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Tuberculosis; TLR2; IL1 β and genetic polymorphism.

Association of TLR2 and IL1B Genetic Variants with Pulmonary Tuberculosis Susceptibility in the Iraqi Population.

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ABSTRACT: Tuberculosis susceptibility results from the complex interaction of host immune responses and genetic factors. This study used a case-control design to assess immunologic biomarkers and polymorphisms in the TLR2 and IL1B genes among Iraqi patients with pulmonary tuberculosis. 50 patients with tuberculosis and 50 apparently healthy controls were recruited from specialised centres in Kerbala and Baghdad. Mean serum TLR2 concentration was higher in patients carrying TLR2 sequence variants than in non- carrier patients (15.71 vs. 12.28 ng/mL), although the difference was not statistically significant ($p = 0.158$). However, Serum IL-1 β concentration was lower in variant-carrier patients than in wild-type patients and controls, but the difference was not statistically significant ($p = 0.470$). Genetic analysis of the studied genes showed that TLR2 rs5743708 was monomorphic G>G in all patients and the control; Meanwhile, many previously studied SNPs were identified in the target sequence. The IL-1B gene showed multiple variants at the target SNP rs1143627, Among TB patients, G>T-related variants were observed in 10 individuals and G>A-related variants in 5 individuals, compared with 4 G>T-related variants among controls; the odds ratio was 4.93, 95% CI: 1.55–15.69, $p = 0.0095$.

INTRODUCTION:

Mycobacterium tuberculosis is an aerobic, non-motile, slow-growing, acid-fast bacillus because its lipid-rich cell envelope contains mycolic acids, which resist acid–alcohol decolourisation and reduce drug penetration, causing tuberculosis, a chronic infectious disease mainly affecting the lungs (Jacob-Delgado *et al.*, 2023). Most importantly, *Mycobacterium tuberculosis* is hazardous because it has the ability to survive inside macrophages, elude the host's immunity, establish a latent infection, and gradually destroy the lung. Treatment is prolonged for many months due to its slow replication, intracellular and granulomatous persistence, drug-tolerant bacterial populations, and the protective lipid (Warner *et al.*, 2025; Sarangi *et al.*, 2024). Epidemiological evidence indicates that approximately one-quarter of the global population is infected with *M. tuberculosis*, representing a large reservoir of latent TB infection. However, only about 5–10% of infected individuals develop active TB during their lifetime, suggesting that host immune and genetic factors strongly influence disease progression (Shrestha *et al.*, 2024). In addition to socioeconomic determinants such as poverty, malnutrition, overcrowding, and limited healthcare access, increasing evidence suggests that host immunological and genetic factors play major roles in determining susceptibility, disease progression, and clinical outcome (Pai *et al.*, 2022). Innate immune recognition of *M. tuberculosis* is initiated through pattern-recognition receptors, particularly Toll-like receptor 2 (TLR2), which recognizes multiple mycobacterial cell wall components including lipoproteins and lipoarabinomannan (Kleinnijenhuis *et al.*, 2011). Activation of TLR2 triggers MyD88-dependent signalling pathways that lead to NF- κ B activation and the induction of pro-inflammatory cytokines such as TNF- α , IL-6, and IL-1 β (Kawasaki and Kawai, 2014). Interleukin-1 β (IL-1 β), encoded by the *IL1B* gene, is an important proinflammatory cytokine in the host response to *Mycobacterium tuberculosis* infection. Inflammasome activation promotes the maturation and release of IL-1 family cytokines, including IL-1 β , and this pathway is considered central to tuberculosis-related inflammatory defense (Theobald *et al.*, 2024;

Zhuang *et al.*, 2024). In addition, recent evidence indicates that cytokine gene polymorphisms are associated with tuberculosis susceptibility and progression, supporting the relevance of *IL1B* genetic variation in the pathogenesis of TB (Fu *et al.*, 2025). Maturation of *IL-1B* is critically regulated by activation of the NLRP3 inflammasome, a cytosolic multiprotein complex composed of NLRP3, ASC, and caspase-1 (Swanson *et al.*, 2019).

METHODOLOGY:

A total of 100 people were recruited between December 2024 and June 2025 from Specialised TB Centers in Karbala and Baghdad to participate in the study. These included 50 patients with active tuberculosis and 50 apparently healthy controls. Controls were age- and sex-matched to the patients. Diagnosis of tuberculosis was both clinical and confirmed by GeneXpert. The serum levels of TLR2 and IL-1 β were measured using enzyme-linked immunosorbent assay. Blood Samples were processed as follows: about ten millilitres of venous blood were withdrawn from Tuberculosis patients and healthy individual volunteers.

Each sample was separated into two tubes. The first (5) was collected into EDTA tubes for genetic analysis. The second was placed in a gel tube (5 mL) to separate serum by centrifugation at 3000 rpm for 15 min, and then kept in Eppendorf tubes at -20 °C. Quantities of TLR2 and IL-1 β serum concentration were performed using the Sandwich ELISA (BT lab kit) following the manufacturer's instructions. Genomic DNA from white blood cells (WBCs) of both patients and control groups was extracted using a DNA extraction kit (Geneaid), according to the manufacturer's instructions. The PCR conditions for amplifying the TLR-2 and IL-1B promoter genes were initial denaturation at 95°C for 5 min, followed by 30 cycles consisting of 30 sec. at 95°C, 35 sec. at 53°C, and 35 sec. at 72°C, with a final extension at 72°C for 10 min. The amplified products were determined by electrophoresis on agarose gel containing 0.5 μ g/ml Ethidium bromide. The PCR product was sent to Promega/Korea for sequencing. After amplification, Sanger sequencing was used to analyse selected regions of the two genes. We used BLAST to align our sequences with reference sequences to identify nucleotide substitutions and used genetic code to find their effects on amino acid sequences.

EXCLUSION CRITERIA:

Patients with HIV infection, autoimmune diseases, chronic inflammatory diseases, malignancy, or those receiving immunosuppressive therapy were excluded from the study.

INCLUSION CRITERIA:

Newly diagnosed Pulmonary TB patients.

Table 1. Shows the SNP ID and primer sequence 5'- 3' and size for two candidate genes.

SNP ID	Primer sequence 5'- 3'	Primer length	Ref.
TLR2 rs5743708	F: 5'-GTT GTG TCT TCA TAA GCG GGA CT-3'	23 bp	Moghaddam <i>et al.</i> ,2018
	R: 5'- AGT CCT CAA ATG ACG GTA CAT CC-3'	23 bp	
IL-1 β rs1143627	F: 5'-ATGACGGCTACGTTTCATGTGT -3'	21 bp	Primer design
	R: 5'CTGTGTGTCTTCCACTTTGTCC- -3'	22 bp	

Table (2): Recommended volumes and concentration for applying PCR into PCR tubes.

Components	Volume (μ l)	Concentration
Master Mix	12.5	X1
Forward primer	1.5	10 pmol
Reverse primer	1.5	10 pmol
Template DNA	3	50 ng
Nuclease-free water	1.5	
Total Volume	20	

RESULTS:

Genomic DNA was extracted from the frozen blood of the 50 samples and 50 controls. Primer pairs (Table 1) were used to amplify a specific SNP region of the *TLR2* gene (rs5743708) and the *IL-1 β* gene (rs1143627) using a conventional PCR technique. The results of PCR electrophoresis showed that all samples gave true amplification with the expected PCR product size (Fig. 1, 2) for the target gene for the specific SNP. All patients and controls had the GG genotype at *TLR2* rs5743708, showing that this locus was monomorphic in the study population. Sequencing of the adjacent *TLR2* region, however, revealed seven previously reported SNPs at other loci (Table 3). Mean serum *TLR2* concentrations were 15.71 ng/mL among variant-carrier patients and 12.28 ng/mL among non-carrier patients, compared with 14.09 ng/mL in the control group, but the difference was not statistically significant ($p = 0.158$). (Figure 3). While 15 patients had variations at *IL1B* rs1143627. Analysis of *IL1 β* rs1143627 genotyping identified as follows, in tuberculosis (TB) patients, the GG genotype was most prevalent (70.0%), followed by TT (14.0%), GA (8.0%), GT (6.0%), and AA (2.0%). Within the control group, the GG genotype was present in 92.0% of individuals, while GT and TT genotypes were each observed in 4.0% of cases. Giving OR = 4.93, 95% CI: 1.55–15.69, $p = 0.0095$. Serum *IL-1 β* protein concentrations in the wild-type TB patients were 1887.93 pg/mL, whereas mutant-type TB patients had the lowest mean concentration at 1627.61 pg/mL, while the control group had 2316.93 pg/mL, but the difference was not statistically significant ($p = 0.470$) as shown in Figure 4.

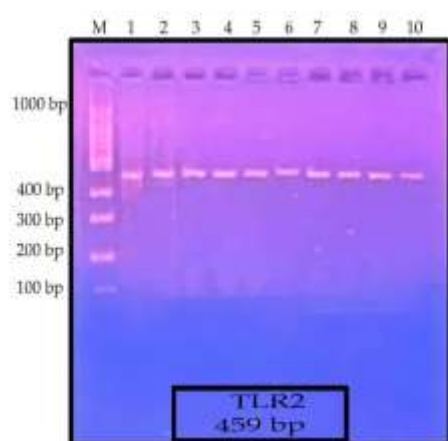


Fig.1: *TLR2* gene bands as appeared in gel electrophoresis, Lane 1-6 P; 6-10 C

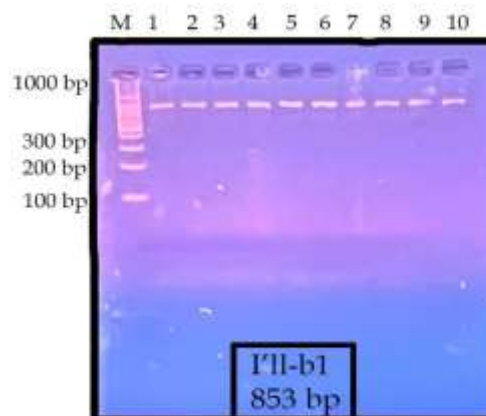


Fig.2: *IL-1 β* gene bands as appeared in gel electrophoresis, Lane 1-6 P and 6-10 C

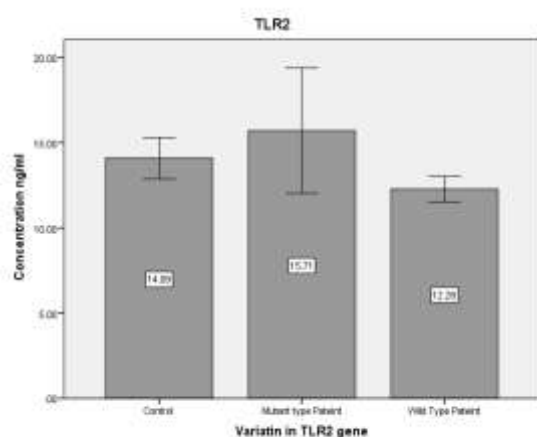


Fig. 3: shows variation in the *TLR2* gene.

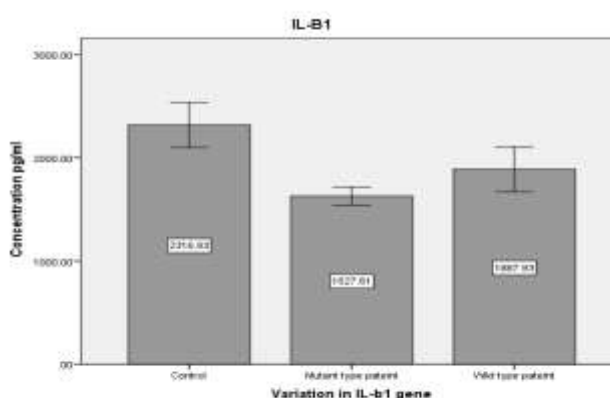


Fig.4: shows variation in the *IL-1 β* gene

Table(3) shows all previously studied SNPs in the TLR2 gene as identified by Sanger Sequencing.

Location	SNPs	Reference Seq.		Variation		Previously Recorded SNPs
		Code	Amino acid(AA)	Code	Amino acid(AA)	
153705048 Exon	A>G	AAG	Lys	AGG	Arg	rs1737239629
1.154E+09 Exon	C>T	TGC	Cys	TGT	Cys	rs66474962
187930060 Exon	T>C	TTT	Phe	CTT	Leu	rs947903940
154626079 Exon	C>T	TCT	Ser	TTT	Phe	rs2535435478
153705091 Exon	C>A	AAC	Asn	AAA	Lys	rs2535437230
153704927 Exon	C>T	CTT	Leu	TTT	Phe	rs25354354
153705056 Exon	C>T	CTG	Leu	TTG	leu	rs55693043
Location	SNPs	Reference Seq.		Variation		Previously Recorded SNPs
		Code	Amino acid(AA)	Code	Amino acid(AA)	
153705048 Exon	A>G	AAG	Lys	AGG	Arg	rs1737239629
Exon	C>T	TGC	Cys	TGT	Cys	rs66474962
187930060 Exon	T>C	TTT	Phe	CTT	Leu	rs947903940
154626079 Exon	C>T	TCT	Ser	TTT	Phe	rs2535435478
153705091 Exon	C>A	AAC	Asn	AAA	Lys	rs2535437230
153704927 Exon	C>T	CTT	Leu	TTT	Phe	rs25354354
153705056 Exon	C>T	CTG	Leu	TTG	leu	rs55693043

DISCUSSION:

Genetic variation in immune-related genes has been shown to influence host resistance to *M. tuberculosis* infection, disease severity, and drug resistance (Gao *et al.*, 2024). Variations in susceptibility to TB may arise from the expression of genetic polymorphisms in humans (Cubillos-Angulo *et al.*, 2019). Epidemiological and molecular studies across different regions have demonstrated associations between specific SNPs and increased risk of active TB, progression from latent to active infection, and more severe clinical phenotypes. However, these findings are often inconsistent across populations due to genetic diversity, ethnic background, and methodological differences (Chen *et al.*, 2023).

Toll-like receptor 2 (TLR2) is essential for recognizing mycobacteria and inducing anti-mycobacterial cytokines, including IFN γ and TNF α , with TLR2 deficiency linked to poor Th17 differentiation and suboptimal immune responses (Khan *et al.*, 2017). Although the targeted rs5743708 locus showed no polymorphism, other previously reported TLR2 variants were found in the sequenced region. Patients with one or more of these variants had a higher mean serum TLR2 concentration than those without detected TLR2 variation. This finding is supported by a study performed by Proença *et al.* (2015), who found that carriers of the TLR2 -196/-174 deletion variant had approximately twofold higher TLR2 mRNA expression and significantly higher protein expression than wild-type carriers. However, many variations were observed in the targeted region of the TLR2 gene, including previously reported SNPs (Table 3). The current study agrees with a study by Davoodi *et al.* (2018) re, which reported that Arg753Gln was absent among Iranian TB patients and controls.

In this study, the TLR2 rs5743708 locus showed no polymorphism: all patients and controls were homozygous GG. A similar result was reported by Wubete *et al.* (2024), who found that TLR2 G2258A (rs5743708) was monomorphic in a Northwest Ethiopian population. The GG genotype occurred in 100% of pulmonary tuberculosis patients, individuals with latent tuberculosis infection, and healthy controls; the A allele was not detected in any study group.

Interleukin beta one (IL- β 1) plays an essential role in host defence against *Mycobacterium tuberculosis* by promoting inflammatory cell recruitment, enhancing antimicrobial activity, regulating granuloma formation, and supporting communication between innate and adaptive immunity. Proper IL- β 1 signalling is considered critical for early control of mycobacterial infection and maintenance of protective immune responses (Mayer-Barber and Sher, 2015; Moreira *et al.*, 2022).

The present study shows that the mutant-type patients have a lower mean serum IL- β 1 concentration compared with wild-type patients, suggesting that this polymorphism may influence IL- β 1 production or regulation during TB infection. Since IL- β 1 is an important cytokine involved in antimycobacterial immunity, reduced IL- β 1 levels among carriers of rs1143627 may reflect impaired inflammatory signalling, altered cytokine transcription, or dysregulated inflammasome-related immune responses.

The IL β gene variation showed a strong association with increased tuberculosis susceptibility. The variation was detected in 15 of 50 TB patients compared with only 4 of 50 controls, giving an odds ratio of 4.93 with a 95% confidence interval of 1.55–15.69 and a p-value of approximately 0.0095. Therefore, this IL β variation may be interpreted as a susceptibility-associated genetic factor in the studied population. The current study agrees with a study by Zhang *et al.* (2014), who provided strong evidence for the effect of IL β rs1143627 on IL- β expression and its association with TB susceptibility and disease severity, thereby directly supporting the biological interpretation of our finding for rs1143627. In an Iraqi study, Ali and Mankhi (2022) examined IL-37 gene polymorphisms in relation to pulmonary TB susceptibility. It's not IL- β 1, but it's from the IL-1 cytokine family. This provides local evidence that genetic variation within members of the IL-1 family may influence susceptibility to TB among Iraqi patients. Similarly, Nosik *et al.* (2024) reported significantly decreased IL- β 1 levels in tuberculosis-associated disease cohorts and proposed that reduced IL- β 1 may reflect altered immune responsiveness during chronic infection.

Another study conducted by Hall *et al.* (2015) also reported that polymorphisms in IL β 1 and TICAM2 were associated with TB, further supporting the contribution of innate immune gene variation to TB susceptibility. Conversely, increased IL- β 1 levels reported in some TB studies may result from intense macrophage activation, high bacterial burden, acute inflammatory responses, or early-stage disease. During active pulmonary tuberculosis, strong innate immune activation can stimulate excessive cytokine release, leading to elevated circulating IL- β 1 concentrations (Stanciu *et al.*, 2025)

STATISTICAL ANALYSIS

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 22. Data were presented as the mean $\pm$ standard error of the mean (SEM). Serum TLR2 and IL- β 1 concentrations in variant-carrier and non-carrier patients were compared with an independent-samples t-test. Associations with pulmonary tuberculosis were reported as odds ratios with 95% confidence intervals. Statistical significance was determined at various levels of probability: *P < 0.05, **P < 0.01, ***P < 0.001, and ****P < 0.0001.

ETHICS APPROVAL:

The current study was approved by the Research Ethics Committee of the College of Science, University of Kerbala, as documented in the approval letter (No. 0048CSE, dated 17/6/2025)

LIMITATIONS OF THE CURRENT STUDY:

- 1- the relatively small sample size (50 patients and 50 controls).
- 2- Sanger sequencing made it possible to identify genetic variations in the regions studied, but the functional effects of these variants were not examined directly.

CONCLUSION:

In the Iraqi population studied, non-GG genotypes appeared more often in tuberculosis patients than in controls and were associated with increased susceptibility to pulmonary tuberculosis (OR = 4.93, 95% CI: 1.55–15.69, p = 0.0095). While patients

with the variant genotypes had lower serum IL-1 β concentrations compared to wild-type patients and controls, this difference was not statistically significant ($p = 0.470$).

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