Association of IL-4 and IL-6 Gene Polymorphism with Pulmonary Tuberculosis

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ABSTRACT

The case-control study was aimed to evaluate the effect of IL-4 and IL-6 gene polymorphism on susceptibility to pulmonary tuberculosis in patients in Babylon province and also measure the serum level of these cytokine in in sera of studied group. The genotype association of rs2243250 (C/C, C/T, T/T) were significant (P<0.05) with (46.7, 38.3, 15)% respectively for PTB cases and (36.7, 26.6, 36.7)% respectively for control group. Allele's frequency for patients and control for IL-4 (rs2243250) were also significant (P<0.05) and the C allele represent the risk allele for PTB patients with odd ratio (95% CI) of 1.93(1.15-3.24), while the T allele represent protective allele for control group 0.52 (0.31-0.87). The genotype association of rs1800796 (C/C, G/C, G/G) were significant (P<0.05) with (43.3, 38.3, 18.4)% respectively for PTB cases and (50, 15, 35)% respectively for control group, whereas, the allele's frequency for patients and control of IL-6 (rs1800796) were insignificant with (P>0.05). There was a significant difference in mean level of both IL-4 and IL-6 serum concentration between pTB patients and controls (P<0.01). Also, there were an insignificant effect of IL-4 (rs2243250) and IL-6 (rs1800796) gene polymorphism on the difference in serum level of both IL-4 and IL-6 respectively in studied groups (P>0.05).

Keywords: IL-4, IL-6, rs2243250, rs1800796, MTB and ELISA.

INTRODUCTION

The bacterial genus Mycobacterium belongs to the family Mycobacteriaceaea, More than 223 *Mycobacterium* species have been validly published to date, according to the List of Prokaryotic names with Standing in Nomenclature (LPSN) website. To these, a number of non-officially recognized species can be added. According to the International Committee on Systematic Bacteriology, species whose descriptions are published in the *International Journal of Systematic and Evolutionary Microbiology* are automatically validated. The validation of species described elsewhere can be requested at the office of the above-mentioned journal and is subject to evaluation. The species have been divided into three groups: rapidly growing NTM, slowly growing NTM, and members of the *Mycobacterium tuberculosis* complex (Enrico 2014).

There were many factors that influence the nature of cytokine response to MTB, such as polymorphisms of cytokine genes, will result in modification of host immunological response. Although mechanisms of altered gene expression associated with polymorphisms are still poorly understood (Dejan et al. 2009).

IL-4 gene polymorphism could be a potential candidate to play a role in the susceptibility of individuals to brucellosis. The IL-4 gene is located on the long arm of chromosome 5, where it lies in close proximity to the genes for other Th2 cytokines such as IL-5 and IL-13 (Mehdi et al. 2006). Polymorphisms in the IL-4 promoter (rs2243250 C/T) could effect on the transcription levels of the gene. Specifically, a functional SNP, located 589bp upstream of the transcriptional site, has been related with increased promoter strength, stronger binding of transcription factors to the promoter and also with different levels of IL-4 activity (Sivangala et al. 2014).

The gene encoding IL-6 is located on chromosome 7p21, and contains 6 exons with a 1.3 kb coding sequence (size 6119 base pairs). Most studies have focused on the promoter region of the IL-6 gene as many polymorphisms are known in this region, including -174G/C (NCBI ID:rs1800795), and -572G/C (NCBI ID:rs1800796) (Yaping et al. 2017).

To date, large numbers of epidemiological studies have been performed to examine the relationship between the IL-6 gene polymorphisms and the risk of TB, but different studies reached different conclusions. The differences in results may be due to a possible small effect of the polymorphism on TB risk and the relatively small sample sizes in the published studies (Yaping et al. 2017).

MATERIAL AND METHOD

Samples Selection and MTB Detection

A case-control study involved 60 newly diagnostic pulmonary tuberculosis and 60 samples of apparently healthy persons were taken as a control group.

A blood and sputum samples were collected from all study cases at the center of chest and respiratory disease in AL-Hillah / Babylon province, during the period from November 2018 to July 2019.

The sputum sample was subjected to direct smear examination by Ziehl-Neelsen technique (Tille Bailey

2014), routine culture by use Lowenstein-Jensen medium Bhawan (2009) and use of GeneXpert for detection of MTB (Pandey et al. 2017).

The blood samples were used for genotyping study, as the DNA extraction was achieved according to the method recommended by the manufacturing company (favorgene) in the user manual of Favor Prep Genomic DNA Mini Kit general protocol for fresh and frozen blood samples. The extracted blood genomic DNA was tested by using nanodrop spectrophotometer which measured DNA concentration (ng/µL) and check the DNA purity by reading the absorbance at (260 /280 nm). All the primers that used in this study for detection IL-4 (rs2243250) and IL-6 (rs1800796) were listed in table (1.1).

Table 1: Primers of PCR

No.	Primer name	Primer sequence 5′ to 3′	Product size	Reference
1	IL-4 rs2243250	F- AGGTGTCGATTTGCAGTGAC R-ACTAGGCCTCACCTGATACG	646bp	Sivangala *et al*., 2013
2	IL-6 rs1800796	F-GGAGACGCCTTGAAGTAACTGC R- GAGTTTCCTCTGACTCCATCGCAG	163bp	Feng *et al*., 2014

F= forward, R= reverse, temp = temperature, bp= base pair

The PCR technique was done on all samples by use (Promega master mix,USA) and then the amplified products were subjected to RFLP technique to determine SNPs.

The PCR-RFLP of rs2243250 and rs1800796 was done for all sample by using *BsmF I* and *Mbi I* endonucleases respectively and according to instructions of manufactured company (New England Biolabs Inc./USA) by add 5 µl amount DNA from PCR product to 4 µl restriction enzyme buffer and 1 µl of the selected restriction enzyme *BstDE I* and the reaction mixture then completed to 15 µl by Free nuclease water.

The level of IL-4 and IL-6 in the serum of PTB patients and healthy control was measured according to the instructions of the manufacturer by the using of specific human serum ELISA kit from (MELSIN Medical Co. / China) (Günay et al. 2018).

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS version 23; variables were described as T-test, mean, standard deviation, number and percentage. Risk was estimated using odds ratio and the level of significance was set at P <0.05.

RESULTS AND DISCUSSION

DNA Extraction and PCR Products Detection

Human DNA genome was extracted from whole blood of all the 60 samples of PTB patients and 60 samples of apparently healthy control, the concentration was (50-150 ng) and purity was (1.8-2.0). These DNA was subjected to PCR amplification using specific primers targeting specific regions in the DNA and then enrolled for detection of single nucleotide polymorphisms (SNPs) by RFLP techniques. Then the optimized of PCR products of the designed primers pair which would be used in IL-4 (rs2243250) and IL-6 (rs1800796) genotyping was done by the gradient-PCR at (55-66 C^0) and then the PCR product were electrophoresed to evaluate the most appropriate condition for PCR technique. The most appropriate annealing temperature was 60C^0 for both (rs2243250) and (rs1800796).

Genotypic Characterization of IL-4 (Rs2243250)

The amplification of IL-4 gene at region rs2243250 appeared the presence of gene amplicons on electrophoresis gel for all groups of study.

Genotype association and allele's frequency for patients and control are listed in table (1.2). The results showed that there were significant allele frequency differences between patients and control group (P=0.018). Allele C represents the risk allele with odd ratio (95% CI) of 1.93(1.15-3.24), while allele T represents the protective allele with odd ratio (95% CI) of 0.52(0.31-0.87).

The restriction fragment length polymorphism of PCR products of IL-4 (rs2243250) gene revealed three genotypes; C/C, C/T and T/T (figure 1.1).

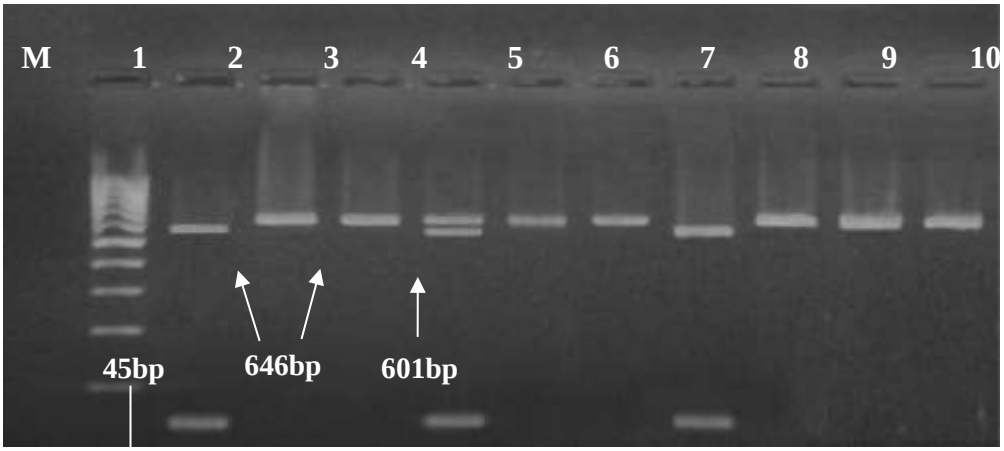

Figure 1: Gel electrophoresis carried on (agarose gel (2%), 75% V, 20 Am for 1hr.) for IL-4 (rs2243250) gene. PCR products visualized under U.V. light after staining with ethidum promaide. M: 100 bp DNA marker; the size of product is 646bp and 601+45 bp. The T/T(1,7), C/T(4) and C/C(2,3,5,6,8,9,10).

The result of association of IL-4 (rs2243250) genotypes with PTB showed a significant association between these genotypes with pulmonary tuberculosis and it was revealed that C/C and C/T genotype was more associated with pulmonary tuberculosis, while T/T genotype conferring lesser pulmonary tuberculosis susceptibility for the carrier individuals with odd ratio (95% CI) of 0.32 (0.12-0.84), (P=0.048).

Table 2: Genotype association and allele's frequency of IL-4 (rs2243250) with PTB.

Genotypes	Control	Case	OR (95% CI)	P-value
C/C	22 (36.7%)	28 (46.7%)	1.00	
C/T	16 (26.6%)	23 (38.3%)	1.13 (0.48-2.64)	0.048
T/T	22 (36.7%)	9 (15%)	0.32 (0.12-0.84)	
Allele Frequency				
T	60 (50%)	41 (34.2%)	0.52 (0.31-0.87)	0.018
C	60 (50%)	79 (65.8%)	1.93 (1.15-3.24)	

*(P<0.05), OR: odd ratio, CI: confidence interval

The results of this study was agreed with (Sivangala et al. 2014) who found that gene polymorphisms in promoter region (CC genotype) of IL-4 rs2243250 (-589 C/T) was associated in patients (P<0.03) when compared to healthy control and also reported that the genotype distributions of IL-4 (-589C/T) were in Hardy–Weinberg equilibrium (HWE) for health control but not for patient (Takzare et al. 2018).

Other studies in Russian population showed significance difference for C/C, C/T genotypes in patients compared with controls (Naslednikova et al. 2009).

Trajkov *et al.* (2009) observed that homozygous genotypes C/C of IL-4 polymorphisms were clearly associated with TB infection with OR (95% CI) of 1.856 (1.108-3.108), (p=0.018), while heterozygous genotypes C/T of the same IL-4 polymorphisms showed protective association with OR (95% CI) of 0.489 (0.292-0.817), (p=0.006).

Trajkov *et al.,* (2009) also mention that polymorphism at position -590 in the IL-4 promoter region is associated with enhanced IL-4 promoter strength and altered IL-4 level and activity, and thereby influences on IL-4 related activities that determine the diseases progression.

Another study has shown that patients with pulmonary tuberculosis has significantly more frequent heterozygous C/T genotype of IL- 4 (-589C/T) gene location than healthy control group Vidyarani *et al*. (2006) and this result agree with our finding.

On the other hand, studies by Amirzargar *et al.* (2006) in Iranian population found an insignificant association of IL-4-590 T/T in patients with TB.

Genotypic Characterization of IL-6 (Rs1800796)

The amplification of IL-6 gene at region rs1800796 appeared the presence of gene amplicons on electrophoresis gel for all groups of study.

Genotype association and allele's frequency for patients and control are listed in table (1.3). The results showed that there were insignificant allele frequency differences between patients and control group (P=0.51).

The restriction fragment length polymorphism of PCR products of IL-6 (rs1800796) gene revealed three genotypes; C/C, G/C and G/G (figure 1.2).

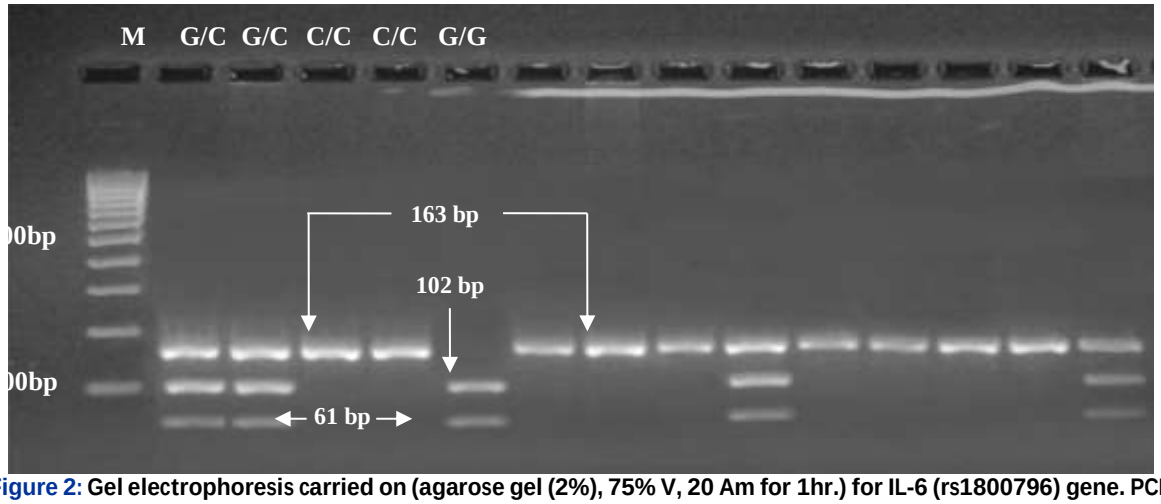

Figure 2: Gel electrophoresis carried on (agarose gel (2%), 75% V, 20 Am for 1hr.) for IL-6 (rs1800796) gene. PCR products visualized under U.V. light after staining with ethidum promaide. M: 100 bp DNA marker; the size of product is 163 and 102+61 bp. The C/C(3,4,6,7,8,10,11,12,13), G/C(1,2,914) and G/G(5).

Association of IL-6 (rs1800796) genotypes with PTB was further tested, and the results revealed that G/C genotype was more associated with pulmonary tuberculosis with odd ratio (95% CI) of 2.95 (1.16-7.49), (P=0.019), while G/G genotypes conferring lesser pulmonary tuberculosis susceptibility for the carrier individuals.

Table 3: Genotype association and allele frequencies of IL-6 (rs1800796) with PTB.

Genotypes	Control	Case	OR (95% CI)	P-value
C/C	30 (50%)	26 (43.3%)	1.00	
G/C	9 (15%)	23 (38.3%)	2.95 (1.16-7.49)	0.019
G/G	21 (35%)	11 (18.4%)	0.60 (0.25-1.48)	
		Allele Frequency		
C	69 (57.5%)	75 (62.5%)	1.232 (0.734-2.066)	0.51
G	51 (42.5%)	45 (37.5%)	0.81 (0.48-1.36)	

*(P<0.05), OR: odd ratio, CI: confidence interval

The finding of this study was in agreement with Zhang *et al.* (2012) who found that IL-6 rs1800796 G/G genotype is largely associated with reduced risk to tuberculosis (OR: 0.621; 95% CI, 0.460–0.838) but, Interestingly, CD14+ monocytes isolated from individuals with G/G genotype produced significantly lower IL-6 in response to *M. tuberculosis* 19-kDa lipoprotein.

Sun and Wang, (2017) also shown that genotype CC is associated with less risk of pulmonary tuberculosis and these results was in agreement with our finding.

On the other hand, the our finding was disagree with Wang *et al.* (2017) who found in their meta-analysis that genotype GG is associated with significantly more susceptibility to pulmonary TB than both GC and CC genotypes, however, Wang *et al*. (2017) suggest to performed more study to investigate the mechanism how IL-6 polymorphism regulates IL-6 production and plays a role in tuberculosis susceptibility.

Several independent genetic studies reported an associated of IL-6 rs1800796 (-572G/C) SNP with the susceptibility to inflammatory conditions in the Chinese Han population, which include type-II diabetes, coronary heart disease, idiopathic membranous nephropathy and chronic periodontitis and these study suggesting that IL-6 rs1800796 (-572G/C) is a common genetic SNPs in the Chinese Han population that causes susceptibility to a broad spectrum of inflammatory diseases, including mycobacterial infection (Chen et al. 2010; Zhang et al. 2011).

Concentration Level of Interleukin-4

The mean level of IL-4 concentration in serum of pTB patients was 231.04 pg/ml, while in controls was 372.58 pg/ml, with significant difference (P<0.01), as shown in table (1.4).

Table 4: Concentration of IL-4 pg/ml for TB patients and control group.

	group	N	Mean	Std. Deviation	Std. Error Mean	T- Value	P-Value
IL-4	case	60	231.04	96.37	12.44	6.57	0.001
	control	30	372.58	96.18	17.56		

In the this study, serum levels of IL-4 was significantly lower in TB patients than in control group ($P < 0.01$); and this results was agreed with results of Dmytro *at al.* (2016) who found that patients with pTB showed significant decrease of IL-4 levels compared to apparently healthy subjects.

The correlations between IL-4 (rs2243250) gene polymorphism and the level of IL-4 in sera of patients and control group was demonstrated in table (1.5) and the results revealed an insignificant effect of IL-4 (rs2243250) on the concentration level of IL-4 in sera of studied groups.

Table 5: Correlations between IL-4 gene polymorphism and serum IL-4 levels.

IL4 Genotypes		Mean Difference	Std. Error	P-value	95% Confidence Interval	
					Lower Bound	Upper Bound
C/C	C/T	15.87	28.62	0.58	41.02	72.16
	T/T	34.21	31.33	0.27	96.49	28.06
C/T	C/C	15.87	28.62	0.58	72.77	41.02
	T/T	50.08	33.70	0.14	117.08	16.90
T/T	C/C	34.21	31.33	0.27	28.06	96.49
	C/T	50.08	33.70	0.14	16.90	117.08

Wenjuan *et al.,* (2020) show no significant detectable IL-4 level between TB patients and controls and also conclude that serum level of IL-4 might not serve as a useful biomarker for predicting bacillary burden.

On the other hand, Pooran *et al.* (2019) and Wassie *et al.,* (2008) found different results in which the levels of IL-4 in the sera of patients was increased in the peripheral blood of TB patients than in control group. Also, Van *et al.,* (2000) have observed increased IL-4 production in human TB patients, especially those with cavitary disease.

Conversely, some studies failed to show significant correlation in IL-4 levels between TB patients and those of healthy donor group (Bai et al. 2004; Ruolan et al. 2019).

IL-4 is known as a regulatory cytokine that share in control of the immune response against infection (Domingo-Gonzalez et al. 2016). In addition, it has a role in the development of immunopathology through its regulation of TNF-α activity during progressive disease. Actually, IL-4 produced in response to TB infection may down-regulate the immune response to limit tissue injury; nevertheless, excessive production of this cytokine may result in failure to control infection (Sharma & Bose 2001).

The finding of our study may be related to the fact that the effective immune response against tuberculosis is achieved by Th1 T cell cytokines and through cell mediated immunity rather than humeral immunity represented by Th2 T cell cytokines.

Concentration Of Interleukin-6

The mean of IL-6 concentration in serum of pTB patients was 365.29 pg/ml, while in controls was 252.08 pg/ml, with significant difference (P<0.01), as shown in table (1.6).

Table 6: Concentration of IL-6 pg/ml for TB Patients and Control.

	GROUP	No.	Mean	Std. Deviation	Std. Error Mean	T-Value	P-Value
IL-6	Case	60	365.29	136.37	17.60	4.11	0.001
	Control	30	252.08	90.37	16.50		

The finding of this study were in agreement with Fakhri *et al*. (2019) who reported that IL-6 plasma level was higher in the newly diagnostic TB patients than healthy subjects ($P = 0.002$).

The correlations between IL-6 (rs1800796) gene polymorphism and the level of IL-6 in sera of patients and control group was demonstrated in table (1.7) and the results revealed an insignificant effect of IL-6 (rs1800796) on the concentration level of IL-6 in sera of studied groups.

Table 7: Correlations between IL-6 gene polymorphism and serum IL-6 levels.

IL6 Genotype		Mean Difference	Std. Error	P-value	95% Confidence Interval	
					Lower Bound	Upper Bound
C/C	C/G	39.54	33.07	0.23	105.27	26.18
	G/G	23.23	35.44	0.51	47.21	93.67
C/G	C/C	39.54	33.07	0.23	26.18	105.27
	G/G	62.77	39.05	0.11	14.85	140.40
G/G	C/C	23.23	35.44	0.51	93.67	47.21
	C/G	62.77	39.05	0.11	140.40	14.85

Jang *et al.* (2004) demonstrated that IL-6 is secreted by TLR -2 expressing cells in response to the presence of MTB early in infection and is involved in anti-tuberculosis immunity in the body. Also, Joshi *et al*., (2015) declared that serum levels of IL-6 are elevated in patients with active TB comparison with control subjects.

Interestingly, interleukin-6 is a pro-inflammatory cytokine, which is secreted by T cells and macrophages and it has been reported the involvement of this cytokine in the pathogenesis of TB by stimulating the secretion of IFN-γ, which plays a crucial role in the activation of MTB-infected macrophages (Singh 2016).

An Asian study, displayed that high IL-6 concentration in patients with pulmonary cavities than those without cavities signifying the disease severity (Karyadi et al. 2007).

Another Chinese study also reported an elevated IL-6 concentration in active TB compared with latent TB infections (Shu et al. 2013). The increased IL-6 concentration in patients when compared with controls may be due to release of IL-6 into circulation during early stages of infection causing systemic symptoms and hence the levels may also vary depending upon the clinical status of the patients.

CONCLUSION

There were a significant association of IL-4 (rs2243250) genotypes (C/C and C/T) with pulmonary tuberculosis and also, there were significant allele frequency differences between patients and control group (*P*=0.018) and the allele C represents the risk allele with odd ratio (95% CI) of 1.93(1.15-3.24).

There were a significant association of IL-6 (rs1800796 G/C) genotypes with PTB with pulmonary tuberculosis with odd ratio (95% CI) of 2.95 (1.16-7.49), (*P*=0.019), while there were insignificant allele frequency differences were observed between patients and control group (*P*=0.51).

A significant difference in the mean level of IL-4 and IL-6 concentration in serum of PTB patients and controls were observed with (P<0.01).

CONFLICT OF INTEREST: Nil

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