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Association of SLC11A1 gene polymorphisms and Tuberculosis susceptibility among HIV-negative population: Evidence through systematic review and meta-analysis

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 December 2023 and was last updated on 30 December 2023.

INTRODUCTION

Review question / Objective Review Aim: Detecting whether there is association of the SLC11A1 gene polymorphisms with tuberculosis susceptibility within HIV-negative population. if there is, has the investigation on association changed over the decades?
Objectives : (1) To explore the association between SLC11A1 3'UTR, D543N, INT4 gene polymorphisms and the risk of TB developing (2) To dectect any correlations between SLC11A1 gene polymorphisms and TB susceptibility in the different ethnicity.

Condition being studied 1. Tuberculosis: TB is one of the major causes for global mortality, and it is resulted from Mycobacterium tuberculosis (MTB) .According to 'Global Tuberculosis Report 2022' from World Health Organization (WHO), approximately 10.6 million people worldwide fell ill with TB in 2021, which had a 4.5% rise from the 10.1 million records in 2020. One third of the population of the world is infected with the bacillus, but only 5% to 10% of them may progress to active TB disease. Some risk factors might increase the risk of the TB developing such as age, gender, environment, cellular immune system, although the mechanisms of TB suscepbility is unclear.
2. Solute Carrier Family 11-member 1 Protein (SLC11A1) : it was formerly named as Natural Resistance Associated Macrophage Protein (NRAMP1), and it is located on the human chromosome 2q35 region. This protein plays an essential role of immune system response to MTB as the protein where the SLC11A1 gene encodes is involved in macrophage activation and intracellular elimination of pathogens. It is known that macrophages are the main host cells of MTB in the body, as well as the main effector cells to eliminate MTB. Moreover, SLC11A1 gene affects the production of various cytokines and reactive oxygen species, which are the main components

for immune system response, thereby impacting on infectious disease control. For the past decades, the polymorphisms in the SLC11A1 gene have been learnt to cause differences in the expression or function of the protein, which ultimately have an impact on the body's ability to control MTB. Given evidence has supported that the polymorphisms of rs17235416 (3'UTR), rs17235409 (D543N), and rs3731865 (INT4) may be related to TB susceptibility. The 3'UTR polymorphism is characterized by a TGTG deletion (TGTG-) in the 3' untranslated region of the SLC11A1 gene. Furthermore, the polymorphisms of D543N represents the missense mutation site at codon 543, whereas the INT4 polymorphism indicates the change of G/C in intron 4 of the SLC11A1 gene. Since the past 2 decades, various investigations have been conducted to detect any association between SLC11A1 gene polymorphisms and the risk of TB. However, the findings of these reports are controversial due to variations in the sample sizes, screening criteria, genetic context, and other factors such as publication year which could influence on report standards.

METHODS

Search strategy The studies for the present meta-analysis were searched through three databases via PubMed, Embase and Medline. These databases were searched with the keywords "SLC11A1"、"NRAMP1"、"tuberculosis"、"gene" and "polymorphism". The reference lists of review articles were also manually searched for additional pertinent publications.

Participant or population Population: All participants in studies ensured as HIV-negative through a certain diagnostic criterian of laboratary or antibody test.

Intervention No intervention was performed as case-control studies were included in final our analysis only.

Comparator No comparative intervention was applicable.

Study designs to be included Case-control study.

Eligibility criteria The inclusion criteria: i) Case-control study assessing the association of SLC11A1 (NRAMP1) gene polymorphisms with TB risk; ii) All participants in studies ensured as the negative human immunodeficiency virus (HIV-negative) which could be examined by a certain diagnostic criterion of laboratory or antibody tests. iii) Providing sufficient data of alleles and genotypes for the case and control groups to calculate the odd ratio (OR) and its 95% confidence intervals (CIs).The exclusion criteria were: i) Studies of control groups with gene distributions that deviate from the Hardy-Weinberg equilibrium (HWE) [15]. ii) Low-quality Studies (i.e., scores of Newcastle-Ottawa Scale (NOS) [16] below 6). iii) review articles, abstracts, animal experiments, letters, editorials, case report, and non-English publications.

Information sources All eligible articles were acquired from the Pubmed, Medline and Embase electronic databases.

Main outcome(s) The primary outcome is the pooled effects with ORs and its 95% Confidence Interval (CI) for all genotype models (i.e., allele model, recessive model, dominant model, homozygous model) of the SLC11A1 gene polymorphisms (i.e., 3'UTR, D543N, INT4). The second outcome is the pooled effects based on ethnicity (i.e., Asian, African, South American, European) for the SLC11A1 3'UTR, D543N, INT4 gene polymorphisms.

Quality assessment / Risk of bias analysis We applied the Newcastle-Ottawa Scale (NOS) to appraise the quality for screening articles. The assessment was divided as 4 components which are sample selection(Scores 0-4), comparability between cases and controls (Scores 0-2), exposure (Scores0-3) respectively. Two categories in which all relevant articles had been stratified as were low quality (scores 0-5) and high quality (scores ≥6) respectively.

Strategy of data synthesis The strength of association between SLC11A1 gene polymorphisms and TB susceptibility was evaluated by calculating Pooled odds ratio (OR) and its 95% confidence interval (CI). Data were extracted to build different comparison genotype models for the Polymorphisms (i.e., 3'UTR, D543N, INT4) of SLC11A1 gene, which were as follow: i) 3'UTR: allele model (TGTG- vs TGTG+), dominant model (TGTG-/- + TGTG+/- vs TGTG+/+), recessive model (TGTG-/- vs TGTG+/- + TGTG+/+), homozygote model (TGTG-/- vs TGTG+/+); ii) D543N: allele model (A vs G), dominant model (AA+GA vs GG), recessive model (AA vs GA+GG), homozygote model (AA vs GG); iii) INT4: allele model (C vs G), dominant model (CC+GC vs GG), recessive model (CC vs GC+GG), homozygote model (CC vs GG). The heterogeneity among studies was measured based on Q statistic (a P-value with significance level at 0.05) and I^2

statistic which was used to quantify the inconsistence of between study results. Commonly, a fixed-effects model for pooled OR is used if Q statistic with P>0.05 and I^2<50%. Otherwise, a random-effects model would be used to combine the data if P≤0.05 and I^2≥50%.

Subgroup analysis Subgroup analysis was operated to evaluate the source of heterogeneity from the perspective of ethnicity. In addition, we also performed meta-regression analysis to explore the potential heterogeneity source based on publication year as well as ethnicity.

Sensitivity analysis Sensitivity analysis was performed to evaluate the impact of an individual article on pooled ORs by adopting the Leave-one-out method which means omitting a single article each time.

Language restriction English only.

Country(ies) involved Corporations under the multiple institutions or departments in China.

Keywords Tuberculosis; SLC11A1; NRAMP1; Susceptibility; Polymorphism; Meta-analysis.

Contributions of each author

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