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The influence of single nucleotide polymorphisms of *NOD2* or *CD14* on the risk of *Mycobacterium tuberculosis* diseases: a systematic review

Juan M. Cubillos-Angulo^{1,2,3†}, Catarina D. Fernandes^{1,3,4†}, Davi N. Araújo^{1,2,3†}, Cristinna A. Carmo⁴,
María B. Arriaga^{1,2,3} and Bruno B. Andrade^{1,2,3,4,5,6,7,8*} 

Abstract

Background: Tuberculosis (TB) is still one of the leading causes of death worldwide. Genetic studies have pointed to the relevance of the *NOD2* and *CD14* polymorphic alleles in association with the risk of diseases caused by *Mycobacterium tuberculosis* (*Mtb*) infection.

Methods: A systematic review was performed on PubMed, EMBASE, Scientific Electronic Library Online (SciELO), and Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs) to examine the association between single nucleotide polymorphisms (SNP) and risk of *Mtb* diseases. Study quality was evaluated using the Newcastle-Ottawa Quality Scale (NOQS), and the linkage disequilibrium was calculated for all SNPs using a webtool (Package LDpop).

Results: Thirteen studies matched the selection criteria. Of those, 9 investigated *CD14* SNPs, and 6 reported a significant association between the T allele and TT genotypes of the rs2569190 SNP and increased risk of *Mtb* diseases. The genotype CC was found to be protective against TB disease. Furthermore, in two studies, the *CD14* rs2569191 SNP with the G allele was significantly associated with increased risk of *Mtb* diseases. Four studies reported data uncovering the relationship between *NOD2* SNPs and risk of *Mtb* diseases, with two reporting significant associations of rs1861759 and rs7194886 and higher risk of *Mtb* diseases in a Chinese Han population. Paradoxically, minor allele carriers (CG or GG) of rs2066842 and rs2066844 *NOD2* SNPs were associated with lower risk of *Mtb* diseases in African Americans.

Conclusions: The *CD14* rs2569190 and rs2569191 polymorphisms may influence risk of *Mtb* diseases depending on the allele. Furthermore, there is significant association between *NOD2* SNPs rs1861759 and rs7194886 and augmented risk of *Mtb* diseases, especially in persons of Chinese ethnicity. The referred polymorphisms of *CD14* and *NOD2* genes likely play an important role in risk of *Mtb* diseases and pathology and may be affected by ethnicity.

* Correspondence: bruno.andrade@focruz.br

†Juan M. Cubillos-Angulo, Catarina D. Fernandes and Davi N. Araújo contributed equally to this work.

¹Instituto Gonçalo Moniz, Fundação Oswaldo Cruz, Salvador, Bahia, Brazil

²Faculdade de Medicina, Universidade Federal da Bahia, Salvador, Bahia, Brazil

Full list of author information is available at the end of the article



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Background

Tuberculosis (TB) is one of the 10 leading causes of death around the world [1]. Approximately 1.7 billion people are infected by *Mycobacterium tuberculosis* (*Mtb*) worldwide [1]. The occurrence of this infection at different rates across countries and ethnicities indicates that genetic determinants may underlay the risk of developing diseases caused by *Mtb* infection such as pulmonary or extrapulmonary TB (referred hereafter as *Mtb* diseases) [2]. Work to date has highlighted notable gaps in factors that influence the risk of *Mtb* diseases [3]. For example, the associations of host genetic factors with *Mtb* infection have not been validated in multiple populations, and some study findings are inconsistent [3].

The immune system has a fundamental role in response to *Mtb* [4]. Thus, it is expected that polymorphisms in immune-related genes may directly affect the capacity of a host exposed to *Mtb* to control infection. Indeed, many studies have reported relationships between SNPs of immune-related genes and risk of *Mtb* diseases, such as the association between SNPs in *TLR4* [5], *TNFA* [6], and increased risk of active TB among highly exposed individuals. In addition to these genes, the nucleotide-binding oligomerization Domain-Containing protein 2 (*NOD2*) and Cluster Differentiation antigen 14 (*CD14*) genes are frequently studied in this setting, as these genes account for proteins that act in the recognition of mycobacterial molecular patterns and lead to immune activation against *Mtb* [7, 8]. While prior studies reported on the role of *NOD2* and *CD14*, many have disparate results, and often are restricted to certain populations [9].

The *CD14* gene codifies a glycosylphosphatidylinositol-anchored surface molecule present on the surface of monocytes, macrophages, and polymorphonuclear leukocytes, which functions as a key pattern recognition receptor (PRR) protein in innate immunity. CD14 plays a role in mediating signals from Toll-like receptors (TLRs) that recognize *Mtb* [10]. Additionally, *CD14* is critical to mounting an adequate innate response to aerogenic infection with *Mtb* [11]. Several studies have investigated whether risk of *Mtb* diseases is influenced by polymorphisms of this gene, though results have been inconsistent and inconclusive [4, 12]. For that reason, it remains difficult to determine the role of CD14 on risk of *Mtb* diseases in different populations, as studies with distinct ethnicities have conflicting results.

NOD2 is expressed in numerous cell types of the immune system, including macrophages, neutrophils, and eosinophils [13, 14]. It encodes a specialized

protein that functions as an intracellular PRR of peptidoglycan through the recognition of muramyl dipeptide (MDP), a motif common to all bacteria [15], with a stimulating signal towards activation of immune responses [16]. When *NOD2* is activated by specific substances produced by bacteria, it turns on a protein complex named nuclear factor kappa-B (NFkB), resulting in transcription of pro-inflammatory mediators [17]. As such, there is mounting evidence that deregulation of *NOD2* signaling causes or contributes to a variety of human diseases, including asthma [18], cancer [19], inflammatory bowel disease [20], and TB [21]. Of note, studies have reported conflicting results on the relationship between *NOD2* SNPs and TB infection, finding mutations in the *NOD2* gene that may lead to both the increased and decreased risk of *Mtb* diseases [22]. Notwithstanding, like studies of *CD14* SNPs, most results diverge depending on the investigated population, leaving several knowledge gaps for a complete understanding of these relationships.

The present study aimed to evaluate work published to date on the influence of polymorphisms of the above-mentioned PRRs on risk of *Mtb* diseases. We performed a systematic review to evaluate the association between all reported polymorphisms of *CD14* and *NOD2* and occurrence of *Mtb* diseases, and how such association may differ in distinct ethnic populations.

Methods

Study aim

We performed a systematic review on the influence of *CD14* and *NOD2* SNPs on the risk of *Mtb* diseases following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.

Literature search

A systematic search was conducted between June 01, 2019, and June 25, 2020, by two independent researchers (the authors JMC-A and DNA) in the following databases: PubMed, EMBASE, Scientific Electronic Library Online (SciELO), and Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs). The keywords used in the search were '*Mycobacterium tuberculosis*', 'tuberculosis'; '*CD14*' or '*NOD2*'; and 'polymorphism', 'SNPs' or 'genetic polymorphism' with various combinations. The exact search strategy per database and the number of hits per database are illustrated in the Additional File 1.

Every original research article found in the search that was in English, Spanish, or Portuguese was considered, with no restriction on the publication date. Reviews, letters to the editor, and comments were not included but were sources of additional references that did not appear in the first search.

Selection of studies

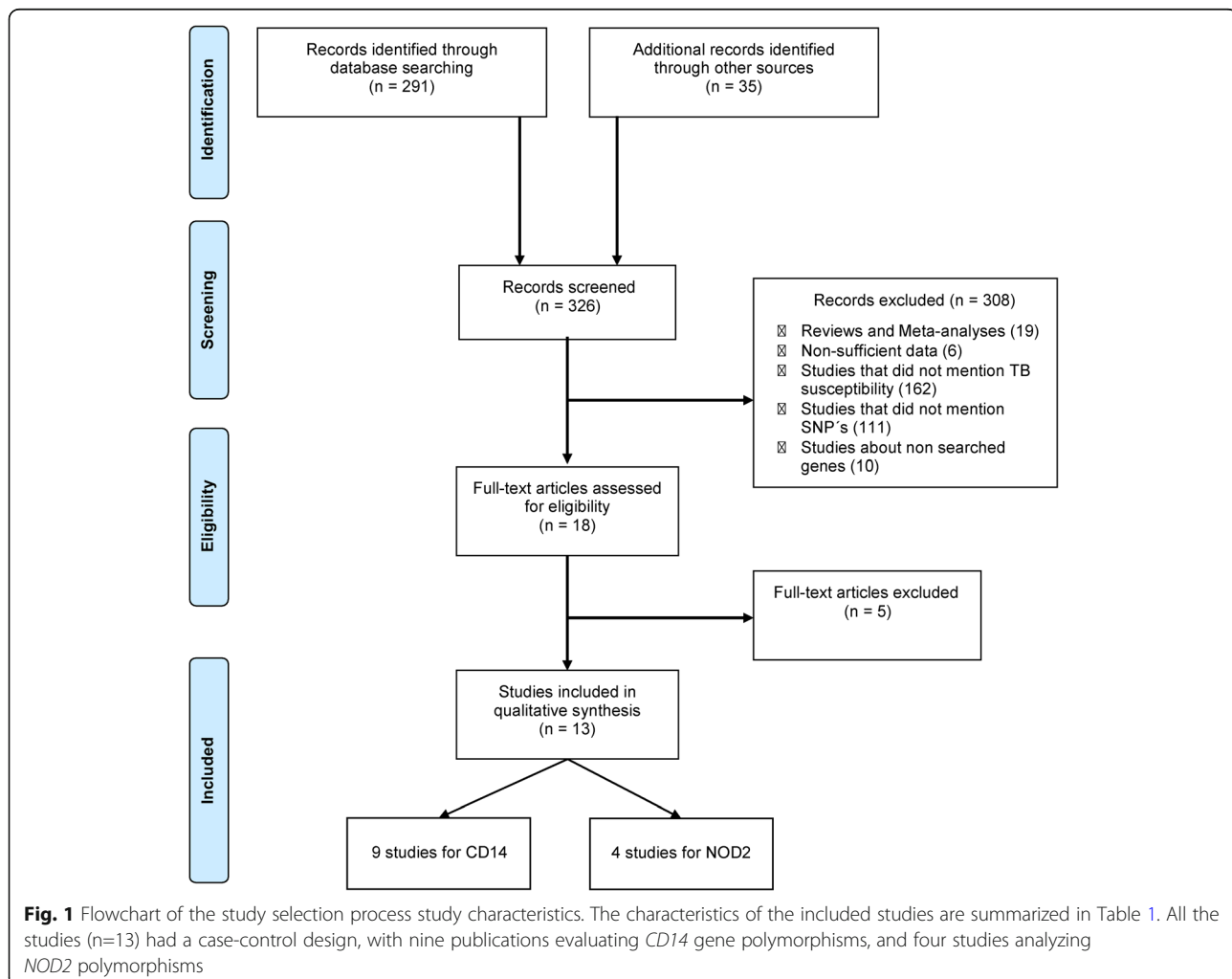
Initially, titles and abstracts were reviewed and analyzed for eligibility (Fig. 1). Thereafter, all the eligible articles were fully read. These two steps were performed by two independent reviewers (JMC-A and DNA). The inclusion criteria were (1) the main subject of the article must have been the genetic influence on TB and (2) the study must have been related to a SNP in *CD14* and/or *NOD2* genes. Articles that did not mention TB susceptibility or risk of *Mtb* diseases, polymorphism in the genes indicated above, had non-sufficient data, reviews, meta-analyses, animal model studies, letters to the editor, or which were clearly not related to the theme were excluded.

Data extraction

Data extraction was performed individually by two researchers (DNA and CDF), and discrepancies between them were resolved by a third reviewer (JMC-A). All the information on important variables, publication date, methods, results, and conclusions of the included articles were registered in tables built in Microsoft Excel, made by two different researchers. Lastly, the content of those Excel tables was checked by a third reviewer (JMC-A), attesting the registry compliance.

Quality assessment

The quality assessment of each individual study was further performed according to the Newcastle-Ottawa Quality Scale (NOQS) [34] (Table 2), which measures the quality of a study based on three aspects: selection (maximum, 4 stars), comparability (maximum, 2 stars), and exposure (maximum, 3 stars). Thus, in the processing of the article quality analysis, a maximum of 9 stars could be obtained. Publication with a total score of 0–3



was classified as low quality, 4–6 as moderate quality, and ≥ 7 as high quality.

Linkage disequilibrium

Linkage disequilibrium coefficients were calculated and reported in only three studies [24, 30, 32]. In order to examine the overall profile of the linkage disequilibrium of the SNPs reported in our systematic review, we calculated the linkage disequilibrium for all SNPs of *CD14* and *NOD2* using the Package LDpop [35], establishing an R^2 cutoff of ≥ 0.8 . LDpop takes as input two dbSNP reference SNP numbers and a selection of desired populations from the 1000 Genomes Project which includes sequencing data for 2504 individuals in 26 ancestral populations which are divided into 5 “super populations” [35]. In this approach, we used for the linkage disequilibrium the R^2 values for all individuals that had reported information for the SNPs.

Results

Selection of articles

Our primary search identified a total of 326 articles (Fig. 1). Through the study selection process, 13 articles met the inclusion criteria and were included in the systematic review [4, 12, 23–33]. The majority of the studies evaluated *CD14* gene polymorphisms ($n = 9$), whereas four studies analyzed *NOD2* polymorphisms. All of the selected studies adopted the case-control design, in which the case was defined as patients with tuberculosis, whether pulmonary, extrapulmonary, or both, and controls were defined as individuals not infected with *Mtb*. The majority of articles investigated the relationship between presence of polymorphisms and the risk of *Mtb* diseases ($n = 7$), whereas five studies tested association of SNPs with pulmonary and other forms of TB, and one assessed the relationship with spinal TB (Table 1).

In this systematic review, data on 4054 TB patients were examined, whereas 3993 individuals were identified as controls. The median sample size (IQR) per study was 267 (123–401) and 187 (127–413) for TB patients and healthy controls, respectively. The detailed characteristics of each study are shown in Table 1.

As observed in Fig. 2, most studies originated from Asia ($n = 8$) [23–28, 31, 32], with China leading as the most frequent study site ($n = 5$) [23–25, 31, 32], followed by Turkey ($n = 1$) [27], Iran ($n = 1$) [26], and South Korea ($n = 1$) [28]. The American continent also contributed to studies ($n = 3$): 1 in the USA [33], 1 in Mexico [4], and 1 in Colombia [12]. Only one study was set in Africa, specifically in Uganda [30], and Europe was represented by one study from Poland [29]. It is also possible to visualize in Fig. 2 that the *CD14* polymorphisms were studied in diverse populations from various ethnicities, including Mexican, Colombian, Polish, Turkish, Iranian,

South Korean, and Chinese. In contrast, the *NOD2* polymorphisms were studied in 3 restricted populations: North Americans, Chinese, and Ugandan.

Quality assessment and sensitivity analysis

The quality scores of the studies, assessing the risk of bias, are displayed in Table 2. All the studies were of moderate quality (Table 2). Of note, 5 studies [12, 27, 28, 30, 33] were clear about the procedures used to test the control populations (persons without TB infection/exposure), affecting the quality score with regard to comparability between the experimental groups (Table 2).

We performed sensitivity analysis with five studies [12, 27, 28, 30, 33] that specifically mentioned use of tuberculin skin test to exclude TB in the control groups. The five studies investigated different SNPs, and only 3 studies [12, 27, 28] reported results from the same SNP (rs2569190). A summary of the observations is illustrated in Additional File 2. Hence, a sensitivity analysis could not be performed for the other SNPs.

CD14 polymorphisms and risk of *Mtb* diseases

In the present review, *CD14* polymorphisms were the most frequently studied in the context of the risk of *Mtb* diseases. In total, 9 studies reported potential associations, presenting data for different populations. The sample sizes in total were 1976 TB cases and 2011 controls. The studies reported data on 7 *CD14* SNPs: rs2569190 [4, 12, 23, 24, 26–29, 31], rs2569191 [24, 31], rs3138078 [24], rs2915863 [24], rs3138076 [24], rs5744455 [24], and rs5744454 [24].

Linkage disequilibrium

The study of Xue et al. [24] was the only one that evaluated the magnitude of linkage disequilibrium and found that rs2569191 and rs2569190 were in high linkage disequilibrium ($R^2 = 0.90$). We next examined effects of linkage disequilibrium and SNP-SNP interactions in the *CD14* gene with the Package LDpop as described in the “Methods” section [35]. The SNPs rs2569190-rs2569191 ($R^2 = 0.9715$), rs3138078-rs3138076 ($R^2 = 0.9924$), rs3138078-rs5744454 ($R^2 = 0.9924$), and rs3138076-rs5744454 ($R^2 = 1$) were in high linkage disequilibrium and represented a haplotype block. The tables with all values of linkage disequilibrium for all SNPs can be found in supplementary information Additional File 3.

The findings on linkage disequilibrium are described below narratively for each SNP of *CD14* identified in the search from here onwards as subsections. Likewise, given the heterogeneity in populations and SNPs, only a narrative description was feasible.

Table 1 Characteristics of included studies

| Author/year | Country | Study design | Ethnicity | Gene/ studied SNP | TB diagnosis | Sample size | Type of study/ resistance to <i>Mtb</i> diseases or risk of <i>Mtb</i> diseases) | Type of control | TB screening controls (Tuberculin (TST) or Interferon-gamma Release Assay (IGRA)) | Inclusion and exclusion criteria cases | Inclusion and exclusion criteria controls | Outcomes |
|-------------------------|---------|--------------|-------------|---|--------------|---------------------------------|--|--|--|---|--|--|
| Zheng et al., 2018 [23] | China | Case control | Chinese Han | CD14 rs2569190 C>T | Spinal | 240 TB and 150 controls; N= 390 | Risk of <i>Mtb</i> diseases | Healthy controls | Not reported | Patients diagnosed with extra-pulmonary TB, who tested negative for PTB. Every included patient is free of co-morbidities. The spinal TB patients with comorbid disorders or other complications, such as rheumatoid arthritis, congenital cervical anomalies, trauma, prior spinal cervical surgery, HIV-positive, or ankylosing spondylitis were excluded from the present study. | Age- and sex-matched healthy subjects were enrolled as controls. | The frequency of the rs2569190 T allele was significantly higher in spinal TB patients than in controls (OR= 1.97, 95% CI= 1.24–3.42) (p< 0.01), and the frequency of the CT+TT genotypes (OR=2.10, 95% CI= 1.09–3.85) was also significantly higher in spinal TB patients than in controls (p< 0.05). |
| Xue et al., 2012 [24] | China | Case control | Chinese Han | CD14 rs2915863 G>A; rs3138078 T>G; rs2569190 C>T; rs2569191 A>G; rs3138076 T>C; rs5744454 T>G, rs5744455 G>T | Pulmonary | 318 TB and 380 controls; N= 698 | Risk of <i>Mtb</i> diseases | The control group was unrelated blood donors with no history of TB or other immune diseases. | Not reported | Patients with PTB confirmed by clinical, radiological, and bacteriological investigation. Patients were excluded if they tested positive for HIV or if they were undergoing immunosuppressive agents. | Healthy individuals, with no history of TB or immune diseases. | The G allele of rs2915863 (OR=1.41, 95% CI=1.12–1.76), G allele of rs3138078 (OR=1.77, 95% CI=1.39–2.24), G allele of rs2569191 (OR=1.78, 95% CI=1.43–2.22), and T allele of rs2569190 (OR=1.73, 95% CI=1.40–2.15, |

Table 1 Characteristics of included studies (Continued)

| Author/year | Country | Study design | Ethnicity | Gene/ studied SNP | TB diagnosis | Sample size | Type of study/ resistance to <i>Mtb</i> diseases or risk of <i>Mtb</i> diseases) | Type of control | TB screening controls (Tuberculin skin test (TST) or Interferon-gamma Release Assay (IGRA)) | Inclusion and exclusion criteria cases | Inclusion and exclusion criteria controls | Outcomes |
|------------------------|---------|--------------|-------------|--|---------------------------------|------------------------------------|--|--|--|--|---|---|
| Zhao et al., 2012 [25] | China | Case control | Chinese Han | CD14 rs2569190 C>T; rs2569191 G>A | Pulmonary and extrapulmonary TB | 432 TB and 404 controls; N= 836 | Risk of <i>Mtb</i> diseases | The control group comprised unrelated blood donors with no history of TB or other immune diseases. | Not reported | Patients were undergoing standard TB treatment at the TB clinic of the Sixth Hospital of Shaoying and Hangzhou Red Cross Hospital between October 2005 and October 2009. They were excluded if HIV+ or were taking immunosuppressive agents. | Healthy, unrelated blood donors with no history of TB or other immune diseases. All control subjects were from the same ethnic population and geographical origin and were living in the same region as the patients with TB. | Both the frequency of allele T in the rs2569190 (OR= 1.4, 95% CI = 1.148–1.708) and allele G in the rs2569191 (OR = 1.512, 95% CI = 1.236–1.849) were significantly more frequent in cases than in controls and were also significantly associated with TB. The frequencies of genotypes CT and CC in the rs2569190 (OR = 0.46 and 0.63, respectively; 95% CI = 0.34–0.63 and 0.42– |

Table 1 Characteristics of included studies (Continued)

| Author/year | Country | Study design | Ethnicity | Gene/ studied SNP | TB diagnosis | Sample size | Type of study (Susceptibility/ resistance to <i>Mtb</i> diseases or risk of <i>Mtb</i> diseases) | Type of control | TB screening controls (Tuberculin skin test (TST) or Interferon-gamma Release Assay (IGRA)) | Inclusion and exclusion criteria cases | Inclusion and exclusion criteria controls | Outcomes |
|-------------------------------|---------|--------------|---------------------------------------|---------------------------------|--------------|------------------------------------|--|---|--|---|--|---|
| Alavi-Naimi et al., 2012 [26] | Iran | Case control | Persian, Balouch, and Afghan Iranians | CD14 rs2569190 C>T | Pulmonary | 120 TB and 131 controls; N= 251 | Risk of <i>Mtb</i> diseases | The control group was healthy subjects with absence of clinical symptoms and signs suggestive of pulmonary TB and normal chest X-ray. | Not reported | Culture-positive PTB patients were included. They had no other comorbidities such as myocardial infarction, septic shock, liver cirrhosis, or pancreatitis. | Healthy subjects matched for age, sex, and ethnicity. The inclusion criteria were absence of clinical symptoms or signs for active TB and normal chest X-ray, no medical history of TB or other infectious or autoimmune diseases. | The frequency of the rs2569190 T allele was 57% in TB patients and 44% in controls and was significantly different ($p < 0.002$). The risk of <i>Mtb</i> diseases was 2.3-fold greater in individuals with the T-allele (CT + TT) than in those without (OR= 2.3, 95% CI= 1.2–4.3, $p = 0.006$). |

0.93), as well as the frequencies of genotypes AG and AA in the rs2569191 (OR = 0.60 and 0.44, respectively; 95% CI = 0.44–0.83 and 0.29–0.65) were lower in cases than in controls and were also protective against the disease.

Table 1 Characteristics of included studies (Continued)

| Author/year | Country | Study design | Ethnicity | Gene/ studied SNP | TB diagnosis | Sample size | Type of study (Susceptibility/ resistance to <i>Mtb</i> diseases or risk of <i>Mtb</i> diseases) | Type of control | TB screening controls (Tuberculin skin test (TST) or Interferon-gamma Release Assay (IGRA)) | Inclusion and exclusion criteria cases | Inclusion and exclusion criteria controls | Outcomes |
|-------------------------------|-------------|--------------|---------------------------|---------------------------------|---------------------------------|----------------------------------|--|--|--|---|--|---|
| Rosas-Taraco et al., 2007 [4] | Mexico | Case control | White and Mestizo Mexican | CD14 rs2569190 C>T | Pulmonary | 111 TB and 174 controls; N = 285 | Risk of <i>Mtb</i> diseases | Healthy individuals as control subjects | Not reported | All patients had active pulmonary TB diagnosed on the basis of clinical findings and smear or culture positive for PTB. Also, 67 were household contacts who were or were not genetically related to the patients. All participants were negative for HIV and diabetes and not treated with steroids or immunosuppressive agents. | 114 healthy individuals. All of them were Mexican older than 18 years. | The frequency of the rs2569190 homozygous TT genotype was highest in patients with pulmonary TB (OR= 3.37, 95% CI= 1.58–7.19 p=<0.002). The frequency of the rs2569190 allele T had a significantly higher risk for the development of pulmonary TB (OR= 2.267; 95% CI= 1.5–3.3). |
| Ayasioglu et al., 2012 [27] | Turkey | Case control | Turkish | CD14 rs2569190 C>T | Pulmonary and extrapulmonary TB | 88 TB and 116 controls; N = 204 | Risk of <i>Mtb</i> diseases | Control group was selected from the adult population who had no underlying comorbidity and no diagnosis of tuberculosis. | Tuberculin skin test (TST) | Subjects who had a diagnosis of tuberculosis; age ≥ 16 years; and consented to be included into the study. Patients who had infectious diseases in the last 6 weeks, had significant chronic immunosuppressive systemic diseases, was pregnant, or HIV+ were excluded. | Subjects with no known diseases. Patients who had infectious diseases in the last 6 weeks, had significant chronic immunosuppressive systemic diseases, was pregnant, or HIV+ were excluded. | There was no significant difference in terms of genotype distribution between patients with tuberculosis and controls. |
| Kang et al., 2009 [28] | South Korea | Case control | Korean | CD14 rs2569190 | Pulmonary and extrapulmonary | 274 TB and 422 controls | Risk of <i>Mtb</i> diseases | A control group | Tuberculin skin test | Patients with confirmed | A group of healthy blood donors with | The frequency of the |

Table 1 Characteristics of included studies (Continued)

| Author/year | Country | Study design | Ethnicity | Gene/ studied SNP | TB diagnosis | Sample size | Type of study (Susceptibility/ resistance to <i>Mtb</i> diseases or risk of <i>Mtb</i> diseases) | Type of control | TB screening controls (Tuberculin skin test (TST) or Interferon -gamma Release Assay (IGRA)) | Inclusion and exclusion criteria cases | Inclusion and exclusion criteria controls | Outcomes |
|--------------------------------|----------|--------------|---------------------------------|---------------------------|---------------------------------|----------------------------------|--|---|---|--|---|---|
| | | | | C>T | TB | controls; N = 696 | | consisting of 422 healthy blood donors with normal chest X-ray and without respiratory symptoms and signs | (TST) | tuberculosis were enrolled from Seoul National University Hospital in Korea. Patients with a positive HIV test were excluded. | normal chest X-ray and without respiratory symptoms and signs were recruited from medical students and employees of Seoul National University College of Medicine/Seoul National University Hospital. | rs2569190 T allele was higher in tuberculosis patients than in healthy controls (64% vs. 57%; p = 0.01), and rs2569190 TT genotypes (OR= 1.60; 95% CI, 1.01–2.54) were over-represented among tuberculosis patients (43% vs. 32%; p = 0.016). |
| Druszczyńska et al., 2006 [29] | Poland | Case control | Caucasian Polish | CD14 rs2569190 C>T | Pulmonary TB | 126 TB and 122 controls; N = 248 | Risk of <i>Mtb</i> diseases | Healthy volunteers who had no past history of TB | Not reported | Not reported | Not reported | No association was found between the rs2569190 and the presence of TB. |
| Pacheco et al., 2004 [12] | Colombia | Case control | Caucasian and Mestizo Colombian | CD14 rs2569190 C>T | Pulmonary and extrapulmonary TB | 267 TB and 112 controls; N = 379 | Risk of <i>Mtb</i> diseases | Healthy control individuals were recruited | Tuberculin skin test (TST) | Patients were recruited from different health units in the metropolitan area of Medellín, Colombia. Individuals, who were HIV+, or with a history of cancer, autoimmune, metabolic, or endocrine diseases, as well as pregnant women, were | Tuberculin-positive healthy control individuals were recruited from the Facultad de Medicina at the Universidad de Antioquia, and the institutions from where the patients were recruited. | No association was found between the allele and genotype frequencies and the presence of TB or between the different forms of the disease. |

Table 1 Characteristics of included studies (Continued)

| Author/year | Country | Study design | Ethnicity | Gene/ studied SNP | TB diagnosis | Sample size | Type of study (Susceptibility/resistance to <i>Mtb</i> diseases or risk of <i>Mtb</i> diseases) | Type of control | TB screening controls (Tuberculin skin test (TST) or Interferon-gamma Release Assay (IGRA)) | Inclusion and exclusion criteria cases | Inclusion and exclusion criteria controls | Outcomes |
|------------------------|---------|--------------|------------------------------|---|-----------------|---|---|--|--|---|--|--|
| Hall et al., 2015 [30] | Uganda | Case control | USA | NOD2 rs6500328 A>G; rs2111234 G>A and rs17313265 C>T | TB ^a | 240 TB 595 controls; N= 835 | Risk of <i>Mtb</i> diseases | Healthy household contacts without active disease were included in the control group | Tuberculin skin test (TST) | Analysis was gathered from two phases of a household contact study conducted in Kampala, Uganda. Subjects from the Household Contact Study were enrolled from 1995 to 1999. Individuals who presented at the study clinic with active culture-positive pulmonary TB were enrolled as index cases. | Analysis was gathered from two phases of a household contact study conducted in Kampala, Uganda. Subjects from the Household Contact Study were enrolled from 1995 to 1999. Healthy household contacts underwent a follow-up evaluation every 3 months for the first 6 months and were enrolled as control | rs17313265 association with TB in adults (examination of age-specific effects with TB) (OR= 2.82, 95% CI= 1.05–7.53). rs6500328 (OR= 2.44, 95% CI=1.01–5.88) and rs211234 (OR= 1.56 95% CI= 1.07–2.28) showed a nominal association with resistance to <i>Mycobacterium tuberculosis</i> (Mtb) infection. |
| Zhao et al., 2012 [31] | China | Case control | Chinese Han, Uyгур and Kazak | NOD2 rs1861759 T>G | Pulmonary | 425 TB and 380 controls; N=805 | Risk of <i>Mtb</i> diseases | Healthy controls were HIV negative and none was known to present any autoimmune, chronic inflammatory or any other disease conditions. | Not reported | Han population 219 PTB and 215 healthy controls; For the Uyгур population 86 PTB patients and 72 controls; for the Kazak 120 PTB patients and 93 healthy controls. The patients were diagnosed based on the TST test, chest X-ray, or sputum smear culture results. | They were HIV-negative patients and controls without any autoimmune, chronic inflammatory, or any other disease condition. All selected patients had no mixed descendants within 3 generations. | By comparing the TG genotype frequencies of rs1861759 in the Han population, a significant difference was observed between the patients with TB and the healthy controls (OR= |

Table 1 Characteristics of included studies (*Continued*)

| Author/year | Country | Study design | Ethnicity | Gene/ studied SNP | TB diagnosis | Sample size | Type of study/ resistance to <i>Mtb</i> diseases or risk of <i>Mtb</i> diseases) | Type of control | TB screening controls (Tuberculin skin test (TST) or Interferon-gamma Release Assay (IGRA)) | Inclusion and exclusion criteria cases | Inclusion and exclusion criteria controls | Outcomes |
|--------------------------|---------|--------------|-------------------|---|------------------------------|-----------------------------------|--|--|--|---|---|--|
| Pan et al., 2012 [32] | China | Case control | Chinese Han | NOD2 rs7194886 C>T and rs9302752 T>C | Pulmonary | 1043 TB and 808 controls; N= 1851 | Risk of <i>Mtb</i> diseases | The controls were selected from a pool of individuals who participated in the local community-based health examination programs. None of controls had a history of active tuberculosis and/or a malignancy | Not reported | Patients older than 15 years, Han Chinese. They were divided in 3 groups: clinical symptoms of TB, sputum smear positive, and bacteriologically confirmed TB. 234 of 1043 TB patients were sputum smear negative. | Every control was older than 15 years, without history of TB and/or a malignancy. | 2.16; 95% CI= 1.31–3.58; p= 0.0023). The individuals carrying the CT/TT genotype of rs7194886 had an increased risk of pulmonary tuberculosis (OR= 1.35, 95% CI= 1.05–1.72). Allele frequency analysis found that variant allele T of rs7194886 (OR= 1.25, 95% CI= 1.00–1.57) was associated with an increased risk of tuberculosis. Haplotype rs9302752 C–rs7194886 T was associated with an increased risk of being sputum culture-positive tuberculosis (p = 0.039). |
| Austin et al., 2008 [33] | USA | Case control | African Americans | NOD2 rs2066842 | Pulmonary and extrapulmonary | 377 TB and 187 | Risk of <i>Mtb</i> diseases | Control subjects for malignancy | Tuberculin skin test | All cases patients were HIV negative | African Americans without history of | Minor allele carriers |

Table 1 Characteristics of included studies (Continued)

| Author/year | Country | Study design | Ethnicity | Gene/ studied SNP | TB diagnosis | Sample size | Type of study/ resistance to <i>Mtb</i> diseases or risk of <i>Mtb</i> diseases) | Type of control | TB screening controls (Tuberculin skin test (TST) or Interferon-gamma Release Assay (IGRA)) | Inclusion and exclusion criteria cases | Inclusion and exclusion criteria controls | Outcomes |
|-------------|---------|--------------|-----------|--|--------------|----------------------|--|---|--|--|--|--|
| | | | | C>T rs2066844 C>T, and rs5743278 C>G | TB | controls; N = 564 | (Susceptibility/ resistance to <i>Mtb</i> diseases or risk of <i>Mtb</i> diseases) | this study were recruited without a history of TB, autoimmune disease, or other infectious diseases | (TST) | and had their ethnicities determined by self-indication. TB diagnosis was given based on bacille culture (286/312 PTB cases and 33/43 of EPTB), in these negative patients, diagnosis was based on clinical manifestations, chest X-ray, and clinical improvement to anti-mycobacterial treatment. | TB, autoimmune disease, or other diseases. | (heterozygous and homozygous) of rs2066844 (OR= 0.55, 95% CI=0.32–0.94, p= 0.02) and rs2066844 (OR= 0.27, 95% CI= 0.08–0.88; p= 0.01) presented decreased risks for TB disease. Conversely, the minor allele carrier (heterozygous) of rs2066844 (OR= 2.16, 95% CI= 1.10–4.72; p= 0.03) showed an increased risk for TB disease. |

Abbreviations: *MOD2* nucleotide-binding oligomerization domain-containing protein 2, *CD14* Cluster Differentiation antigen 14, *TB* tuberculosis, *PTB* pulmonary tuberculosis, *EPTB* extrapulmonary tuberculosis, *OR* odds ratio, *CI* confidence intervals, *USA* United States of America

^aDid not specify the TB type

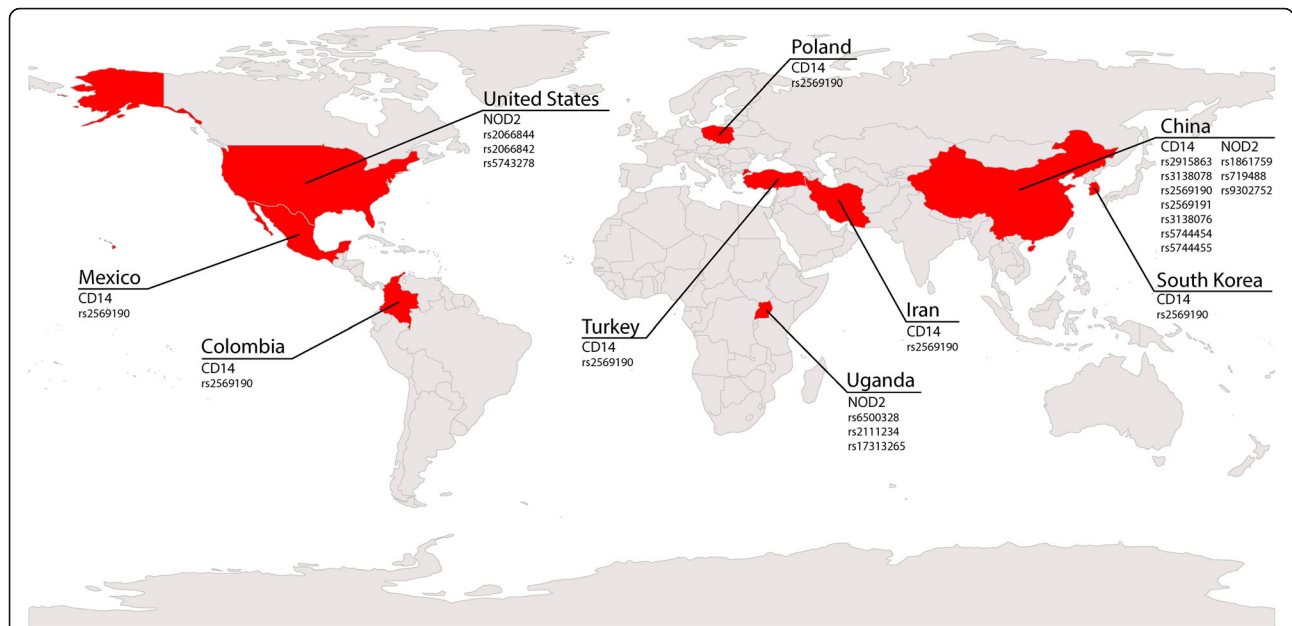


Fig. 2 Geographical distribution of CD14 and NOD2 SNPs associated with risk of *Mtb* diseases. Studies originated from nine different countries. Most studies were from Asia (n=8), with China leading as study site (n=5) followed by Iran (n= 1), Turkey (n= 1), and South Korea (n= 1). Three studies were performed in the American continent: one in the USA, one in Mexico, and one in Colombia. Only one study was set in Europe (Poland), and one was performed in Africa (Uganda)

SNP rs2569190

Of the 9 publications which investigated this gene locus, six studies reported a significant association between the T allele of SNP rs2569190 and higher odds of TB [4, 23, 24, 26, 28, 31].

Zhao et al. identified the T allele as the major allele of the cases that was higher in TB cases compared to

healthy controls (63.53% vs 55.44%, respectively) [31]. Hence, the frequencies of the allele C in the rs2569190 polymorphism were lower in TB cases than in controls suggesting that CT and CC genotypes are likely protective against TB (OR = 0.46 and 0.63, respectively) [31]. Similarly, Alavi-Naini et al. observed that the risk of *Mtb* diseases was greater in individuals with the T-allele (CT

Table 2 Quality assessment of studies included in the systematic review by Newcastle-Ottawa Scale

| N° | Source | Selection | | | | Comparability | | Exposure | | | Overall score ^a |
|----|--------------------------|-----------|---|---|---|---------------|----|----------|---|----|----------------------------|
| | | 1 | 2 | 3 | 4 | 5A | 5B | 6 | 7 | 8 | |
| 1 | Zhao et al. [25] | * | * | 0 | 0 | * | NA | * | * | NA | 5 |
| 2 | Kang et al. [28] | * | * | * | 0 | * | NA | * | * | NA | 6 |
| 3 | Alavi-Naini et al. [26] | * | * | 0 | 0 | * | NA | * | * | NA | 5 |
| 4 | Zhao et al. [31] | * | * | * | 0 | * | NA | * | * | NA | 6 |
| 5 | Rosas-Taraco et al. [4] | * | * | * | 0 | * | NA | * | * | NA | 6 |
| 6 | Pacheco et al. [12] | * | * | * | 0 | * | NA | * | * | NA | 6 |
| 7 | Austin et al. [33] | * | * | 0 | 0 | * | NA | * | * | NA | 5 |
| 8 | Zheng et al. [23] | * | * | 0 | 0 | * | NA | * | * | NA | 5 |
| 9 | Xue et al. [24] | * | * | * | 0 | * | NA | * | * | NA | 6 |
| 10 | Hall et al. [30] | * | * | * | 0 | * | NA | * | 0 | NA | 5 |
| 11 | Pan et al. [32] | * | 0 | * | 0 | * | NA | * | * | NA | 5 |
| 12 | Ayaslioglu et al. [27] | * | * | * | 0 | * | NA | * | * | NA | 6 |
| 13 | Druszczynska et al. [29] | * | 0 | 0 | 0 | * | NA | * | * | NA | 4 |

Abbreviations: NA not applicable

Star (*) indicates the score given to the study according to the NOS quality assessment scale

^aDetermined by the total number of stars assigned to study: 0–3 stars = poor; 4–6 stars = moderate; ≥7 stars = good quality

and TT) than in those without, finding that the T allele was more common in TB patients (57%) than in controls (44%) [26]. Moreover, in this same study, the C allele in homozygosis was a protective factor in a sub-analysis of Iranian subjects, with an OR of 0.44 (95% CI 0.23–0.83; $p=0.006$) [26].

Zheng et al. [23] found that the frequency of the rs2569190 T allele was significantly higher in spinal TB patients compared to healthy controls (57.5% v 44%; $p<0.01$), demonstrating that those with TT and CT genotypes was more frequent in spinal TB patients than in healthy controls (85% vs 44.17%; $p<0.05$) [23]. In contrast, Rosas-Taraco et al. [4] found that the most frequent allele of the rs2569190 was allele C in all study population, but the highest frequency of the rs2569190 T allele was 71% in household contacts of TB index cases who developed active TB, and 60% in those with pulmonary TB. In contrast, this allele was present in only 40% the healthy controls and 39.2% in the household contacts without TB ($p<.0001$) [4].

Xue et al. [24] observed allele T as the common allele of rs2569190 in the study population [24]. The TT genotype of rs2569190 was significantly associated with increased risk of *Mtb* diseases, present in 46% in patients diagnosed with pulmonary TB and 30% in healthy controls ($p<0.001$) [24]. Finally, Kang et al. [28] identified that the TT genotypes increased the risk of *Mtb* diseases and was significantly more frequent in TB patients than in healthy controls (43% vs 32%; $p=0.016$) [28].

Notably, two articles, by Ayaslioglu et al. [27] and Pacheco et al. [12], described more reliably “control” groups; in such studies, the authors found no statistically significant difference between the presence of SNP rs2569190 and increased TB risk. Moreover, another study [29] also did not find any evidence of a significant association between SNP rs2569190 and TB development. Furthermore, no association was found between the *CD14-159C/T* polymorphism and TB clinical severity in studies that evaluated Turkish [27], Caucasian Polish [29], or White and Mestizo Colombian patients [12]. In the Turkish study performed by Ayaslioglu et al. [27], one hypothesis for the lack of association was the small sample size (88 TB cases and 116 controls). While investigating Caucasian Polish individuals, Druszczynska et al. [29] did not specify whether TB patients and controls were from the same region, which could possibly account for the lack of association.

SNP rs2569191

Additional investigations evaluating the *CD14* SNP rs2569191 revealed significant associations with odds of TB in 2 distinct publications from China [24, 31]. In one of these studies [24], individuals with the GG genotype of A-1145G were more likely to present with TB ($p<$

0.001), and this genotype was more common in the patients diagnosed with pulmonary TB (46%) than the healthy controls (28%). The second investigation [31] suggested that the frequencies of genotypes AG and AA were lower in TB cases compared to healthy controls [AG=181 (41.90%) vs 174 (47.41%) and AA= 65 (15.05%) vs 85 (23.16%) respectively], arguing for a protective role against TB and not found significance with the GG genotype. Both studies reported that the G allele of A-1145G was more prevalent in TB cases than in controls, indicating an increased risk of *Mtb* diseases.

Other SNPs

CD14 SNPs (rs3138078, rs2915863, rs2569192, rs3138076, rs5744455, and rs5744454) were evaluated by only one study [24], finding the following alleles to be significantly associated with TB: G allele of rs2915863 and the G allele of rs3138078. For the SNPs rs2569192, rs3138076, rs5744455, and rs5744454, there were no statistically relevant associations

NOD2 polymorphisms and risk of *Mtb* diseases

In regard to the *NOD2* gene, the results from the studies were diverse, with SNPs associated with either an increased or decreased risk of *Mtb* diseases in each of the study populations based on ethnicity, age group, or biological sex. In such studies, a total of 2085 TB cases and 2347 controls were investigated. These studies were performed in different countries including China, Uganda, and North America, with the last being focused on African Americans. Two publications reported data on *NOD2* SNPs in China [25, 32], with a total of 2651 individuals.

Linkage disequilibrium

The study of Hall et al. [30] used the linkage disequilibrium for selected SNPs with linkage disequilibrium $R^2 \geq 0.8$. The other study that used linkage disequilibrium was Pan et al. [32]. In such investigation, the selected haplotype blocks where haplotype rs9302752C–rs7194886T (block 1) which was associated with an increased risk of being a case of sputum culture-positive tuberculosis. We next examined the effects of linkage disequilibrium and SNP-SNP interactions in the *NOD2* gene with the Package LDpop [35]. Here, we found that no reported SNP was in high linkage disequilibrium. The tables with all values of linkage disequilibrium for all SNPs can be found in supplementary information Additional File 4.

Hereafter, the findings on linkage disequilibrium will be reported narratively for each *NOD2* SNP identified in the search as subsections. Once again, given the heterogeneity in populations and SNPs, only a narrative description was feasible.

SNP rs1861759

Zhao et al. [25] showed that in the Han population, the T allele frequency of the SNP rs1861759 in the patient group and in the control group was the most common. The TG genotype in rs1861759 SNP was substantially associated with TB ($p = 0.0023$) in the Han population with a frequency of 53 (24.2%) in pulmonary TB patients and 28 (13%) in healthy controls. Interestingly, the same study did not identify this relationship between the TG genotype and TB in Chinese participants of Kazak or Uygur ancestry.

SNP rs7194886

A different study by Xue et al. investigating Han Chinese individuals [24] found that the frequency of the rs7194886 T allele was associated with risk of *Mtb* diseases ($p=0.042$), but allele C was the most common in all study subjects. Patients who presented CT or TT genotypes of rs7194886 were more likely to present with TB when compared to individuals with the CC genotype ($p=0.018$). The genotype CT was more frequent in the pulmonary TB case compared with uninfected controls (CT= 271 [26.03%] vs 179 [22.43%]). Furthermore, the study found a higher frequency of rs7194886 polymorphism in either smokers ($p=0.019$) or men ($p=0.014$) [28].

SNP rs9302752

In the same study [32], the haplotype rs9302752 C–rs7194886 T was linked with a higher risk of presenting with sputum culture-positive TB ($p = 0.039$).

SNPs rs2066842, rs2066844, and rs5743278

The study by Austin et al., which predominantly recruited African Americans in the USA [33], found C allele of the SNPs rs2066842, rs2066844, and rs5743278 in all case patients and control subjects. This study reported an association between NOD2 SNPs rs2066842, rs2066844, and rs5743278 and odds of TB. The study participants who were carriers of the CC genotype in SNPs rs2066842 ($p=0.02$) and rs2066844 ($p=0.01$) were less likely to have TB. The frequencies of the CC genotype (340 vs 156) in rs2066842 and in rs2066844 (372 vs 178) were higher in patients with TB compared with control subjects. Moreover, individuals who were heterozygous (CG) in rs5743278 were more frequent in those with TB compared to the control group (39 vs 10) and exhibited an increased chance of having TB ($p=0.03$).

SNPs rs17313265, rs6500328, and rs2111234

The study by Hall et al. in the adult African population from Uganda [30] reported that presence of the SNP rs17313265 was associated with increased risk of *Mtb* diseases (OR= 2.82, 95% CI= 1.05, 7.53; $p= 0.0052$). Notably, increased frequency of the rs6500328 and rs2111234 SNPs was found in those without TB,

suggesting that such SNPs may protect against *Mtb* infection, with OR of 2.44 (95% CI= 1.01, 5.88; $p= 0.047$) and 1.56 (95% CI= 1.07, 2.28, $p=0.020$), respectively.

Discussion

The molecular basis of immune response to infectious diseases is an indispensable approach to understand how gene regulation ultimately may impact clinical outcomes. In recent decades, a great deal of research has sought to identify associations between genetic polymorphisms and risk of *Mtb* diseases [36, 37]. Most of the target loci are PRRs contributing to control of mycobacterial diseases, especially TB [38]. *CD14* and *NOD2* are considered to be key PRRs in the innate immune system [9]. In this systematic review, a variety of studies were identified evaluating seven *CD14* SNPs and four evaluating nine *NOD2* SNPs, finding several genetic variants associated with *Mtb* infection.

We identified studies that found significant association between the T allele of *CD14* SNP rs2569190 and increased risk of *Mtb* diseases in different ethnic groups. This polymorphism is located in the promoter region of the *CD14* gene [9], and the T allele seems to act as a negative regulator of in vitro T-cell proliferation and decreased production of cytokines, including interferon- γ (IFN- γ) [28]. IFN- γ is an essential cytokine for the control of mycobacterial infection [39], and therefore, rs2569190 may produce an environment that favors development of TB. Interestingly, other studies found this SNP associated with ischemic stroke [40], cardiovascular disease [41], and asthma [42], indicating that these polymorphisms could actually lead to a more profound alteration in immune responses that may affect a large number of clinical conditions.

Another important association of *CD14* polymorphism with TB was described in this review, involving the SNP rs2569191. In this setting, the G allele of A-1145G was more prevalent in TB cases than in controls in two Chinese studies. An interesting link between such SNP and circulating concentrations of IgE has been proposed. In a study performed in patients with asthma, the authors identified heightened IgE concentrations in those who had the G allele of A-1145G [43]. Moreover, other studies identified IgE as a marker of *Mtb* infection, in which pre-treatment levels of serum total IgE concentrations in TB patients were significantly higher than in healthy individuals; such levels decreased after successful antitubercular treatment [44, 45]. It is possible that the polymorphism rs2569191 plays an important role in TB infection which may be related to IgE concentrations. Future studies in other ethnic groups are warranted to directly test this hypothesis. Interestingly, the two SNPs rs2569191 and rs2569190 are found to be in linkage disequilibrium [46]. For this reason, future studies will need

to determine whether these SNPs influence risk of *Mtb* diseases individually when solely associated.

NOD2 is one of the most well-studied genes in the context of the innate immune response against microbial pathogens [47]. This gene accounts for a cytoplasmic receptor belonging to the NOD-like receptor family [48] and is known to participate in the induction of inflammation during *Mtb* infection [49]. In experimental conditions, *Mtb* recognition is *NOD2*-dependent [50]. Mice genetically deficient in *NOD2* are shown to be more susceptible to TB [51]. Here, we found two studies [25, 32] in the Chinese population that reported three different polymorphisms (rs1861759, rs7194886, and rs9302752) associated with increased risk of *Mtb* diseases. The rs1861759 (synonymous variant) TG genotype is associated with increased risk of *Mtb* diseases [25]. Individuals with the rs7194886 CT or TT genotype are more likely to develop TB [32]. The rs9302752 C allele has been linked to a higher risk of being sputum culture-positive TB. To our knowledge, these three polymorphisms do not appear in other TB studies. Curiously, such SNPs have been also related to increased risk of leprosy [52].

In an African-American study [33], it was observed that the three *NOD2* polymorphisms exhibit impact on risk of *Mtb* diseases. The polymorphism rs2066844 represents missense mutations whose variants are located in the C-terminal region and cause defective production of proinflammatory mediators [53]. The rs2066842 is a missense variant but, when presented alone, does not alter gene function [54]. Importantly, the two polymorphisms in our systematic review appear to protect against TB when in the presence of allele C [33]. In contrast, the presence of the T allele in such mutations was associated with increased risk of *Mtb* diseases. The association between the presence of the T allele and augmented pathology has been described for other diseases such as Crohn's disease [55] and gastric cancer [56]. The genotyping heterozygous (CG) of rs5743278 has been linked to higher risk of *Mtb* diseases [55]. It is possible that the rs5743278 SNP causes an amino acid change from a low hydrophobic arginine to a highly hydrophobic tryptophan, modifying the stability of the *NOD2* structure or its ability to properly interact with *Mtb* ligands [55]. Finally, one study in a population from Uganda described the *NOD2* rs17313265 polymorphism associated with increased risk of *Mtb* diseases in adults whereas the SNPs rs6500328 and rs2111234 exhibited decreased risk of *Mtb* diseases [30]. Furthermore, these three polymorphisms have not been reported in other studies with TB patients. These findings indicate that *NOD2* polymorphisms may be dramatically affected by ethnicity and/or ancestry. This scenario reinforces the need of additional investigations performed in a variety of ethnic populations, particularly when study design

uses family-based control subjects to eliminate the bias in stratification of the populations.

To our knowledge, the present study is the first systematic review to explore the relation of all *CD14* and *NOD2* SNP polymorphisms with the risk of *Mtb* diseases in different ethnicities. A strength of our study was the comprehensive search strategy, which used detailed inclusion and exclusion criteria. Moreover, methodological quality was assessed in duplicate using the Newcastle-Ottawa scale [34], which reduced the subjectivity of the selection of studies and allowed for precise evaluation of the risk of bias in several domains. There was no report categorized as low quality, resulting in a review with reduced risk of bias. Another important strength is that the inclusion of the SNPs was not limited to one specific locus or ethnicity, allowing the study to observe different loci associated with risk of *Mtb* diseases or not in various populations.

Our study has some limitations. It was not possible to perform a meta-analysis and, consequently, a sensitivity analysis, mainly because a considerable part of the SNP polymorphisms appeared in only one study at a time. Only two SNPs, rs2569191 which was seen in two studies and rs2569190 which was reported in nine publications were consistently investigated. However, the need for a study to compile and critically revise these results in different ethnicities reinforces the importance of our work, regardless of quantitative analyses. Another limitation was the moderate quality of those studies included in the systematic review. One reason for this quality is the ambiguous concept of the control groups reported in most of the studies where the precise screening method to categorize these groups was not specifically described. To circumvent such concern, we have contacted the authors individually but obtained replies from just two articles. Only 5 of the 13 included studies reported active TB screening of asymptomatic individuals with either tuberculin skin test (TST) or interferon-gamma releasing assay (IGRA). This imprecision in the definition of control groups may limit the full interpretation of the study results. Our study highlights the need of studies standardizing description of the control groups to more accurately delineate the associations between SNPs and risk of *Mtb* diseases. Other determinants for the moderate quality were the small sample size of some studies and lack of clarity regarding description of the tools/approaches used to choose the SNPs, such as the examination of the linkage disequilibrium.

This review identified multiple studies that determined an association of the minor allele T at position chr5:140633331 of rs2569190 *CD14* polymorphism with increased risk of *Mtb* diseases in persons from different ethnicities. In addition, the *CD14* SNP rs2569191 and

the *NOD2* SNPs rs1861759 and rs7194886 are shown here to be associated with a high risk of *Mtb* diseases in the Chinese population. In contrast, genotypes CG or GG of rs2066842 and rs2066844 were at low risk of *Mtb* diseases in African Americans. Since such genes account for key molecules of the immune system, the referred polymorphisms of *CD14* and *NOD2* genes likely play an important role in TB physiopathology. These results add knowledge to the field by reinforcing the genetic influence on the risk of *Mtb* diseases. Such knowledge, if validated by larger studies, may help development of tools for assessment of the risk of *Mtb* diseases and hopefully predict clinical outcomes in precision medicine approaches.

Abbreviations

MONSTER: Multinational Organization Network Sponsoring Translational and Epidemiological Research; UNIFACS: Universidade Salvador; FTC: Faculdade de Tecnologia e Ciências; TB: Tuberculosis; SNP: Single nucleotide polymorphisms; NOQS: Newcastle-Ottawa Quality Scale; *Mtb*: *Mycobacterium tuberculosis*; *NOD2*: Domain containing protein 2; *CD14*: Cluster differentiation antigen 14; PRR: Pattern recognition receptor; TLRs: Toll-like receptors; MDP: Muramyl dipeptide; NFκB: Nuclear factor kappa-B; PRIS MA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SciELO: Scientific Electronic Library Online; Lilacs: Literatura Latino-Americana e do Caribe em Ciências da Saúde; IQR: Median sample size; OR: Odds ratio; IFN-γ: Interferon-γ; CNPq: *Conselho Nacional de Desenvolvimento Científico e Tecnológico*; OAS-PAEC: Organization of American States - Partnerships Program for Education and Training; CAPES: *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—Brazil*; FAPESB: *Fundação de Amparo à Pesquisa da Bahia*; PTB: Pulmonary tuberculosis; EPTB: Extrapulmonary tuberculosis; CI: Confidence intervals; TST: Tuberculin skin test; IGRA: Interferon-γ releasing assay; USA: United States of America; NA: Not applicable

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13643-021-01729-y>.

Additional file 1. Table with the exact search strategy per database and the number of hits per database.

Additional file 2. Table of the five studies that evaluated the control groups with the tuberculin skin test.

Additional file 3. Tables describing the frequencies and the linkage disequilibrium of the seven *CD14* SNPs.

Additional file 4. Tables depicting the frequencies and the linkage disequilibrium of the nine *NOD2* SNPs.

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Authors' contributions

JMC-A, CDF, and DNA conceived the study. JMC-A, CDF, DNA, and MBA were responsible for the data collection. JMC-A, CDF, DNA, MBA, and BBA analyzed the data and built the figures and tables. JMC-A, CDF, and DNA performed the scientific literature search. JMC-A, CDF, and DNA participated in the writing of the first draft of the manuscript. BBA critically revised the article. The authors read and approved the final version of the manuscript.

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Availability of data and materials

All data used in the present study were retrieved from the publications used in the systematic review and are publicly available.

Declarations

Ethics approval and consent to participate

There were no patients directly involved in the research. The present study used public data from previously published studies to perform a systematic review. All information given to the research team was de-identified. Thus, the study was exempted from revision by the Institutional Review Board of the Instituto Gonçalo Moniz, Fundação Oswaldo Cruz, Salvador, Brazil, and did not require signed consent forms.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

¹Instituto Gonçalo Moniz, Fundação Oswaldo Cruz, Salvador, Bahia, Brazil. ²Faculdade de Medicina, Universidade Federal da Bahia, Salvador, Bahia, Brazil. ³Multinational Organization Network Sponsoring Translational and Epidemiological Research (MONSTER) Initiative, Salvador, Bahia, Brazil. ⁴Curso de Medicina, Universidade Salvador (UNIFACS), Laureate Universities, Salvador, Bahia, Brazil. ⁵Curso de Medicina, Faculdade de Tecnologia e Ciências (FTC), Salvador, Bahia, Brazil. ⁶Curso de Medicina, Escola Bahiana de Medicina e Saúde Pública, Salvador, Bahia, Brazil. ⁷Division of Infectious Diseases, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA. ⁸Wellcome Centre for Infectious Disease Research in Africa, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa.

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