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Research Article

The relationship between IL23R 1142G / A (*Arg381Gln*) and GM-CSF 3928 C / T (*Ile117Thr*) gene polymorphism in Iranian patients with tuberculosis disease

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ABSTRACT

The DNA polymorphisms found in clinical strains of *Mycobacterium tuberculosis* drive altered physiology, virulence, and pathogenesis in them. This study aimed to investigate the association between IL23R 1142 G/A (*Arg381Gln*) and GM-CSF 3928 C/T (*Ile117Thr*) gene polymorphisms with the incidence rate of tuberculosis in the population of Sistan. This study was based on the descriptive and applied type. All patients with active pulmonary tuberculosis were referred to the tuberculosis center of Zabol city for one year, with an equal number of healthy people adapted to the patients examined in terms of age. After data collecting to compare the frequency of polymorphisms, the chi-square test and OR index were used using SPSS software version 16. We have found that the IL23R reduced-function allele 1142A and genotypes CC and TC were overrepresented, especially in the Pad subgroup compared with the control group (44% versus 42%, 21% versus 22%, and 44% versus 39%, respectively. Increased risks of TB with minimal/moderate lung involvement, respectively. Our results demonstrate that the reduced-function polymorphism 1142G ¡ A encoded by IL23R influences the outcome of disease severity of active pulmonary TB in ZABOL patients. The genotypic and allelic frequency of IL23R 1142 G/A, and GM-CSF 3928 C/T (*Ile117Thr*) polymorphism in patients with tuberculosis was significantly different from the control group and this polymorphism was associated with the incidence of tuberculosis in the population of Sistan.

1. Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB) infection, affects approximately one-quarter of the world population [1]. Although the majority of infected individuals are asymptomatic, known as latent TB infection (LTBI), around 5–10% of them would tend to active TB (ATB) during their lifetime [2].

M. tuberculosis is an intracellular bacterial pathogen that itself and its anti gens can stimulate the production of cytokines by mononuclear phagocytes [3]. Today, based on Whole-Genome Sequencing (WGS), *M. tuberculosis* is divided into seven genera [4]. Molecular typing techniques are a reliable tool for the epidemiological study tuberculosis due to their power in diagnosing transmission and re-differentiation of infection and recurrence [5]. There are several molecular typing techniques for the epidemiological study of *M.*

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tuberculosis . The two most important typing methods are PCR, MIRU and spoligo typing, which are the most widely used in this field. Cellular immunity plays an important role in controlling the growth of *M. tuberculosis* [6].

Therefore, effective host defense against M. tuberculosis infection requires coordinated measures of innate and adaptive immune systems [7]. T lymphocytes exert cellular immunity and these lymphocytes are divided into two main groups Auxiliary T lymphocytes and lethal T lymphocytes. Auxiliary T cells secrete proteins called "cytokines" in response to antigen stimulation. Cytokines play a central role in regulating the species and the rate of immune responses in mycobacterial infections [8].

In mycobacterial infections, the number of cells from two newly discovered subpopulations of $CD3^+$ myeloid cells are increased at the infection site; one type expresses the T cell receptor ($CD3^+TCR\alpha\beta^+$) and the other does not ($CD3^+TCR\alpha\beta^-$) [9]. The role of *M. tuberculosis* (Mtb) virulence in generating these subpopulations and the ability of these cells to migrate remains unclear [10].

IL-17, which often is produced by Th17, plays an important role in controlling M. tuberculosis infection [11]. In addition, IL-23 is required for long-term control of M. tuberculosis. The granulocyte-macrophage gene colony-stimulating factor (GM-CSF) is located on chromosome 5q31 [12]. GM-CSF plays a key role in the balanced defense of host innate immunity against tuberculosis, which its role is associated with maintaining the integrity of alveolar epithelial cells and regulating the levels of macrophages and dendritic cells to facilitate inhibition of virulent mycobacteria in lung granulomas [13]. Prolonged impairment of GM-CSF expression causes pulmonary tuberculosis in immunocompromised individuals. Defective GM-CSF signaling causes defective innate immune activity in alveolar macrophages, leading to a high susceptibility to lung infections [14]. GM-CSF expression is a host defense response against TB infection. GM-CSF is expressed within human TB granuloma, which is secreted by human macrophages and lung epithelial cells after exposure to M. tuberculosis cells [15]. GM-CSF is also expressed when by addition to M. tuberculosis-infected human macrophage cultures, which leads to reducing the infection rate of this bacterium. In the absence of GM-CSF, mice could not limit the rate of M. tuberculosis infection since they are unable to absorb lymphocytes and cannot form normal granulomas [16]. In addition to the proliferative effects of GM-CSF on alveolar macrophages (AMs), GM-CSF increases the AMs phagocytic capacity, as well as accelerates the division of lung dendritic cells (DCs) that accumulate during TB [17, 18]. The results of limited studies conducted have shown that single nucleotide polymorphism (SNP) in IL-23R is associated with susceptible to tuberculosis (TB) disease [19, 20]. So far, no study in relation to single nucleotide polymorphism located in the GM-CSF gene susceptible to tuberculosis (TB) disease has been performed. The purpose of this study is to investigate the association between IL23R 1142G / A (Arg381Gln) and GM-CSF 3928 C / T (Ile117Thr) gene polymorphisms with the incidence rate of tuberculosis in the population of Sistan.

2. Materials and Methods

2.1. Sample Collection

The case-control study was performed with the approval of the ethics committee of the Zabol University of Medical Science, and written informed consent was collected from all the participants.

The diagnosis of different clinical forms of active pulmonary and extrapulmonary TB was established according to the criteria defined by the American Thoracic Society for the diagnosis of disease caused by MT [21]. Patients included were clinically and radiologically diagnosed with pulmonary tuberculosis and confirmed by sputum smear and culture for M. tuberculosis. TB patients with other comorbidities such as myocardial infarction, liver cirrhosis, acute pancreatitis, and septic shock were excluded. The inclusion criteria for the control group were the absence of clinical symptoms of active PTB and normal CXR. Also, the controls had no medical history of TB, other infectious and

autoimmune diseases, cancer and other diseases affecting host immunity.

2.2. Study populations

Peripheral blood samples were collected in EDTA tubes. From 177 patients with active pulmonary TB from Zabol, Iran, which is in the central region of the country, were enrolled in this study. 160 healthy blood donors (97 males and 63 females) were studied as controls (Table1). Patients and healthy blood donors were selected over the period from January 2019 to June 2020. Individuals with a history of severe pathologies, including HIV infection, cardiovascular disease, asthma, or atopy autoimmune diseases, and cancer, were excluded from the study. Informed written consent was obtained from all individuals prior to blood sampling. Moreover, our study was approved by the Zabol University Medical Science Ethics Committee.

Patients were recruited from the Pneumology Unit, Zabol, and the health care service, Zabol, Iran. Inclusion criteria for the patients in this group were determined according to the criteria defined by the American Thoracic Society [22].

Diagnosis of active pulmonary TB was based on clinical symptoms, the presence of acid-fast bacilli in sputum smears, and culture on Lowenstein-Jensen and Coletsos medium in all cases. All controls had the same ethnic and geographic origins and lived in the same city as the TB patients. The inclusion criteria for the control group were the absence of acute or chronic pulmonary disease, a negative history of TB, and proof of being healthy.

This study is based on the descriptive and applied type and all patients with active pulmonary tuberculosis were referred to the tuberculosis center of Zabol city for one year with an equal number of healthy people adapted to the patients examined in terms of age (figure 1). The obtained information is based on direct observation of the results obtained from laboratory evaluation.

2.3. Steps of extraction and preparation of samples

2.3.1. DNA extraction and genotyping

Genomic DNA was extracted from peripheral blood lymphocytes using the commercially available kit (Roche, Germany) in accordance with the manufacturer's instructions, and extracted DNA was stored at −20°C until analysis.

Blood cell DNA (According to the manufacturer's factory instructions) was extracted using the DNG-plus kit. The primers were designed using Oligo7 software by referring to the NCBI site and dbSNP database and obtaining the upstream sequence of IL23R and GM-CSF genes. The alleles of IL23R and GM-CSF gene polymorphisms were detected using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) according to previously described methods [23, 24]. to investigate the specificity and non-binding of primers to other parts of the genome, the BLAST software from NCBI site was used and finally they were made by Sina gen Company Iran.

2.3.2. Optimal conditions for Reproduction of each gene by gradient PCR method

PCR reactions were performed in a 25 μL reaction volume containing 200 ng genomic DNA, 25 ρM of each primer, 2.5 mM deoxyribonucleoside triphosphates (dNTPs), 1.5 mM MgCl2, and 1 U thermostable Taq DNA polymerase (Fermentas, Lithuania).

Reactions were run on MyCycler Thermal cycler, BIO-RAD PCR system (BIO-RAD Co., USA), using the following conditions: initial denaturation at 95◦C for 5 minutes followed by 35 cycles of denaturation at 94◦C for 30 seconds, annealing at 61◦C for 30 seconds, and extension at 72◦C for 1 minute. A final extension step was at 72◦C for 10 minutes. The PCR products were held at 4◦C until analysis.

When the appropriate temperature is reached for the primer binding step, the IL23R and GM-CSF genes are proliferated by polymerase chain reaction (PCR)(Table 2). To ensure proper proliferation of the desired gene, 2 µl of PCR product on agarose gel is loaded. The study of Gene polymorphism was evaluated by the RFLP method. At this stage, about 5 µl of the proliferated fragments were influenced by the restricting enzymes

Hpy188I and BsmAI, which were purchased from Thermo Scientific Company and exposed to a temperature of 37 ° C for 16 hours. Finally, they were loaded to analyze and cut the amplified fragment by restricting enzymes to the products obtained from the reaction on an agarose gel. To ensure good performance, 10% of the samples were randomly selected and sequenced.

2.3.3. Data analysis

After data collecting to compare the frequency of polymorphisms, the chi-square test and OR index were used using SPSS software version 16.

3. Results

We have found that the IL23R reduced-function allele 1142A and genotypes CC and TC were overrepresented, especially in the Pad subgroup compared with the control group (44% versus 42%, 21% versus 22%, and 44% versus 39%, respectively. Increased risks of TB with minimal/moderate lung involvement, respectively. The frequency distributions of different GM-CSF 3606T / C and 3928C / T genotypes are summarized in Table 3.

Table 1. Demographic and clinical data for tuberculosis patients and controls*

Study group	No. of cases	Female/Male (No. (%))	Age (mean ± SD, Y)
pTB	177	105 (59.65) / 71 (40.34)	45.06 ± 8.23
Pmd	114	75 (66.37) / 38 (33.62)	43.15 ± 6.54
Pad	63	39 (61.90) / 24 (38.09)	48.46 ± 11.31
Healthy	160	97 (60.62)/63 (39.37)	44.93 ± 5.87

* pTB, pulmonary tuberculosis; Pmd, pulmonary patients with minimum/moderate lung involvement; Pad, pulmonary patients with extensive lung involvement; M, male; F, female.

Table 2. Primers, PCR conditions, and restriction enzymes used for genotyping genes GM-CSF

SNPs product	Primer sequence 5`-3	PCR product	Tm
3606T/C (rs25881)	F-81: TTCTGGCAGGACTTTCCTCTGG C 81: AGGGCAGAGCAGGGCAGCTaG T 81: AGGGCAGAGCAGGGCAGCTaA	191bp	68.3
3928C/T (rs25882)	T-82: AAACTTCCTGTGCAACCCAGcA A-82: AAACTTCCTGTGCAACCCAGcT R-82: TTTCATGAGAGAGCAGCTCCCC	156bp	65.6

AT: annealing temperature;

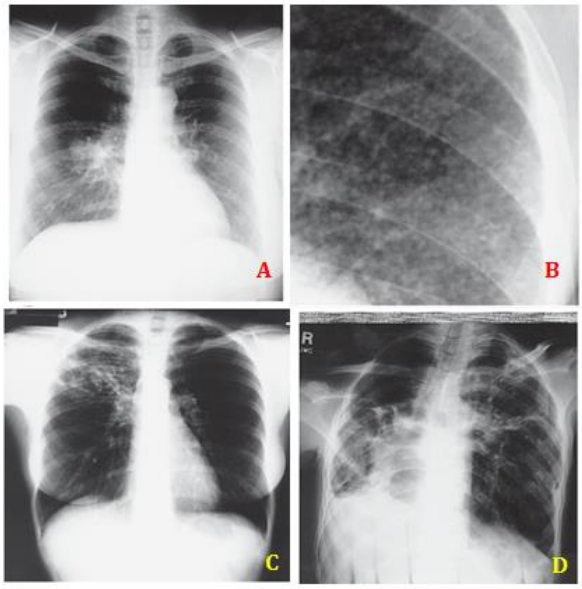

Fig. 1. Chest radiography showing marked right hilar lymph-adenopathy and lower lobe opacity in a 58-year-old woman with primary tuberculosis (A); Detail of a chest radiography (left midlung zone) showing countless 0.5- to 1.0-mm nodules typical of miliary tuberculosis (B); Chest radiography showing a right apical infiltrate in a patient with moderately advanced postprimary tuberculosis (C); Chest radiography showing far-advanced bilateral apical cavitary pulmonary tuberculosis in a 32-year-old woman (D)

Table 3. Genotype and allele frequencies GM-CSF 3606*T/C* and 3928*C/T* gene polymorphisms in controls and pulmonary tuberculosis patients.

Genotype	Control (n = 160) n (%)	Patients*			*p*-value [OR (95% CI)]			
		Total pTB (n = 177) n (%)	Pmd (n = 114) n (%)	Pad (n = 63) n (%)	Controls vs. Total pTB	Controls vs. Pmd	Controls vs. Pad	Pad vs. Pmd
GM-CSF 3606T / C SNP								
Codominant								
TT	66 (41.25)	62 (35.02)	38 (33.33)	24 (38.09)				
TC	73 (45.62)	76 (42.93)	51 (44.73)	25 (39.68)	0.669 [1.108 (0.690-1.777)]	0.479 [1.213 (0.710-2.073)]	0.856 [0.941 (0.490-1.806)]	0.478 [1.288 (0.639-2.594)]
CC	21 (13.12)	39 (22.03)	25 (21.92)	14 (22.22)	0.035 [1.977 (1.049-3.725)]	0.043 [2.067 (1.022-4.181)]	0.148 [1.833 (0.805-4.170)]	0.776 [1.127 (0.491-2.587)]
Dominant								
TT	66 (41.25)	62 (35.02)	38 (33.33)	24 (38.09)				
TC+CC	94 (58.75)	115 (64.97)	76 (66.66)	39 (61.90)	0.240 [1.302 (0.838-2.024)]	0.189 [1.404 (0.851-2.316)]	0.665 [1.141 (0.627-2.074)]	0.525 [1.230 (0.648-2.335)]
Recessive								
TC+CC	94 (58.75)	115 (64.97)	76 (66.66)	39 (61.90)				
CC	21 (13.12)	39 (22.03)	25 (21.92)	14 (22.22)	0.170 [1.518 (0.836-2.756)]	0.246 [1.472 (0.765-2.832)]	0.228 [1.606 (0.742-3.479)]	0.228 [1.606 (0.742-3.479)]
Alleles								
T	205 (64.06)	200 (56.49)	127 (55.70)	73 (57.93)				
C	115 (35.93)	154 (43.50)	101 (44.29)	53 (42.06)	0.045 [1.372 (1.006-1.872)]	0.048 [1.417 (1.002-2.005)]	0.229 [1.294 (0.849-1.971)]	0.684 [0.912 (0.588-1.417)]
GM-CSF 3928C / T SNP								
Codominant								
CC	61 (38.12)	55 (31.07)	35 (30.70)	20 (31.74)				
CT	74 (46.25)	79 (44.63)	53 (46.49)	26 (41.26)	0.493 [1.184 (0.730-1.919)]	0.425 [1.248 (0.723-2.153)]	0.840 [1.071 (0.546-2.103)]	0.679 [1.164 (0.565-2.399)]
TT	25 (15.62)	43 (24.29)	26 (22.80)	17 (26.98)	0.038 [1.907 (1.033-3.521)]	0.009 [1.812 (0.910-3.608)]	0.072 [2.073 (0.935-4.600)]	0.748 [0.873 (0.384-1.988)]
Dominant								
CC	61 (38.12)	55 (31.07)	35 (30.70)	20 (31.74)				
CT+TT	99 (61.87)	122 (68.92)	79 (69.29)	43 (68.25)	0.174 [1.366 (0.870-2.145)]	0.205 [1.390 (0.835-2.316)]	0.373 [1.324 (0.713-2.460)]	0.885 [1.049 (0.540-2.037)]
Recessive								
CT+TT	99 (61.87)	122 (68.92)	79 (69.29)	43 (68.25)				
TT	25 (15.62)	43 (24.29)	26 (22.80)	17 (26.98)	0.243 [1.395 (0.797-2.442)]	0.405 [1.303 (0.698-2.431)]	0.217 [1.565 (0.767-3.192)]	0.615 [0.832 (0.407-1.702)]
Alleles								
C	196 (61.25)	189 (53.38)	123 (53.94)	66 (52.38)				
T	124 (38.75)	165 (46.61)	105 (46.05)	60 (47.61)	0.039 [1.379 (1.015-1.875)]	0.089 [1.349 (0.956-1.903)]	0.087 [1.437 (0.948-2.177)]	

*****PTB, pulmonary tuberculosis; PMD, pulmonary patients with minimal/moderate lung involvement; Pad, pulmonary patients with extensive lung involvement.

Table 4. The combination effects of GM-CSF 3606T / C and 3928C / T gene polymorphism polymorphisms on total, PMD and Pad pulmonary risk*

GM-CSF 3606T / C	GM-CSF 3928C / T	Control (n = 160) n (%)	Patients			*p*-value [OR (95% CI)]		
			Total PTB (n = 177) n (%)	PMD (n = 114) n (%)	Pad (n = 63) n (%)	Controls vs. total pTB	Controls vs. PMD	Controls vs. Pad
TT	CC	23	18	11 (12.28)	7	1	1	1
TT	CT	34	34	22	12	0.537 [1.277 (0.586-2.783)]	0.508 [1.352 (0.551-3.316)]	0.786 [1.159 (0.283-2.667)]
TT	TT	9	10	5	5	0.529 [1.419 (0.476-4.229)]	0.822 [1.161 (0.314-4.297)]	0.393 [1.825 (0.458-7.273)]
TC	CC	25	29	17	12	0.344 [1.482 (0.655-3.353)]	0.466 [1.421 (0.551-3.663)]	0.412 [1.577 (0.529-4.694)]
TC	CT	37	31	22	9	0.863 [1.070 (0.490-2.335)]	0.632 [1.243 (0.509-3.031)]	0.694 [0.799 (0.261-2.440)]
TC	TT	11	16	12	4	0.217 [1.858 (0.694-4.975)]	0.137 [2.281 (0.767-6.776)]	0.806 [1.194 (0.287-4.958)]
CC	CC	13	8	7	1	0.661 [0.786 (0.268-2.304)]	0.842 [1.125 (0.350-3.614)]	0.221 [0.252 (0.027-2.287)]
CC	CT	3	14	9	5	0.011 [5.963 (1.483-23.96)]	0.015 [6.272 (1.412-27.86)]	0.045 [5.476 (1.038-28.87)]
CC	TT	5	17	9	8	0.014 [4.344 (1.345-14.03)]	0.047 [3.763 (1.017-13.92)]	0.020 [5.257 (1.294-21.35)]

*PTB, pulmonary tuberculosis; PMD, pulmonary patients with minimal/moderate lung involvement; Pad, pulmonary patients with extensive lung involvement.

4. Discussion

Histological studies show that GM-CSF facilitates the formation of initial epithelioid granulomas in the lung parenchyma during the intrinsic phase of M. tuberculosis infection. So far, only two studies have been performed on the association of IL-23 gene polymorphisms with the incidence of tuberculosis disease. In the first study, which was conducted by Ben-Selma and Boukadida in 2012 on tuberculosis patients in the Tunisia population, a significant association between IL23R 1142G / A polymorphism and an increased risk of tuberculosis disease in these patients was observed [25]. In the next study, which was conducted by Jiang et al., in 2015 in the Chinese population, a significant association between IL23R 1142G / A polymorphism and an increased risk of tuberculosis disease and its severe clinical forms [26]. In a study which was conducted by Essam Bakr Abdelaal et al., in 2021, it was found that it is the first report that investigates the association of a new granulocyte-macrophage colony-stimulating factor (GM-CSF) -3928C / T and GM-CSF gene polymorphisms (3606T/C) with the pathogenesis and severity of acne vulgaris and showed that the frequency of GM-CSF 3928 C / T polymorphism is statistically different in acne patients compared to healthy individuals who may be susceptible to acne vulgaris [27].

In a study which was conducted by Richard T. Robinson in 2017, it was found that by producing GM-CSF T cells from the host, can be shown that vaccine-mediated proliferation of GM-CSF-producing T cells could be an effective preventive or therapeutic strategy for tuberculosis [28]. In a study which was conducted by H. Saeki et al. in 2006, it was found that there was a strong link imbalance between 3606 and 3928 polymorphisms which were proposed two common GM-CSF haplotypes, 3606 * T-3928 * C and 3606 * C-3928 * T. However, there was no significant difference in genotype or allele frequency between patients with atopic dermatitis and the control group for each of these two polymorphisms, so it doesn't seem that GM-CSF SNPs have an association with susceptibility to atopic dermatitis in Japanese patients. A large-scale study is necessary to confirm these findings [29].

5. Conclusion

These findings indicate that vaccine-mediated proliferation of GM-CSF-producing T cells could be effective prevention or therapeutic strategy for tuberculosis. Prior to performing this study, no report regarding an association between GM-CSF 3928 C/T polymorphism (Ile117Thr) and the incidence of tuberculosis has published.

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Ethics in research

All patients underwent blood sampling consciously and for scientific purposes. Participation in this plan has any cost for patients and the names and details of patients will not be reported. In this research, the rules approved by the National Ethics Committee in medical sciences research according to codes 1, 2, 3, 12-5, 14, 15, 17, and 22-19, which are included in this research, will be observed. This research was accepted by the ethics

committee of Zabol University of Medical Sciences with ID: IR.ZBMU.REC.1398.161.

Authors' Contributions

KH. R, L.R, and A.K prepared the draft manuscript; KH. R, L.R, Revised the paper; L.R and K.R Collected the data, performed experiments, evaluated the results, and analysed the data.

Conflicts of Interest

All authors declare that they have no competing interests.

Consent for publications

All authors have read and approved the final manuscript for publication.

Availability of data and material

The authors have embedded all data in the manuscript.

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