Research Article

**IL-10 -1082 A>G (rs1800896) polymorphism confers susceptibility to pulmonary tuberculosis in Caucasians but not in Asians and Africans: a meta-analysis**

Mohammed Y. Areeshi1, Raju K. Mandal1, Sajad A. Dar1,2, Arshad Jawed1, Mohd Wahid1, Mohtashim Lohani1, Aditya K. Panda3, Bhartendu N. Mishra4, Naseem Akhter5 and Shafiul Haque1

1Research and Scientific Studies Unit, College of Nursing and Allied Health Sciences, Jazan University, Jazan 45142, Saudi Arabia; 2The University College of Medical Sciences and GTB Hospital, University of Delhi, Delhi 110095, India; 3Centre for Life Sciences, Central University of Jharkhand, Ranchi 835205, Jharkhand, India; 4Department of Biotechnology, Institute of Engineering and Technology, Lucknow 226021, Uttar Pradesh, India; 5Department of Laboratory Medicine, Faculty of Applied Medical Sciences, Albaha University, Albaha 65431, Saudi Arabia

**Correspondence:** Shafiul Haque (shafiul.haque@hotmail.com)

**Background:** Earlier studies have shown that *interlukin-10* (*IL-10*) -1082 A>G gene polymorphism is implicated in susceptibility to pulmonary tuberculosis (PTB), but their results are inconsistent and inconclusive. In the present study, a meta-analysis was performed to analyze the potential association between *IL-10* -1082 A>G gene polymorphism and PTB susceptibility.

**Methods:** A quantitative synthesis was done using PubMed (Medline), EMBASE, and Google Scholar web databases search and meta-analysis was performed by calculating pooled odds ratios (ORs) and 95% confidence intervals (95% CIs) for all the genetic models.

**Results:** A total of 22 eligible studies comprising 4956 PTB cases and 6428 healthy controls were included in the analysis. We did not observe any increased or decreased risk of PTB in allelic contrast (G vs. A: \(P = 0.985; \ OR = 1.001, 95\% \ CI = 0.863–1.162\)), homozygous (GG vs. AA: \(P = 0.889; \ OR = 1.029, 95\% \ CI = 0.692–1.529\)), heterozygous (GA vs. AA: \(P = 0.244; \ OR = 0.906, 95\% \ CI = 0.767–1.070\)), dominant (GG + AG vs. AA: \(P = 0.357; \ OR = 1.196, 95\% \ CI = 0.817–1.752\)), and recessive (GG vs. AA + AG: \(P = 0.364; \ OR = 0.921, 95\% \ CI = 0.771–1.100\)) genetic models. Likewise, no association of *IL-10* -1082 A>G polymorphism with PTB risk was observed in Asian and African population for all the genetic models. Interestingly, the dominant model (GG + AG vs. AA: \(P = 0.004; \ OR = 1.694, 95\% \ CI = 1.183–2.425\)) demonstrated increased risk of PTB in Caucasian population.

**Conclusions:** This meta-analysis concludes that *IL-10* -1082 A>G gene polymorphism is not significantly associated with overall, Asian and African population. However, this polymorphism is associated with Caucasian population.

**Introduction**

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (*M. tuberculosis* or *M. tb*) is mainly a disease of the lungs mostly of pulmonary type tuberculosis (PTB), which can easily be spread to others by coughing and breathing. Regardless of availability of various effective treatment strategies, which were assumed to eliminate this disease, recent epidemiological figures of the year 2016 shown that TB is once more on the upsurge [1]. Globally, there is a large burden of disease with 9.6 million new cases and 1.5 million people are reported to deaths in the year 2014 [1].
Approximately one-third of the world’s population is thought to be affected with *M. tuberculosis* but relatively large number of population remains with no clinical sign of the disease. However, remaining 5–15% of the infected individuals develop active disease later in life [2]. This suggests that besides *Mycobacteria* itself, the host genetic factors may regulate the differences in host susceptibility to TB [3]. The identification of host genes and genetic variations that are important in susceptibility and resistance to tuberculosis would lead to a better understanding of the pathogenesis of PTB and perhaps lead to new approaches of the disease treatment or prophylaxis.

Immune response to PTB is regulated by interactions between lymphocytes with antigen-presenting cells and the cytokines secreted by these cell types. Cytokines, their genes and receptors have been implicated in the protective immunity, pathophysiology and in the development of tuberculosis [4]. Manifestation of clinical PTB depends on balance between *T* helper 1 (*Th1*) cytokines associated with resistance to infection and *Th2* cytokines with progressive disease [5].

*IL-10* gene maps on the long arm of chromosome 1 (1q31-1q32) locus and produced by both myeloid cells and T cells. *IL-10* signals through a receptor complex consisting of two subunits: *IL-10R1*, induced on stimulated hematopoietic cells, and the *IL-10R2*, constitutively expressed on most cells and tissues [6].

*IL-10*, an anti-inflammatory cytokine prevents the protective immune response to pathogens by blocking the production of proinflammatory cytokines, such as *TNF-α* and *Th1*-polarizing cytokine *IL-12*, by directly acting on antigen-presenting cells such as macrophages and dendritic cells [7]. *IL-10* may also inhibit phagocytosis and microbial killing by limiting the production of reactive oxygen and nitrogen intermediates in response to *IFN-γ* and *Th1* induced response to TB [8,9]. *IL-10* was shown to be elevated in the lungs and serum of PTB patients [10].

The production of cytokines can be modulated both by the stimuli present in the local environment as well as by the genetic factors. Both, *in vitro* and *in vivo* studies have demonstrated that the presence of polymorphisms within the coding or noncoding sequences of cytokine genes can alter the efficiency of transcription of these genes and thus the production of cytokines. Interindividual variations in *IL-10* production are genetically contributed by polymorphisms within the promoter region. The polymorphism -1082 A>G occurs within a putative Ets (E2F transformation-specific) transcription factor-binding site and may affect the binding of this transcriptional factor and therefore altered levels of this cytokine and may alter *Th1/Th2* balance with major implications in tuberculous infection [11,12].

A number of clinical and genetic studies have been performed to consider the effect of *IL-10* -1082 A>G (rs1800896) gene polymorphism on the development of PTB [13-34]. Results published from previous studies are either conflicting or contradictory in nature and still it is unclear whether this polymorphism is associated with increased or decreased risk of PTB infection [13-34]. Inconsistency in the results across many of the studies could possibly be due to the ethnicity of the population, sample size, and individual studies that have low power to evaluate the overall effect. To overcome this situation, nowadays meta-analysis statistical tool is in use to explore the risk factors associated with the genetic diseases, because it employs a quantitative method of pooling the data collected from individual studies where sample sizes are small to provide reliable conclusions. Hence, in the present study, a meta-analysis was performed to evaluate the effect of *IL-10* -1082 A>G gene polymorphism on the risk of overall PTB development and its ethnicity-wise distribution.

**Materials and methods**

**Literature search strategy**

We performed a PubMed, Medline, EMBASE, and Google Scholar web databases search covering all research articles published with a combination of the following key words, i.e. *IL-10, Interleukin-10* gene (polymorphism OR mutation OR variant) AND tuberculosis susceptibility OR TB OR Pulmonary tuberculosis OR PTB (last updated on June 2016). We examined potentially pertinent genetic association studies by examining their titles and abstracts, and procured the most relevant publication matching with the eligible criteria for a closer examination. Besides the online database search, the references given in the selected research articles were also screened for other potential articles that may have been missed in the primary search.

**Inclusion and exclusion criteria**

In order to minimize heterogeneity and facilitate the proper interpretation of this study, published articles included in the current meta-analysis had to meet all the following criteria, i.e.

- they must have done case–control studies between *IL-10* -1082 A>G gene polymorphism and PTB risk,
- clearly described confirmed PTB patients and PTB free controls
Table 1 Main characteristics of all studies included in the present meta-analysis

| First author and year [Ref.] | Country | Ethnicity | Controls | Cases | Study | Genotyping technique |
|------------------------------|---------|-----------|----------|-------|-------|----------------------|
| Hu et al., 2015 [13]         | China   | Asian     | 480      | 120   | HB    | ARMS PCR             |
| Feng et al., 2014 [14]       | China   | Asian     | 191      | 191   | HB    | PCR-RFLP             |
| García-Elorriaga et al., 2013 [15] | Mexico | Mixed    | 47       | 40    | HB    | TaqMan               |
| Akgunes et al., 2011 [16]    | India   | Asian     | 30       | 30    | HB    | PCR Probe            |
| Liang et al., 2011 [17]      | China   | Asian     | 78       | 112   | HB    | SNaPshot assay       |
| Ansari et al., 2011 [18]     | Pakistan| Asian     | 166      | 102   | HB,PB | ARMS PCR             |
| Ben-Selma et al., 2011 [19]  | Tunisia | African   | 95       | 76    | HB    | ARMS PCR             |
| Taype et al., 2010 [20]      | Peru    | Caucasian | 510      | 500   | PB    | PCR-RFLP             |
| Mosaad et al., 2010 [21]     | Egypt   | African   | 98       | 26    | HB    | ARMS PCR             |
| Thye et al., 2009 [22]       | Ghana   | African   | 1968     | 1541  | HB    | FRET                 |
| Ansari et al., 2009 [23]     | Pakistan| Asian     | 188      | 111   | HB    | ARMS PCR             |
| Trajkov et al., 2009 [24]    | Macedonia| Caucasian | 301      | 75    | HB,PB | PCR-SSP              |
| Selvaraj et al., 2008 [25]   | India   | Asian     | 183      | 155   | HB    | ARMS PCR             |
| Wu et al., 2008 [26]         | China   | Asian     | 111      | 183   | PB    | PCR RFLP             |
| Anand et al., 2007 [27]      | India   | Asian     | 143      | 132   | HB    | ARMS PCR             |
| Oh et al., 2007 [28]         | Korea   | Asian     | 117      | 145   | HB    | ARMS PCR             |
| Amirzargar et al., 2006 [29] | Iran    | Asian     | 123      | 41    | HB    | PCR-SSP              |
| Shin et al., 2005 [30]       | Korea   | Asian     | 871      | 459   | HB    | MAPA                 |
| Scola et al., 2003 [31]      | Italy   | Caucasian | 114      | 45    | HB    | ARMS PCR             |
| López-Maderuelo et al., 2003 [32] | Spain | Caucasian | 100      | 113   | HB    | ARMS PCR             |
| Delgado et al., 2002 [33]    | Cambodia| Asian     | 106      | 358   | HB    | PCR-SSP              |
| Bellamy et al., 1998 [34]    | Gambia  | African   | 408      | 401   | HB    | Hybridization         |

Abbreviations: ARMS PCR, amplification-refractory mutation system polymerase chain reaction; FRET, fluorescence resonance energy transfer; HB, hospital based; MAPA, multiplex automated primer extension analysis; PB, population based; PCR-SSP, polymerase chain reaction with a sequence specific primers.

- have available genotype frequency in the both cases and controls
- published in the English language
- data collection and analysis methodology should be statistically acceptable
- additionally, when the case–control study was included in more than one research article using the same subject series, we selected the research study that incorporated the largest number of individuals.

The major reasons for study exclusion were:

- duplicate or overlapping publication
- study design based on only PTB cases
- genotype frequency not reported
- data of review or abstract

Data extraction and quality assessment

For each retrieved study, the methodological quality assessment and data extraction were independently abstracted in duplicate by two independent investigators (SAD & RKM) using a standard protocol. Data collection form was used to confirm the accuracy of the collected data by strictly following the inclusion/exclusion criteria as stated above. In case of disagreement between the above mentioned two investigators on any item related with the data collected from the selected studies, the issue was fully debated and deliberated with the investigators to attain a final consensus. Also, in case failure of reaching consensus between the two investigators, an agreement was achieved following an open discussion with the adjudicator (SH). The major characteristics abstracted from the retrieved publications included the name of first author, publication year, the country of origin, source of cases and controls, number of cases and controls, study type, genotype frequencies, and association with pulmonary TB.
Quality assessment of the included studies

Methodological quality evaluation of the selected studies was performed independently by two investigators (RKM & SAD) by following the Newcastle–Ottawa Scale (NOS) of quality assessment [35]. The NOS quality assessment criteria included three major aspects: (i) subject selection: 0–4 points, (ii) comparability of subject: 0–2 points, and (iii) clinical outcome: 0–3 points. Selected case–control studies that gained five or more stars were considered as of moderate to good quality [36].

Statistical analysis

In order to evaluate the association between the IL10 -1082 A>G gene polymorphism and risk of developing PTB, pooled ORs and their corresponding 95% CIs were estimated. Heterogeneity assumption was examined by the chi-square-based Q-test [37]. Heterogeneity was considered significant at P-value < 0.05. The data from single comparison were combined using a fixed effects model [38], when no heterogeneity was obtained. Otherwise the random-effects model was used for the pooling of the data [39]. Moreover, I² statistics was employed to quantify interstudy variability and larger values suggested an increasing degree of heterogeneity [40]. Hardy–Weinberg equilibrium (HWE) in the controls was calculated by chi-square test. Funnel plot asymmetry was measured by Egger’s regression test, which is a type of linear regression approach to measure the funnel plot asymmetry on the natural logarithm scale of the OR. The significance of the intercept was measured by the t-test (P-value < 0.05 was considered as a representation of statistically significant publication bias).

A comparative assessment of ‘meta-analysis’ based programs was done by using weblink http://www.meta-analysis.com/pages/comparisons.html. The Comprehensive Meta-Analysis (CMA) Version 2 software program (Biostat, U.S.A.) was utilized to perform all the statistical analysis involved in this meta-analysis.

Results

Characteristics of the published studies

A total of 22 articles were lastly selected after literature search from the PubMed (Medline), EMBASE, and Google Scholar web databases. All retrieved articles were inspected carefully by reading their titles and abstracts, and the full-texts for the potentially relevant publications were further checked for their aptness of inclusion in this meta-analysis (Figure 1: PRISMA 2009 Flow Diagram). All the included 22 studies follow the preset eligible crite-
Table 2 Genotypic distribution of *IL-10* -1082 A>G (rs1800896) gene polymorphism included in the meta-analysis

| First author and year | Controls | Cases |
|-----------------------|----------|-------|
|                       | AA       | GA    | GG    | Minor allele MAF | AA | GA | GG | Minor allele MAF | HWE |
| Hu et al., 2015       | 262      | 196   | 22    | 0.250          | 82 | 34 | 4 | 0.175 | 0.35 |
| Feng et al., 2014     | 171      | 18    | 2     | 0.057          | 164 | 24 | 3 | 0.078 | 0.08 |
| Etorriaga et al., 2013 | 25    | 18    | 4     | 0.276          | 27 | 11 | 2 | 0.187 | 0.01 |
| Akgunes et al., 2011  | 17       | 13    | 0     | 0.216          | 15 | 9  | 6 | 0.350 | 0.26 |
| Liang et al., 2011    | 69       | 9     | 0     | 0.057          | 100 | 12 | 0 | 0.053 | 0.11 |
| Ansari et al., 2011   | 31       | 118   | 17    | 0.457          | 23 | 64 | 15 | 0.460 | 0.04 |
| Ben-Seina et al., 2011| 60      | 26    | 9     | 0.231          | 30 | 33 | 13 | 0.388 | 0.01 |
| Taye et al., 2010     | 347      | 153   | 10    | 0.169          | 333 | 147 | 20 | 0.187 | 0.28 |
| Mosaad et al., 2010   | 8        | 88    | 2     | 0.469          | 0  | 16 | 10 | 0.692 | 0.13 |
| Thye et al., 2009     | 1048     | 783   | 140   | 0.269          | 794 | 620 | 117 | 0.280 | 0.27 |
| Ansari et al., 2009   | 32       | 136   | 20    | 0.468          | 21 | 71 | 19 | 0.490 | 0.03 |
| Trakovic et al., 2009 | 70      | 212   | 17    | 0.411          | 17 | 48 | 10 | 0.453 | 0.04 |
| Selvaraj et al., 2008 | 108    | 69    | 6     | 0.221          | 102 | 42 | 5 | 0.174 | 0.83 |
| Wu et al., 2008       | 104      | 18    | 0     | 0.073          | 48 | 12 | 1 | 0.114 | 0.98 |
| Anand et al., 2007    | 73       | 61    | 6     | 0.260          | 74 | 55 | 3 | 0.231 | 0.01 |
| Oh et al., 2007       | 45       | 53    | 19    | 0.388          | 98 | 43 | 4 | 0.175 | 0.95 |
| Amrizarzgar et al., 2006 | 18  | 79    | 5     | 0.436          | 7  | 31 | 2 | 0.437 | 0.04 |
| Shin et al., 2005     | 718      | 124   | 9     | 0.083          | 394 | 53 | 2 | 0.063 | 0.47 |
| Scola et al., 2003    | 13       | 77    | 24    | 0.548          | 6  | 22 | 17 | 0.822 | 0.05 |
| Maderuelo et al., 2003| 21     | 50    | 29    | 0.540          | 33 | 47 | 33 | 0.501 | 0.91 |
| Delgado et al., 2002  | 39       | 64    | 3     | 0.330          | 86 | 259 | 11 | 0.394 | 0.06 |
| Bellamy et al., 1998  | 179      | 184   | 45    | 0.335          | 165 | 185 | 11 | 0.286 | 0.07 |

Abbreviations: HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency.

...ria of the study inclusion and clearly stated about sample sizes, genotypes, inclusion criteria of PTB patients, and healthy controls. All the studies included in this meta-analysis had recruited HIV free subjects.

Research articles either showing *IL-10* polymorphism to predict survival in PTB patients or considering *IL-10* variants as indicators for response to therapy were excluded straightaway. Similarly, studies investigating the levels of *IL-10* mRNA or protein expression or relevant review articles were also excluded from this meta-analysis. We included only case–control or cohort design studies stating the frequency of all three genotypes. Besides the database search, the supporting references available in the retrieved articles were also checked for potential studies. After careful screening and following the inclusion and exclusion criteria, 22 eligible original published studies were finally considered for the present study (Table 1). Distribution of genotypes, HWE *P*-values in the controls, and susceptibility toward PTB have been shown in Table 2. All the selected studies (22 in number) were examined for the overall quality following the NOS and most of the studies (>80%) scored five stars or more, indicating a modest to good quality (Table 3).

**Publication bias**

Begg’s funnel plot and Egger’s test were performed to examine the publication bias among the selected studies for the present meta-analysis. The funnel plots were almost symmetric for both the Begg’s test and Egger’s test (Figure 2). The findings showed lack of publication bias among all comparison models (Table 4).

**Test of heterogeneity**

In order to test heterogeneity among the selected studies, *Q*-test and *I*² statistics were employed. Significant heterogeneity was detected in all models. Therefore, random effects model was applied to synthesize the data (Table 4).

**Sensitivity analysis**

Sensitivity analysis was performed to assess the influence of each individual study on the pooled OR by deleting one single study each time. The results showed that no individual affected the pooled OR significantly, suggesting stability of this meta-analysis (Figure 3).
Figure 2. Funnel plot: Begg’s Funnel plot for overall analysis.
Figure 3. Forest Plot: Sensitivity analysis for overall analysis.
Table 3 Quality assessment conducted according to the NOS for all the studies included in the meta-analysis

| First author and year [Ref.] | Selection | Comparability | Exposure |
|------------------------------|-----------|---------------|----------|
| Hu et al., 2015 [13]         | ***       | *             | **       |
| Feng et al., 2014 [14]       | ***       | *             | **       |
| García-Elorriaga et al., 2013 [15] | ***  | *             | **       |
| Akgunes et al., 2011 [16]    | **        | *             | **       |
| Liang et al., 2011 [17]      | ****      | **            | **       |
| Ansari et al., 2011 [18]     | ***       | *             | **       |
| Ben-Selma et al., 2011 [19]  | ****      | *             | **       |
| Taype et al., 2010 [20]      | ****      | *             | **       |
| Mosaad et al., 2010 [21]     | ***       | *             | **       |
| Thye et al., 2009 [22]       | ****      | *             | **       |
| Ansari et al., 2009 [23]     | ****      | *             | **       |
| Trajkov et al., 2009 [24]    | ***       | *             | **       |
| Selvaraj et al., 2008 [25]   | ***       | *             | **       |
| Wu et al., 2008 [26]         | ***       | *             | **       |
| Prabhu Anand et al., 2007 [27]| ***   | *             | **       |
| Oh et al., 2007 [28]         | *         | *             | **       |
| Amirzargar et al., 2006 [29] | *         | *             | **       |
| Shin et al., 2005 [30]       | ****      | *             | **       |
| Scota et al., 2003 [31]      | *         | *             | **       |
| López-Maderuelo et al., 2003 [32]| *** | *             | **       |
| Delgado et al., 2002 [33]    | ***       | *             | **       |
| Bellamy et al., 1998 [34]    | ***       | *             | **       |

Quantitative synthesis
We pooled all the 22 studies together which resulted into 4956 confirmed PTB cases and 6428 controls, for the assessment of overall association between the *IL-10* -1082 gene polymorphism and risk of developing PTB. The pooled ORs from the overall studies indicated no association with increased or decreased risk between *IL-10* -1082 A>G gene polymorphism and PTB susceptibility in allelic contrast (G vs. A: P=0.985; OR = 1.001, 95% CI = 0.863–1.162), homozygous (GG vs. AA: P=0.889; OR = 1.029, 95% CI = 0.692–1.529), heterozygous (GA vs. AA: P=0.244; OR = 0.906, 95% CI = 0.767–1.070), dominant (GG + AG vs. AA: P=0.357; OR = 1.196, 95% CI = 0.817–1.752), and recessive (GG vs. AA + AG: P=0.364; OR = 0.921, 95% CI = 0.771–1.100) genetic models, respectively (Figures 3 and 4).

Subgroup analysis
We have performed subgroup analysis based on ethnicity to explore the effect of ethnicity (Asian, African, and Caucasian) in the risk between *IL-10* -1082 A>G and PTB risk.

Asian population
In Asian population, 13 studies were included and heterogeneity was observed in all the genetic models (Table 5). We
Figure 4. Forest plot: Overall analysis showing OR with 95% CI to evaluate the association of the IL10 -1082 A>G (rs1800871) gene polymorphism and PTB risk. Black squares represent the value of OR and the size of the square indicates the inverse proportion relative to its variance. Horizontal line is the 95% CI of OR.
performed analyses using random effect models for all the genetic models and no significant association of PTB susceptibility in all genetic models was detected in allele model (G vs. A: $P=0.466$; OR = 0.917, 95% CI = 0.726–1.158), homozygous model (GG vs. AA: $P=0.602$; OR = 0.853, 95% CI = 0.4710–1.547), heterozygous model (GA vs. AA: $P=0.170$; OR = 0.839, 95% CI = 0.652–1.078), dominant model (GG + AG vs. AA: GG vs. AA + AG: $P=0.836$; OR = 0.945, 95% CI = 0.554–1.613), and recessive model (GG vs. AA + AG: $P=0.282$; OR = 0.858, 95% CI = 0.650–1.134) (Figure 5).

**African population**

In African population four studies were found. Publication bias was not significant but heterogeneity was found significant and conducted analyses using random effect models for all the genetic models (Table 6). We found no association with PTB risk in allele model (G vs. A: $P=0.165$; OR = 1.300, 95% CI = 0.898–1.883), homozygous model (GG vs. AA: $P=0.569$; OR = 1.407, 95% CI = 0.434–4.562), heterozygous model (GA vs. AA: $P=0.128$; OR = 1.101, 95% CI = 0.973–1.246), dominant model (GG + AG vs. AA: $P=0.438$; OR = 1.614, 95% CI = 0.482–5.412), and recessive model (GG vs. AA + AG: $P=0.244$; OR = 1.240, 95% CI = 0.863–1.783) genetic models (Figure 6).

**Caucasian population**

In Caucasian population four studies were included. Publication bias and heterogeneity were not significant, hence fixed effect models were applied for all the genetic models (Table 7). We potentially found association of PTB risk with dominant model (GG + AG vs. AA: $P=0.004$; OR = 1.694, 95% CI = 1.183–2.425). Whereas, other genetic models, i.e. allele (G vs. A: $P=0.236$; OR = 1.103, 95% CI = 0.938–1.298), homozygous model (GG vs. AA: $P=0.098$; OR = 1.439, 95% CI = 0.935–2.215), heterozygous model (GA vs. AA: $P=0.446$; OR = 0.915, 95% CI = 0.729–1.150), and recessive model (GG vs. AA + AG: $P=0.926$; OR = 0.990, 95% CI = 0.794–1.233) did not show any increased or decreased risk of PTB with IL-10 -1082 A>G gene polymorphism (Figure 7).

**Discussion**

Although various mechanisms have been described for the development of a protective immune response that restricts and controls the infection and thus prevents the progression of the active disease, the reasons underlying active disease progression remain poorly understood [41]. Candidate gene approach and association studies have identified various host genetic factors that affect the susceptibility to TB [41]. As an immune response modulator, IL-10 has a crucial role to suppress proinflammatory cytokine responses by the innate and adaptive immune systems [42]. **IL-10**

### Table 6 Statistics to test publication bias and heterogeneity in the present meta-analysis: African population

| Comparisons     | Intercept | 95% confidence interval | P-value | Q-value | $P_{heterogeneity}$ | $I^2$ (%) | Model used for the present meta-analysis |
|-----------------|-----------|-------------------------|---------|---------|---------------------|----------|----------------------------------------|
| G vs. A         | 2.415     | -7.48 to 12.31          | 0.403   | 21.824  | 0.001               | 86.254   | Random                                 |
| GG vs. AA       | 1.047     | -11.12 to 13.21         | 0.746   | 26.345  | 0.001               | 88.613   | Random                                 |
| AG vs. AA       | 1.562     | -2.28 to 5.40           | 0.222   | 6.846   | 0.084               | 54.862   | Fixed                                  |
| GG + AG vs. AA  | 1.610     | -4.12 to 7.34           | 0.350   | 10.073  | 0.018               | 70.216   | Random                                 |
| GG vs. AA + AG  | 1.486     | -13.42 to 16.40         | 0.709   | 35.484  | 0.001               | 91.545   | Random                                 |

### Table 5 Statistics to test publication bias and heterogeneity in the present meta-analysis: Asian population

| Comparisons     | Egger's regression analysis | Heterogeneity analysis | Model used for the meta-analysis |
|-----------------|-----------------------------|------------------------|----------------------------------|
|                 | Intercept                   | 95% confidence interval| P-value | Q-value | $P_{heterogeneity}$ | $I^2$ (%) |
| G vs. A         | 1.686                       | -2.38 to 5.75          | 0.380   | 44.674  | 0.001               | 73.139   | Random |
| GG vs. AA       | 1.018                       | -1.08 to 3.88          | 0.446   | 24.674  | 0.010               | 55.419   | Random |
| AG vs. AA       | 0.883                       | -2.29 to 4.06          | 0.552   | 28.851  | 0.004               | 58.409   | Random |
| GG + AG vs. AA  | 1.672                       | -1.85 to 5.19          | 0.318   | 37.372  | 0.001               | 67.890   | Random |
| GG vs. AA + AG  | 0.025                       | -2.42 to 2.47          | 0.981   | 22.603  | 0.020               | 51.334   | Random |
Figure 5. Forest plot: Data from the Asian population showing OR with 95% CI to evaluate the association of the \textit{IL10} -1082 A>G (rs1800871) gene polymorphism and PTB risk. Black squares represent the value of OR and the size of the square indicates the inverse proportion relative to its variance. Horizontal line is the 95% CI of OR.
Figure 6. Forest plot: Data from the African population showing OR with 95% CI to evaluate the association of the \(IL10\) -1082 A>G (rs1800871) gene polymorphism and PTB risk. Black squares represent the value of OR and the size of the square indicates the inverse proportion relative to its variance. Horizontal line is the 95% CI of OR.
Figure 7. Forest plot: Data from the Caucasian population showing OR with 95% CI to evaluate the association of the IL10 -1082 A>G (rs1800871) gene polymorphism and PTB risk. Black squares represent the value of OR and the size of the square indicates the inverse proportion relative to its variance. Horizontal line is the 95% CI of OR.
Table 7 Statistics to test publication bias and heterogeneity in the present meta-analysis: Caucasian population

| Comparisons       | Egger's regression analysis | Heterogeneity analysis | Model used for the present meta-analysis |
|-------------------|-------------------------------|------------------------|------------------------------------------|
|                   | Intercept | 95% confidence interval | P-value | Q-value | $P_{het}$ | $I^2$ (%) |               |
| G vs. A           | 0.158     | -8.42 to 8.74            | 0.940    | 2.616   | 0.455    | 0.001     | Fixed         |
| GG vs. AA         | 2.859     | -16.58 to 22.30          | 0.590    | 5.366   | 0.147    | 44.089    | Fixed         |
| AG vs. AA         | -1.361    | -4.15 to 1.42            | 0.170    | 2.446   | 0.485    | 0.001     | Fixed         |
| GG + AG vs. AA    | -1.031    | -4.68 to 2.62            | 0.348    | 2.235   | 2.235    | 0.5250    | Fixed         |
| GG vs. AA + AG    | 8.205     | 3.75 to 12.65            | 0.015    | 4.744   | 0.192    | 36.760    | Fixed         |

is also thought to play an important regulatory role in many bacterial infections [43,44]. Immunoregulatory genes are very important in modulating the host susceptibility to PTB because the first line of defense against *M. tuberculosis* involves the identification and uptake of the bacterium by macrophages and dendritic cells [45].

As we know that PTB is one of the most common infectious diseases with a high morbidity and mortality [1]. A well-established genetic marker surely would have a significant influence in screening and prevention of PTB. Cytokine polymorphism has been considered to be of important roles in host genetic factors. Among them, *IL-10* is an essential pleiotropic cytokine which takes part in immunoregulatory activities. Lately, *IL-10* gene has been widely studied and some studies suggested that the *IL-10 -1082 A>G* polymorphism is associated with PTB susceptibility, but the results are inconsistent. The results of studies generated could be having insufficient statistical power of individual studies with small sample sizes or variations that existed in different population. Therefore, we conducted this meta-analysis to provide more accurate statistical evidence of association between *IL-10 -1082 A>G* polymorphism and PTB susceptibility. Pooled ORs generated from large sample size and sufficient statistical power from various studies have the advantage of reducing random errors [46].

In the present study, we have included 22 studies with all the preset eligible criteria of sample size, genotype, inclusion criteria of PTB patients, and healthy controls. Most of the included studies scored five or more stars in NOS quality score assessment and suggested good to moderate quality by clearly stating about the sample size, genotype, inclusion criteria of PTB patients, and healthy controls.

Overall, we found that there was no association between *IL-10 -1082 A>G* polymorphism and PTB susceptibility under any genetic models in overall analysis.

These observations suggested that the *IL-10 -1082 A* allele leads to increased resistance to PTB. Studies carried out on mice observed that overexpression of *IL-10* may not be important for susceptibility to initial infection with *M. tuberculosis* but may play a role in reactivation of the latent disease [47]. Other studies also reported no association between the said polymorphism and resistance to TB [48,49].

During the subgroup analysis, we found that *IL-10 -1082 A>G* polymorphism has no role of increasing or decreasing PTB susceptibility in Asian and African populations. Interestingly, significant association was found with dominant model. This result implied that among different ethnicities, the same gene polymorphism may act differently in PTB susceptibility. Tuberculosis report clarified racial differences of susceptibility to TB [50]. Thus, the current results of the present study might attribute the racial differences and reflect the existence of racial differences of TB.

However, the susceptibility toward PTB is polygenic and multiple candidate genes are likely to be involved in determining resistance or susceptibility to TB [51]. Due to multifactorial nature of TB infection and complex nature of the immune system, *IL-10 -1082 A>G* genetic polymorphism cannot be solely responsible for the predisposition of PTB.

In the present study, significant heterogeneity was found between the selected studies in the test of heterogeneity. This discordance may be related to the ethnic origin of the patients as ethnicity-specific genetic variations may influence the host immunity to PTB. Nevertheless, some limitations also need to be addressed. First, we only included studies published in the English language, abstracted and indexed by the selected electronic databases were included for data analysis; it is possible that some pertinent studies published in other languages and indexed in other electronic databases may have missed. Second, the abstracted data were not stratified by other factors, e.g. HIV status or severity of the TB infection, and our results were based on unadjusted parameters. Third, we did not test for gene–environment interactions because of inadequate data available in the published reports. Despite above limitations, there are some advantages of the present study. First, the present meta-analysis was comprised with more number of studies which
increased the statistical power of the study and ultimately reached at robust conclusion. Second, no publication bias was observed and further sensitivity analysis also supported our results more reliably.

Also, all the included studies were of good to modest quality fulfilling the preset needful criteria as tested by NOS quality score evaluation scale.

**Conclusions**

In conclusion, this meta-analysis demonstrated that IL-10 -1082 A>G gene polymorphism is not associated with PTB risk in overall, Asian and African population. Our result provided evidence that G allele carrier is associated with PTB in Caucasian population. In the near future, because of significant public health impact of PTB, larger studies are warranted to identify the host genes with their functional allele controlling the response to mycobacterial infections. This will help in the identification of the host genetic factors for the susceptibility to PTB, and would greatly help in the global control of this infectious disease.

**Acknowledgments**

The authors are thankful to the Deanship of Scientific Research, Jazan University, Jazan, Saudi Arabia for providing the necessary facilities for this research study.

**Competing Interests**

The authors declare that there are no competing interests associated with the manuscript.

**Funding**

The authors declare that there are no sources of funding to be acknowledged.

**Author Contribution**

M.Y.A., R.K.M., S.A.D., A.J., M.W., M.L., A.K.P., B.N.M., N.A., and S.H. conceived and designed the study. M.Y.A., R.K.M., S.A.D., A.J., and M.W. searched the literature for selection of relevant studies. M.L., A.K.P., B.N.M., N.A., and S.H. verified the selection and extracted the required data from the articles. R.K.M., S.A.D., A.J., A.K.P., and S.H. performed the analysis. R.K.M., S.A.D., and S.H. wrote the paper. All the authors reviewed and approved the final manuscript.

**Abbreviations**

Cl, confidence interval; HWE, Hardy–Weinberg equilibrium; IFN-y, Interferon gamma; IL-10, interleukin-10; NOS, Newcastle–Ottawa Scale; OR, odds ratio; PTB, pulmonary tuberculosis; Th1, T helper 1; TNF-a, Tumor necrosis factor - alpha.

**References**

1. World Health Organization. Global Tuberculosis Report (2016). World Health Organization, http://www.who.int/tb/publications/global_report/gtbr2016_executive_summary.pdf
2. Andrews, J.R., Noubary, F., Walensky, R.P., Cerda, R., Losina, E. and Horsburgh, C.R. (2012) Risk of progression to active tuberculosis following reinfection with Mycobacterium tuberculosis. *Clin. Infect. Dis.* 54, 784–791
3. Bellamy, R. (2003) Susceptibility to Mycobacterial infections: the importance of host genetics. *J. Leukoc. Biol.* 70, 3815–3822
4. Flynn, J. and Chan, J. (2001) Immunology of tuberculosis. *Annu. Rev. Immunol.* 19, 93–129
5. Hallis, R.S. and Ellner, J.J. (1994) Cytokines and tuberculosis. *J. Leukoc. Biol.* 55, 676–681
6. Moore, K.W., de Waal Malefyt, R., Coffman, R.L. and O’Garra, A. (2001) Interleukin-10 and the interleukin-10 receptor. *Annu. Rev. Immunol.* 19, 683–765
7. Fiorentino, D.F., Zlotnik, A., Mosmann, T.R., Howard, M. and O’Garra, A. (1991) IL-10 inhibits cytokine production by activated macrophages. *J. Immunol.* 147, 3815–3822
8. Gazzinelli, R.T., Osvald, J.P., James, S.L. and Sher, A. (1992) IL-10 inhibits parasite killing and nitrogen oxide production by IFN-gamma-activated macrophages. *J. Immunol.* 148, 1792–1796
9. Gong, J.H., Zhang, M., Modlin, R.L., Linsley, P.S., Iyer, D., Lin, Y. et al. (1996) Interleukin-10 downregulators Mycobacterium tuberculosis-induced Th-1 responses and CTLA-4 expression. * Infect. Immun.* 64, 913–918
10. Verbon, A., Juffermans, N., Van Deventer, S.J., Speelman, P., Van Deutekom, H. and Van Der Poll, T. (1999) Serum concentrations of cytokines in patients with active tuberculosis (TB) and after treatment. *Clin. Exp. Immunol.* 115, 110–113
11. Vidyarani, M., Selvaraj, P., Abaad, A.P., Jawahar, M.S., Adhilakshmi, A.R. and Narayanan, P.R. (2006) Interferon gamma (IFNc) & interleukin-4 (IL-4) gene variants & cytokine levels of pulmonary tuberculosis. *Indian J. Med. Res.* 124, 403–410
12. Ates, O., Muselium, B., Ongen, G. and Topal-Sarikaya, A. (2008) Interleukin-10 and tumor necrosis factor-alpha gene polymorphisms in tuberculosis. *J. Clin. Immunol.* 28, 232–236

© 2017 The Author(s). This is an open access article published by Portland Press Limited on behalf of the Biochemical Society and distributed under the Creative Commons Attribution License 4.0 (CC BY).
45 Rockett, K.A., Brookes, R., Udalova, I., Vidal, V., Hill, A.V. and Kwiatkowski, D. (1998) 1,25-Dihydroxyvitamin D3 induces nitric oxide synthase and suppresses growth of Mycobacterium tuberculosis in a human macrophage-like cell line. Infect. Immun. 66, 5314–5321
46 Ioannidis, J.P., Boffetta, P., Little, J., O’Brien, T.R., Uitterlinden, A.G., Vineis, P. et al. (2008) Assessment of cumulative evidence on genetic associations: interim guidelines. Int. J. Epidemiol. 37, 120–132
47 Turner, J., Gonzalez-Juarrero, M., Ellis, D.L., Basaraba, R.J., Kipnis, A., Orme, I.M. et al. (2002) In vivo IL-10 production reactivates chronic pulmonary tuberculosis in C57BL/6 mice. J. Immunol. 169, 6343–6351
48 Bidwell, J., Keen, L., Gallagher, G., Kimberly, R., Huizinga, T., McDermott, M.F. et al. (1999) Cytokine gene polymorphism in human disease: on-line databases. Genes Immun. 1, 3–19
49 Zhang, J., Chen, Y., Nie, X.B., Wu, W.H., Zhang, H., Zhang, M. et al. (2011) Interleukin-10 polymorphisms and tuberculosis susceptibility: a meta-analysis. Int. J. Tuberc. Lung Dis. 15, 594–601
50 Stead, W.W., Senner, J.W., Reddick, W.T. and Lofgren, J.P. (1990) Racial differences in susceptibility to infection by Mycobacterium tuberculosis. N. Engl. J. Med. 322, 422–427
51 Bellamy, R. (2006) Genome-wide approaches to identifying genetic factors in host susceptibility to tuberculosis. Microbes Infect 8, 1119–1123