ZIBELINE INTERNATIONAL™ PUBLISHING

ISSN: 2521-5051 (Print)
ISSN: 2521-506X (Online)
CODEN: ASMCCQ

Acta Scientifica Malaysia (ASM)

DOI: http://doi.org/10.26480/asm.01.2026.26.30

REVIEW ARTICLE

TNF-A PROMOTER POLYMORPHISMS (-308G/A AND -238G/A) AND SUSCEPTIBILITY TO TUBERCULOSIS: A NARRATIVE REVIEW AND META-SYNTHESIS

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ARTICLE DETAILS

Article History:

Received 10 January 2026
Revised 15 February 2026
Accepted 19 March 2026
Available online 17 April 2026

ABSTRACT

Tumor necrosis factor-α (TNF-α) is central to antimycobacterial immunity yet dysregulated signaling can promote immunopathology. Two TNF promoter variants, −308G/A (rs1800629) and −238G/A (rs361525), have been widely investigated for associations with tuberculosis susceptibility. This narrative review synthesizes evidence from 2000 to 2025 across diverse populations, integrating meta-analyses, case-control cohorts, and functional studies. Pooled analyses show no consistent overall association for either variant, with small and context-dependent signals in some subgroups. Functional assays indicate that −308A can increase promoter activity under defined stimuli, but genotype-phenotype relationships in patients are inconsistent and likely depend on cellular state, infection stage, and environment. Population differences in allele frequencies and linkage disequilibrium, together with variable study design and phenotyping, contribute to heterogeneous findings. Current data do not support clinical use of these variants as stand-alone biomarkers. The most promising applications involve research stratification within multi-ancestry, multi-omics frameworks and continued emphasis on latent tuberculosis infection screening before anti-TNF-α therapy. Priorities include adequately powered cohorts in high-burden regions, standardized phenotypes, and stimulus-aware functional genomics to resolve context-specific regulatory effects and guide pathway-focused interventions.

KEYWORDS

tuberculosis, TNF-alpha, genetic polymorphism, susceptibility, immune response, meta-analysis, population genetics

1. INTRODUCTION

Tuberculosis (TB) remains a leading cause of death from infectious disease globally despite advances in prevention and treatment (Chakaya et al., 2021). The World Health Organization reported 10.8 million newly diagnosed TB cases in 2023—the highest since monitoring began in 1995—with 1.25 million deaths making it the top infectious disease killer globally (WHO, 2024). Disease burden is particularly severe in low- and middle-income countries where socioeconomic factors, limited healthcare resources, and coinfections with HIV/AIDS compound TB control challenges (Osman et al., 2021). Infection with Mycobacterium tuberculosis does not lead to uniform clinical outcomes. The spectrum from sterilizing immunity to latent infection and progressive disease reflects contributions from pathogen diversity, environmental exposures, and host genetics (Möller et al., 2017). Multi-ancestry syntheses support a heritable component to TB susceptibility and emphasize immune pathways as plausible determinants, though replication is often inconsistent (Cai et al., 2019).

Tumor necrosis factor-alpha represents one of the most extensively studied cytokines in tuberculosis immunity (Yuk et al., 2024). This pleiotropic pro-inflammatory cytokine orchestrates multiple critical functions including granuloma formation and maintenance, macrophage activation, and coordination of innate and adaptive immune responses (Kireev et al., 2025). While TNF-α is indispensable for protective immunity, dysregulation contributes to immunopathology including tissue damage and cachexia (Flynn and Chan, 2001). The fundamental importance of TNF-α is highlighted by substantially increased TB risk in patients receiving TNF-α inhibitor therapies for autoimmune conditions (Queiroz et al., 2022). Single nucleotide polymorphisms within the TNF-α gene promoter can significantly influence cytokine production levels, potentially affecting immune responses against M. tuberculosis (Wu et al.,

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Cite The Article: Olawuyi Abdullahi Olaleye, Olaniyan Mathew Folaranmi, Ijeoma Evangeline Umeche, Busira Tijani Adesina, Abdulwaheed Adewale Ademosun, Adeosun O. Ganiyu, Ademuyiwa Isaac Adewole, Olaosun Olufunke Ayobami (2026). Tnf-A Promoter Polymorphisms (-308g/A And -238g/A) And Susceptibility To Tuberculosis : A Narrative Review And Meta-Synthesis. *Acta Scientifica Malaysia (ASM)*, 9(1): 26-30.

2019 ; Adane et al., 2021). Two specific variants have received particular focus: the -308G/A polymorphism (rs1800629) and -238G/A polymorphism (rs361525), investigated for their functional significance in cytokine regulation and clinical relevance in TB susceptibility (Qidwai and Khan, 2011).

2. Search Strategy And Methodological Approach

We conducted a narrative search across PubMed/MEDLINE, Embase, Web of Science, Scopus, Google Scholar, and AJOL to improve recall and regional coverage. Database selection reflects evidence that no single index captures full biomedical literature and mixed strategies improve retrieval for genetics and epidemiology (Bramer et al., 2017 ; Asubiaro, 2023). Searches covered January 2000 to September 2025 using controlled terms and keywords: TNF, TNF-α, TNFA, rs1800629, rs361525, −308G/A, −238G/A, tuberculosis, susceptibility, polymorphism, promoter, case-control, cohort, meta-analysis, and functional.

Inclusion criteria encompassed human studies evaluating TNF-α promoter polymorphisms −308G/A and/or −238G/A with TB phenotypes; case-control, cohort, or relevant GWAS designs; extractable genotype or effect estimates; and specified study setting or ancestry. Functional studies assessing promoter activity, transcription-factor binding, or TNF-α production by genotype under defined stimuli were included. Exclusion criteria included animal or in-vitro-only studies without human genetic data; non-extractable information; non-peer-reviewed opinion; non-TB phenotypes; and duplicate data.

From each genetic study we extracted setting, ancestry, TB phenotype, design, sample sizes, genotype distributions or effect sizes, Hardy-Weinberg equilibrium, genotyping platform, covariates, and principal findings. We used STREGA extension to STROBE to guide assessment of transparency and common risks including population stratification, selective reporting, and HWE violations (Little et al., 2009).

3. TNF-A Biology And Functional Significance In Tuberculosis

3.1 Molecular structure and signaling pathways

TNF-α exists as a 26-kDa transmembrane protein (mTNF-α) that undergoes enzymatic cleavage by TACE to generate a 17-kDa soluble form (sTNF-α) capable of systemic circulation (Bhattacharyya and Ghosh, 2020). These isoforms exert opposing biological effects through differential receptor binding : sTNF-α binds primarily to TNFR1 mediating inflammatory responses, while mTNF-α interacts with TNFR2 promoting cellular proliferation and survival (Qu et al., 2017). Two distinct receptors—p55 (TNFR1) and p75 (TNFR2)—are differentially expressed across cell types with structurally different intracellular domains suggesting distinct signaling pathways (Wallach et al., 1991).

Differential signaling through TNFR1 and TNFR2 results in distinct outcomes, with TNFR1 primarily mediating pro-inflammatory and apoptotic responses while TNFR2 promotes cell survival and tissue healing (Gough and Myles, 2020). This receptor-specific diversity contributes to complex context-dependent effects in tuberculosis pathogenesis and immune modulation (Atretkhany et al., 2020).

3.2 TNF-α and Its Role in anti-mycobacterial immunity

TNF-α is critical for controlling Mycobacterium tuberculosis by promoting granuloma formation and maintaining structural integrity, creating localized immune responses that contain bacteria through immune cell recruitment, cell-cell interactions, and extracellular matrix organization (Lin et al., 2007 ; Cavalcanti et al., 2012). Without proper TNF-α signaling, granulomas disorganize allowing bacterial dissemination and increased mortality. Live imaging approaches reveal dynamic nature of these structures and TNF-α's critical role in maintaining functional integrity (You et al., 2021).

TNF-α enhances macrophage antimicrobial programs and cooperates with IFN-γ to promote phagosome-lysosome fusion, acidification, and hydrolase delivery that restrict M. tuberculosis (Hackam et al., 1999). The cytokine also interfaces with canonical autophagy and LC3-associated phagocytosis pathways contributing to cell-autonomous defense and tempering excessive inflammation (Upadhyay and Philips, 2019). Additionally, TNF-α promotes antigen presentation and costimulation supporting Th1-biased responses while shaping tissue-resident and regulatory T-cell networks within granulomas (Cilfone et al., 2013).

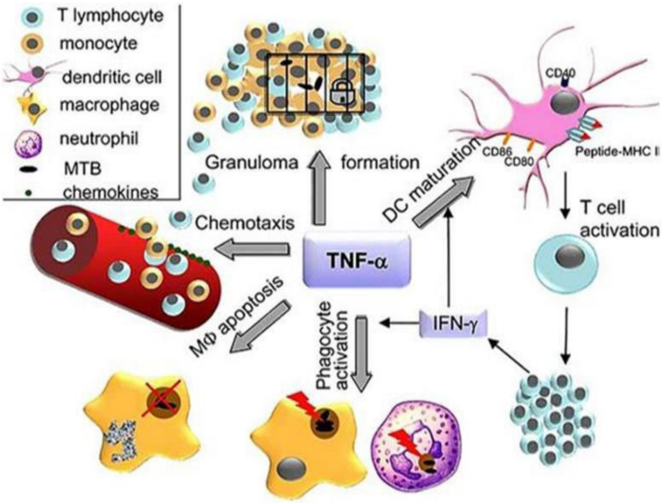

Figure 1: Schematic representation of multiple roles of TNF-α in immune response to *M.tb* infection. Each separate role is represented by a block arrow (Flynn et al., 1995; Mootoo et al., 2009).

3.3 Dual Nature in Tuberculosis Pathogenesi

Properties making TNF-α essential for granuloma integrity and intracellular killing can drive immunopathology when signaling is excessive or mistimed (Elkington et al., 2022). Observational and mechanistic data show systemic TNF inhibition increases TB reactivation risk, first recognized with infliximab and confirmed across classes, emphasizing need to preserve sufficient TNF-dependent host defense (O'Garra et al., 2013). Conversely, hyper-inflammatory states elevating TNF can worsen lung damage, so therapeutic strategies sparing or modulating TNFR1 versus TNFR2 or localizing effects are explored to balance antimicrobial efficacy with tissue protection (Gough & Myles, 2020). These observations explain why TNF-α's net effect in TB depends on dose, timing, receptor bias, and broader immune milieu.

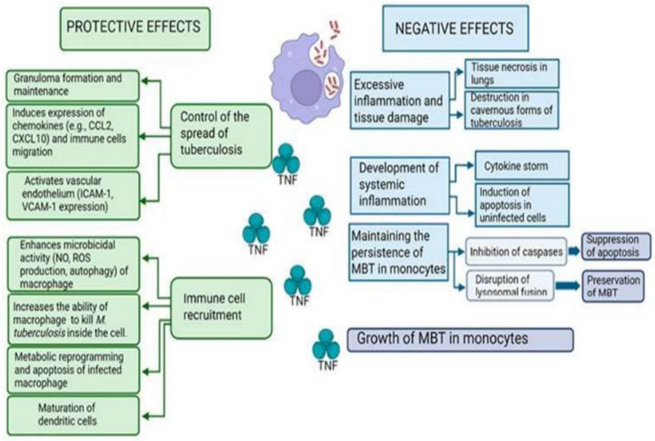

Figure 2: Protective and negative effects of TNF during M. tuberculosis infection. Created in https://BioRender.com (Kireev et al., 2025).

4. Genetic Architecture And Global Epidemiology Of TNF-A Promoter Polymorphisms

4.1 Chromosomal Location and Promoter Regulation

TNF is located on chromosome 6p21.3 within the MHC class III region, near HLA loci and other inflammatory genes (You et al., 2021). This

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genomic neighborhood creates extensive linkage disequilibrium and regulatory crosstalk complicating single-variant associations. The core promoter contains multiple binding sites assembling stimulus-dependent enhanceosome complexes tuning transcription in cell- and context-specific manner (Cruz-Tapias et al., 2013).

4.2 Functional Impacts of -308G/A and -238G/A Polymorphisms

The −308G/A variant has been proposed as a regulatory allele. Reporter assays and binding studies demonstrated −308A allele can increase promoter activity and alter transcription-factor interactions in stimulated cells, though some experiments showed modest or context-dependent effects (Wilson et al., 1997 ; Abraham and Kroeger, 1999). For −238G/A, functional results are less consistent; several studies report limited or stimulus-restricted effects on TNF-α production suggesting smaller or context-specific regulatory role compared with −308G/A (Gane et al., 2015).

4.3 Global Population-Specific Allele Frequency Patterns

Public population resources indicate −308A (rs1800629 A) allele occurs at different frequencies across ancestries. It is generally more common in European and admixed American populations and less frequent in East Asian and several African populations, though notable substructure exists within continents (The 1000 Genomes Project Consortium, 2015 ; Karczewski et al., 2020). The −238A (rs361525 A) allele is globally rare compared with −308A, with very low frequencies in East Asian populations and low frequencies in most African and European datasets, again with heterogeneity across subgroups. These differences affect statistical power, transferability of effect estimates between regions, and risk of confounding by population stratification.

5. GENETIC ASSOCIATION EVIDENCE AND MECHANISTIC INSIGHTS

5.1 Critical appraisal of meta-analyses and major studies

Across pooled analyses, TNF −308G/A shows no consistent overall association with TB susceptibility, with several meta-analyses reporting null effects in combined populations and mixed signals in ethnicity-stratified subgroups (Wang et al., 2012 ; Lee and Song, 2015). Wang et al.'s 2012 meta-analysis reported no global association, with suggestive risk increase in some Asian cohorts not uniformly reproduced in later updates. For TNF −238G/A, a focused meta-analysis of nine case-control studies found no significant association in any genetic model (Zhang et al., 2012). Recent efforts re-aggregating post-2018 studies highlight heterogeneity and instability of effect estimates, reinforcing that sample size, population structure, and phenotype definition drive discordant findings.

5.2 Population-specific association studies

Ethnicity-stratified analyses align with allele-frequency differences. In Asian cohorts, some early case-control studies suggested modest risk with −308A, but ethnicity-stratified meta-analyses found attenuation or no association after pooling larger datasets (Wang et al., 2012). In African populations, single-center studies reported both positive and null findings for −308G/A; Ethiopian data linked −308G with disease in relatively small series, illustrating estimate volatility when samples are limited (Adane et al., 2021). In European and American datasets, meta-analyses generally report null associations with wide confidence intervals for −238A due to rarity (Zhang et al., 2012).

5.3 Bridging genotype and phenotype

Classical promoter assays showed −308A can increase transcriptional activity under defined stimuli, providing mechanistic route for altered inducible TNF production, while −238A shows weaker or context-limited effects in vitro (Wilson et al., 1997). In patient-based work, functional bridges are less consistent. Recent South African study measuring plasma cytokines in TB, HIV, and TB-HIV groups found no robust correlation between TNF −308G/A or −238G/A genotypes and circulating TNF-α levels, underscoring systemic cytokine concentrations may not reflect local granuloma expression or cell-context regulation (Manabile et al., 2024).

6. CLINICAL IMPLICATIONS AND RESEARCH TRANSLATION

6.1 Risk stratification and predictive biomarkers

Current evidence does not support using TNF-α −308G/A or −238G/A as stand-alone clinical biomarkers for TB risk. Meta-analyses consistently report no reproducible overall association and only unstable subgroup-limited signals, implying effect sizes are small and context dependent (Lee and Song, 2015 ; Zhang et al., 2012). Allele-frequency gradients across ancestries complicate transportability of findings and increase potential for confounding without ancestry-aware analyses. A more realistic role for these promoter variants is research stratification within multivariable models also considering epidemiologic risk factors, co-morbidities, and other host loci showing stronger consistent signals including HLA regions (Schurz et al., 2024).

6.2 TNF-α inhibitors and TB reactivation risk

Clinical literature demonstrates clear increase in TB reactivation among patients treated with TNF-α antagonists for immune-mediated diseases. Early pharmacovigilance identified strong signal with infliximab, followed by similar concerns with other agents (Lorenzetti et al., 2014). Meta-analysis of randomized trials confirmed higher TB incidence in anti-TNF-treated populations versus controls, supporting causal relationship between TNF blockade and impaired control of latent M. tuberculosis (Zhang et al., 2017). These data underpin routine screening and treatment of latent TB infection before initiating anti-TNF therapy.

6.3 Potential roles in personalized medicine

Personalized applications for −308G/A and −238G/A remain limited. Available data suggest these variants could be incorporated as exploratory covariates in research frameworks integrating clinical risk, environmental exposure, pathogen lineage, and host multi-omics to refine mechanistic hypotheses rather than guide bedside decisions (McHenry et al., 2020). In host-directed therapies, TNF-α's centrality to protection and pathology argues for precision approaches modulating pathway activity without global suppression, but TNF promoter genotypes have not shown actionable predictive value for response or safety.

7. RESEARCH GAPS, LIMITATIONS, AND FUTURE DIRECTIONS

7.1 Addressing population underrepresentation

Large portions of global TB burden occur in regions underrepresented in human genetic studies, particularly sub-Saharan Africa and parts of South and Southeast Asia. Underrepresentation reduces discovery power, impairs fine-mapping because of distinct linkage disequilibrium patterns, and limits portability of effect estimates across ancestries (Sirugo et al., 2019). Increasing representation requires equitable investments in cohort recruitment, biobanking, sustained local analytics capacity, and data-governance frameworks co-designed with communities.

7.2 Integration of functional genomics

A key gap is the link between genotype and mechanism in cell types relevant to TB. Stimulus-aware eQTL and chromatin studies demonstrate regulatory variant effects are often context specific, emerging only under immune activation or infection, implying functional follow-up must model appropriate stimuli and cellular states (Fairfax et al., 2014). Integrating transcriptomics, epigenomics, and proteomics from blood and lung compartments with pathogen data can provide holistic view of host-pathogen interactions and help explain heterogeneity in genetic associations (Mehta et al., 2024).

7.3 Recommendations for future study design

Future studies should target larger multi-site sample sizes with explicit ancestry modeling and replication across regions reflecting global TB distribution. Designs should use standardized phenotyping distinguishing infection, incipient disease, pulmonary TB, and extrapulmonary forms, with harmonized covariates such as HIV status, diabetes, malnutrition, and smoking. Transparent reporting of genotyping QC and Hardy-Weinberg equilibrium in controls, along with pre-specified statistical models, will improve reproducibility.

8. Conclusion

TNF-α promoter polymorphisms -308G/A and -238G/A show no consistent population-wide association with tuberculosis susceptibility after more than two decades of research. While functionally plausible, their effects appear small, context-dependent, and insufficient for clinical application. Future progress requires adequately powered multi-ancestry cohorts, standardized phenotyping, and functional genomics examining stimulus-specific effects in relevant biological contexts. Such approaches are more likely to yield insights for risk stratification and therapeutic development than continued focus on these individual promoter variants.

Acknowledgments

The authors gratefully acknowledge Mrs Oyebanji-Olawuyi Mariam for her technical and logistical support.

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Cite The Article: Olawuyi Abdullahi Olaleye, Olaniyan Mathew Folaranmi, Ijeoma Evangeline Umeche, Busira Tijani Adesina, Abdu lwaheed Adewale Ademosun, Adeosun O. Ganiyu, Ademuyiwa Isaac Adewole, Olaosun Olufunke Ayobami (2026). Tnf-A Promoter Polymorphisms (-308g/A And -238g/A) And Susceptibility To Tuberculosis : A Narrative Review And Meta-Synthesis. *Acta Scientifica Malaysia (ASM),* 9(1): 26-30.