HLA-DQ Allele Carriers as Genetic Risk Factors for Pulmonary Tuberculosis: A Meta-Analysis

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Abstract: Several studies have shown that pulmonary tuberculosis (PTB) is a major global health issue, affecting various countries around the world. Susceptibility to the disease has been reported to be influenced by host genetic variables, including Human Leukocyte Antigen (HLA) class II genes, specifically HLA-DQ. Despite the association, studies on the relationship between HLA-DQ allele carriers and the risk of PTB are still not consistent among various populations. This meta-analysis aims to assess the association between carrier status (phenotype frequency) of HLA-DQA1 and HLA-DQB1 alleles and susceptibility to pulmonary tuberculosis. Several HLA-DQ alleles were examined, and the pooled effect size estimates were calculated based on carrier (phenotype) frequencies of HLA-DQA1 and HLA-DQB1 alleles, using odds ratios (ORs) and 95% confidence intervals (CI). A total of 21 high-quality studies (NOS ≥7) were included in the review, with 25,896 controls and 3,927 cases. The results showed that the risk of PTB was significantly increased by allele carriers of HLA-DQA1*01:01 (OR = 1.79; 95% CI: 1.22–2.62) and HLA-DQA1*03:01 (OR = 1.64; 95% CI: 1.08–2.48). Risk factors for HLA-DQB1 allele carriers were also found to be the *02:01 (OR = 1.36; 95% CI: 1.04–1.79), *05:03 (OR = 1.35; 95% CI: 1.01–1.80), and *06:01 (OR = 1.41; 95% CI: 1.00–1.97) allele carriers. Meanwhile, HLA-DQA1*02:01, *04:01, *05:01, and *06:01 allele carriers had protective effects. The majority of analyses found no indications of publication bias. This meta-analysis demonstrates that carrier status of specific HLA-DQA1 and HLA-DQB1 alleles is significantly associated with susceptibility to pulmonary tuberculosis

Keywords: PTB, allele carriers, HLA-DQ, HLA-DQA1, HLA-DQB1, meta-analysis.

1. INTRODUCTION

As one of the leading causes of death worldwide and a significant public health concern, pulmonary tuberculosis (PTB) is a major infectious disease [1]. Approximately 10.8 million cases have been recorded globally, representing an increase over the previous year (95% Uncertainty Interval [UI]: 10.1–11.7 million) [2]. Despite the implementation of several preventative, diagnostic, and therapeutic techniques, the incidence of PTB has been reported to be high and varies by population [3, 4], suggesting that host variables have a significant influence on infection susceptibility and response [5].

According to previous studies, susceptibility to PTB is influenced by host genetic variables [6, 7]. One of the most extensively studied genetic factors is the major histocompatibility complex (MHC) class II, particularly Human Leukocyte Antigen (HLA)-DQ genes [8, 9]. This genes plays a role in the presentation of antigen to Cluster of Differentiation ($CD4^+$) cells and triggers an adaptive immune response [10]. In addition, important elements of the immune system, HLA-DQ genes, such as HLA-DQA1 and HLA-DQB1, can affect the course of active pulmonary tuberculosis by either enhancing susceptibility or offering protection [11].

Several observational studies have reported associations between carriers of specific HLA-DQ alleles and the risk of active pulmonary tuberculosis; however, the findings remain inconsistent across populations and ethnic groups [12, 13]. For example, carriers of the HLA-DQA1*01:01 [14, 15] and HLA-DQB1*02:01 [16, 17] alleles have been reported to have an increased risk of tuberculosis in certain populations, whereas other alleles, such as HLA-DQA1*05:01 [18], appear to confer a protective effect. These inconsistencies highlight the influence of population-specific genetic backgrounds and methodological heterogeneity, including differences in outcome definitions, HLA genotyping approaches, and units of genetic analysis. Although several meta-

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analyses have previously examined associations between HLA class II polymorphisms and tuberculosis, substantial heterogeneity remains unresolved. The inconsistency indicates the need for a more comprehensive synthesis of evidence through a systematic approach [19].

Therefore, the present meta-analysis aims to systematically evaluate the association between HLA-DQA1 and HLA-DQB1 allele carrier status (phenotype frequency) and susceptibility to HIV-negative active pulmonary tuberculosis by adopting a conservative, carrier-based analytical framework to harmonize allele-specific data across studies using different genotyping methods. By integrating evidence from diverse ethnic groups and geographical regions through standardized data extraction and analysis, this study seeks to provide a more interpretable and robust synthesis of the role of HLA-DQ allele carriers in tuberculosis susceptibility

2. MATERIAL AND METHODS

2.1. Search Strategy and Eligibility Criteria

PubMed, ProQuest, and ScienceDirect databases, as well as additional sources such as WHO, Directory of Open Access Journals (DOAJ), and BioMed Central, were searched for articles about HLA-DQ and PTB up until May 2025. This was in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The terms "TBC," "TB," "tuberculosis," "pulmonary," "HLA," "HLA-DQ," "HLA-DQA1," "HLA-DQB1," "polymorphism," and "genetic" were used in the search process. PICOS strategy (Population, Intervention, Comparison, Outcome, Study Design) was used in the selection process [20] to ascertain the studies' general eligibility. HIV-negative active pulmonary tuberculosis patients made up the population, and the intervention involved the presence of HLA-DQ (DQA1 and DQB1) gene polymorphisms, which were confirmed by molecular biology techniques and characterized as particular alleles. Furthermore, the comparison group comprised both PTB cases and non-PTB cases, and the study design included cohort or case-control studies. The inclusion criteria were (1) studies that measured HLA-DQA1 and HLA-DQB1 genes in cohort or case-control studies including PTB cases; (2) English-language articles; (3) case-control or cohort study design; (4) human subjects studies; (5) adult patients; (6) non-specific populations (excluding HIV-positive individuals); (7) full-text availability; and (8) data presented in numerical values. Meanwhile, exclusion criteria included (1) review articles, cross-sectional studies, case reports, case series, and meta-analyses; (2) duplicate studies; (3) specific populations (HIV-positive); (4) non-English articles; and (5) insufficient data. A study was deemed PTB-positive when it satisfied at least one of the following requirements: (1) a positive culture; (2) a positive result from a molecular rapid test (MRT), such as GeneXpert; and (3) PTB symptoms (such as a cough that lasted longer than 2 weeks) along with suggestive radiological results. Newcastle-Ottawa Quality Scale (NOQS) was used to assess the quality and evaluate observational or non-randomized studies [21] (Appendix **1**).

2.2. Data Collection

The literature search and data extraction were carried out independently by 2 study teams, and the papers were vetted by another 2. Furthermore, the full texts of pertinent papers were assessed in accordance with eligibility requirements, and any possible duplicate articles were thoroughly examined. Final judgments were reached by consensus in the study team, and studies that satisfied the criteria were included in the meta-analysis.

In studies reporting allele-specific variability in sample size, particularly those employing PCR sequence-specific primer (PCR-SSP)-based HLA genotyping, allele-specific numbers of cases and controls were extracted and retained for each corresponding forest plot. To ensure a conservative and non-inflated presentation of study characteristics, Table **1** summarizes the minimum available number of cases and controls per study, based on the smallest allele-specific datasets reported

Genetic association analyses were conducted using carrier (phenotype) frequency data, in which individuals were classified as positive or negative carriers of a specific HLA-DQA1 or HLA-DQB1 allele. Accordingly, the denominator represents the number of subjects rather than the number of chromosomes (2N). True allele frequency-based analysis was not feasible due to inconsistent reporting of genotype-level data across the included studies

2.3. Statistical Analysis

A meta-analysis approach for categorical data was used for statistical analysis, and 95% CI and odds ratios (OR) were used to represent effect sizes. The degree of correlation between HLA-DQA1 and HLA-DQB1 allele carrier status (phenotype frequency) and

Table 1: Characteristics of the Included Studies on HLA-DQA1 and HLA-DQB1 Genes

No	First author Year	Population	Ethnicity	Sample size		Detection methods for genotype	Study design	NOS score*		
				Case (N=3927)	Control (N=25896)			S	C	E
1.	[10]	Uganda	African	43	42	PCR-SSP	Case-control	4	1	3
2.	[14]	Canada	America	34	71	PCR-SSP/PCR-SSO	Case-control	4	1	3
3.	[15]	Latvian	European	80	200	PCR-SSP	Cohort	4	2	2
4.	[16]	Iranian	Asian	50	100	PCR-SSP	Case-control	4	1	2
5.	[17]	USA South Africa	America African	433	203	PCR-SSP	Case-control	3	2	2
6.	[18]	Thailand	Asian	185	811	PCR-SSOP	Case-control	4	1	3
7.	[27]	China	Asian	1178	21343	GWAS/WES	Case-control	4	2	2
8.	[28]	Cambodia	Asian	156	98	PCR-SSO	Case-control	4	1	3
9.	[29]	India	Asian	120	83	PCR-SSP PCR-SSO	Case-control	3	2	2
10.	[30]	Mexico	America	50	95	PCR-SSP	Case-control	4	2	2
11.	[31]	Thailand	Asian	82	160	PCR-SSO	Case-control	4	1	3
12.	[32]	Indian	Asian	54	58	PCR-SSOP	Case-control	4	1	3
13.	[33]	Iranian	Asian	40	100	PCR-SSP	Case-control	4	1	3
14.	[34]	Korea	Asian	160	200	PCR-SSO	Case-control	4	1	2
15.	[35]	Poland	European	38	125	PCR-SSP	Case-control	4	1	3
16.	[36]	South Africa	African	95	117	PCR-SSP	Case-control	4	1	3
17.	[37]	India	Asian	110	112	PCR-SSOP	Case-control	4	1	2
18.	[38]	China	Asian	176	189	PCR/SSP	Case-control	4	1	3
19.	[39]	China	Asian	402	420	PCR-SSP	Case-control	4	1	2
20.	[40]	Kazakhstan	Asian	76	157	PCR-SSP	Case-control	4	2	2
21.	[41]	China	Asian	365	1212	GWAS	Case-control	4	2	2

*Newcastle-Ottawa Scale [21]; S selection, C comparability, E exposure, with a maximum score of four, two, and three for each, respectively
Note: For studies reporting variable sample sizes across different HLA alleles, the minimum available number of cases and controls was reported in this table to avoid overestimation of sample size.

the risk of PTB was evaluated using the OR value. An elevated risk was indicated by an OR > 1 with a 95% CI that included 1, a protective effect was suggested by an OR < 1, and no significant association was shown by an OR = 1.

The I^2 statistic and the Chi-square test (also known as Cochran's Q test) were used to examine study heterogeneity. Significant heterogeneity was evaluated as an $I^2 > 50\%$ and a p-value < 0.10 in the Q test. The Mantel-Haenszel approach, a fixed-effect model, was

used when heterogeneity was modest (I^2 < 50%) [22]. Meanwhile, a random-effects model was applied to account for differences between studies where heterogeneity was large (I^2 ≥ 50%). When heterogeneity was significant (I^2 > 50%), sensitivity analysis was conducted by eliminating studies one at a time (leave-one-out approach) and comparing the fixed-effect and random-effects models while tracking changes in the overall OR values. Egger's regression test [23] analyses were performed to evaluate possible publication bias for factors with more than 2 studies. Publication bias was shown by an asymmetric funnel plot and a significant Egger's test result (P < 0.05). Review Manager version 5.4.1 (The Cochrane Collaboration, Oxford, UK) was used to conduct statistical analyses [24], while Jeffreys's Amazing Statistics Program (JASP) version 0.18.3.0 (University of Amsterdam) was used for this meta-analysis.

3. RESULTS

3.1. Study Characteristics

A total of 545 studies were found up until the May 2025 literature search deadline using the WHO registry, DOAJ, and BioMed Central (n = 34), as well as PubMed, ProQuest, and ScienceDirect databases (n = 511). A total of 179 studies were eliminated before screening because of incompatibility found by automated tools (n = 57), duplication (n = 103), and other reasons (n = 19). Meanwhile, 219 studies were left for eligibility evaluation after 76 of the 366 screened studies were eliminated, and 29 of the 42 requested studies could not be retrieved. Lack of full text (32), non-English language (22), non-cohort/case-control design (37), non-human subjects (17), non-adult patients (15), irrelevant populations (29), and irrelevant themes (46) led to the exclusion of studies during the

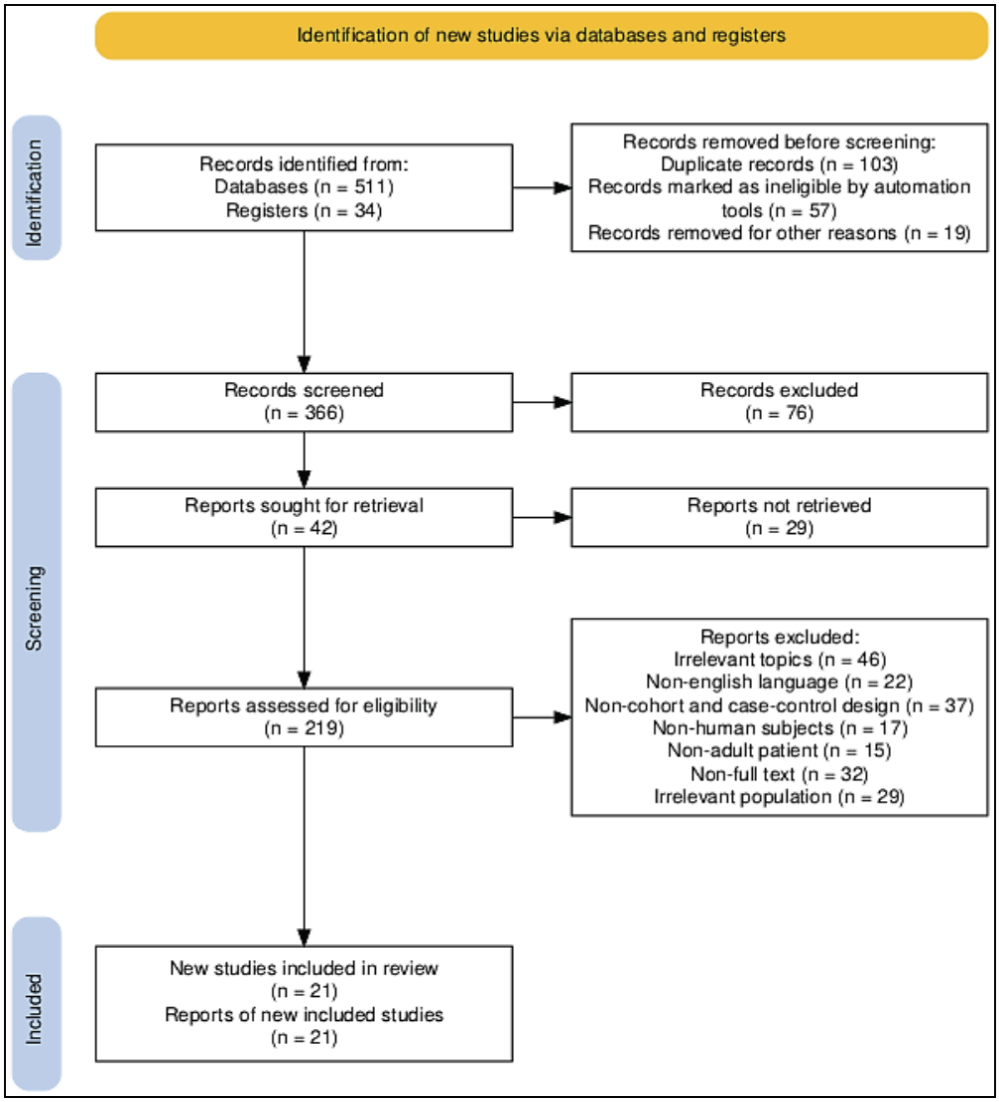

Figure 1: PRISMA flow diagram of the literature search [25].

full-text review stage. A total of 21 studies, 12 on HLA-DQA1 allele carriers and 18 on HLA-DQB1 allele carriers, met the inclusion criteria and were incorporated into this systematic review (Figure **1**).

The study covered 21 observational studies, with 3,927 cases and 25,896 controls. A total of 12 studies (n = 1,666 cases and 2,626 controls) on HLA-DQA1 allele carriers and 18 studies (n = 3,346 cases and 24,395 controls) on HLA-DQB1 allele carriers were included. These studies represented a range of ethnic groups and geographical areas, including Asia (India, Thailand, Korea, China, Iran, Kazakhstan), Africa (South Africa, Uganda), Americas (Mexico, Canada, the United States), and Europe (Poland, Latvia). The results showed that 1 study used a cohort design, while

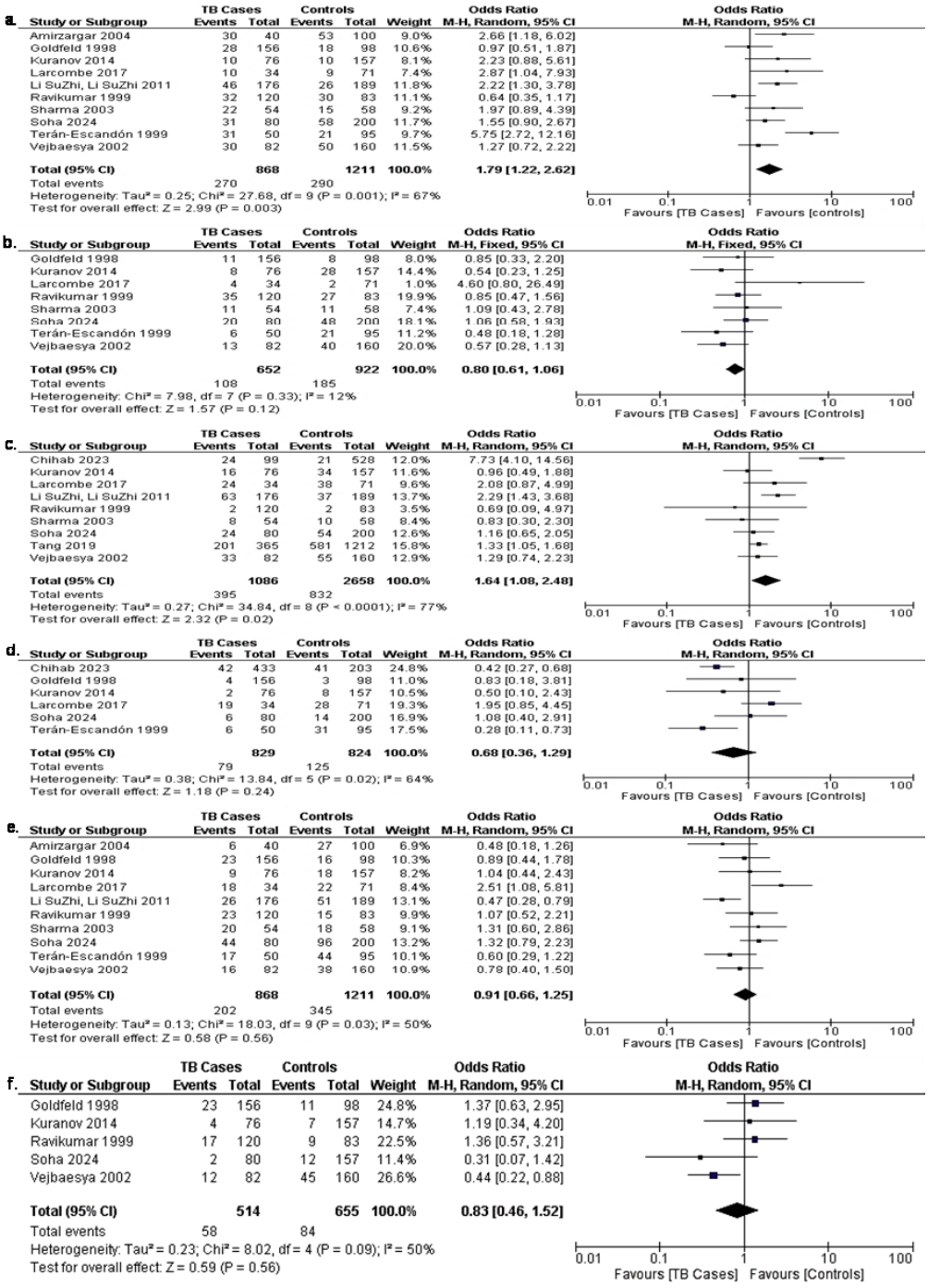

Figure 2: Forest plot of the Mantel-Haenszel odds ratio with 95% confidence intervals for carrier (phenotype) of HLA-DQA1 alleles in PTB cases and healthy controls: (**a**) HLA-DQA1*01:01; (**b**) HLA-DQA1*02:01; (**c**) HLA-DQA1*03:01; (**d**) HLA-DQA1*04:01; (**e**) HLA-DQA1*05:01; (**f**) HLA-DQA1*06:01.

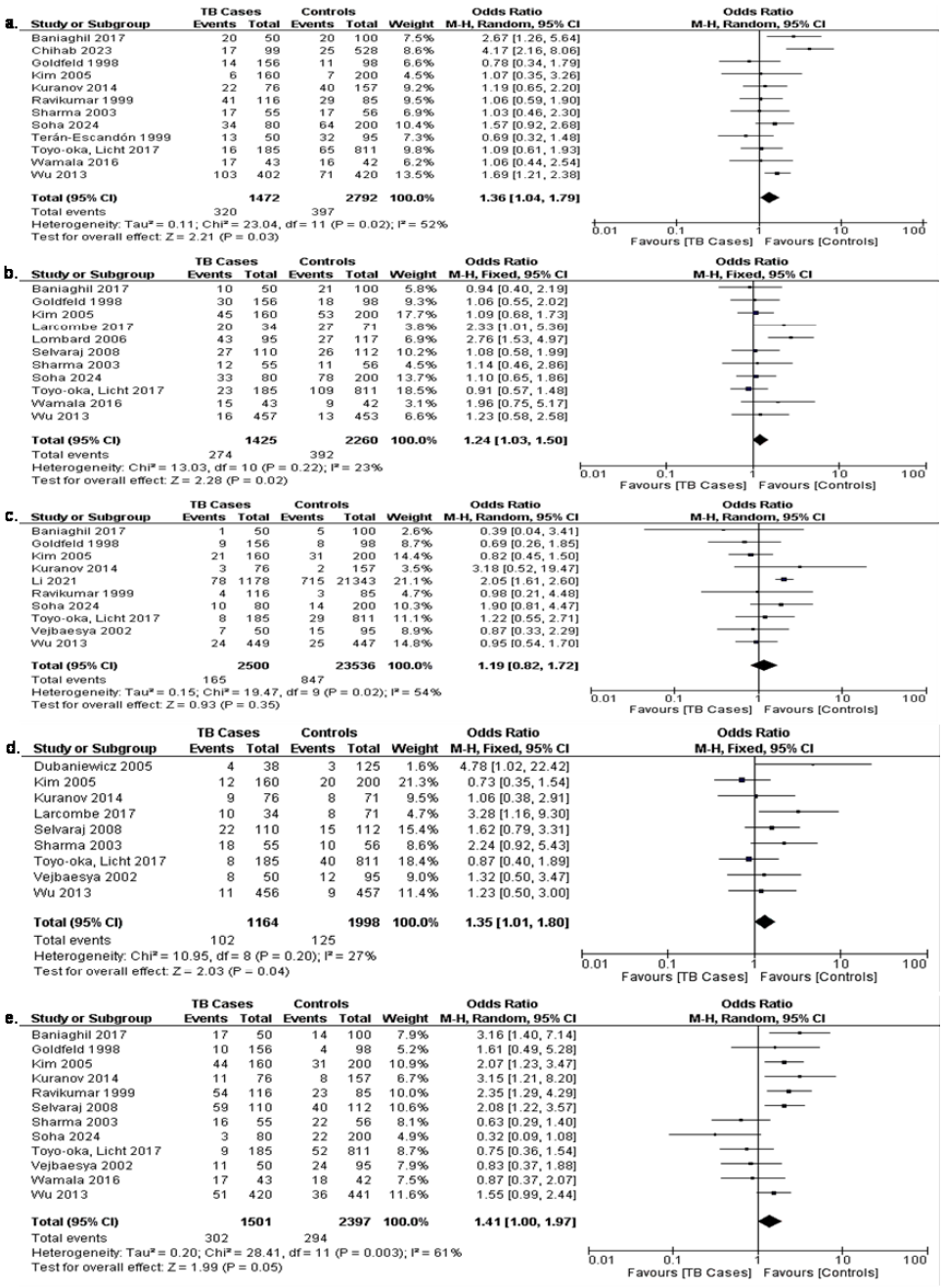

Figure 3: Forest plot of the Mantel-Haenszel odds ratio with 95% confidence intervals for carrier (phenotype) of HLA-DQB1 alleles in PTB cases and healthy controls: (**a**) HLA-DQB1*02:01; (**b**) HLA-DQB1*03:01; (**c**) HLA-DQB1*04:01; (**d**) HLA-DQB1*05:03; (**e**) HLA-DQB1*06:01.

the remainder used a case-control strategy [15]. Polymerase Chain Reaction Sequence-Specific Primers (PCR-SSP) and Polymerase Chain Reaction Sequence-Specific Oligonucleotides (PCR-SSO) were the most widely used genotyping methods, but 2 recent Chinese studies [26, 27] used large-scale genomic techniques such as Weighted Allele Score (WAS) and Genome-Wide Association Study (GWAS). Newcastle-Ottawa Scale (NOS) was used to assess the quality, and all of the included studies had scores of at least 7, indicating good quality. A thorough picture of the relationship between HLA-DQA1 and HLA-DQB1 genes and susceptibility to PTB in various populations was given by the variety of ethnic backgrounds and genotyping techniques in the compiled studies (Table **1**).

3.2. HLA-DQ Alleles and Pulmonary Tuberculosis

The degree of risk between HLA-DQ gene and the incidence of PTB was investigated in this meta-analysis. Furthermore, HLA-DQA1 allele carriers

Table 2: Summary of Findings Based on Carrier (Phenotype) Frequency Analysis

Groups	Number of studies	OR M-H	95% CI	I^2 (%)	P	Egger's test
HLA-DQA1*01:01	10	1.79	1.22 – 2.62	67	<0.003	0.139
HLA-DQA1*02:01	8	0.80	0.61 – 1.06	12	0.12	0.310
HLA-DQA1*03:01	9	1.64	1.08 – 2.48	77	<0.02	0.485
HLA-DQA1*04:01	6	0.68	0.36 – 1.29	64	0.24	0.867
HLA-DQA1*05:01	10	0.91	0.66 – 1.25	50	0.56	0.596
HLA-DQA1*06:01	5	0.83	0.46 – 1.52	50	0.56	0.790
HLA-DQB1*02:01	12	1.36	1.04 – 1.79	52	<0.03	0.463
HLA-DQB1*03:01	11	1.24	1.03 – 1.50	23	<0.02	0.232
HLA-DQB1*04:01	10	1.19	0.82 – 1.72	54	0.35	0.263
HLA-DQB1*05:03	9	1.35	1.01 – 1.80	27	<0.04	0.012
HLA-DQB1*06:01	12	1.41	1.00 – 1.97	61	<0.05	0.151
Sensitivity analysis DQA1*01:01	9	1.55	1.12 - 2.15	51	<0.008	0.151
Sensitivity analysis DQA1*03:01	8	1.38	1.16 - 1.64	16	<0.0002	0.453
Sensitivity analysis DQB1*02:01	11	1.31	1.09 - 1.57	17	<0.004	0.106
Sensitivity analysis DQB1*03:01	10	1.20	1.01 - 1.46	16	<0.05	0.565
Sensitivity analysis DQB1*05:03	8	1.29	1.01 - 1.74	16	<0.05	0.035
Sensitivity analysis DQB1*06:01	11	1.32	0.93 - 1.86	60	0.12	0.213

showed an increased PTB risk including HLA-DQA1*01:01 with an effect size of OR-MH = 1.79, 95% CI (1.22–2.62), p = 0.003, and heterogeneity values of (p = 0.0001; I^2 = 67%), as well as HLA-DQA1*03:01 with OR-MH = 1.64, 95% CI (1.08 –2.48), p = 0.02, and heterogeneity (p = 0.0001; I^2 = 77%). HLA-DQA1*02:01, *04:01, and *05:01 alleles consistently showed protective effects, lowering the incidence of PTB. Meanwhile, HLA-DQA1*06:01 allele was comparatively less studied but displayed a possible trend of association with PTB risk (Figure **2**).

HLA-DQB1 allele carriers linked to a higher risk of PTB included HLA-DQB1*02:01, which had heterogeneity (p = 0.02; I^2 = 52%), an effect size of OR-MH = 1.36, 95% CI (1.04–1.79), and p = 0.03. HLA-DQB1*03:01 allele was homogeneous across study (p = 0.22; I^2 = 23%) and had an OR-MH = 1.24, 95% CI (1.03–1.50), p = 0.02. This showed homogeneity across studies (p = 0.20; I^2 = 27%) and an OR-MH = 1.35, 95% CI (1.01–1.80), p = 0.04. With OR-MH = 1.41, 95% CI (1.00 –1.97), p = 0.05, and heterogeneity (p = 0.003; I^2 = 61%), HLA-DQB1*06:01 allele carrier demonstrated an elevated risk. However, there was no correlation between HLA-DQB1*04:01 allele carrier and the risk of PTB (Figure **3**).

3.3. Publication Bias and Sensitivity Analysis

The meta-analysis's potential for publication bias was evaluated using Egger's test. For both HLA-DQA1 and HLA-DQB1 allele carriers, the results demonstrated that all p-values were more than 0.05 (range from 0.012 to 0.867), suggesting that publication bias had minimal effect on the majority of the meta-analysis results. For HLA-DQB1*05:03 allele carrier, a p-value < 0.05 (p = 0.012) indicated a possible imbalance in study reporting.

When heterogeneity was quite large (I^2 > 50%), sensitivity analysis was performed by comparing the fixed-effect and random-effects models after deleting 1 study at a time using the leave-one-out technique. Except for HLA-DQB1*06:01 allele carrier group, which was unstable, the data demonstrated that the majority of the results were resilient (remained significant) (Table **2**). However, the results were steady and consistent after using the fixed-effect model (OR-MH = 1.46, 95% CI [1.18–1.81], p < 0.0004) (Appendix **2**).

4. DISCUSSION

This meta-analysis demonstrates that carrier status of specific HLA-DQA1 and HLA-DQB1 alleles is associated with susceptibility to pulmonary tuberculosis, supporting the role of host immunogenetic variation as a determinant of tuberculosis risk. By applying a carrier (phenotype)–based analytical framework, this study emphasizes interpretability and methodological consistency across heterogeneous studies, particularly those employing different HLA genotyping approaches. Consequently, the observed

associations should be understood as reflecting phenotypic expression of HLA-DQ variants rather than precise allele dosage effects. Compared with previous meta-analyses that pooled allele or genotype frequencies across heterogeneous analytical units, the present approach offers a more conservative and harmonized synthesis, thereby reducing potential inflation of genetic effect estimates [42].

HLA-DQ molecules are integral components of the major histocompatibility complex (MHC) class II pathway [43], which orchestrates antigen presentation to $CD4^+$ T helper cells and initiates adaptive immune responses against *Mycobacterium tuberculosis* [44-46]. Structural polymorphisms within HLA-DQA1 and HLA-DQB1 genes influence peptide-binding properties of the DQαβ heterodimer, thereby modulating antigen recognition efficiency and downstream immune activation [13]. Variability in these mechanisms provides a biologically plausible explanation for differential susceptibility or resistance to tuberculosis among individuals and populations [47].

The increased susceptibility associated with certain HLA-DQA1 allele carriers observed in this meta-analysis aligns with prior evidence indicating that specific DQα variants may exhibit reduced efficiency in presenting mycobacterial antigens to $CD4^+$ T cells [48]. Rather than reiterating quantitative effect estimates, these findings suggest that functional differences in antigen presentation may impair macrophage activation and Th1-mediated immune responses, which are critical for intracellular mycobacterial control [14, 30, 33, 38, 49]. Age-related interactions reported in large population-based studies further indicate that genetic factors may play a more prominent role in primary tuberculosis, whereas environmental and clinical factors contribute more substantially to disease reactivation in older individuals [41]. Importantly, while such age- and population-specific effects were evident in individual studies, the present meta-analysis highlights consistent directional trends across diverse geographic regions, suggesting a shared immunogenetic mechanism underlying tuberculosis susceptibility.

Conversely, several HLA-DQA1 allele carriers were consistently associated with a protective effect against pulmonary tuberculosis [41, 50]. This pattern supports the hypothesis that certain HLA-DQ variants enhance antigen presentation efficiency, resulting in more effective immune surveillance and pathogen clearance [15]. Such protective associations reinforce the concept that HLA-DQ polymorphisms do not uniformly confer risk but instead operate along a functional spectrum ranging from susceptibility to resistance [51]. These findings underscore the need to interpret protective alleles within specific population contexts, as their frequency and impact may vary substantially across ethnic groups while still contributing to broader global trends.

Regarding HLA-DQB1, the present analysis indicates that selected allele carriers are linked to increased tuberculosis susceptibility, consistent with earlier systematic reviews and population-specific studies [16, 48]. Functional studies suggest that alterations in the β-chain of HLA-DQ molecules may affect peptide-binding stability and T-cell receptor engagement, thereby weakening immune responsiveness to Mycobacterium tuberculosis. In contrast, the absence of association for certain HLA-DQB1 variants underscores the allele-specific nature of immunogenetic risk and highlights the importance of distinguishing between susceptibility-conferring and neutral variants within the same gene locus.

Importantly, the functional HLA-DQ molecule is formed through the heterodimerization of HLA-DQA1 and HLA-DQB1 gene products, emphasizing that tuberculosis susceptibility is likely influenced by combined α- and β-chain interactions rather than isolated allelic effects [52]. This interaction may partially explain inconsistencies across individual studies and populations, particularly where haplotype structures and linkage disequilibrium patterns differ.

Overall, this meta-analysis reinforces the biological relevance of HLA-DQ–mediated antigen presentation in tuberculosis pathogenesis while acknowledging substantial population-specific and methodological heterogeneity [53]. By focusing on carrier status, the present study provides a pragmatic synthesis of existing evidence and avoids overinterpretation of allele frequency data that are inconsistently reported across studies. From a clinical and public health perspective, these findings suggest that HLA-DQ allele carrier status may contribute to future risk stratification models and inform population-level tuberculosis susceptibility research, although direct clinical application will require further validation in large, prospective, and ethnically diverse cohorts.

5. LIMITATION

With 21 distinct studies included, this meta-analysis was the largest to assess HLA-DQ allele carriers as

genetic risk factors for PTB, with a few drawbacks. Initially, most studies did not screen the control groups for latent PTB using methods such as Interferon Gamma Release Assay (IGRA) or the tuberculin skin test. This could cause affected people to contaminate the control group, which reduced the strength of the relationships that were found [14, 15, 17, 27, 49]. Furthermore, the accuracy of determining HLA alleles had been impacted by the third limitation, which was related to the genotyping techniques used in previous studies. Some of these methods used low-resolution techniques (such as serological methods) or failed to provide adequate information on technical quality control, including sample replication [30]. More studies are required to have a more thorough understanding of the genetic pathways driving PTB. Hardy-Weinberg Equilibrium (HWE) testing could not be uniformly assessed, as most included studies did not report genotype distributions required for HWE calculation. This limitation may affect the ability to detect potential genotyping errors or population stratification [54].

6. CONCLUSION

This meta-analysis demonstrates a significant association between susceptibility to active pulmonary tuberculosis and the carrier status of specific HLA-DQA1 and HLA-DQB1 alleles. Carrier status of HLA-DQA1*02:01, HLA-DQA1*04:01, HLA-DQA1*05:01, and HLA-DQA1*06:01 was associated with a protective effect against tuberculosis, whereas carriers of HLA-DQA1*01:01, HLA-DQA1*03:01, HLA-DQB1*02:01, HLA-DQB1*05:03, and HLA-DQB1*06:01 showed an increased risk of developing active pulmonary tuberculosis. These findings support the biological role of the HLA-DQ complex in presenting Mycobacterium tuberculosis antigens to $CD4^+$ T cells and highlight how genetic polymorphisms in HLA-DQ genes may influence the effectiveness of adaptive immune responses, thereby contributing to inter-individual variability in tuberculosis susceptibility or resistance. By applying a carrier-based analytical framework to harmonize data across heterogeneous studies, the present meta-analysis provides an overall synthesis of the existing evidence while acknowledging substantial population-specific and methodological variability. Accordingly, the observed associations should be interpreted as general trends rather than population-specific effects. Further large-scale studies using standardized HLA typing methods and including diverse ancestral populations are warranted to clarify ancestry-specific genetic risks and to better define the role of HLA-DQ polymorphisms in tuberculosis pathogenesis.

SUPPLEMENTAL MATERIALS

The supplemental materials can be downloaded from the journal website along with the article.

CONFLICT OF INTEREST

None declared.

ETHICAL APPROVAL

Not applicable.

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