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A meta-analysis of P2X7 gene-1513A/C polymorphism and pulmonary tuberculosis susceptibility

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ABSTRACT

Objective: A meta-analysis was performed to determine the association between P2X7-1513A/C polymorphism and pulmonary tuberculosis susceptibility.
Methods: Based on comprehensive searches of the MEDLINE, EMBASE and ISI Web of knowledge, China National Knowledge Infrastructure (CNKI) and Wanfang Database, we identified eligible studies about the association between P2X7-1513A/C polymorphism and pulmonary tuberculosis susceptibility.
Results: A total of 1916 cases and 2194 controls in 10 studies were pooled together for evaluation of the overall association between P2X7-1513A/C polymorphism and susceptibility of pulmonary tuberculosis. Allele model (A vs. C: $p = 0.15$; OR = 0.86, 95% CI = 0.69–1.06), homozygous model (AA vs. CC: $p = 0.22$; OR = 0.78, 95% CI = 0.53–1.16), and heterozygous model (AC vs. CC: $p = 0.23$; OR = 0.80, 95% CI = 0.56–1.15) did not show decreased risk of developing pulmonary tuberculosis. Similarly, dominant model (AA + AC vs. CC: $p = 0.19$; OR = 0.80, 95% CI = 0.56–1.12) and recessive model (AA vs. AC + CC: $p = 0.21$; OR = 0.85, 95% CI = 0.66–1.10) failed to show decreased risk of developing pulmonary tuberculosis. In Indians, allele model (A vs. C: $p = 0.0006$; OR = 0.69, 95% CI = 0.55–0.85), and recessive model (AA vs. AC + CC: $p = 0.0003$; OR = 0.62, 95% CI = 0.48–0.80) indicated significant association between P2X7-1513A/C polymorphism and susceptibility to pulmonary tuberculosis.
Conclusions: Our pooled data suggest a association between P2X7-1513A/C polymorphism and the prevalence of pulmonary tuberculosis among Indian populations.

1. Introduction

Tuberculosis (TB) is a significant global public health problem, especially in Asia and Africa [1]. It is caused by the bacillus *Mycobacterium tuberculosis*, with an estimated 8.6 million incident case of tuberculosis and 1.3 million deaths in 2012 [2].

Although one third of the population is infected by *Mycobacterium tuberculosis*, only 5–10% of those develop the clinical disease [3]. TB is likely influenced by the molecular (including genetic, genomic, epigenetic and others) background and environment of the patients [4–7]. Human P2X7 gene encoding the P2X7 receptor contains 13 exons and is localized on chromosome 12q24 [8]. Activation of P2X7 by adenosine triphosphate (ATP) causes an immediate opening of a cation selective channel, permitting the influx of Ca2+ and Na+ and the efflux of K+. In *M. tuberculosis* infection, activating the P2X7 receptor may prove beneficial in bacilli eradication by encouraging infected macrophages to die by apoptosis. Various single-nucleotide polymorphisms (SNPs) in P2X7 gene lead to the loss of receptor function, and the most common SNP is the 1513A/C [9].

However, the role of P2X7-1513A/C polymorphism in the development of pulmonary tuberculosis has been investigated with conflicting results. Previous studies have suggested an association between the P2X7-1513A/C polymorphism and pulmonary tuberculosis [10,11]. However, other studies have failed to confirm such an association [12–14]. The exact relationship between the P2X7-1513A/C polymorphism and susceptibility to pulmonary tuberculosis is not entirely established. Therefore, we performed a meta-analysis of all eligible studies to derive a more precise estimation of the association between the P2X7-1513A/C polymorphism and pulmonary tuberculosis.

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2. Methods

2.1. Publication search

The electronic databases MEDLINE, EMBASE and ISI Web of knowledge, China National Knowledge Infrastructure (CNKI) and Wanfang Database were searched for studies to include in the present meta-analysis, using the terms: "P2X7," "genotype," "tuberculosis," "TB," "pulmonary tuberculosis," "polymorphism," "A1513C," and "mutation." An upper date limit of June 30, 2014 was used, but no earlier date limit was applied. The search was conducted without any restrictions on language but focused on studies that had been conducted on human subjects. Only published studies with full text articles were included.

2.2. Inclusion and exclusion criteria

Included studies in this meta-analysis met the following criteria: (a) a human study on the association between P2X7-1513A/C polymorphism and the risks of pulmonary tuberculosis; (b) containing available genotype data in cases and controls for estimating an odds ratio (OR) and 95% confidence interval (CI); (c) genotype distributions of control population were consistent with Hardy–Weinberg equilibrium (HWE). The exclusion criteria were: (a) reviews, letters, editorial articles and case reports; (b) studies on the association between other gene polymorphisms and pulmonary tuberculosis risks. This study was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for meta-analysis of randomized clinical trials (http://prisma-statement.org/statement.htm).

2.3. Data extraction

The following information was extracted from each study: first author, year of publication, ethnicity of study population, and the number of TB cases and controls for the A1513C genotype. We did not define a minimum number of patients as a criterion for a study's inclusion in our meta-analysis.

2.4. Statistical analysis

The association between P2X7-1513A/C polymorphism and tuberculosis risks was estimated by calculating pooled ORs and 95% CI in the allele model (A vs. C), co-dominant model (AA vs. CC and AC vs. CC), dominant model (AA/AC vs. CC), and recessive model (AA vs. AC/CC). The effect of the association was indicated as an odds ratio (OR) with its corresponding 95% confidence interval (CI). Pooled OR was estimated using fixed and random effects models. Heterogeneity between studies was tested using the Q statistic. Heterogeneity was considered statistically significant if $P < 0.10$. Heterogeneity was quantified using the I^2 metric, which was independent of the number of studies in the meta-analysis ($I^2 < 25\%$ no heterogeneity; $I^2 = 25–50\%$ moderate heterogeneity; and $I^2 > 50\%$ large or extreme heterogeneity). An estimate of potential publication bias was performed using the funnel plot. All calculations were performed using ReviewManager 5.0 and STATA10.0 software.

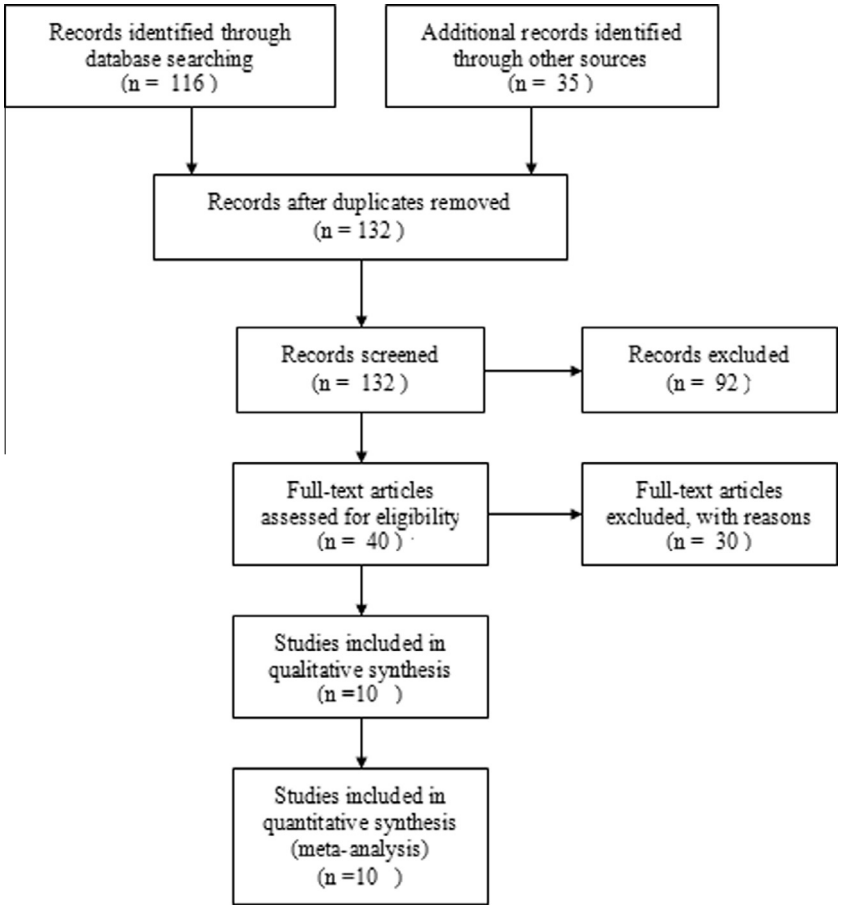

Fig. 1. Process of identification and selection of the relevant randomized, controlled trials according to the PRISMA statement.