minutes. Restriction fragment length polymorphism (RFLP) digestion was performed in a 25 mL reaction mixture containing 5 U of the PVUII restriction enzyme (Fermentase, USA) incubated at 37 °C for 16-18 h, followed by 2% agarose gel electrophoresis. The undigested PCR product with 236 bp represented the A allele. The presence of the G allele was confirmed by visualizing two fragments of the digested PCR product of 182 bp and 54 bp.

The amplification-refractory mutation system (ARMS) with allele-specific primers was used to detect IFNγ (+874 T/A) rs62559044 SNP. The PCR was performed in a final volume of 25 mL of the reaction mixture containing 50 ng of the template DNA, 10X PCR buffer (GENET BIO, Korea), 2 mM MgCl2, 0.5 mM of each primer (generic: 5´-TCAACAAAGCTGATACTCCA-3´; A allele-specific: 5´-TTCTTACAACACAAAATCAAATCA-3´; T allele-specific: 5´-TTCTTACAACACAAAATCAAATCT-3´), and 1.5 U of the Taq polymerase (GENET BIO, Korea). Reactions were then incubated at 95 °C for 3 min, 10 cycles of 95 °C for 15 s, 65 °C for 50 s, 72 °C for 40 s, followed by 20 cycles of 95 °C for 20 s, 55 °C for 50 s, 72 °C for 50 s, and final extension at 72 °C for 7 minutes, on a Biorad Thermal Cycler, MJ Mini (Biorad, USA). The PCR products were run on 1.5% agarose gel electrophoresis [26]. The human growth hormone (hGH) gene with the following primers (forward: 5´-TTCCCAACCATTCCCTTA-3´; reverse: 5´-GGATTTCTGTTGTGTTTC-3´) was utilized as an internal control in the reaction. The PCR product with 262 bp represented both alleles (C and T), and the size of the internal control PCR product was 422 bp.

Table 1. Clinical findings and laboratory parameters of pulmonary tuberculosis (TB) patients and healthy subjects

Characteristics*		TB patients (N=124)	Related healthy controls (N=121)	Unrelated healthy controls (N=123)	P-value
Age		51.26±1.88	33.71±1.61	46.07±1.34	<0.0001
Sex	Male	62 (50.4%)	52 (43.7%)	69 (56.1%)	0.155
	Female	61 (49.6%)	67 (56.3%)	54 (43.9%)	
Ethnicity	Fars	18 (14.5%)	18 (14.9%)	27 (22.0%)	0.399
	Sistani	62 (50.0%)	61 (50.4%)	58 (47.2%)	
	Turkmen	27 (21.8%)	27 (22.3%)	30 (24.4%)	
	Other	17 (13.7%)	15 (12.4%)	8 (6.5%)	
History of the disease	New case	105 (85.4%)	.	.	
	Recurrent	18 (14.6%)	.	.	
BCG Vaccination	Yes	47 (38.2%)	.	.	
	No	76 (61.8%)	.	.	
MDR TB	Yes	4 (3.3 %)	.	.	
	No	119 (96.7%)	.	.	
Treatment	Successful	110 (89.4 %)	.	.	
	Unsuccessful	13 (10.6 %)	.	.	

* Data are demonstrated as Mean±SE (Standard Error) or number (Percentage). Significant associations are shown in bold. Differences in the number of some variables with the total number of participants in each group are due to missing data. MDR TB: Multi-drug-resistant tuberculosis; BCG: Bacillus Calmette-Guerin.

2.3. Statistical analyses

The Hardy-Weinberg equilibrium was checked for each polymorphic site by Pearson's goodness-of-fit test using SNPStats software (2006, Catalan Institute of Oncology, Barcelona, Spain) (http://bioinfo.iconcologia.net/SNPStats) [27]. SPSS v. 22.0 (SPSS, Chicago, USA) was used to statistically analyze the data. The odds ratio (OR) and 95% confidence interval (CI) were determined to evaluate case-control study associations. The chi-square goodness-of-fit test was used to compare genotype frequencies between groups, while Fisher's exact test was applied when the necessary conditions for the chi-square test were not met. The nonparametric Kruskal-Wallis test with the Dunn-Bonferroni post-hoc test was used to compare the means of multiple samples. The independent samples *t*-test or the nonparametric Mann-Whitney U test was used to compare the means between the two groups. P-values lower than 0.05 were considered statistically significant.

Results

We evaluated the association of MCP1 (-2518 A/G) and IFNγ (+874 T/A) polymorphisms with the susceptibility to TB. The distribution of all alleles and genotypes under different inheritance models (codominant, dominant, recessive, and overdominant) in TB patients and healthy subjects (both groups) were in the Hardy–Weinberg equilibrium (HWE) (Tables 2-3). The comparison of the MCP1 (-2518 A/G) alleles showed that the allele A was more frequently observed in normal subjects. When the AA genotype was set as the reference under the

codominant model, neither the AG genotype [OR = 1.18, 95% CI (0.75–1.88)] nor the GG genotype [OR = 1.12, 95% CI (0.53–2.36)] was associated with the altered risk of TB development (P-value = 0.77) (Table 2). As illustrated in Table 2, no significant association was observed under the other inheritance models. Regarding the IFNγ (+874 T/A) polymorphism, the frequency of allele T was higher in normal subjects. When TT was set as the reference genotype, no significant association was observed between AT [OR = 1.05, 95% CI (0.65–1.72)] and AA [OR = 0.84, 95% CI (0.45–1.59)] genotypes with TB susceptibility (P-value = 0.76) (Table 3) under the codominant model. Moreover, no significant association was shown under the other inheritance models.

We also analyzed the association of all genotypes and alleles of TB patients within the 2 subgroups of normal subjects. The comparison of the MCP1 (-2518 A/G) genotypes in TB patients with both subgroups of related and unrelated normal subjects showed no significant association. Moreover, the IFNγ (+874 T/A) polymorphism was not associated with TB susceptibility in the two subgroups of normal subjects. Other subgroup analyses were also conducted regarding MDR TB patients and their response to treatment, and no significant association was found.

Table 2. The genotype and allele frequencies of MCP1 (-2518 A/G) single-nucleotide polymorphism (SNP) in tuberculosis patients and all healthy subjects under different inheritance models

Genotypes and alleles		TB patients (n=124)	Normal subjects (n=244)	OR (95% CI)	P-value
		Number (%)	Number (%)		
	A	163 (66%)	311 (64%)	Reference	
	G	85 (34%)	177 (36%)		0.57
	Codominant model				
	AA	52 (41.9%)	93 (38.1%)	Reference	
	AG	59 (47.6%)	125 (51.2%)	1.18 (0.75-1.88)	0.77
	GG	13 (10.5%)	26 (10.7%)	1.12 (0.53-2.36)	0.96
	Dominant model				
rs1024611	AA	52 (41.9%)	93 (38.1%)	Reference	
	AG+GG	72 (58.1%)	151 (61.9%)	1.17 (0.75-1.82)	0.48
	Recessive model				
	AA+AG	111 (89.5%)	218 (89.3%)	Reference	
	GG	13 (10.5%)	26 (10.7%)	1.02 (0.5-2.06)	0.96
	Overdominant model				
	AA+GG	65 (52.4%)	119 (48.8%)	Reference	
	AG	59 (47.6%)	125 (51.2%)	1.16 (0.75-1.78)	0.51
X2 HWE* (P-value)		(0.69)	(0.13)		

*P-values lower than 0.05 are considered to be statistically significant. No significant association was observed. The exact test for the Hardy-Weinberg equilibrium was also conducted. OR: Odds ratio; CI: Confidence interval; TB: Tuberculosis.

Table 3. The genotype and allele frequencies of IFNγ (+874 T/A) single-nucleotide polymorphism (SNP) in TB patients and all healthy subjects under different inheritance models

Genotypes and alleles		TB patients (n=124)	Normal subjects (n=244)	OR (95% CI)	P-value
		Number (%)	Number (%)		
	T	140 (56%)	283 (58%)	Reference	
	A	108 (44%)	205 (42%)	0.94 (0.69-1.28)	0.69
	Codominant model				
	TT	40 (32.3%)	79 (32.4%)	Reference	
	AT	60 (48.4%)	125 (51.2%)	1.05 (0.65-1.72)	0.69
	AA	24 (19.4%)	40 (16.4%)	0.84 (0.45-1.59)	
	Dominant model				
rs62559044	TT	40 (32.3%)	79 (32.4%)	Reference	
	AT+AA	84 (67.7%)	165 (67.6%)	0.99 (0.63-1.58)	0.98
	Recessive model				
	TT+AT	100 (80.7%)	204 (83.6%)	Reference	
	AA	24 (19.4%)	40 (16.4%)	0.82 (0.47-1.43)	0.48
	Overdominant model				
	TT+AA	64 (51.6%)	119 (48.8%)	Reference	
	AT	60 (48.4%)	125 (51.2%)	1.12 (0.73-1.73)	0.61
X2 HWE* (P-value)		(0.86)	(0.51)		

*P-values lower than 0.05 are considered statistically significant. No significant association was observed. The exact test for the Hardy-Weinberg equilibrium was also conducted. OR: Odds ratio; CI: Confidence interval; TB: Tuberculosis.

Discussion

We evaluated IFNγ (+874 T/A) rs2430561 and MCP1 (-2518 A/G) rs1024611 polymorphism with the susceptibility to pulmonary TB in an Iranian population.

Several studies have explored the association of MCP1 (-2518 A/G) polymorphism and susceptibility to pulmonary TB in different populations and ethnicities, which have resulted in controversial findings. A study by Naima Arji et al. in a Moroccan population showed a higher prevalence of homozygous GG genotype in healthy individuals, suggesting a potential protective effect of the G allele (14). However, A meta-analysis was conducted by Feng et al. to assess the association of MCP1 (-2518 A/G) alleles and genotypes with pulmonary TB and showed that the G allele increases the risk of developing TB in Asians and Hispanics (15), in accordance with a most recent meta-analysis by Gong et al. (16).

In the present study, we found no significant association between MCP1 (-2518 A/G) alleles and genotypes with the risk of pulmonary TB, which was consistent with the results of Naderi et al. in Zahedan, Iran, which did not support the association of MCP1 (-2518 A/G) polymorphism with pulmonary TB susceptibility (22). Ganachari et al. demonstrated that the joint effects of MCP1 (-2518 A/G) GG genotype and MMP-1 2G/2G genotype could be associated with an increased likelihood of developing pulmonary TB in BCG-vaccinated individuals in Mexico and Peru (28). Another study on an African population by Ben-Selma et al. revealed that MCP1 (-2518 A/G) G allele and GG genotype frequencies were significantly higher in active pulmonary TB patients. They also proposed a protective role for allele A and the AA genotype with higher frequencies in healthy subjects (29). The increased frequency of MCP1 (-2518 A/G) G allele has also been linked to a positive tuberculin test and elevated MCP1 serum levels among TB patients in the latent phase (30).

Similar to the MCP1 (-2518 A/G) polymorphic region, numerous population-based studies have been conducted to evaluate the association of IFNγ (+874 T/A) SNP with the susceptibility to pulmonary TB. A cohort study by Larcombe et al. showed that the higher frequencies of allele G in MCP1 (-2518 A/G) and allele A in IFNγ (+874 T/A) SNPs were associated with an increased risk of pulmonary TB (18). An African-based population study in Mozambique by Mabunda et al. found no significant association between IFNγ (+874 T/A) alleles and genotypes with the susceptibility to pulmonary TB and altered expression of IFNγ (31). The association of IFNγ (+874 T/A) alleles and genotypes has also been investigated in an Iranian population by Hashemi et al. (21), which showed a significant functional association between allele A and AA genotype overrepresentation in patients and an increased risk of TB. Their findings were in accordance with those of Ben-Selma et al., who presented the association of AA genotype with pulmonary TB development in Tunisian patients (20). Although other recent studies have highlighted the association of AA genotype in the IFNγ (+874 T/A) SNP with an increased risk of pulmonary TB (32), we found no significant relationship regarding the abovementioned polymorphism. Our results were consistent with those of Beiranvand et al. (23) and Muller et al. (33). Overall, the relationship between these gene polymorphisms and TB deserves further investigation. Current pharmacogenetic/pharmacogenomic strategies are largely based on the identification of known polymorphisms (34). Although the results of this study can be used in pharmacogenetic studies both in the clinic and in research, further studies with larger samples are recommended.

Conclusion

Our findings revealed that MCP1 (-2518 A/G) and IFNγ (+874 T/A) polymorphisms were not related to PT susceptibility in northeastern Iran. In the absence of previous reports of these associations in Iran, and based on conflicting results, the differences in allele, genotype, and haplotype frequencies and associations may be due to ethnic differences. Together with previous findings, this study contributes to the understanding of genetic susceptibility to TB; still, further clinical and molecular studies are needed to better explain the role of the investigated polymorphisms in the pathogenesis of TB.

Acknowledgement

Declaration

We declare that we have no conflict of interest.

Funding sources

Ethical statement

This study was approved by the Ethics Committee of Golestan University of Medical Sciences (Ethics Code: 1599012257).

Conflicts of interest

We declare that we have no conflict of interest.

Author contributions

AK: Writing the proposal and initial draft of the manuscript, Editing and finalizing the manuscript. AJ: Study design and supervision. MZ: Performed experiments, data extraction and data analysis. All authors read and approved the final manuscript.

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