



OPEN Association of *CD14* rs2569190 and rs2569191 polymorphisms with tuberculosis susceptibility in the Kurdish population of Iran

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Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*Mtb*), remains a leading cause of infectious disease mortality globally. Host genetic factors, particularly those involved in innate immunity like Cluster of Differentiation 14 (*CD14*), may influence susceptibility to TB. This study investigated the association of two *CD14* promoter polymorphisms, rs2569190 (C-159 T) and rs2569191 (A-1145G), with TB susceptibility in the Kurdish population of Iran. A prospective case-control study was conducted, enrolling 303 newly diagnosed TB patients (280 drug-sensitive, 23 MDR-TB) and 288 age- and sex-matched healthy Kurdish controls from Ilam, Iran. Genotyping for rs2569190 and rs2569191 was performed using PCR-RFLP. The TT genotype of rs2569190 and the GG genotype of rs2569191 were significantly more frequent in both drug-sensitive and MDR-TB patient groups compared to controls ($P < 0.05$). Under the codominant model, the TT genotype of rs2569190 (OR = 1.68, 95% CI 1.15–2.45) and the GG genotype of rs2569191 (OR = 1.55, 95% CI 1.06–2.26) were associated with increased TB susceptibility. Haplotype analysis revealed a higher prevalence of the CG haplotype in TB patients and an association of the TG haplotype with increased TB risk. In conclusions, this study suggests that the *CD14* promoter polymorphisms rs2569190 and rs2569191 are associated with increased susceptibility to tuberculosis in the Kurdish population of Iran. These findings highlight the potential role of *CD14* genetic variations in TB pathogenesis and warrant further investigation in other populations and functional studies to elucidate the underlying mechanisms.

Keywords *Mycobacterium tuberculosis*, Cluster of differentiation 14, MDR-TB, rs2569190, rs2569191

The *Mycobacterium tuberculosis* (*Mtb*) is the causative agent of tuberculosis (TB), which remains one of the deadliest infectious diseases worldwide. In 2023, an estimated 10.8 million TB cases were reported, with an incidence rate of 134 new cases per 100,000 people. To meet the targets outlined in the “End TB Strategy”—including a 10% annual reduction in TB cases by 2025 and an average yearly decline of 17% between 2025 and 2035—intensified efforts are essential¹. In 2022, an estimated 410,000 individuals worldwide were diagnosed with multidrug- or rifampicin-resistant TB (MDR/RR-TB). In 2024, the World Health Organization (WHO) designated MDR-TB as a priority pathogen on its list of antibiotic-resistant bacteria, citing its substantial impact on morbidity and mortality, long-term health consequences, high financial burden, and the complexity of mounting an effective health response^{1,2}.

To identify genes critical for effective host defense mechanisms, host genetics may offer valuable insights into susceptibility to TB. However, this approach has had limited success in TB research, as susceptibility loci identified through genome-wide association studies (GWAS) have often failed to replicate across different populations—despite GWAS proving effective in uncovering genetic associations in other diseases^{3,4}. Nevertheless, several studies have reported associations between specific alleles within the human leukocyte antigen (HLA) class II region and pulmonary TB, possibly due to reduced T cell-mediated presentation of protective *Mtb* antigens^{5,6}.

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Additionally, other GWAS have identified loci related to innate immunity, which are known to play key roles in determining the risk of Mtb infection and disease outcomes^{4,7}.

Macrophage activation is a critical early event in the innate immune response to intracellular infections. Cluster of differentiation 14 (CD14), primarily expressed by cells of the monocyte/macrophage lineage, plays a key role in the innate recognition of bacterial cell wall components. Acting as a co-receptor for toll-like receptors (TLRs), CD14 facilitates the detection of microbial components, leading to cellular activation and the initiation of various effector functions, including cytokine secretion and cell proliferation^{8–10}.

Numerous single nucleotide polymorphisms (SNPs) within the promoter region of the *CD14* gene have been identified as influencing *CD14* expression or being associated with various diseases. However, previous studies have been limited in scope, often lacking a comprehensive analysis of all SNPs within this region. To date, eight common SNPs—such as C-159 T (rs2569190) and A-1145G (rs2569191)—with minor allele frequencies greater than 10% have been identified within the *CD14* promoter region, spanning the DNA sequence from –4000 bp to +1 bp¹¹. In this regard, two SNPs, rs2569190 and rs2569191, have been shown to influence immune responses and play a key role in modulating the risk of developing TB^{11,12}.

The role of these SNPs in susceptibility to TB remains poorly understood. This study aimed to investigate the association between the rs2569190 and rs2569191 polymorphisms in the *CD14* gene and susceptibility to tuberculosis in the Kurdish population of Iran.

Material and methods

Patients and controls

A prospective case–control study was conducted at a hospital in Ilam, Iran, from May 2020 to April 2024. A total of 303 newly diagnosed TB patients were enrolled, including 23 cases of MDR-TB and 280 cases of drug-sensitive TB. Pulmonary TB was diagnosed based on clinical evaluation, positive sputum smears for acid-fast bacilli, culture on Löwenstein–Jensen medium, and chest X-ray findings. Additionally, 288 healthy control individuals were recruited from the same geographic region. All participants were of Kurdish ethnicity. Individuals who tested positive for human immunodeficiency virus (HIV), coronavirus disease 2019 (COVID-19), had a history of cancer, autoimmune, metabolic, or endocrine disorders, or were pregnant were excluded from the study. All methods were carried out in accordance with relevant guidelines and regulations. Written informed consent was obtained from all participants after providing a thorough explanation of the study and ensuring complete confidentiality. The study was approved by the Ethics Committee of Ilam University of Medical Sciences (IR.MEDILAM.REC.1403.018).

Genotyping of *CD14* rs2569190 and rs2569191 polymorphisms

Total genomic DNA was extracted from EDTA-treated blood samples using the Yekta Tajhiz DNA extraction kit (Yekta Tajhiz, Tehran, Iran). Genotyping was conducted using the polymerase chain reaction–restriction fragment length polymorphism method (PCR–RFLP) as follows: the rs2569190 polymorphism was analyzed using the forward primer 5′-GTGCCAACAGATGAGGTTCAC-3′ and reverse primer 5′-GCCTCTGACAGT TTATGTAATC-3′ with an annealing temperature of 65 °C. After PCR amplification, the product (497 bp) was digested with 2 units of *AvaII* (New England Biolabs, Frankfurt, Germany) for 4 h. The resulting fragments were then visualized on a 2% agarose gel. Three distinct banding patterns were observed: a single band at 497 bp, indicating CC homozygotes; three bands at 144, 353, and 497 bp, representing CT heterozygotes; and two bands at 144 and 353 bp, corresponding to the TT homozygous mutant¹³.

The rs2569191 polymorphism was identified using the forward primer 5′-CTCAGGAATCTGAGGCAAGA-3′ and reverse primer 5′-AGTACAATCTCTGTGCCCTA-3′ with an annealing temperature of 65 °C. After PCR amplification, the product was digested with 1 unit of *HpyCH4V* (New England Biolabs) for 4 h. Digestion of the wild-type allele (AA) resulted in three fragments of 230 bp, 70 bp, and 71 bp, consistent with complete digestion at both recognition sites. In heterozygous individuals (AG), four fragments were observed: 300 bp, 230 bp, 71 bp, and 70 bp, indicating the presence of both digested and undigested products. Homozygous mutant genotypes (GG) displayed two bands of 300 bp and 71 bp, representing the digestion pattern specific to the polymorphic allele¹³.

A minimum of 10% of the samples were randomly selected and genotyped using the Sanger sequencing method to confirm the PCR–RFLP results. The results of the sequencing were fully concordant with those obtained by PCR–RFLP, supporting the reliability of the genotyping method used in this study.

Statistical analysis

Continuous data are presented as mean ± standard deviation (SD), while categorical variables are expressed as percentages. Pearson's chi-squared test was used to assess the relationship between demographic factors and TB susceptibility, along with Hardy–Weinberg equilibrium (HWE). The Mann–Whitney U-test was employed to evaluate the impact of age and blood parameters on TB susceptibility. Two-tailed *P*-values were calculated, with values below 0.05 considered statistically significant (SPSS v.22.0, Inc., Chicago, IL, USA). The study also examined the associations between various genotypes and the likelihood of TB susceptibility by calculating odds ratios (ORs) and 95% confidence intervals (CIs) across four distinct inheritance models: dominant, co-dominant, over-dominant, and recessive. Additionally, haplotype analysis was conducted using the SNPStats web software (<https://www.snpstats.net/snpstats/start.htm>).

Results

Clinical and demographic characteristics of TB patients and healthy controls

Table 1 summarizes the clinical characteristics of both the patient and healthy control groups. Of the 303 TB patients, 280 were diagnosed with drug-sensitive TB, while 23 had MDR-TB. The study also included 288 age- and sex-matched healthy control. The mean age was 56.5 ± 11.8 years for drug-sensitive TB patients, 57.1 ± 10.4 years for MDR-TB patients, and 56.5 ± 12.0 years for the control group. In the TB group, 64.7% were male, compared to 64.6% in the control group. There were no significant differences in mean age or gender distribution between the TB patient and healthy control groups ($P > 0.05$). The body mass index (BMI) and vitamin D levels differed significantly between the TB patient groups and the healthy control group ($P < 0.05$).

Genotype frequencies of CD14 rs2569190 and rs2569191 polymorphisms

Figure 1 illustrates the frequencies of CD14 rs2569190 and rs2569191 genotypes in TB patients and healthy controls. The TT genotype of rs2569190 and the GG genotype of rs2569191 were significantly more frequent in both drug-sensitive TB and MDR-TB groups compared to the healthy control group ($P < 0.05$).

Table 2 presents the genetic distribution of TB patients in comparison to the healthy control group. The codominant model provided the best fit for CD14 rs2569190, with the TT genotype significantly associated with an increased risk of TB susceptibility. Additionally, the frequency of the minor allele (T) of the rs2569190 SNP was higher among TB patients compared to healthy controls. The HWE was not observed in either the patient or healthy control group.

The codominant model yielded the best results for CD14 rs2569191, with the G allele linked to increased susceptibility to tuberculosis, while the A allele was associated with resistance to TB infection. The minor allele frequency (A) of the rs2569191 SNP was higher in the healthy control group. The HWE was observed in the healthy control group ($P = 0.91$), but not in the TB patient group.

Haplotype distribution of CD14 rs2569190 and rs2569191 polymorphisms

The haplotype association analyses were performed for the genetic SNPs under investigation and their potential link to TB susceptibility (Table 3). The analysis of CD14 polymorphisms revealed a higher prevalence of the CG haplotype in both TB patient groups. Additionally, a correlation was observed between the TG haplotype and increased susceptibility to TB.

Discussion

The results indicate that the CD14 rs2569190 and rs2569191 polymorphisms are associated with an increased susceptibility to TB in the Kurdish population, aligning with the role of CD14 in innate immunity. CD14, primarily located on monocytes and macrophages, is essential for recognizing bacterial components through TLRs, triggering immune responses such as cytokine secretion and cell proliferation^{8–10}. Variations in the CD14 promoter region, including rs2569190 and rs2569191, have been shown to affect CD14 expression, potentially influencing immune responses to Mtb^{11,12}.

This study found that the T allele and TT genotype of the rs2569190 polymorphism in the CD14 gene are associated with an increased risk of TB, particularly within the Iranian population. Consistent with these findings, Alavi-Naini et al. reported that individuals carrying the TT genotype had a 3.5-fold higher risk of developing TB compared to those with the CC genotype¹⁴.

A meta-analysis of seven studies involving various populations (Iran, Turkey, China, Korea, Mexico, Poland, and the USA) also showed a significant association between the T allele/TT genotype and increased TB risk. However, results were not consistent across all populations—e.g., a study in Turkey found no significant link—indicating potential population-specific differences^{15,16}. The deviation from HWE in the TB patient group for rs2569190 may suggest a potential association between this polymorphism and disease susceptibility. However, factors such as population stratification and other confounding variables must also be taken into account, which calls for further investigation.

This study is the first to suggest a potential association between the CD14 rs2569191 polymorphism and susceptibility to TB. Our findings indicate that the G allele is linked to an increased risk of TB infection. Evidence regarding rs2569191 remains relatively limited. Two studies that reported a significant association between the G allele and an increased risk of tuberculosis, consistent with the present study’s observation of a higher frequency of the GG genotype among TB patients. These findings suggest that rs2569191 may play a role

Variables	Subjects			P-value
	MDR (n = 23)	Sensitive (n = 280)	Healthy control (n = 288)	
Mean age ± SD	57.1 ± 10.4	56.5 ± 11.8	56.5 ± 12.0	0.972
Gender (male/female)	18/5 (78.3/21.7%)	178/102 (63.6/36.4%)	186/102 (64.6/35.4%)	0.367
BMI	19.7 ± 1.5	20.3 ± 2.3	23.2 ± 1.7	<0.001*
Smoking users (Yes/No)	13/10 (56.5/43.5%)	115/165 (41.1/58.9%)	135/153 (46.9/53.1%)	0.189
25-hydroxy vitamin D, ng/mL (mean ± SD) (Sufficiency: 21–150)	17.4 ± 3.1	24.8 ± 8.6	31.7 ± 11.7	<0.001*

Table 1. Comparison of clinical laboratory parameters between TB patients and healthy controls. TB tuberculosis; MDR multi-drug resistance; BMI body mass index; SD standard deviation; *Statistically significant (<0.05).

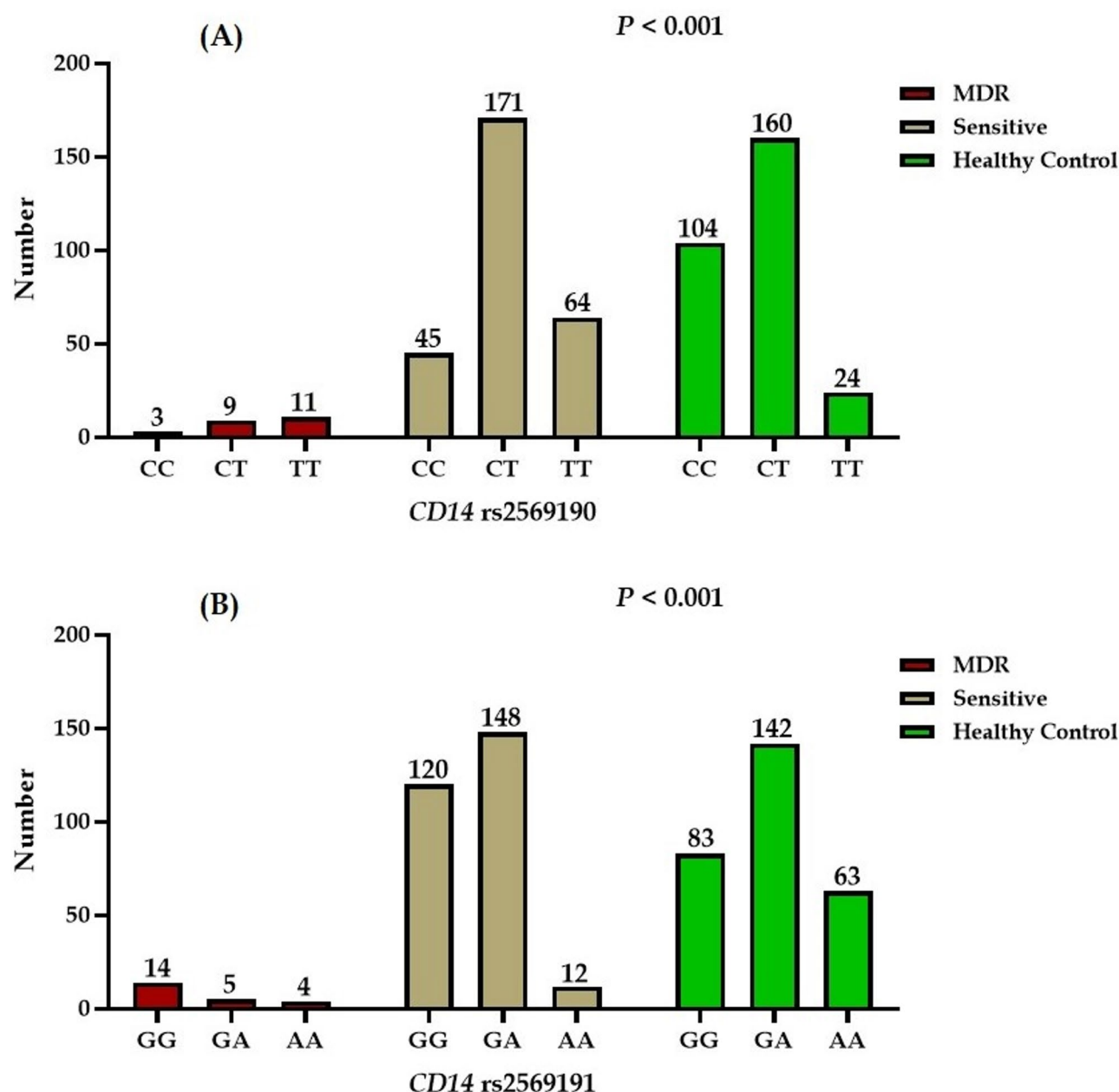


Fig. 1. The frequencies of CD14 rs2569190 and rs2569191 genotypes in TB patients and healthy controls.

in TB susceptibility; however, further research is needed to confirm its impact across different populations^{11,12}. The presence of HWE in the healthy control group for rs2569191 strengthens the significance of the deviation observed in the tuberculosis patient group, suggesting a potential role for this polymorphism in the pathogenesis of TB within this population.

Haplotype analysis showed that the CG haplotype was more frequent among TB patients, while the TG haplotype was associated with an increased risk of developing TB. These findings suggest a possible interaction or synergistic effect between the two *CD14* promoter polymorphisms in influencing TB susceptibility. Further functional research is needed to clarify how these specific haplotypes affect *CD14* gene expression and the resulting protein function in response to *Mtb* infection.

According to Gu et al. both SNPs (rs2569190 and rs2569191) have the potential to significantly influence the transcriptional activity of the *CD14* promoter, which may, in turn, affect *CD14* expression. As a result, individual differences in *CD14* expression and the inflammatory response to TB could be attributed to *CD14* polymorphisms. However, the study also found that TB patients with the *CD14* rs2569191 GG genotype exhibited similar levels of membrane-bound CD14 and soluble CD14 compared to those with other genotypes, suggesting that the functional consequences of these polymorphisms may be context-dependent or influenced by additional regulatory factors¹⁷.

CD14 rs2569190		Groups		OR (95% CI)	P-value	AIC	BIC
Model	Genotype	Healthy control	TB patients				
Allele	C	368 (64.0%)	276 (46.0%)	–	–	–	–
	T	208 (36.0%)	330 (54.0%)	–	–	–	–
Codominant	C/C	104 (36.1%)	48 (15.8%)	1.00	< 0.0001*	752.1	769.7
	C/T	160 (55.6%)	180 (59.4%)	3.54 (2.29–5.45)			
	T/T	24 (8.3%)	75 (24.8%)	18.58 (9.12–37.87)			
Dominant	C/C	104 (36.1%)	48 (15.8%)	1.00	< 0.0001*	785.8	799.0
	C/T-T/T	184 (63.9%)	255 (84.2%)	3.79 (2.46–5.82)			
Recessive	C/C-C/T	264 (91.7%)	228 (75.2%)	1.00	< 0.0001*	784.7	797.9
	T/T	24 (8.3%)	75 (24.8%)	5.65 (3.19–10.02)			
Overdominant	C/C-T/T	128 (44.4%)	123 (40.6%)	1.00	0.34	824.0	837.2
	C/T	160 (55.6%)	180 (59.4%)	1.17 (0.84–1.62)			
Minor allele frequency (T)		0.36	0.54	–	–	–	–
CD14 rs2569191							
Allele	G	308 (53.0%)	421 (69.0%)	–	–	–	–
	A	268 (47.0%)	185 (31.0%)	–	–	–	–
Codominant	G/G	83 (28.8%)	134 (44.2%)	1.00	< 0.0001*	753.6	771.1
	G/A	142 (49.3%)	153 (50.5%)	0.37 (0.25–0.57)			
	A/A	63 (21.9%)	16 (5.3%)	0.04 (0.02–0.09)			
Dominant	G/G	83 (28.8%)	134 (44.2%)	1.00	< 0.0001*	802.8	815.9
	G/A-A/A	205 (71.2%)	169 (55.8%)	0.37 (0.25–0.57)			
Recessive	G/G-G/A	225 (78.1%)	287 (94.7%)	1.00	< 0.0001*	773.7	786.9
	A/A	63 (21.9%)	16 (5.3%)	0.11 (0.06–0.21)			
Overdominant	G/G-A/A	146 (50.7%)	150 (49.5%)	1.00	0.77	824.8	838.0
	G/A	142 (49.3%)	153 (50.5%)	1.05 (0.76–1.46)			
Minor allele frequency (A)		0.47	0.31	–	–	–	–

Table 2. Association of *CD14* rs2569190 and rs2569191 polymorphisms with susceptibility to TB. *CD14* cluster of differentiation 14; *TB* tuberculosis; *OR* odds ratios; *CI* confidence intervals; *AIC* Akaike information criterion; *BIC* Bayesian information criterion; *Statistically significant (<0.05).

Haplotypes	Frequency	Healthy control	TB patients
		OR (95% CI)	OR (95% CI)
CG	0.477	1.00	1.25 (0.68–2.28)
TA	0.3154	1.00	0.76 (0.43–1.33)
CA	0.0678	1.00	0.85 (0.60–1.18)
TG	0.1397	1.00	3.02 (2.21–4.11)

Table 3. *CD14* SNP haplotypes in healthy controls and TB patients. Significant values are in bold. *CD14* cluster of differentiation 14; *SNPs* single nucleotide polymorphisms; *TB* tuberculosis; *OR* odds ratios; *CI* confidence intervals.

There is increasing evidence suggesting that CD14 signaling plays a crucial role in the host response to intracellular bacterial pathogens such as *Mtb*. Elevated levels of soluble CD14 have been detected in the sera and bronchoalveolar lavage fluid of patients with active TB^{18,19}. However, the exact impact of *CD14* expression levels on the progression of TB remains insufficiently understood. It is hypothesized that an increase in *CD14* expression induced by *Mtb* could contribute to the immune pathogenesis of TB by enhancing interactions with mannoseylated lipoarabinomannan. This interaction may lead to increased production of transforming growth factor β , which could suppress immune responses²⁰. Additionally, there is evidence indicating that CD14 plays a significant role in regulating immunoglobulin E (IgE) responses, as it promotes T helper 1 (Th1) differentiation while inhibiting Th2-dependent IgE responses^{21,22}.

This investigation has several limitations. First, the study was conducted at a single center and focused specifically on Iranian Kurds, which may limit the applicability of the findings to other ethnic groups. Iran is a genetically diverse country, comprising Persians, Azeris (Turks), Arabs, Baluchis, Gilaks, Mazandarani, Lors, Turkmen, and others. Given the heterogeneity in genetic susceptibility to tuberculosis across different populations and geographic regions, the results may not be fully representative of the broader Iranian population or other ethnic backgrounds. Second, while the sample size is sufficient for a candidate gene association study, larger, multi-center studies are necessary to confirm these findings and explore potential interactions with other

genetic and environmental factors. The study focused solely on two polymorphisms within the *CD14* promoter, but further research should investigate additional SNPs within the *CD14* gene and its regulatory regions, as well as their functional implications on *CD14* expression and protein function. Finally, this study did not include functional studies assessing *CD14* expression levels in individuals with different genotypes or their in vitro responses to Mtb infection. Such investigations are essential to validate the biological significance of the observed associations.

In summary, our results highlight a significant association between the rs2569190 and rs2569191 polymorphisms in the *CD14* gene promoter and the risk of tuberculosis in the Kurdish population of Iran. The TT genotype of rs2569190, the GG genotype of rs2569191, and the TG haplotype were all linked to an increased risk of developing TB. These findings deepen our understanding of the genetic factors that may influence susceptibility to TB and suggest a potential role for *CD14* in the pathogenesis of this critical global health issue. Further research is needed to validate these results across diverse populations and to elucidate the functional mechanisms behind these genetic associations, which may eventually pave the way for the development of novel diagnostic and therapeutic strategies for TB.

Data availability

The datasets generated and/or analysed during the current study are available in the PubMed SNP repository, [<https://www.ncbi.nlm.nih.gov/snp/rs2569190>, <https://www.ncbi.nlm.nih.gov/snp/rs2569191>]

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Author contributions

FS and MGJ: Performed the experiments and manuscript preparation; IA and SB: Clinical sample and data acquisition; EA: analyzed data and interpreted data; AF: designed and supervised clinical study, interpreted data, read and approved manuscript. All authors reviewed the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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