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REVIEW PAPER

P2X7 GENE POLYMORPHISMS AND PULMONARY TUBERCULOSIS SUSCEPTIBILITY: A GLOBAL SYSTEMATIC REVIEW

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Summary

Several studies have recently demonstrated the roles of purinergic receptor P2X ligand-gated ion channel 7 (P2X7) polymorphisms in pulmonary tuberculosis, yet these were controversial and inconclusive (inconsistent). Thus, the present study was designed to systematically assess the relationship between P2X7 gene polymorphisms and pulmonary tuberculosis susceptibility. Eligible studies were searched through the PubMed, Web of Science, Semantic Scholar, Elsevier and Google Scholar databases until 2024. The systematic review was performed according to the PRISMA guidelines. The review of literature included 20 case-control, pilot, and meta-analysis studies on pulmonary tuberculosis that included a total of 50,359 cases and 57,375 controls. The particular studies included in this review were conducted between 2014 and 2024, shortlisted during the current study to investigate the association of P2X7 gene polymorphisms with susceptibility to tuberculosis infection. The knowledge of the impact of P2X7 gene polymorphisms on susceptibility to pulmonary tuberculosis is relevant for better management of this disease and for determining the most appropriate therapy.

Keywords: P2X7, polymorphism, pulmonary tuberculosis, susceptibility, systematic review

Introduction

Tuberculosis (TB) is a serious public health challenge. Worldwide, an estimated 10 million people or more are afflicted with TB every year according to the World Health Organization (WHO) [1]. We need action urgently to rush to an end to the global TB epidemic by 2030, an aspiration adopted by all United Nations (UN) Member States and the WHO [2,3]. The WHO End TB Strategy goal of an 80% reduction by 2030 was not fulfilled by the 8.3% net reduction between 2015 and 2023. The greatest impact was made in the European and African regions, where declines were 27% and 24%, respectively [3]. Infection of *Mycobacterium tuberculosis* (M.tb) is associated with different host immune responses due to the host genetic factor and its response to the infection [3,4].

TB remains a major global public health concern. According to the WHO Global Tuberculosis Report 2024, approximately 10.8 million people worldwide developed TB in 2023, translating to an incidence rate of 134 cases per 100,000 people. The burden of the disease is unequally distributed, with over 70% of cases occurring in South-East Asia and Africa, followed by the Western Pacific (17%), Eastern Mediterranean (8.6%), Americas (3.2%), and Europe (2.1%). These regional differences highlight the need to investigate environmental and genetic factors that affect different groups' susceptibility to TB [5].

TB is a highly common chronic infectious disease and often presents as pulmonary tuberculosis (PTB) [6,7]. The scientific community has made significant progress in mapping the innate and adaptive immunity pathways that protect against PTB while discovering that specific SNPs in innate immunity genes serve as candidate biomarkers for PTB susceptibility [8].

The human P2X7 gene encoding the P2X7 receptor consists of 13 exons and is localized on chromosome 12q24. It encodes a polypeptide of 595 amino acids composed of 2

trans-membrane domains [9]. Purinergic receptor P2X ligand-gated ion channel 7 (P2X7) is encoded by the P2X7 gene on chromosome 12q24 [10]. This receptor is richly expressed on the surface of blood cells, immune cells, and especially on mono-nuclear lymphocytes. Thus, it functions through secretion of pre-inflammatory cytokines from monocytes, and macrophage P2X7 is predominantly expressed on the macrophage surface and can be activated through binding with adenosine-5 triphosphate (ATP) [11-13]. The P2X7 receptor is mostly expressed in hematological, mesenchymal, and epithelial cells, as well as neural lineages, and plays an important role in immunity, inflammation, neurological function, bone homeostasis, and neoplasia [12].

Activation of P2X7 generates the opening of a cation selective channel, allowing Ca2+ and Na+ to enter and K+ to exit [9]. This ion exchange triggers apoptosis in M.tb-infected macrophages, resulting in the pathogen's elimination. As a result, functional P2X7 polymorphisms are considered to be potential genetic indicators for TB. The involvement of P2X7R in the intracellular death of M.tb has received a lot of attention at present. It has been reported that polymorphisms in their canonical areas result in their loss of activity and, as a result, increase their vulnerability to M.tb infection. In earlier research, the significance of SNPs in P2X7, particularly rs3751143, in TB susceptibility was thoroughly examined [14]. We conducted this systematic review to improve our understanding of how P2X7 polymorphisms influence TB development.

Following *M. tuberculosis* inhalation, P2X7 receptor activation may play a role in the initial control of infection in alveolar macrophages. A lack of P2X7-mediated control of mycobacterial infection within macrophages in the lungs may allow for transmission to extrapulmonary tuberculosis (EPTB) locations, where the infection either proceeds to post-primary TB illness or is controlled by the developing specialized T-cell response. With

diminishing T-cell immunity, reactivation of latent TB infection (LTBI) may result in an increase in the prevalence of EPTB in people with non-functioning SNPs in P2X7.

The P2X7 gene plays an essential role in how the immune system responds to TB. The P2X7 gene produces the P2X7 receptor, which is located on many cell types including macrophages. When ATP binds to the P2X7 receptor, it starts a chain reaction that eliminates intracellular pathogens, including the TB-causing bacterium Mtb [15]. Changes in the P2X7 gene called polymorphisms have effects on how the P2X7 receptor functions. Research shows that certain polymorphisms reduce P2X7 receptor function, which weakens macrophages' ability to eliminate *M. tuberculosis*. This outcome may lead to greater TB risk while complicating infection management. The connection between P2X7 gene polymorphisms and TB vulnerability has been examined by numerous studies. While the results have been somewhat inconsistent, several studies have discovered that specific polymorphisms are related to an increased risk of TB, notably EPTB [16].

The P2X7 receptor is involved in the pathogenesis of several diseases, ranging from inflammatory to autoimmune disorders and from altered neurological conditions to cancer. This suggests that P2X7 blocking drugs have high pharmacological potential in a wide range of settings, particularly in disorders where other clinical trials have failed [17]. However, additional research is required to completely understand the significance of P2X7 gene polymorphisms in TB etiology. It is crucial to emphasize that genetics are only one of several factors that influence TB susceptibility. Environmental factors, including *M. tuberculosis* exposure and immunological state, are also relevant. TB is the top infectious disease leading to deaths worldwide, claiming 1.25 million lives each year [5,18,19].

M.tb may not be completely eradicated during the first phagocytosis step. Interleukin-12 (IL-12), IFN-γ production, suppression of macrophage apoptosis, and inhibition of phagosome fusion are some of the reasons that can lead to this failure. A variety of chemokines

including CCL2, CCL3, CCL5, CXCL8, and CXCL10 and cytokines such as IL-1β, IL-6, TNF-α, IL-12, IL-23, IL-17, and IFN-γ are released by the bacteria that survive. These chemicals are essential for attracting and stimulating various leukocyte populations at the infection site, which aids in the development of granulomas. Usually, two to three weeks after the innate immune response, the adaptive immune response starts. Naive CD4 + T cells in the closest regional lymph node are activated by antigen-presenting cells displaying bacterial antigens on MHC class II molecules. These T cells move to the lungs after becoming activated in order to aid in limiting M.tb growth [20].

This systematic review fills a vital need by integrating and critically evaluating previous studies on the association between P2X7 gene polymorphisms and TB susceptibility, highlighting inconsistencies in the findings.

Aim of the work

This review aims to evaluate the relationship between P2X7 gene polymorphisms and TB susceptibility. It also looks for possible causes of discrepancies in the results and assesses the methodological caliber of the examined studies. Identifying and suggesting possible biomarkers linked to TB susceptibility based on P2X7 polymorphisms is another goal of this review. The review's goal is to provide a better understanding of the genetic pathways influencing TB susceptibility by combining findings from multiple populations. The ultimate objective is to advance our knowledge of how genetic variables, particularly those pertaining to immune response pathways, affect the likelihood of contracting TB.

Methods

Literature search and inclusion criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in the current review. To minimize selection bias and guarantee a thorough evaluation of pertinent studies, a thorough and methodical search of many databases was conducted. From 2014 to 2024, the following keywords were used to search PubMed, Web of Science, Semantic Scholar, Elsevier, Gene Cards, and Google Scholar: "P2X7", "P2X7R", "purinergic receptor P2X7", "pulmonary tuberculosis", and "polymorphism or variant". This method was developed to find research investigating the connection between TB susceptibility and P2X7 gene variations. The review includes a total of 20 studies.

The inclusion criteria were: (1) case-control studies that specifically examined the relationship between P2X7 polymorphisms and PTB incidence; (2) studies that reported on genotype and allele frequencies in patients and controls that could be obtained for additional analysis; and (3) studies that used meta-analysis methodology.

The exclusion criteria were: (1) research that was not directly connected to P2X7 polymorphisms and PTB risk; (2) research that had data that overlapped; and (3) conference abstracts or research that was published in non-peer-reviewed journals.

A broad range of sources, including both more regionally specific sites (Semantic Scholar, Google Scholar) and major scientific databases (PubMed, Web of Science, etc.), were specifically covered by the search method.

Search strategy and evaluation criteria

A computer-assisted search was performed across multiple platforms to identify studies investigating the relationship between P2X7 gene polymorphisms and PTB susceptibility. In addition to PubMed, Web of Science, and Google Scholar, databases like SCI Hub and regional journals were included to capture studies that might be overlooked otherwise. The search terms used included: “P2X7 or P2X7R”, “purinergic receptor P2X7”, “pulmonary tuberculosis”, and “polymorphism or variant”, with added terms like [susceptibility or resistance] to ensure comprehensive coverage of relevant articles. The study selection process is summarized in Figure 1.

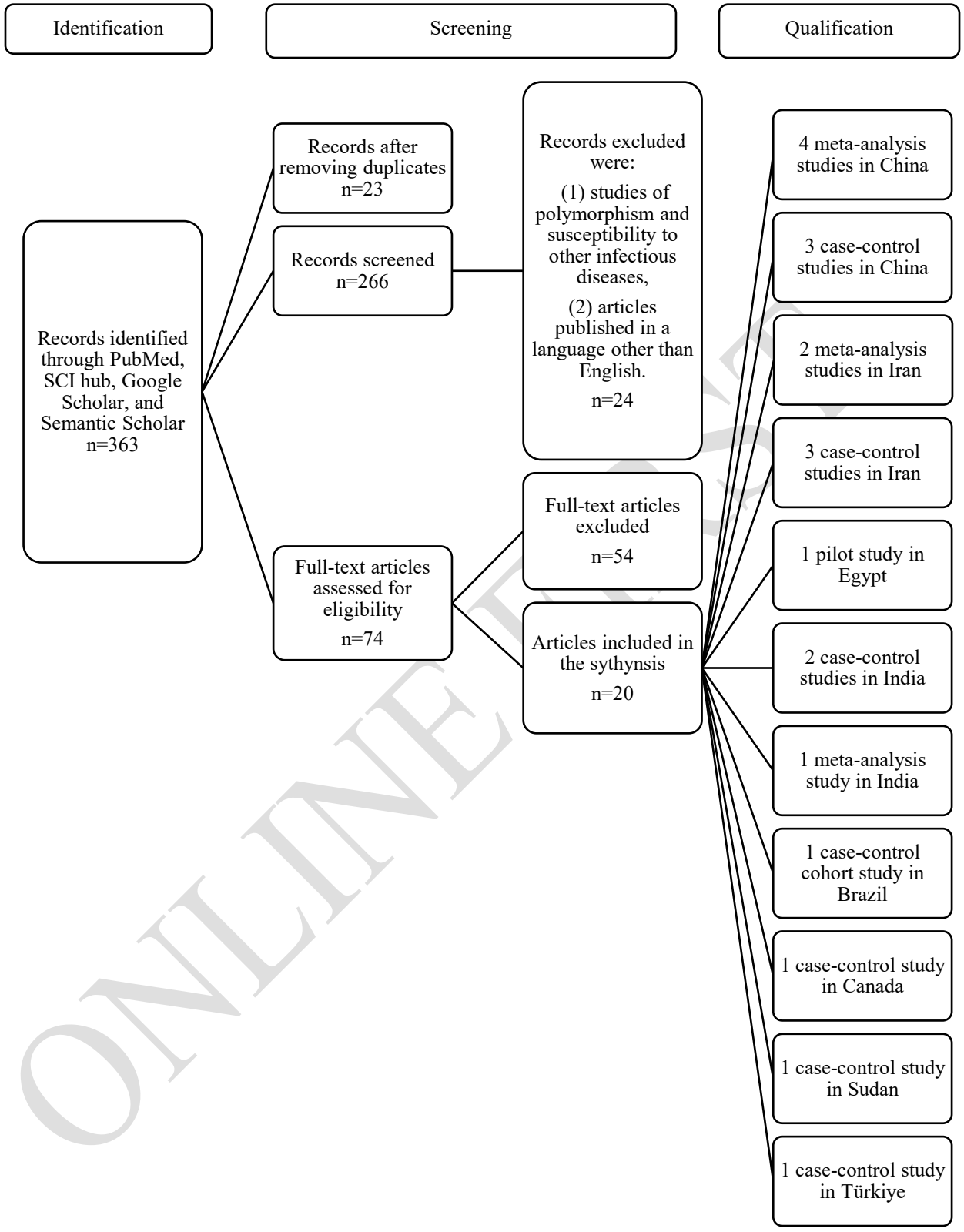

Figure 1. Flow chart illustrating the detailed study selection process of this systematic review

Eligibility criteria

Studies were considered eligible if they met the following criteria: (1) all eligible case-control studies that evaluate the relationship between P2X7 gene polymorphism and risk of susceptibility or resistance in PTB patients; (2) articles that examine genotypic and allelic distribution of patients and healthy individuals for P2X7 gene polymorphism; (3) case-control articles published in the English language. The exclusion criteria included: (1) studies of polymorphism and susceptibility to other infectious diseases; (2) articles published in a language other than English.

Data extraction

In this review, all data was extracted using the following criteria: the author's name, journal name, year of publication, country of origin, ethnicity, number of cases for every gender separately, genotyping method, polymorphism type, and total sample size of case and control.

This review included studies from a variety of populations, including Chinese, Iranian, Indian, Brazilian, and Sudanese, each having their own genetic backgrounds that could influence the results. Furthermore, multiple genotyping technologies (such as PCR-RFLP, TaqMan tests, and sequencing) were used across investigations, with differing sensitivity and accuracy. To account for these differences, results were examined by demographic group where applicable, and studies using better accuracy methods, like sequencing, were given priority in the study.

Literature review results

In this systematic review, 363 publications were gathered from Google Scholar, Elsevier and PubMed. Only 20 were examined for a systematic review based on the assessment of the titles and abstracts. Based on the defined inclusion and exclusion criteria, 20 eligible studies were identified that explored the association between P2X7 receptor gene polymorphisms and susceptibility to PTB. The majority of the research used TaqMan-assay, ARMS-PCR, PCR-RFLP, allele comparisons, real-time PCR, sequencing, and gene expression (Table 1).

Table 1. Characteristics of the 20 studies included in the systematic review

Authors	Year of publication	Country	Host ethnicity	Sample size	Genotyping method	Type of study
Chi et al. [6]	2019	China	Caucasian	16138 cases, 20133 controls	Allele comparisons rs208294, rs1718119, rs2230911, rs2393799, rs3751143, rs7958311	Meta-analysis
Yi et al. [21]	2014	China	Caucasian, Asian and mixed populations	2207 cases, 2220 controls	ARMS-PCR, PCR-RFLP, allele specific PCR, sequencing	Meta-analysis
Wu et al. [22]	2014	China	Asian, African and Latin	2195 cases, 2036 controls	RFLP–PCR, ARMS-PCR, RTFQ PCR	Meta-analysis
Ge et al. [9]	2016	China	Indian	1916 cases, 2194 controls	Allele comparisons	Meta-analysis
Zheng et al. [23]	2017	China	Chinese Han	1601 cases, 1526 healthy controls	TaqMan Real-Time PCR System	Case-control
Zhu et al. [8]	2016	China	Tibetan Chinese	467 patients with active PTB, 504 healthy controls	Sequenom mass ARRAY	Case-control

Jiangdong et al. [12]	2015	China	Xinjiang province population	103 TB patients, 87 healthy individuals	PCR-RFLP	Case-control
Varahram et al. [24]	2015	Iran	Iranian	80 PTB patients, 50 controls	PCR-RFLP and allele specific PCR	Case-control
Shamsi et al. [13]	2016	Iran	Iranian	100 patients, 100 healthy individuals	PCR-RFLP	Case-control
Amiri et al. [11]	2018	Iran	Lur population	100 unrelated pulmonary TB patients, 100 unrelated controls	PCR-RFLP	Case-control
Taheri et al. [25]	2019	Iran	Asian	16514 cases, 20246 controls	TaqMan Real-Time PCR System, PCR-RFLP, ARMS-PCR, mass spectrometry, mass array	Meta-analysis of case-control studies
Keikha et al. [26]	2021	Iran	Asian	5324 TB patients (both pulmonary and extra-pulmonary TB), 5220 controls	PCR-RFLP, ARMS-PCR, and TaqMan methods	Meta-analysis of 20 case-control studies
Konuk et al. [27]	2016	Türkiye	Turkish	188 TB patients, 81 healthy individuals	RFLP-PCR	Case-control
Alshammari et al. [28]	2016	India	Caucasian, Asian and mixed populations	2113 PTB patients, 2678 controls	PCR-RFLP, ABI-PRISM	Meta-analysis
De et al. [29]	2017	India	Tribal population of Jhargram, West Bengal	56 TB patients, 60 non-TB individuals	PCR-RFLP	Case-control
Chaudhary et al. [14]	2018	India	North Indian Punjabi	145 PTB patients, 247 healthy controls	ARMS-PCR	Case-control
Shafiek et al. [30]	2022	Egypt	Egyptian	25 PTB patients 25 controls	PCR-RFLP	Pilot

Mukhtar et al. [31,32]	2018, and 2020	Sudan	Sudanese	120 TB patients, 46 healthy controls	PCR–RFLP and confirmed by sequencing	Case-control
Souza de Lima et al. [33]	2016	Brazil	South American	288 unrelated individuals with active PTB, 288 unrelated individuals	TaqMan Real-Time PCR	Case-control cohort
Semple et al. [34]	2019	Canada	Canadian (Dene, Inuit and non-indigenous Canadian participants)	114 self-identified Dene, 99 self-identified non-indigenous individuals	SNP genotyping-PCR	Cohort

Notes: TB – tuberculosis, PTB – pulmonary tuberculosis, PCR – polymerase chain reaction, RFLP – restriction fragment length polymorphism, MALDI-TOF – chip-based matrix-assisted laser desorption ionization time-of-flight, ARMS-PCR – amplification-refractory mutation system-PCR, TaqMan – probes used in quantitative PCR, T-ARMS-PCR –Multiplex Tetra-Primer Amplification Refractory Mutation System-PCR, MassARRAY – non-fluorescent detection platform utilizing mass spectrometry to accurately measure PCR-derived amplicons.

13 case-control studies investigating the relationship between P2X7 gene polymorphisms and TB across different populations revealed several significant findings.

There was research conducted in China, such as in the Han population. Zheng found that the rs1718119 allele A was substantially linked to a lower risk of sputum smear-positive TB (OR=0.78, p=0.005) and active TB (OR=0.81, p=0.006). Among tobacco smokers, the protective impact was higher, according to stratified analysis. Additionally, the study found that rs7958311 was linked to a better chance of a successful course of treatment, albeit this result was not maintained after Bonferroni correction [23]. The best medications are no longer effective against TB. Drug-resistant TB is more deadly, expensive, and challenging to cure. In 2023, there were 400,000 new cases of MDR/RR TB in every nation [19].

3 P2X7 gene polymorphisms were identified to be significantly associated with an elevated risk of PTB in another study conducted in the Tibetan Chinese population [8]. There

is a genetic predisposition to TB in this population, as evidenced by the substantial associations of the rs656612, rs208290, and rs7958311 polymorphisms, with an increased chance of contracting the disease. Even after Bonferroni adjustment, the rs208290 polymorphism remained significant.

In addition, Wu et al. discovered that TB patients had greater frequencies of the rs1513A/C and rs762T/C polymorphisms than controls [12]. According to the study, the rs762T/C polymorphism may play a part in TB susceptibility, as it was linked to increased IgG responses to M.tb and more M.tb in sputum.

Studies highlight the complex role that genetic variations in the P2X7 gene play in influencing susceptibility to TB and the outcomes from TB across diverse populations (Table 2).

Table 2. Characteristics of included studies for P2X7 polymorphisms and PTB

Country/year	Population	Genotype/ allele/reference sequence	Findings
Iran (2021) [26]	Asian	rs3751143	Although rs3751143 polymorphism plays an important role in the susceptibility of individuals to TB, at the same time, according to the results of the study, this polymorphism cannot be considered as a biomarker for predicting TB.
Iran (2019) [25]	Asian	rs2393799, rs1718119, rs208294, rs7958311, rs2230911, and rs3751143	The study did not support an association between the rs2393799, rs1718119, rs208294, rs7958311, and rs2230911 polymorphisms of P2X7 and TB risk. P2X7 rs3751143 polymorphism may play a role in susceptibility to TB in the Asian population.
Iran (2018) [11]	Lur population of Iran	1513A/C, 762T/C	AA genotype was associated with TB susceptibility (OR=4.75), AC protective (OR=0.19), A allele was associated with susceptibility (OR=2.879).
Iran (2016) [13]	Iranian	SNP-762, and 1513	A significant association of IFN-γR1 and P2X7 gene polymorphisms with a risk of developing TB was found in the Iranian population.
Iran (2015) [24]	Iranian	SNPs in P2X7 (+1513, -762)	P2X7 (1513) and the TNF-a (238) gene were associated with a risk of developing PTB. Additionally, distribution of haplotype

			and diplotype variables appeared to be more specific than SNPs.
Türkiye (2016) [27]	Turkish	A1513C	Polymorphisms rarely appear in the Turkish population. However, although the P2X7 A1513C polymorphism that changes glutamine to alanine at codon 496 was detected in both groups. There was no significant relationship between the occurrence of this polymorphism and resistance/or susceptibility to TB.
Egypt (2022) [30]	Egyptian	1513A/C	AC and CC genotypes are more frequent in active TB and are associated with smoking, though not with gender or previous TB cases.
Sudan (2018) [32]	Sudanese	1513A/C, rs2230912	Polymorphism rs2230912 was detected from sequencing, and the results may be associated with TB infections.
India (2018) [14]	North Indian Punjabi	+1513(A/C), +946(G/A), +1729(T/A)	C allele at +1513 associated with TB risk, and +946 and +1729 were monomorphic. There was no significant difference for +489 and -762.
India (2017) [29]	Tribal population of Jhargram, West Bengal	1513 A/C	P2X7 1513A/C gene polymorphism has been studied in TB infected (n=56) and non-TB (n=60) individuals, and the CC genotype has a significantly higher risk of developing TB (p<0.05). The results of this research established that the CC genotype of P2X7 polymorphism is related with susceptibility to TB among infected individuals.
India (2016) [28]	Caucasian, Asian and mixed populations	A1513C	The study did not suggest an association of P2x7, A1513C polymorphism with PTB risk in overall population or among Caucasian population. However, it plays a significant risk factor for predisposing PTB in Asians.
China (2019) [6]	Caucasian	rs1718119, rs3751143	The study indicates that the rs1718119 polymorphism may serve as a potential biological marker of TB in Asians, and the rs3751143 polymorphism as a potential biological marker of TB in Caucasians.
China (2017) [23]	Chinese Han	rs1718119, rs7958311	A allele of rs1718119 was associated with reduced TB risk (OR=0.81), with a stronger effect in smokers; rs7958311 was weakly associated with treatment outcomes.
China (2016) [8]	Tibetan	rs656612, rs208290, rs7958311	C allele of rs656612 and A allele of rs208290 was associated with increased TB risk (rs656612 OR=1.307, rs208290 OR=1.418).
China (2015) [12]	Xinjiang Province, China	1513A>C, 762T>C	P2X7 SNPs, 1513A>Cand-762T>C, may be associated with a susceptibility to TB, and -762T>C SNP may contribute to the development of M.tb. The mutant genotype of-762T>C (TC and CC) may lower human

			capability of phagocytosis to M.tb, leading to an increased morbidity from TB.
China (2016) [9]	Indian	1513A>C, 762T>C	P2X7 SNPs, 1513A>Cand-762T>C, may be associated with a susceptibility to TB, and -762T>C SNP may contribute to the development of M.tb. The mutant genotype of -762T>C (TC and CC) may lower the human capability of phagocytosis to M.tb, leading to an increased morbidity from TB.
China (2014) [21]	Caucasian, Asian and mixed populations	762T/C, 1513A/C	P2X7, 762T/C gene polymorphism is not associated with PTB susceptibility.
China (2014) [22]	Asian, African, and Latin	1513A/C	The study indicates that the C allele of P2X7 receptor gene 1513A/C polymorphism is a risk factor for PTB in Asians, though not in Africans or Latinos, and a risk factor for EPTB.
Brazil (2016) [33]	South American	rs2230911	Loss-of-function SNP rs2230911 in P2X7 that negatively affects NLRP3-inflammasome activation, confers a susceptibility toward active PTB in Brazilian Amazonian cohorts.
Canada (2019) [34]	Canadian (Dene, Inuit and non-indigenous Canadian participants)	rs3751143	A higher frequency of non-functional P2X7 receptors may influence the activity of downstream immune mediators required for resolution of infections such as pro-inflammatory cytokines and CHDP defensins, thus contributing to a higher burden of infections in indigenous populations.

A study on the Lur population in western Iran by Amiri et al. discovered that the 1513A/C polymorphism of the P2X7 gene is linked to PTB susceptibility in the Lur community [11]. The AC genotype served as a protective factor (OR=0.192, p=0.0001), whereas the AA genotype was associated with increased vulnerability (OR=4.750, p=0.0001). The C allele offered protection (OR=0.347, p=0.0001), but the A allele was linked to increased vulnerability (OR=2.879, p=0.0001). There were no noteworthy discoveries about the 762T/C polymorphism. The heterozygous AC genotype and the 1513A allele were more common in TB patients than in controls.

According to another study by Shamsi et al. this difference was statistically significant (p=0.00) [13]. Furthermore, none of the patients had the wild-type T/T genotype, while the

majority of TB patients (99%) carried the heterozygote T/C mutation at the 762 location. The above findings imply that variations in the P2X7 gene are substantially linked to TB susceptibility. Additionally, Varahram et al. found that the P2X7 gene's 1513 polymorphism was more common in TB patients (35%-44.3%) than in controls (12-24%) (p=0.026, OR=2.45) [24]. TNF-α polymorphisms and allele frequencies at the 762 location did not differ significantly. TB patients were more likely to have the 238 allele of TNF-α (72.1%, p=0.000, OR=5.85). The study found that polymorphisms in TNF-α (238) and P2X7 (1513) are linked with PTB vulnerability.

Furthermore, research conducted in India by De et al. [29], on the P2X7 1513A/C polymorphism among the West Bengali Jhargram tribe revealed a strong correlation between the C allele and active TB (0.37% vs. 0.23%, p=0.013). A greater risk of developing TB was associated with the C allele (OR=2.067, 95% CI=1.16-3.67) [29]. Furthermore, TB patients had a higher prevalence of the CC genotype than healthy people (OR=5.54, CI=1.42–21.63, p=0.01). There was no discernible difference between the two groups' heterozygous AC genotypes. A study conducted in a Punjabi community in North India, Chaudhary, discovered a strong correlation (p<0.05) between TB susceptibility and the P2X7 A1513C polymorphism. The 1513 site's C allele was found to be a TB risk factor, whereas other polymorphisms (such as 946, 1729, 489, and 762) did not exhibit any noteworthy correlations. In this cohort, the polymorphism at the 1513 location was identified as a major risk factor for TB (Table 2) [14].

Different studies carried out in different countries have explored the association between P2X7 polymorphisms and susceptibility to TB, revealing diverse findings across different populations, such as in Egypt, Sudan, Türkiye, Brazil, and Canada. A study conducted among Egyptians by Shafiek et al. [30] examining the P2X7 1513A/C polymorphism in Egyptian individuals found a significant association between the AC and CC genotypes and active TB cases (both PTB and EPTB). The distribution of these genotypes was more frequent in TB

patients than in healthy controls (p<0.05). However, no association was found between the P2X7 genotypes and gender or in those with a previous history of TB. P2X7 polymorphisms and smoking history were shown to be significantly correlated (p=0.036), indicating that the P2X7 1513A/C polymorphism may contribute to Egyptians' susceptibility to TB (Table 2) [30].

The P2X7 1513A/C polymorphism, more especially the CC and AC genotypes, was found to be strongly linked to a higher susceptibility to TB, including both pulmonary and extrapulmonary forms, in a study conducted on Sudanese populations by Mukhtar et al. [31,32]. The CC and AC genotypes had odds ratios (OR) of 2.058 and 4.615, respectively. With an OR of 2.65, the study also found that the CC and AC genotypes were more strongly associated with EPTB, suggesting a possible genetic susceptibility to TB in Sudanese people. In Türkiye, a study by Konuk et al. [27] investigated the P2X7 A1513C polymorphism in TB patients and healthy controls. It was found that both TB patients and healthy people have the A1513C polymorphism, which results in alteration of the Glu496Ala amino acid in the P2X7 gene. The lack of significant differences in genotype frequencies between the two groups suggests that the A1513C polymorphism may not be a major factor influencing TB susceptibility or resistance in the Turkish population. However, it may still have an impact on TB susceptibility or resistance.

Souza de Lima et al. [33] investigated the P2X7 gene variant rs2230911 (T357S) in Brazil and found a robust association with an increased risk of active PTB. With an adjusted odds ratio of 3.79, homozygous individuals with the variation (T357S) were more common in TB patients (8%) than controls (2%). According to this finding, those who have a loss-of-function mutation in P2X7 are more vulnerable to TB as it affects their immune response to M.tb. The results highlight the role of P2X7 in immunological protection against TB and corroborate findings seen in Caucasian populations. According to a study [34], in Canada, indigenous communities (Dene and Inuit) had a greater frequency of the C allele in the P2X7

gene than non-indigenous populations [34]. According to the study, these genetic differences may affect how the immune system reacts to illnesses like TB. A greater frequency of the C allele was consistently seen across sample sizes, despite some genetic equilibrium problems in the data. This suggests that there may be a genetic component to indigenous cultures' susceptibility to TB (Table 2).

The populations included in this study are from a variety of geographical areas, including Egypt, Sudan, Türkiye, Brazil, Canada, India (Jhargram tribe, Punjabi), Iran (Lur), and China (Han, Tibetan). Environmental factors, risk factors, and genetic backgrounds vary by community and can affect the impact of genetic variants and susceptibility to TB. For example, in one community, some polymorphisms might be more prevalent or have stronger effects than in another.

The frequency and impact of genetic variants such as the P2X7 polymorphisms (e.g. rs1718119, rs1513A/C, rs7958311) may vary among groups. While the rs1513A/C polymorphism showed a protective effect in the Lur people but a higher susceptibility in other populations, such as the Jhargram tribe in India and Sudanese individuals, the rs1718119 allele A, for instance, was protective in the Han Chinese population. This implies that the impact of a single genetic mutation may differ according on the population under investigation.

The way that genetic variations interact with the environment to affect TB susceptibility may also be influenced by factors like urbanization, smoking, dietary practices, and the local prevalence of TB. For example, the Han Chinese study [16] found a stronger protective effect of the rs1718119 allele among tobacco smokers, suggesting that environmental exposure can modify genetic risk factors.

7 meta-analysis studies investigating the relationship between P2X7 gene polymorphisms and TB across different populations reveal several significant findings.

A meta-analysis of studies conducted in China by Chi et al., identified significant associations between the rs3751143 polymorphism and TB susceptibility [6]. In the overall analysis, all genetic models (dominant, recessive, additive, and allele) showed significant associations, with the dominant model yielding an OR of 1.24 (p=0.01). TB was linked to the rs1718119 polymorphism, according to subgroup studies. TB was associated with rs3751143 in Asians (recessive model: OR=0.64, p=0.03). Furthermore, a meta-analysis of the P2X7-1513A/C polymorphism by Ge et al. revealed no overall significant connection with TB vulnerability [9]. According to subgroup analysis, the rs1513A/C C allele was linked to a higher risk of TB in Indian populations (OR=0.69, p=0.0006) but not in Latino or Caucasian populations. The study noted significant heterogeneity among studies. Significant correlations between the C allele and elevated TB susceptibility in Asians were found in another meta-analysis study of the P2X7-1513A/C polymorphism by Wu et al. [22] (C vs. A: OR=1.42, p=0.001). Stronger correlations with EPTB were found through further analysis, specifically in the CC genotype (OR=3.79, p=0.007) [22]. Furthermore, a meta-analysis of the P2X7-762T/C polymorphism by Yi et al. [21] revealed no significant association between the polymorphism and TB susceptibility in any genetic model. Additionally, subgroup analyses were unable to identify any correlations between various ethnic groups, suggesting that the rs762T/C polymorphism had no bearing on TB susceptibility (Table 2) [21].

The studies by Keikha et al. [26] in Iran showed that the rs3751143 polymorphism was associated with TB susceptibility; however, it is not a reliable diagnostic biomarker, according to a meta-analysis of 20 studies on the polymorphism. For the genetic models AA, AC, and CC, the sensitivity and specificity ranged from 34.3% to 59.4% and 6% to 95%, respectively. The investigation revealed that although the mutation might make Asians more susceptible, it is not a valid biomarker for diagnosing TB (Table 2) [26]. The rs3751143 mutation was found to be significantly associated with an elevated risk of TB in another meta-analysis study by Taheri et

al. [25], with all genetic models indicating positive odds ratios. The heterozygous (OR=1.44) and homozygous (OR=1.87) codominant models, as well as the dominant (OR=1.50) and recessive (OR=1.61) models, all indicated increased susceptibility. The variant was especially significant in the Asian population and was linked to both pulmonary and EPTB. However, other P2X7 polymorphisms were not associated with TB risk [25].

A meta-analysis study in India by Alshammari et al. [28] of 11 studies including 2,678 controls and 2,113 PTB cases found no significant overall association between the P2X7 A1513C polymorphism and PTB risk. On the other hand, the heterozygous AC genotype (OR=1.570, p=0.001) and the C allele (OR=1.375, p=0.001) were substantially linked to a higher incidence of PTB in Asian populations. Asians were likewise at higher risk according to the recessive genetic model (CC+AC vs. AA) (OR=1.540, p=0.001). In the Caucasian population, no correlation was discovered (Tables 2 and 3) [28].

Table 3. Summaries of the studies that support the association of P2X7 gene polymorphism with TB risk and studies that did not state any association

Polymorphism	Studies supporting association with TB Risk	Studies opposing or not supporting association
rs3751143	– Iran (2021): plays a role in susceptibility but not a biomarker for TB prediction. – Iran (2019): associated with TB risk in Asians. – China (2019): associated with TB risk in Caucasians. – Iran (2016): associated with TB risk. – Canada (2019): non-functional P2X7 receptors contribute to TB susceptibility in indigenous populations.	– Iran (2019): no significant association. – Türkiye (2016): no significant relationship with TB susceptibility. – China (2014): no association with PTB susceptibility in Caucasians, Asians, and mixed populations.
1513A/C	– Egypt (2022): AC and CC genotypes more frequent in active TB, associated with smoking. – Sudan (2018): associated with TB infections. – India (2018): C allele associated with increased TB risk.	– China (2014): no association with PTB susceptibility in Asians, Africans, or Latinos, but may be a risk for EPTB in Asians. – China (2014): no association in mixed populations (Caucasians, Asians).

	– India (2017): CC genotype associated with TB susceptibility in Jhargram, West Bengal. – China (2015): associated with TB susceptibility.	
762T/C	– Iran (2014): associated with TB risk. – China (2015): associated with TB susceptibility and decreased phagocytosis.	– China (2014): no significant association with PTB susceptibility in Caucasians, Asians, and mixed populations. – India (2016): no significant findings in the North Indian Punjabi population.
rs1718119	– China (2017): A allele associated with reduced TB risk, stronger in smokers.	– Iran (2019): no association with TB risk.
rs7958311	– China (2017): weak association with treatment outcome.	– Iran (2019): no significant association with TB risk.
rs2230911	– Brazil (2016): loss-of-function SNP associated with susceptibility to active PTB in Brazilian Amazonian cohorts.	– None explicitly opposing for this polymorphism, as it is specific to the Brazilian cohort.
Other SNPs	– Iran (2014): association with TB risk, including TNF-α (238) and P2X7 (+1513, -762) polymorphisms.	– Iran (2021): did not find consistent evidence for several P2X7 polymorphisms (rs2393799, rs1718119, rs208294, rs7958311, rs2230911, rs3751143).

Numerous studies [13,20,21] demonstrate that there are population-dependent relationships between particular P2X7 gene polymorphisms and TB susceptibility. For example, several researchers have found that the rs3751143 polymorphism is significantly linked to TB susceptibility in Asians populations, whereas no significant association was observed among Latino or Caucasian populations. Similarly, the rs1513A/C polymorphism exhibits a greater correlation with TB among Indian populations (C allele), whereas neither Latino nor Caucasian populations exhibit any correlation. As some polymorphisms may be more common or have bigger effects in some populations due to genetic background or environmental exposure, this emphasizes the significance of ethnic variety in genetic investigations.

Research that supported an association: several studies [6,25,26,32,34] indicate that certain P2X7 polymorphisms, in particular rs3751143, 1513A/C, and rs2230911, are associated with an increased risk of TB, notably in populations from Asia, Africa, and Latin America.

Research that found no association: some research [14,20,22], especially from China, Iran, and Türkiye, found no significant relationships, suggesting that the correlation between these polymorphisms and TB risk might not be applicable to other populations or geographical areas.

We examined P2X7 gene variants and identified a few that appear to elevate the risk of PTB. This leads to the question if a doctor's office could use P2X7 genotype checks as a useful early warning system, as well as identifying those variations that genuinely influence immune response mechanisms. This might significantly help in developing optimized solutions, such as vaccinations or therapies, that take into account each person's particular genetic makeup [30,34].

Conclusions

In conclusion, our pooled data suggests an association between P2X7-1513A/C polymorphism and the prevalence of PTB among Indian, Egyptian, and Iranian populations. Other studies in China discussed how rs1718119 was associated with reduced susceptibility to TB, especially among smokers, while rs7958311 had a weak association with TB treatment outcomes. An association of rs656612, rs208290, and rs7958311 with increased TB risk in the Tibetan Chinese population was also seen. Furthermore, a significant association with the susceptibility of PTB was detected for the rs3751143 polymorphism in the dominant, recessive, additive, and allele models in overall analyses, which may serve as a potential biological marker of TB in Caucasians. Further subgroup analyses based on the ethnicity of participants revealed

that the rs1718119 polymorphism is significantly associated with the susceptibility of TB, which may serve as a potential biological marker of TB in Asians.

Furthermore, studies in Egypt, Sudan, Türkiye, Brazil, and Canada collectively suggest that the P2X7 receptor polymorphisms, particularly the 1513A/C and T357S variants, are associated with susceptibility to TB across different populations. While some studies found a significant association, others, such as the Turkish study, did not observe a major impact on TB susceptibility. However, the findings from Egypt, Sudan, Brazil, and Canada highlight the potential role of these genetic variants in modulating immune responses to TB, particularly in specific ethnic or geographic groups.

Understanding how variations in the P2X7 gene affect PTB is important for medical practice. The P2X7 receptor is key in controlling how immune cells, called macrophages, respond and die when fighting the bacteria that cause TB. Differences in this gene might change how likely someone is to become infected. By identifying these variations in gene expression, medical professionals could more effectively identify individuals who are at higher risk, strengthen prevention programs, and develop treatments that are specific to each patient's need. Furthermore, since P2X7 is a potential therapeutic target, knowledge of its variations may help develop novel host-directed therapies and vaccines [22,25].

Future research should focus on confirming whether differences in the P2X7 gene genuinely affect a person's risk of developing TB. This means carrying out in-depth research with participants from various geographic locations and ethnic backgrounds. By combining genetic information with other health and lifestyle factors, researchers may be able to create more precise methods for identifying people who are susceptible to TB. It is also essential to conduct more research on how these gene alterations actually affect our bodies' defenses against the TB bacteria. Ultimately, as genetic research progresses, it could help physicians

create more customized strategies for treating and preventing TB and which are unique to the traits of each patient [5].

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