Association between **CD209 -336A/G** and **-871A/G** Polymorphisms and Susceptibility of Tuberculosis: A Meta-Analysis

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Abstract

**Background:** The association between **CD209** promoter polymorphisms (-336A/G, -871A/G) and tuberculosis (TB) risk has been widely reported, but results of previous studies remain controversial and ambiguous. To assess the association between **CD209** polymorphisms and TB risk, a meta-analysis was performed.

**Methods:** Based on comprehensive searches of the PubMed, Embase, Web of Science, Weipu, and CBM databases, we identified outcome data from all articles estimating the association between **CD209** polymorphisms and TB risk. The pooled odds ratio (OR) with 95% confidence intervals (CIs) were calculated.

**Results:** A total of 14 studies with 3,610 cases and 3,539 controls were identified. There was no significant association between **CD209** -336A/G polymorphism and TB risk (OR = 1.04, 95% CI = 0.91–1.19 for G vs. A; OR = 1.13, 95% CI = 0.84–1.53 for GG vs. AA; OR = 1.04, 95% CI = 0.87–1.24 for GG vs. AA; OR = 1.11, 95% CI = 0.88–1.39 for GG vs. AG+AA). However, the significant association was revealed for Asians in GG vs. AA (OR = 2.48, 95% CI = 1.46–4.22, P = 0.0008) and GG vs. AG+AA (OR = 2.10, 95% CI = 1.33–3.32, P = 0.001). For the **CD209** -871A/G polymorphism, lack of an association was also found (OR = 0.81, 95% CI = 0.70–0.95 for G vs. A; OR = 1.00, 95% CI = 0.52–1.93 for GG vs. AA; OR = 0.73, 95% CI = 0.60–0.89 for GG vs. AG+AA).

**Conclusion:** The present meta-analysis suggested that **CD209** promoter polymorphisms (-336A/G, -871A/G) were unlikely to substantially contribute to TB susceptibility. However, the GG genotype of **CD209** -336A/G polymorphism might be a genetic risk factor that increases TB susceptibility for Asians in GG vs. AA and GG vs. AG+AA.

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Introduction

Tuberculosis (TB) constitutes a serious threat to public health throughout the world, particularly in developing countries [1]. Recent data from the World Health Organization (WHO) show that nearly 10 million new cases arise and 1.7 million deaths die of TB annually [2]. It has been reported that one-third of population is infected with **Mycobacterium tuberculosis**; however, only one-tenth of infected individuals will ever develop active TB [3]. Thus, host genetic susceptibility, combined with environmental factors, may play a crucial role in exploring the infection mechanism of **Mycobacterium tuberculosis** [4–5].

The **CD209** gene, located on human chromosome 19p13.2–3, is composed of 7 exons and 6 introns, and is about 13 kb in length [6–7]. This gene encoded Dendritic Cell-Specific ICAM3-Grabbing Non-integrin (DC-SIGN), which is one of the major receptor of **Mycobacterium tuberculosis** on human dendritic cells [8]. In addition, the **Mycobacterium tuberculosis** interacts with DC-SIGN to activate the Raf-1-acetylation-dependent signaling pathway that is involved in the regulation of adaptive immune response to tuberculosis. Furthermore, the DC-SIGN could suppress Toll-like receptor signaling leading to cytokine secretion. This effect may be a part of immune evasion to TB progression [9–10]. Therefore, the **CD209** gene might play a crucial role in host immunity to TB and might be one of the candidate genes for susceptibility of TB.

A relatively large number of studies evaluated the association between **CD209** polymorphisms (-336A/G, -871A/G) and TB risk, but the results have been inconsistent due to limited sample sizes and different study populations. To derive a more comprehensive and precise estimation of the relationship, we carried out a meta-analysis on all eligible case-control studies to estimate the effect of **CD209** polymorphisms on the risk of TB and to quantify the potential between-study heterogeneity.
Table 1. Association between individual study characteristics and CD209 gene polymorphisms.

| Study                        | Origin               | Ethnicity | Male patients (%) | Mean age(years) | Sample types | Sample size | Polymorphisms investigated | Clinical diagnoses performed | Control source | Genotyping method | Score |
|------------------------------|----------------------|-----------|-------------------|-----------------|--------------|-------------|---------------------------|----------------------------|----------------|------------------|-------|
| Kobayashi et al. [12]        | Indonesian           | Asian     | 53.7              | 41.6±1.54       | PTB          | 532         | -336A/G, -871A/G          | Smear, radiologic, clinical symptoms | Healthy individuals | Sequencing | 8     |
| Ogarkov et al. [17]          | Russian              | Caucasian | 76.3              | 42.3±12.1       | PTB          | 101         | -336A/G                  | NR                         | Healthy individuals | Taq Man LNA technology | 7     |
| Zheng et al. [19]            | Chinese              | Asian     | 65.4              | 44.6±17.7       | PTB          | 237         | -336A/G, -871A/G          | Culture, radiologic          | Healthy individuals | Sequencing | 7     |
| Sadki et al. [15]            | Moroccan             | Mixed     | 81.1              | 33.7±13.2       | PTB          | 122         | -336A/G                  | Smear, culture, histology, radiologic, clinical symptoms | Healthy unrelated donors | Taq Man SNP genotyping assays | 8     |
| Selvaraj et al. [13]         | Indian               | Caucasian | 61.2              | 340±8.2         | PTB          | 183         | -336A/G                  | Smear, culture, radiologic, clinical symptoms | Healthy individuals | PCR-RFLP | 7     |
| Zhuang et al. [20]           | Chinese              | Asian     | 65.9              | 43(16–77)       | PTB          | 167         | -336A/G                  | Smear, culture, histology, radiologic, clinical symptoms | Healthy unrelated donors | SSP-PCR | 7     |
| Vannberg et al. (a) [14]     | Gambian              | African   | NR                | NR(15–78)       | PTB          | 676         | -336A/G                  | Smear, culture, histology | Healthy unrelated donors | MALDI-TOF | 8     |
| Vannberg et al. (b) [14]     | Guinean              | African   | NR                | NR              | PTB          | 151         | -336A/G                  | Smear, culture, histology | Healthy unrelated donors | MALDI-TOF | 8     |
| Vannberg et al. (c) [14]     | Guinea-Bissau        | African   | NR                | NR(18–65)       | PTB          | 162         | -336A/G                  | Smear, culture, histology confirmed TB | Healthy unrelated donors | MALDI-TOF | 8     |
| Vannberg et al. (d) [14]     | Malawian             | African   | NR                | NR(25–60)       | PTB          | 244         | -336A/G                  | Smear, culture, histology confirmed TB | Healthy unrelated donors | MALDI-TOF | 8     |
| Ben-Ali et al. [18]          | Tunisian             | Mixed     | NR                | NR(18-65)       | PTB          | 138         | -336A/G, -871A/G          | Smear, culture, radiologic, clinical symptoms confirmed TB | Healthy unrelated donors | Sequencing | 8     |
| Olesen et al. [16]           | Guinea-Bissau        | African   | 60.4              | 37.3            | PTB          | 315         | -336A/G                  | Smear, culture, histology confirmed TB | Healthy unrelated donors | Taq Man SNP genotyping assays | 9     |
| Barreiro et al. [6]          | South African        | African   | 51.8              | 36.7±10.9       | PTB          | 351         | -336A/G, -871A/G          | Smear, culture confirmed TB | Healthy unrelated donors | Taq Man or fluorescence polarization | 8     |
Results

Study Characteristics

Eleven publications, including 3,610 cases and 3,539 controls, met the inclusion criteria [6,11–20]. A flowchart detailing the process for study identification and selection was shown in Fig. S1. The publication of Vannberg et al. presented four independent case-control studies, each study was considered separately for analysis. Therefore, 11 publications including 14 studies were involved in this meta-analysis. The main characteristics of the studies were shown in Table 1. The sample sizes ranged from 273 to 1093 patients (median 390, IQR 324–669). Nine of the 14 included studies reported the proportion of male patients, which ranged from 14.5% to 81.1% (median 62.25%, IQR 53.225%–68.5%). Thirteen of the 14 included studies clearly described the diagnostic criteria. One study didn’t provide the genotype number [18]. Gene frequencies of all the individual studies were shown in Table S1. The NOS scores ranged from 7 to 9, which indicated that the methodological quality was generally good. The quality assessment of included studies was shown in Table S2. The genotype distribution in the controls of all studies was in agreement with HWE.

The CD209 -336A/G Alleles and Tuberculosis Susceptibility

Random effects models were used to calculate the pooled OR in all genetic models. Overall, the combined results showed that no significant association was found in all genetic models (OR = 1.04, 95% CI = 0.91–1.19 for G vs. A, OR = 1.13, 95% CI = 0.84–1.53 for GG vs. AA, OR = 1.04, 95% CI = 0.87–1.24 for GG+AG vs. AA, and OR = 1.11, 95% CI = 0.89–1.39 for GG vs. AG+AA). Forest plots on the basis of all studies were shown in Fig. 1A, B, C, D. When stratified by ethnicity, we observed a wide variation of G allele frequencies between the controls across different ethnicities. The G allele frequencies were significant difference in Africans, Asians, Caucasians and Mixed populations (P = 0.007). Forest plots were shown in Fig. S2. When meta-analysis was performed to assess association between CD209 -336A/G polymorphism and TB risk in different ethnicities, significant association was revealed for Asians in GG vs. AA (OR = 2.48, 95% CI = 1.46–4.22, P = 0.0008) and GG vs. AG+AA (OR = 2.10, 95% CI = 1.33–3.32, P = 0.001) (Fig. S3, Fig. S4, Fig. S5, and Fig. S6). On subgroup analysis by sample types, no evidence of association was found in all genetic models for pulmonary tuberculosis (PTB) and extra-pulmonary tuberculosis (EPTB). The results were shown in Table 2.

The CD209 -871A/G Alleles and Tuberculosis Susceptibility

The results on the CD209 -871A/G polymorphism indicated that the G allele had no significant association to TB susceptibility as compared to the A allele under the fixed effects models (Fig. 2). The results were as followed: G vs. A (OR = 0.81, 95% CI = 0.70–0.93), GG vs. AA (OR = 1.00, 95% CI = 0.52–1.93), GG+AG vs. AA (OR = 0.73, 95% CI = 0.60–0.89), GG vs. AG+AA (OR = 1.09, 95% CI = 0.57–2.10).

Heterogeneity Analysis

For CD209 -336A/G polymorphism, there were statistically significant heterogeneity in G vs. A (I² = 66%, $P_{\text{heterogeneity}} = 0.0003$), GG vs. AA (I² = 60%, $P_{\text{heterogeneity}} = 0.003$), dominant genetic model (I² = 62%, $P_{\text{heterogeneity}} = 0.002$), and recessive genetic model (I² = 47%, $P_{\text{heterogeneity}} = 0.03$). To explain the heterogeneity,
### A

| Study or Subgroup | TB 6 6+A 6 6-A Weight M-H, Random, 95% CI | Odds Ratio | Odds Ratio |
|-------------------|------------------------------------------|------------|------------|
| Kobayashi K 2011  | 133 1064 143 1122 8.2%                  | 0.98 [0.76, 1.28] |            |
| Oganov O 2011     | 81 382 63 354 6.2%                      | 1.24 [0.86, 1.79] |            |
| Zheng R 2011      | 29 474 38 489 4.4%                      | 0.82 [0.49, 1.39] |            |
| Sadiq K 2009      | 55 244 87 302 5.8%                      | 0.72 [0.49, 1.08] |            |
| Selvaraj P 2009   | 95 426 76 314 6.4%                      | 0.86 [0.60, 1.23] |            |
| Zhuang B 2008     | 193 334 146 334 7.2%                    | 1.00 [0.40, 2.58] |            |

**Total (95% CI)**: 7220 7078 100.6% 1.04 [0.91, 1.19]

**Total events**: 2470 2234

**Heterogeneity**:
- $I^2 = 0.04$,
- $X^2 = 3.80$, df = 13 ($P = 0.0033$), $P = 66$

**Test for overall effect**: $Z = 0.64$ ($P = 0.53$)

### B

| Study or Subgroup | TB 6 6+A 6 6-A Weight M-H, Random, 95% CI | Odds Ratio | Odds Ratio |
|-------------------|------------------------------------------|------------|------------|
| Kobayashi K 2011  | 133 1064 143 1122 8.2%                  | 0.98 [0.76, 1.28] |            |
| Oganov O 2011     | 81 382 63 354 6.2%                      | 1.24 [0.86, 1.79] |            |
| Zheng R 2011      | 29 474 38 489 4.4%                      | 0.82 [0.49, 1.39] |            |
| Sadiq K 2009      | 55 244 87 302 5.8%                      | 0.72 [0.49, 1.08] |            |
| Selvaraj P 2009   | 95 426 76 314 6.4%                      | 0.86 [0.60, 1.23] |            |
| Zhuang B 2008     | 193 334 146 334 7.2%                    | 1.00 [0.40, 2.58] |            |

**Total (95% CI)**: 7220 7078 100.6% 1.04 [0.91, 1.19]

**Total events**: 2470 2234

**Heterogeneity**:
- $I^2 = 0.04$,
- $X^2 = 3.80$, df = 13 ($P = 0.0033$), $P = 66$

**Test for overall effect**: $Z = 0.64$ ($P = 0.53$)

### C

| Study or Subgroup | GG 6-A | Total 6 6-A | Weight M-H, Random, 95% CI | Odds Ratio | Odds Ratio |
|-------------------|--------|------------|----------------------------|------------|------------|
| Kobayashi K 2011  | 139 532 | 135 561 | 0.99 [0.74, 1.32] |            |
| Oganov O 2011     | 74 191 | 58 177 | 0.99 [0.85, 1.19] |            |
| Zheng R 2011      | 29 237 | 35 244 | 0.93 [0.49, 1.41] |            |
| Sadiq K 2009      | 46 122 | 18 83 | 0.83 [0.63, 1.10] |            |
| Selvaraj P 2009   | 72 214 | 59 157 | 0.88 [0.57, 1.35] |            |
| Zhuang B 2009     | 132 167 | 108 167 | 0.80 [0.67, 1.00] |            |
| Vanberg FO 2009a  | 491 676 | 255 327 | 0.75 [0.55, 1.02] |            |
| Vanberg FO 2009b  | 108 151 | 128 180 | 0.88 [0.67, 1.13] |            |
| Vanberg FO 2009c  | 109 162 | 105 141 | 0.71 [0.43, 1.16] |            |
| Olesen R 2007     | 138 207 | 100 250 | 0.80 [0.57, 1.14] |            |
| Barreiro LB 2006  | 255 315 | 255 340 | 1.42 [0.88, 2.28] |            |
| Dömmez LM 2006    | 46 110 | 104 299 | 0.91 [0.50, 1.55] |            |

**Total (95% CI)**: 3472 3399 100.0% 1.04 [0.87, 1.24]

**Total events**: 1879 1723

**Heterogeneity**:
- $I^2 = 0.07$,
- $X^2 = 31.54$, df = 12 ($P = 0.002$), $P = 62$

**Test for overall effect**: $Z = 0.39$ ($P = 0.69$)

### D

| Study or Subgroup | GG 6-A | Total 6 6-A | Weight M-H, Random, 95% CI | Odds Ratio | Odds Ratio |
|-------------------|--------|------------|----------------------------|------------|------------|
| Kobayashi K 2011  | 4 532 | 4 581 | 2.3% 1.05 [0.26, 4.24] |            |
| Oganov O 2011     | 7 191 | 6 177 | 3.2% 1.31 [0.41, 4.28] |            |
| Zheng R 2011      | 0 237 | 1 244 | 0.5% 0.34 [0.01, 8.43] |            |
| Sadiq K 2009      | 9 122 | 13 151 | 4.9% 0.85 [0.35, 2.05] |            |
| Selvaraj P 2009   | 11 214 | 11 157 | 5.1% 0.72 [0.30, 1.78] |            |
| Zhuang B 2009     | 51 167 | 32 167 | 10.0% 2.43 [0.49, 1.89] |            |
| Vanberg FO 2009a  | 151 676 | 98 327 | 14.5% 0.67 [0.50, 0.91] |            |
| Vanberg FO 2009b  | 39 151 | 43 180 | 10.0% 1.11 [0.87, 1.43] |            |
| Vanberg FO 2009c  | 45 162 | 37 141 | 9.8% 1.08 [0.65, 1.86] |            |
| Vanberg FO 2009d  | 34 244 | 33 295 | 9.8% 1.29 [0.77, 2.16] |            |
| Olesen R 2007     | 85 315 | 84 340 | 13.3% 1.13 [0.79, 1.60] |            |
| Barreiro LB 2006  | 71 351 | 67 360 | 12.8% 1.11 [0.76, 1.61] |            |
| Dömmez LM 2006    | 6 110 | 10 299 | 3.8% 1.67 [0.95, 2.90] |            |

**Total (95% CI)**: 3472 3399 100.0% 1.11 [0.88, 1.39]

**Total events**: 523 438

**Heterogeneity**:
- $I^2 = 0.07$,
- $X^2 = 22.75$, df = 12 ($P = 0.03$), $P = 47$

**Test for overall effect**: $Z = 0.88$ ($P = 0.38$)
Table 2. Meta-analyses of CD209 -336A/G promoter polymorphism and risk of TB in each subgroup.

| Category   | G vs. A OR (95%CI)  | GG vs.AA OR (95%CI)  | Dominant model OR (95%CI)  | Recessive model OR (95%CI)  |
|------------|---------------------|----------------------|---------------------------|-----------------------------|
| Ethnicity  |                     |                      |                           |                             |
| African    | 1.00 (0.85–1.19)     | 1.03 (0.75–1.42)     | 1.00 (0.76–1.32)          | 0.97 (0.83–1.15)            |
| Asian      | 1.17 (0.71–1.94)     | 2.48 (1.46–4.22)     | 1.17 (0.71–1.93)          | 2.10 (1.33–3.32)            |
| Caucasian  | 1.03 (0.80–1.33)     | 0.91 (0.45–1.82)     | 1.07 (0.79–1.45)          | 0.89 (0.45–1.78)            |
| Mixed      | 1.01 (0.72–1.43)     | 1.03 (0.52–2.05)     | 0.93 (0.44–1.95)          | 1.11 (0.56–2.18)            |
| Sample types |                  |                      |                           |                             |
| PTB        | 1.02 (0.88–1.18)     | 1.08 (0.79–1.48)     | 1.01 (0.83–1.22)          | 1.08 (0.85–1.37)            |
| EPTB       | 1.21 (0.84–1.74)     | 1.51 (0.58–3.92)     | 1.20 (0.77–1.86)          | 1.51 (0.59–3.89)            |

Abbreviations and definitions: PTB, pulmonary tuberculosis; EPTB, extra-pulmonary tuberculosis; CI, 95% confidence intervals; OR, odds ratio.

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Due to different racial or ethnic populations with different frequencies of alleles, different genetic backgrounds may affect TB susceptibilities. Therefore, subgroup analyses were performed according to ethnicity. First, we detected whether there was G allele frequency of variation in different ethnicities. For CD209 -336A/G polymorphism, the G allele frequency has significant differences in different populations. Next, the association between CD209 -336A/G polymorphism and different ethnicities was explored. The significant association was revealed for Asians in GG vs. AA (OR = 2.48, 95% CI = 1.46–4.22, P = 0.0008) and GG vs. AG+AA (OR = 2.10, 95% CI = 1.33–3.32, P = 0.001). The ethic-dependent association may attribute to interplay among different human alleles, locally predominant, and endemic mycobacterial lineages [31]. Ogarkov et al. [17] demonstrated that the G allele of CD209 -336A/G polymorphism could increase the risk of infection with Mycobacterium tuberculosis Beijing but not non-Beijing strain in Russian male population. Thus, the TB...
in different host infected with the same genotype may manifest as different outcome in clinic.

In our meta-analysis, obvious heterogeneity was observed for CD209 -336A/G polymorphism. Then, we used the Galbraith plots to explore the sources of heterogeneity. We found all of the $I^2$ values were less than 50% and $P_{\text{heterogeneity}}$ were greater than 0.1 after excluding the studies of Zhuang et al., Vannberg FO(a) et al. and Barreiro LB et al., respectively. The results indicated that the

Table 3. Meta-analyses of CD209 -336A/G promoter polymorphism and risk of TB after omitting the studies.

| Polymorphism          | OR (95% CI)    | Z   | P OR | $I^2$ (%) | $P_{\text{heterogeneity}}$ | Effect model |
|-----------------------|----------------|-----|------|-----------|---------------------------|--------------|
| G vs. A*              | 1.05 (0.96, 1.14) | 1.12 | 0.26 | 17        | 0.28                      | F            |
| GG vs. AA*            | 1.16 (0.95, 1.42) | 1.46 | 0.15 | 0         | 0.74                      | F            |
| GG+AG vs. AA*         | 0.98 (0.86, 1.11) | 0.29 | 0.77 | 36        | 0.12                      | F            |
| GG vs. AG+AA*         | 1.11 (0.93, 1.32) | 1.14 | 0.26 | 0         | 0.98                      | F            |

Abbreviations and definitions: TB, tuberculosis; CI, 95% confidence intervals; OR, odds ratio; $P_{\text{heterogeneity}}$, P value of Q test for heterogeneity; F, fixed-effect models.

*CD209 -336A/G promoter polymorphism and risk of TB after excluding the two studies of Zhuang et al. and Vannberg FO(a) et al.

**CD209 -336A/G promoter polymorphism and risk of TB after excluding the three studies of Zhuang et al., Vannberg FO(a) et al. and Barreiro LB et al.

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three studies might be the major source of the heterogeneity for the CD209 -336A/G polymorphism. The results of subgroup analyses revealed that the ethnicity and sample type might contribute to the potential heterogeneity. Owing to the limited number of studies in this meta-analysis, we restricted meta-regression analysis to four factors (sample size, control source, NOS scores, and the frequency of G allele), which are the most likely to cause the heterogeneity between studies. However, the four above-mentioned factors had no significant impact on the heterogeneity.

There are some limitations to this meta-analysis. Firstly, the retrieved literature is potentially not comprehensive enough. We did not track the unpublished articles to obtain data for analysis. The potential effect of this publication bias is unknown. Secondly, the small sample sizes in some subgroup analyses may have limited statistical power to estimate the possible risk for CD209 polymorphisms. Thirdly, TB is a multifactorial disease and potential interactions among gene-gene and gene-environment should be considered. Moreover, as many other factors such as age or gender may participate in the progression of TB, we did not carry out subgroup analysis based on these factors due to limited data.

Conclusively, the CD209 promoter polymorphisms (-336A/G, -871A/G) may lack association with genetic susceptibility of TB. However, genotype GG of CD209 -336A/G polymorphism might play a role as risk factor for Asians in GG vs. AA and GG vs. AG+AA, which indicated the different genetic backgrounds may affect TB susceptibilities. Moreover, further studies with large sample size of different ethnic populations will be necessary to combine genetic factors together with poor economic conditions, malnutrition, stress and overcrowding.

Materials and Methods

Data Sources and Search Strategy

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria [32]. Two investigators (K.C. and S.D.) independently performed a systematic electronic search of the PubMed, Embase, Web of Science, Weipu, and CBM databases for original articles published until 1 December, 2011 to identify potentially relevant articles and abstracts. Search terms used were “CD209 or DC-SIGN” and “tuberculosis or TB” and “polymorphism or mutation or variant”. There were no language restrictions. We reviewed the bibliographies of all selection articles to identify additional relevant studies.

Selection of Publications

Two reviewers (K.C. and W.L.) independently screened titles and abstracts of all studies for relevancy. Disagreements were resolved by a third opinion (M.C.). Full-text publications were retrieved for relevant articles. The strength of the individual studies was weighed for relevance, based on the following items: (1) evaluation of the CD209 -336A/G or -871A/G polymorphisms and TB risk, (2) case-control studied (family-based study design with linkage considerations was excluded), (2) sufficient data for estimating an odds ratio (OR) with 95% confidence intervals (CIs), (3) genotype distribution of control population in Hardy-Weinberg equilibrium (HWE), and (4) studies written in English or Chinese. For the studies with the same or overlapping data by the same authors, the most recent or largest population was selected.

Data Extraction

Data were extracted independently from each study by two reviewers (K.C. and S.D.) according to the inclusion criteria listed above. Agreement was reached after discussion for conflicting data. The following data were collected from each study: first author’s name, publication year, original country, ethnicity, sample size, sample types, TB definition, genotyping method, and genotype number in cases and controls.

Quality Assessment

The quality of included studies was assessed independently by the same two investigators using the Newcastle-Ottawa Scale (NOS) (Stang A., 2010). The NOS uses a ‘star’ rating system to judge quality based on 3 aspects of the study: selection, comparability, and exposure. Scores were ranged from 0 stars (worst) to 9 stars (best). Studies with a score of 7 stars or greater were considered to be of high quality. Disagreement was settled as described above.

Statistical Analysis

The strength of association between CD209 polymorphisms and TB risk was estimated by OR and corresponding 95% CIs. The pooled OR was calculated respectively for G vs. A, GG vs. AA, dominant genetic model (GG+AG vs. AA), and recessive genetic model (GG vs. AG+AA). Between-study heterogeneity was assessed by the Q-test and I² test, I² heterogeneity<0.10 and I²>50% indicated evidence of heterogeneity. Then, the random-effects model (the DerSimonian and Laird method) [33–34] was used to calculate the pooled OR. Otherwise, the fixed-effects model (Mantel-Haenszel) [35] was adopted. Subgroup analyses and meta-regression were used to analyze the sources of heterogeneity.

Sensitivity analysis was mainly performed to assess the stability of the results, namely, a single study in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled OR. Asymmetry funnel plots were inspected to assess potential publication bias. The Egger’s linear regression test [36] was also used to assess publication bias statistically.

Data were analyzed by using STATA 11.0 (Stata Corporation, College Station, TX, USA) and Revman 5.0 (The Cochrane Collaboration).

Supporting Information

Figure S1 Flow diagram of the selection of eligible studies.

Figure S2 Frequencies of the minor allele (G allele) of the CD209 -336A/G polymorphism among controls subjects stratified by ethnicity. The G allele frequencies were significant difference in Africans, Asians, Caucasians and Mixed populations (P = 0.007)

Figure S3 Forest plot of CD209 -336A/G promoter polymorphism and risk of TB in G vs. A for each subgroup. No significant association was found between the CD209 -336A/G polymorphism and TB risk in G vs. A.

Figure S4 Forest plot of CD209 -336A/G promoter polymorphism and risk of TB in GG vs. AA for each subgroup. The significant association was revealed for Asians in GG vs. AA (OR = 2.48, 95% CI = 1.46–4.22, P = 0.0008).

Figure S5 Forest plot of CD209 -336A/G promoter polymorphism and risk of TB in dominant model for
each subgroup. No significant association was found between the CD209 -336A/G polymorphism and TB risk in dominant model.

(TIF)

Figure S6 Forest plot of CD209 -336A/G promoter polymorphism and risk of TB in recessive model for each subgroup. The significant association was revealed for Asians in recessive model (OR = 2.10, 95% CI = 1.33–3.32, P = 0.001).

(TIF)

Figure S7 Funnel plots of all genetic models in overall studies. A. G vs. A; B. GG vs. AA; C. dominant model (GG+AG vs. AA); D. recessive model (GG vs. AG+AA). Funnel plots of dominant model seemed asymmetry. Each point represents a separate study for the indicated association.

(TIF)

Figure S8 Forest plot of the overall risk of TB associated with the CD209 -339G/A promoter polymorphism. No significant association was found between the CD209 -339G/A polymorphism and TB risk in all genetic models. Error bars indicate 95% CI. Solid squares represent each study in the meta-analysis. Solid diamonds represent pooled OR.

(TIF)

Table S1 Gene frequencies of all the individual studies used for the meta-analysis.

(DOC)

Table S2 Quality assessment of included studies.

(DOC)

Table S3 Meta-regression analysis of CD209 -336A/G promoter polymorphism and risk of TB after omitting the studies.

(DOC)

Author Contributions

Analyzed the data: KC FW SRJ FKl. Wrote the paper: KC MC LLY. Conceived and designed the meta-analysis: MC KC LLY. Performed a systematic electronic search of databases and extracted the data: KC SLD MC. Screened titles and abstracts of all studies for relevancy: KC WPL MC. Assessed the quality of included studies: KC SLD MC.

References

1. Connel DW, Berry M, Cooke G, Kon OM (2011) Update on tuberculosis: TB in the early 21st century. Eur Respir Rev 20: 71–84.
2. Organization WH (2010) Global Tuberculosis Control 2010.WHO/HTM/TB/ 2010.7. Geneva, World Health Organization.
3. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, et al. (2003) The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Am J Respir Crit Care Med 168: 1808–1817.
4. Hill AV (2000) A study of genetic susceptibility to human infectious diseases. Annu Rev Genet 40: 469–486.
5. Jepson A, Fowler A, Banya W, Singh M, Bennett S, et al. (2001) Genetic regulation of acquired immune responses to antigens of Mycobacterium tuberculosis: a study of twins in West Africa. Infect Immun 69: 3999–3994.
6. Barreiro LB, Neyrolles O, Babb CL, Tailleux L, Quach H, et al. (2006) Genetic regulation of acquired immune responses to antigens of Mycobacterium tuberculosis: a study of twins in West Africa. Infect Immun 69: 3999–3994.
7. Tailleux L, Schwartz O, Herrmann JL, Pivert E, Jackson M, et al. (2005) DC-SIGN is the major Mycobacterium tuberculosis receptor on human dendritic cells. J Exp Med 197: 121–127.
8. Geijtenbeek TB, Van Vliet SJ, Koppel EA, Sanchez-Hernandez M, Vandenbroucke-Grauls CM, et al. (2005) Mycobacteria target DC-SIGN to suppress dendritic cell function. J Exp Med 197: 7–17.
9. Gao L, Tao Y, Zhang L, Jin Q (2010) Vitamin D receptor genetic polymorphisms and tuberculosis susceptibility: an updated meta-analysis. Hum Immunol 72: 1137–1142.
10. Li N, Yang Y, Zhou F, Zhang Y, Lu H, et al. (2011) SLCN1A1 (NRAMP1) polymorphisms and tuberculosis susceptibility: updated systematic review and meta-analysis. PLoS One 6: e15831.
11. Kobayashi K, Kobayashi T, Yanai H, Itoh LT, Hang NT, et al. (2011) Association of CD209 polymorphisms with tuberculosis in an Indonesian population. Hum Immunol 72: 741–745.
12. Selvaraj P, Agaraguru K, Swaminathan S, Harishankar M, Narender G (2009) CD209 gene polymorphisms in South Indian HIV and HIV-TB patients. Infect Genet Evol 9: 236–252.
13. Vannberg FO, Chapman SJ, Khor CC, Toshi K, Floyd S, et al. (2008) CD209 genetic polymorphism and tuberculosis disease. PLoS One 3: e1386.
14. Suidi K, Lamnayi H, Rueba E, Lahnou O, El Aouad R, et al. (2009) CD209 Promoter Single Nucleotide Polymorphism-336A/G and the Risk of Susceptibility to Tuberculosis Disease in the Moroccan Population. Int J Hum Genet 9: 239–243.
15. Olsen R, Weige J, Velez DR, Bissey C, Sodemann M, et al. (2007) DC-SIGN (CD209), pentraxin 3 and vitamin D receptor gene variants associate with susceptibility to Tuberculosis Disease in the Moroccan Population. Int J Hum Genet 9: 239–243.