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Research Article

Genetic Polymorphisms of Toll-like Receptor 2 (rs7656411) among Pulmonary Tuberculosis Patients in Selected Healthcare Facilities in Abeokuta, Ogun State

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ABSTRACT

Toll-like receptor 2 (TLR2) is a key pattern recognition receptor in the innate immune system that detects components of *Mycobacterium* species and initiates immune responses against infection. Dysfunction of TLR2 can impair this recognition, potentially increasing susceptibility to disease. This study investigated whether single nucleotide polymorphisms (SNPs) in the TLR2 gene, specifically rs7656411, are associated with susceptibility to pulmonary tuberculosis (pTB). The research used a case-control design conducted between November 2024 and January 2025. It included 83 patients diagnosed with pTB and 47 healthy controls. Diagnosis of pTB was confirmed using blood and sputum samples through microscopic examination and molecular testing with GeneXpert. DNA was extracted from blood samples, and the TLR2 rs7656411 SNP was genotyped using polymerase chain reaction followed by restriction fragment length polymorphism analysis (PCR-RFLP). The study population was predominantly male, making up 60% of participants, with females accounting for 40%. The largest age group was 31-40 years, representing 40% of the sample. Demographically, 68.5% identified as Christian, 60.8% were married, and 40% worked as traders. Educational attainment was relatively high, with 66.9% having tertiary education. Ethnically, 71% were Yoruba. By comparing the distribution of TLR2 rs7656411 SNPs between pTB patients and healthy controls, the study aimed to determine if this genetic variation impairs TLR2 function and contributes to increased risk of developing pulmonary tuberculosis. The findings clarify the role of host genetic factors in TB susceptibility and inform future research on targeted prevention or treatment strategies for high-risk individuals.

Keywords: Single nucleotide polymorphism; Southwestern Nigeria; Susceptibility; Toll-like receptor 2; Tuberculosis

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INTRODUCTION

Tuberculosis (TB) is a common, preventable, and chronic disease caused by members of the *Mycobacterium tuberculosis* (*Mtb*) family, also called tuberculosis complex (Zhang *et al.*, 2013; Zhou and Zhang, 2020). Tuberculosis complex is a family of closely related species capable of infecting any part of the body of humans and animals (Szacawa *et al.*, 2025). It usually affects the lungs and/or any other part of the body and may manifest as pulmonary or extra pulmonary tuberculosis (Dong *et al*., 2025). *Mycobacterium tuberculosis* is the predominant pathogen in human, although, *M. bovis*, *M. africanum* and *M. canetti* can also infect humans (Adugna *et al*., 2018).

In 2024, an estimated 10.7 million TB cases and 1.23 million deaths were reported worldwide, equivalent to approximately 131 cases per 100,000 population annually (WHO, 2025). South East Asia and Africa share the largest burden of TB in the world (Lee *et al.,* 2025). Despite many public health interventions, Nigeria is among the highest TB prevalent countries in the world, and ranked fourth in Africa (Olaleye *et al*., 2023). This may in part, due to weak healthcare delivery system, inadequate infrastructure and socioeconomic challenges facing low- and middle-income countries (Ogunniyi *et al.,* 2024). Ogun State is located in Southwestern Nigeria and is one of the areas significantly affected by TB (Daniel *et al*., 2023). An estimated 25% of global population are infected with *Mtb* resulting in latent TB (WHO, 2026). Approximately, 5-10% of the infected patients develop active TB symptoms within the first 2 years, while other 5% develop the TB symptoms later (States Geiter, 2000; and CDC, 2025). The risk factor which is the geographical location including South East Asia or Africa, has the highest burden of TB. These risk factors underscore variation in TB risk among exposed individuals (Zhuang *et al*., 2024). The risk of infection following exposure to TB is primarily governed by both endogenous and exogenous factors (Narasimhan *et al*., 2013). Exogenous factors involve a complex interplay between pathogen virulence and invasiveness, proximity to an infected person, length of exposure, social and behavioural factors like smoking, alcoholism and air pollution (Davidson *et al*., 2024). On the other hand, endogenous factors are host related factors involving altered immune responses that increases the risk of progression of latent TB infection to active TB (Asgharzadeh *et al*., 2025).

Host immunity is implicated in human susceptibility to infectious diseases including tuberculosis *(*Zhuang *et al.,* 2024). Innate immunity serves as the first line of defence against pathogenic invasion by mediating recognition of pathogenic-associated molecular patterns via pattern recognition receptors (PRRs) located on immune cells, activation of signalling pathways, upregulation of cytokine and chemokine production, recruitment of adaptor proteins, and development of adaptive immune response (Wang *et al*., 2024).

The Toll-like receptors are group of transmembrane proteins expressed on extracellular surface or cytosol of various immune cells including macrophages (Behzadi *et al.,* 2021). Thirteen different subtypes exist but only 10 are found in humans (TLR-1 –10) and are implicated with different infectious diseases such as leprosy and rhinitis tuberculosis (Behzadi *et al.*, 2021). Studies showed an association between TLR 1, 2, 4, 6, 8 and 9 and TB risk (Zhang, 2020b; Mahmoud, 2023). The TLR2 is the most common of the TLRs due to its ability to recognize the broadest range of pathogen-associated molecular patterns (PAMPs) (Zähringer *et al*., 2008). It is also unique because it interacts with TLR1 and TLR6 to form a heterodimer to recognize pathogen associated molecular patterns (PAMPs) of *Mtb (Triantafilou et al., 2006)*. This interaction results in initiation of downstream signalling pathway, activation of innate immune response, production of cytokines and formation of adaptive immune response *(*Sudarto *et al., 2026)*.

The TLR2, like the other TLRs, is encoded and expressed by *TLR* gene. Mutations in *TLR2* gene may affect TLR2 function as a modulators of immune response *(Mukherjee et al., 2019)*. Hence, single nucleotide polymorphisms (SNPs) in TLR2 gene can alter ligand-receptor binding or modulate receptors signalling, thus influencing TB susceptibility or resistance (Mukherjee *et al.,* 2019).

Three TLR2 (rs7656411) genotypes have been studied (TT, CC and CT) (Kobayashi *et al.,* 2022). The expression of TT (homozygous) genotype is implicated in protective response and exhibit normal TLR2 receptor function by providing effective recognition of *M. tuberculosis* antigens, strong activation of macrophages and adequate production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 (Quesniaux *et al*., 2024). These cytokines promote granuloma formation, which are essential for containing the bacteria within lung tissue (Wong *et al*., 2020). Thus, the TT genotype are often associated with better immune containment of infection, and promoting lower risk of progression from latent TB infection to active cases (Lawn *et al.,* 2021). Conversely, the CC genotype is often associated with altered TLR2 receptor activity by promoting weaker recognition of *M. tuberculosis*, reduced activation of intracellular signalling pathways such as NF-κB and lower production of protective cytokines like TNF-α and IL-12 (Liu *et al., 2022*). These may lead to reduced macrophage activation and the bacteria may survive longer inside the macrophages to multiply and spread within lung tissues, causing an increased risk of active tuberculosis and more severe disease progression (Lawn *et al.,* 2021). The CT is a heterozygous genotype which provide intermediate response (Drenam., 2019). The TLR2 signalling pattern in individuals carrying the CT genotype may be partially altered (Drenam, 2019). Thus, the immune response may be intermediately reduced with variable cytokine production and partial macrophage activation which may lead to intermediate resulted susceptibility to TB (Wong *et al.*, 2020).

Several studies reported links between TLR2 polymorphisms and TB susceptibility (Zaki *et al*., 2018; Liu *et al*., 2020). However, some studies showed no evidence of association between TLR2 polymorphism and TB susceptibility or inconclusive (Jin *et al.,* 2020). Hence, the need for studies from other populations for better elucidation. Few studies have reported on links between TLR2 polymorphism and TB risk among Africans (Ben-Ali *et al*., 2004) but no association studies have been conducted on Nigerian TB patients, particularly in Ogun state. Therefore, this study is designed to evaluate the association between TLR2 gene polymorphism and TB susceptibility among residents of Abeokuta, Ogun State.

MATERIALS AND METHODS

Study Population

A case-control, cross-sectional study was conducted between November, 2024 and January, 2025 at Abeokuta, Ogun state. A total of 130 participants, comprising of 83 pulmonary TB patients and 47 healthy controls, were recruited from three (3) TB treatment facilities within Abeokuta metropolis.

Study Site

Abeokuta is an ancient Yoruba town with rich historical and cultural heritage (Adépégba and Abati, 2024). It is the capital of Ogun state and it is located in Southwest Nigeria. According to 2006 census figures, the town has a population of 449,008 with an annual growth rate of 3.03% and a landmass of 897 square kilometres. Its inhabitants are mostly traders. It geographically lies between latitude 7^0 5' N to 7^0 20' N and longitude 3^0 17' E to 3^0 27' E.

The treatment facilities are Federal Medical Centre (FMC), Abeokuta; State Hospital, Ijaiye, Abeokuta and Sacred Heart Catholic Hospital, Lantoro, Abeokuta.

Abeokuta is home to several public and private hospital that span all three level of healthcare delivery system in Nigeria. Sacred Heart hospital is the first and oldest hospital in Nigeria that was established by the Catholic mission in 1895. It is a private hospital that operates secondary healthcare delivery involve Directly Observed Treatment Short-course (DOTs) for TB patients.

Federal Medical Centre, Abeokuta is a public hospital established by the Federal government of Nigeria in 1993. It offers secondary level of healthcare and also has specialized unit for diagnosis and treatment of TB that serve as DOTs centre.

State Hospital, Ijaiye is a state-owned secondary health facility located in Abeokuta South Local government. It has a DOTs centre that delivers care for TB patients.

Ethical consideration

Ethical approval for the study was obtained from the Research and Ethics Review committee, Federal Medical Centre, Abeokuta, Ogun state (FMCA/470/HREC/01/2023/30). A duly signed and written informed consent was equally obtained from all the participants before enrolment into the study.

Collection of Samples

A well-structured interviewer-administered questionnaire was used to collect socio-demographic, as well as, information on TB risk factors of participants. Blood and two consecutive days early morning sputum samples were also collected and stored at -20^{0}C for further analysis. The sputum samples were used for microscopic detection and cell culture examination of *Mtb* while the blood sample was used to genotype and detect single nucleotide polymorphisms (SNPs) in TLR2 gene.

Microscopic detection of *Mtb*

Sputum smear was prepared using a slightly modified Ziehl-Neelsen (ZN) procedure (Vasanthakumari *et al*., 1986). The sputum was smeared and evenly spread with a sterile bacterial loop on a grease-free glass slide. It was allowed to air-dry for 15-30 mins before fixing by passing the underside of the slide 2-3 times over a blue flame of a Bunsen burner. The smear was then flooded with 1% fuchsin solution and heated for 5 mins. The smear was decolourized with 25% H_2SO_4 solution for 2-3 mins before gently rinsing with water. It was then counterstained with 0.1% methylene blue for 30 secs. The slides were again rinsed with water, air-dried and examined under light microscope by an expert microscopist.

Molecular detection of *M. tuberculosis* (GeneXpert)

Mycobacterium tuberculosis (*Mtb*) was detected in sputum samples using kits (GeneXpert®) as described by the manufacturer.

DNA extraction

Genomic DNA was extracted from blood samples using QIAamp® DNA Mini Kit (Qiagen, Hilden, Germany) as described by the manufacturer. The extracted DNA samples were stored at

-20^{0}C for further analysis.

Single nucleotide polymorphism (SNP) of TLR2 gene

The TLR2 gene polymorphism (rs656411) was detected using polymerase chain reaction (PCR) followed by restriction fragment length polymorphism of the amplified TLR2 gene. The TLR2 gene amplification was done using primers adopted from Mhmoud (2023). Briefly, amplification was performed in a 25µL reaction volume consisting of 5µL FIREPol® master mix (Solis Biodyne, Estonia), 1µL each of forward (5'-ACGTTGGATGCCTTTAAATTACTGTGTATC-3') and reverse primers (5'-ACGTTGGATGGTACATGTGAGCTAAATAG-3'), 13µL of nuclease-free water and 5 µL of genomic DNA as template. The thermocycling conditions for the reaction follow: 4 mins of initial denaturation at 94^{0}C; 30 cycles of 30 secs each of denaturation, annealing and extension at 94^{0}C, 55^{0}C and 72^{0}C; and a final extension step at 72^{0}C for 70 secs.

After amplification, restriction digestion was performed using PciI (New England Biolabs® Inc, Ipswich, Massachusetts, USA; Cat. No. R0655S) following the manufacturer's instructions. Amplicon digestion was performed in a 20 µL reaction volume containing: 2 µL of 10X NEBuffer™ r3.1, 10 units of PciI, 8 µL of nuclease-free water and 10 µL of PCR amplicon. The reaction mixture was then incubated at 37°C overnight. The digested product was electrophoresed on a 1.5% agarose gel pre-stained with SafeView™ Classic DNA dye (Applied Biological Materials Inc., Canada), visualized under a UV trans-illuminator (Dark Reader®, Clare Chemical Research) and photo-documented. The sizes of the fragments were estimated using a 100bp molecular weight ladder (Solis BIODYNE, Tartu, Estonia).

Data Analysis

Data were analysed using Statistical Package for Social Sciences (SPSS v. 26.0). Mean and proportion were obtained using descriptive statistics. Proportion between two groups was compared using Chi-square. Multi-group comparison was done using one-way ANOVA. Differences were considered significant at $p < 0.05$.

RESULTS

Sociodemographic data of participants

The socio-demographic information about the participants is shown in Table 1. The largest pool of participants was between the ages of 31-40 years old and constitute 40% of the pool of participants (n=52). Other age categories – 20-30, 41-50 and > 50 – constitute approximately 17%, 21% and 22% of participants respectively. At $p < 0.05$, there was no significant difference in proportion among the age categories ($p = 0.10$). The predominant gender among the participants were males, constituting 60% (n=78) while the females accounted for 40% (n=52). The difference in proportion between the genders was statistically significant ($p = 0.04$). The religion practiced by the participants were Islam, Christianity and Traditional religion. Most of the participants (68.5%) were Christians while the Muslim participants constituted 29% of participants with few Traditionalist (2.3%, n=3). The difference in the proportion of Muslims, Christian and traditional worshippers was statistically significant ($p=0.00$).

The Yoruba tribe was the predominant ethnic group among the participants making up the majority of participants (71%), followed by the Igbo tribe (19.2%, n=25) then, Hausa tribe (8.5%, n=11). The difference in ethnicity among the participants was significant ($p=0.00$). Most of the participants are married (60.8%) while the remaining 39.2% of participants (n=51) are either single (n =41), divorced (n=8), or widowed (n=2). The marital status among participants was significant ($p=0.00$). Participant's occupation in the study was categorized into 4: artisan, traders, civil servants and unemployed. While the proportion of participants that are artisans, civil servants and traders are 20%, 31% and 40% respectively, only 9.2% are unemployed. There is no difference in proportion among the 4 categories of occupations of participants ($p=0.10$). The proportion of participants increases with increasing level of educational attainment and vice-versa. While only 4.6% (n=6 had no formal education), 8.5% (n=11) completed primary school education, 20% (n=26) completed secondary school education and 66.9% (n=87) completed tertiary education. There was difference in the proportion of participants across the levels of educational attainment ($p=0.00$).

Associated risk factors of tuberculosis

The risk factors of tuberculosis comprising of family size, living condition, and alcohol and smoking history were summarized (Table 2). Family size was grouped into 3 categories: <4, 4-6 and >6 individual. Approximately 37% of participants had less than 4 family members, 55% had 4-6 family members and 8.5% had more than 6 family members. There was significant difference in the proportion of family size of participants. Over half of the participants (51.5%, n=67) lived in a flat, 34.6% (n=45) lived in a self-contained apartment, and 13.9% (n=18) lived in a single room apartment. The living conditions of participants varies significantly ($p=0.01$). While 56.1%

of participants had no history of alcohol consumption, 43.9% had history of alcohol intake. Over 60% of participants (n=84) had never smoked while 35.5% (n=46) had smoking history.

Genotyping of *TLR2*

Three genotypes of the TLR2 gene (TT, CC and CT) were identified by extrapolating the band sizes of the digested products (Table 3). The genotypes (TT, CC and CT) between TB patients and healthy controls were compared. The TT allele (wild type) was the most prevalent allele of the TLR2 gene (res: 7656411) among the TB patients. Out of 83 TB patients, approximately 55.4% (n=46), 23% (n=19) and 8.4% (n=7) had the TT, CC and CT alleles respectively. Eleven of the TB patients (13.3%) had none of the three genotypes. Similar to TB patients, TT genotype was the most prevalent among healthy controls. Out of 47 healthy controls, the frequency of TT, CC and CT genotypes were 33 (70.2%), 2 (4.3%) and 4 (8.5%) respectively. The TB patients had significantly higher proportion of CC genotype compared to Healthy controls (p=0.01), higher proportions of CT and TT genotypes in TB patients against controls were not statistically significant at p< 0.05.

Table 1: Socio-demographic characteristics of participants

Variable	Frequency (n)	Percentage (%)	p-value
Age (years)			0.10
20-30	22	16.9	
31-40	52	40.0	
41-50	27	20.8	
>50	29	22.3	
Gender			0.04
Male	78	60.0	
Female	52	40.0	
Religion			0.00
Islam	38	29.2	
Christianity	89	68.5	
Traditionalist	3	2.3	
Ethnicity			0.00
Yoruba	91	71.0	
Igbo	25	19.2	
Hausa	11	8.5	
Other	3	2.3	
Marital status			0.00
Single	41	31.5	
Married	79	60.8	
Divorced	8	6.2	
Widowed	2	1.5	
Occupation			0.10
Artisan	26	20.0	
Trader	52	40.0	
Civil servant	40	30.8	
Unemployed	12	9.2	
Educational status			0.00
Primary	11	8.5	
Secondary	26	20.0	
Tertiary	87	66.9	
None	6	4.6	

Table 2: Risk factors of Tuberculosis

Variables	Frequency	Percentage (%)	p-value
Family size			0.01
<4	48	36.9	
4-6	71	54.6	
>6	11	8.5	
Living condition			0.01
Self-contained apartment	45	34.6	
Flat	67	51.5	
Single room apartment	18	13.9	
History of Alcohol Intake			0.22
Yes	57	43.9	
No	73	56.1	
History of Smoking			0.00
Yes	46	35.4	
No	84	64.6	

Table 3: Genotype distribution of TLR2 gene

Genotype	Frequency (n, %)		
	TB patients (n=83)	Healthy controls (n=47)	p-value
TT	46 (55.4)	33 (70.2)	0.21
CC	19 (22.9)	2 (4.3)	0.01
CT	7 (8.4)	4 (8.5)	0.75
None	11 (13.3)	8 (17.0)	0.75

None denotes participants whose DNA failed amplification None denotes participants whose DNA failed amplification

DISCUSSION

In this study, we examined and compared TLR2 (rs 7656411) single nucleotide polymorphisms (TT, CC and CT) among pulmonary tuberculosis patients and healthy controls. Evidence from our study shows the TT genotype was well expressed in both groups, while the variant CC genotype was significantly associated with TB. The heterozygous (CT) genotype was also associated with TB but this was not statistically significant. Despite widespread vaccination against TB, Nigeria still experiences high TB morbidity and mortality (Coscolla *et al.,* 2010). Host genetics contribute significantly to modulating and regulating immune responses following exposure to pathogens. However, genetic variations have been implicated in differential severity and susceptibility to infections including TB. Toll-like receptors are one of the key modulators of immune response to Mycobacterium (Faridgohar and Nikoueinejad, 2017). Single nucleotide polymorphism in TLR gene have been associated with variation in TB susceptibility (Mhmoud, 2023). Our findings suggest that participants are mostly Christians, from Yoruba tribe, and most of the female participants were in their reproductive years (21-40 years). This findings corroborate with earlier study that reported patients between 21-40 years had the highest prevalence of tuberculosis (Babajide *et al*., 2014). Our study showed that males are more at risk of TB than females, which aligns with earlier studies (Asmamaw *et al*., 2025). Another study revealed that men are at 53% higher risk of TB than females (Humayun *et al*., 2022). Disproportionately higher TB risk in males may be due to increased social contacts than females (Miller *et al*., 2021). Males are generally more social and engage in outdoor activities which potentially increases the odds of TB exposure. Majority of participants are traders and civil servants. Our findings agrees with studies among attendees of tertiary health facility which showed that Abeokuta residents are mostly civil servants (Oredola and Odusanya, 2017). Historically, Abeokuta is a major hub for trade and cultural arts, especially tie and die" fabric also known in local parlance as "Adire" (Adépégba and Abati, 2024). It is also the state capital and the seat of power of Ogun state government, a major employer of labour in the state. This fact, in addition to absence of big corporations and industries within Abeokuta metropolis, may influence the choice of occupation among its residents, which may explain the reason why most of the study participants are traders and civil servants. Our study showed that most of the participants had tertiary education. The high literacy rate among participants could be as a result of high number of tertiary institutions in Abeokuta and also the convenient sampling technique of recruiting participants in a TB clinic. As such, the sampling technique may be biased toward participants with high educational status due to better health seeking behaviour. A study in Abeokuta South Local government is in agreement with our reported high literacy rate among resident visiting healthcare facilities (Oredola and Odusanya, 2017).

Several factors have been implicated in risk of TB infection and these factors can be broadly categorized into: bacterial, environmental and host factors (Asgharzadeh *et al.,* 2025). Host factors include genetics and socio-behavioural factors e.g. smoking and alcoholism. Smoking and excessive alcohol consumption impairs immune function thus, increasing the risk of infections (Bhatia *et al*., 2020). Unhealthy lifestyle choices are shaped at adolescence and peaks at productive year and increase the risk of diseases in later years (Arafa *et al.,* 2024).

Tuberculosis is transmitted through aerosol or droplets from an infected person (Sarkar, 2025). Therefore, some associated risk factors are based on proximity to infected individuals. Predisposing factors of TB include overcrowding, air pollution, close proximity to TB patients (Menon *et al.*, 2026). Hence, occupation, family size, living conditions are some of those factors that borders on proximity and therefore influence TB risk. Healthcare workers are frontline workers and are at increased risk of TB infection due to occupational exposure to infected patients (Zhen *et al*., 2025). The majority of participants (54.6%) resided in households with 4–6 members, a distribution that differed significantly across family size categories (p = 0.01). Overcrowding correlates positively to TB risk. The lesser the number of inhabitants of a living space, the lower the risk of TB infection. This study showed that more than half of the participants lived in flat hence, the chances of transmission is reduced. However, there was no significant difference in the living conditions of the participants. Our findings support an earlier study conducted among residents of Kemta housing estates, Abeokuta (Odunnaike and Olagoke, 2023).

Other associated risk factors of TB suppress immunity. Human immunodeficiency virus (HIV), smoking and alcohol have been linked to immune suppression in TB patients (Satre *et al*., 2021). TB risk correlates significantly with smoking and alcohol history (Thomas *et al.*, 2019). In this study, a statistically significant difference was observed between smokers and non-smokers (p = 0.00). However, there was no significant difference in alcohol intake history between the groups (p = 0.22), despite the higher number of participants reporting a history of alcohol consumption compared to those with no alcohol intake history.

Toll-like receptor 2 is a critical receptor of recognition during *Mtb* host invasion (Liu *et al*., 2020). Single nucleotide polymorphism in *TLR2* gene may alter the expression, function, recognition and downstream signalling of TLR2. Despite contrasting reports, some studies have demonstrated an association between of TLR2 polymorphism on TB susceptibility (Zaki *et al.,* 2018; Wu *et al.*, 2020; Sudarto *et al.*, 2026). The TT genotype which is the normal genotype was predominant in both TB patients and healthy controls. Despite higher genotypic frequencies of TT, CC and CT in TB patients compared to controls, the difference was not significant in the CT and TT genotypes. However, the CC genotype differs significantly between TB patients and healthy controls, confirming CC variant alters immune response and promote TB susceptibility. A study from Sudanese TB patients showed no significant difference between genotypes of TLR2 (rs7656411) between healthy individuals and TB patients (Mhmoud, 2023). This implies that TLR2 (rs7656411) polymorphism was not associated with TB susceptibility. However, this was contrary to our study findings which shows association between CC genotype and TB susceptibility. In addressing the conflicting findings, further studies involving large sample size across different ethnic populations is needed to establish relationship between TLR2 polymorphism and TB susceptibility.

CONCLUSION

Genetic variations in the Toll-like receptor gene contribute essentially to differential TB susceptibility. Therefore, understanding the influence of these genetic variations on the function of TLR may help to predict susceptibility to tuberculosis and improve treatment outcomes. This may assist healthcare providers and public health professionals in reducing the incidence of TB in the society.

Conflict of Interest

Authors declared no conflict of interest

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