

# Association of Three SNPs Loci of Kelch-Like-ECH-Associated Protein 1 (Human) with Tuberculosis in Chinese Han Population

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**Purpose:** Progression from latent tuberculosis infection (LTBI) to pulmonary TB (PTB) was associated with genetic polymorphisms, but there were limited genetic polymorphism data on LTBI and PTB. We aimed at examining the association of KEAP1 gene polymorphisms with PTB and LTBI.

**Patients and Methods:** PTB patients and close contacts of PTB patients were recruited from West China Hospital of Sichuan University. After obtaining the patient's consent, we draw 2–5mL of blood from the patient's peripheral vein. Tag-SNPs of KEAP1 were chosen according to previous studies. The genotyping was done by improved multiplex ligase detection reaction (iMLDR). We used logistic regression to assess the association of SNPs with LTBI/PTB, with sex and age as covariates.

**Results:** A total of 209 PTB patients, 201 LTBI, and 204 HCS were included in the present study. Three Tag-SNPs were included in this study. Significant association was found for KEAP1 rs1048290 between LTBI and HCS. Compared with the KEAP1 rs1048290 CC genotype, genotype GC had an 38% decreased risk for development LTBI ( $P = 0.043$ , OR = 0.62, 95% CI: 0.039–0.98). We also found that SNPs in KEAP1 were significantly related to PTB compared to LTBI. Compared with the rs11545829G allele, allele A had an 30% decreased risk for development PTB ( $P = 0.034$ , OR = 0.70, 95% CI: 0.51–0.97). We also found the rs11668429 polymorphism was related to PTB. Compared with TT, GT had a significantly increased risk of LTBI developing into PTB ( $P = 0.041$ , OR = 1.68, 95% CI: 1.02–2.77).

**Conclusion:** Our study suggested that KEAP1 polymorphisms were significantly related to susceptibility to PTB and LTBI subjects.

**Keywords:** latent tuberculosis infection, pulmonary tuberculosis, SNPs, association study

## Introduction

Tuberculosis (TB), caused by *Mycobacterium TB*, is a serious infectious disease with a mortality rate second only to COVID-19.<sup>1</sup> TB is a serious infectious disease worldwide, causes 1.3 million deaths every year. In 2020, 9.87 million TB patients were diagnosed worldwide, with an incidence rate of 1.27/100,000. In China, the estimated number of new TB cases in 2020 is 842,000 second only to India.<sup>1</sup> However, only 5–15% of infected people progress to TB.<sup>2</sup> It is unclear why only a small number of infected people progress to active disease.

Previous researches have shown that host genetics, specific strains of *Mycobacterium TB* (MTB) and environmental factors may explain why TB incidence varies across specific ethnic groups, geographic regions, genders and age groups.<sup>3,4</sup> It was suggested that different host gene polymorphisms were closely associated with TB.<sup>5</sup> Our previous basic research also confirmed the role of gene polymorphism in TB.<sup>6</sup> The study of various host genes associated with TB can improve the understanding of the pathogenesis TB and the development of prevention or treatment strategies.

MTB infection can lead to oxidative stress in the intracellular environment, which can hinder the progress of TB.<sup>7</sup> Nuclear factor erythroid 2-related factor 2 (Nrf2) protein is the main mediator of many anti-oxidant pathway genes

expression. Our previous studies have shown that Nrf2 is associated with TB.<sup>6</sup> NRF2 is commonly present in the cytoplasm and forms a complex with Kelch-like ECH-associated protein 1 (KEAP1), which leads to inhibition of Nrf2 activity temporarily.<sup>8</sup> KEAP1 is located on the short arm of chromosome 19. The C-terminal Kelch domain of Keap1 binds Nrf2 through the evolutionarily conserved kelch repeat sequence motif. As a sensor of ROS, KEAP1 plays an important role in protecting cells from oxidative damage.<sup>9</sup> Study has shown that Keap1 is involved in the repair process of MTB infection in macrophages.<sup>10</sup> Keap1 gene polymorphisms have been reported to be associated with multiple diseases.<sup>11–13</sup> However, the association between KEAP1 gene polymorphisms and TB is currently lacking.

Therefore, in this study, we hypothesized that KEAP1 genetic polymorphisms might play an important role in TB susceptibility. To test this hypothesis, 3 tag single-nucleotide polymorphisms (Tag-SNPs) in KEAP1 were analyzed to determine the role of Tag-SNPs in pulmonary TB (PTB) and latent TB infection (LTBI) in Chinese population.

## Materials and Methods

### Inclusion of Objects

A total of 209 PTB patients and 405 close contacts of PTB patients were recruited from West China Hospital of Sichuan University. Sample size calculations were from our previous studies.<sup>14</sup> All participants were genetically unrelated Chinese Han people, and they were over 16 years old. The diagnosis of PTB was through sputum culture and/or lung lavage by bronchoscopy and/or lung percutaneous biopsy. Patients with complications of diabetes, hepatitis B and/or C, chronic obstructive pulmonary disease, immune-mediated disease and HIV were excluded.

The close contacts of PTB in this study included accompanying persons, colleagues, spouses, and staff of the TB ward. We followed up for one year, excluding those who progressed to TB. Finally, based on interferon gamma release assay results, chest imaging, and symptoms, the 405 close contacts were finally divided into LTBI and healthy control (HCS) at enrolment and at one-year follow-up. Definition of close contacts is based on our previously published research.<sup>14</sup>

After obtaining the patient's consent, we draw 2–5 mL of blood from the patient's peripheral vein. The blood collection tubes contained ethylenediamine tetra acetic acid (EDTA) and the whole blood was subsequently stored in a –80°C freezer. DNA was extracted from whole blood using a genomic DNA purification kit (Axygen Scientific, Inc., Union City, CA, USA) according to the instructions. The DNA samples were stored at –80°C for further investigation. All participants signed an informed consent form. Parents or legal guardians of participants under the age of 18 signed the informed consent form. This study has passed ethical review. This study was approved by the ethical committee of the West China Hospital Institutional Review Board (ethics number: 2019;761). Our study complies with the Declaration of Helsinki.

Tag-SNPs (SNP with high linkage disequilibrium in a genome and can represent multiple SNPs) of KEAP1 were chosen according to previous studies.<sup>15</sup>

### Genotyping

The genotyping was done by improved multiplex ligation detection reaction (iMLDR), and the Shanghai Genesky Biotechnology company provides technical support. 5% of the samples were repeated for verification. The genotyping steps are briefly described below. The iMLDR process begins with multiplex PCR amplification of the mutant region. The amplification products are purified by exonuclease and shrimp alkalase. The purified product is used in a double ligation reaction. During the reaction, each locus contains a 5' terminal allele-specific probe and an immediately following 3' terminal site-specific probe. A specific ligating sequence is added to the 5' termina of each allele-specific primer and ligated to the specifically fluorescently labeled primer to achieve labeling. The tested allelic site ligation products are obtained in 2 ligation reactions, including the fluorescent labeling reaction and the allele-specific ligation reaction. The allele-specific ligation products of each locus are distinguished by labeling with different fluorescence, while the different loci are distinguished by 3' terminal probes and different length ligation sequences.

### Statistical Analysis

Continuous variables were calculated using the Student's *t*-test and displayed as means. Categorical variables and Weinberg equilibrium (HWE) were assessed using the  $\chi^2$ -test and displayed as counts and percentages. We used logistic

regression to assess the association of SNPs with LTBI/PTB, with sex and age as covariates. The relationship of haplotypes between each group was analyzed using online software (<http://analysis.bio-x.cn>). P values smaller than 0.05 were considered statistically significant. SPSS software (SPSS, Inc., Chicago, IL, USA) was used for all statistics analysis.

## Results

### Demographics of the Participants and results of Quality Control

A total of 209 PTB patients, 201 LTBI, and 204 HCS between the age group of 16 and 87 years were included in the present study. The male to female ratio of the three groups did not differ significantly; However, the mean age of the groups was observed to be significantly higher in PTB and HCS ( $P=0.027$ ) (Table 1).

A total of 3 Tag-SNPs were included in this study. According to the 5% samples repeat genotyping, the genotyping call rate of the three SNPs was 99.78%, and the accuracy rate was 100%. All 3 SNPs did not deviate from HWE in the control subjects. All SNPs information is shown in Table 2.

### Polymorphisms of the KEAP1 in the Three Groups

Three SNPs in the KEAP1 gene was evaluated for associations with LTBI or PTB. We compared genotypes of LTBI with PTB and HCS, respectively. The distribution of genotypes among different groups is shown in Table 3. Significant association was found for KEAP1 rs1048290 between LTBI and HCS. Compared with the KEAP1 rs1048290 CC genotype, genotype GC had an 38% decreased risk for development LTBI ( $P = 0.043$ , OR = 0.62, 95% CI: 0.039–0.98). We also found that SNPs in KEAP1 were significantly related to PTB compared to LTBI. Compared with the rs11545829G allele, allele A had an 30% decreased risk for development PTB ( $P = 0.034$ , OR = 0.70, 95% CI: 0.51–0.97). We also found the rs11668429 polymorphism was related to PTB. Compared with TT, GT had a significantly increased risk of LTBI developing into PTB ( $P = 0.041$ , OR = 1.68, 95% CI: 1.02–2.77). Finally, we compared the

**Table 1** Baseline Information of the Participants

|                    | PTB (n=209)       | LTBI (n=201)      | HCS (n=204)       | PTB vs LTBI<br>p value | LTBI vs HCS<br>p value |
|--------------------|-------------------|-------------------|-------------------|------------------------|------------------------|
| Male, N (%)        | 107 (0.51)        | 83 (0.48)         | 84 (0.46)         | 0.539                  | 0.750                  |
| Age, mean $\pm$ SD | 38.76 $\pm$ 16.97 | 49.09 $\pm$ 15.91 | 45.71 $\pm$ 14.90 | <0.001                 | 0.027                  |
| Lung rale          | 37                |                   |                   |                        |                        |
| Hemoptysis         | 31                |                   |                   |                        |                        |
| Cough              | 153               |                   |                   |                        |                        |
| Night Sweats       | 68                |                   |                   |                        |                        |
| Dyspnea            | 51                |                   |                   |                        |                        |
| Thoracalgia        | 31                |                   |                   |                        |                        |
| Fever              | 82                |                   |                   |                        |                        |

**Abbreviations:** SD, standard error; PTB, pulmonary tuberculosis; LTBI, latent tuberculosis infection; HCS, healthy controls.

**Table 2** Basic Information of All SNPs in Our Study

| SNPs       | Chromosome | Location   | Functional Consequence | MA   | MAF   | MA  | MAF   | HWE   |       |
|------------|------------|------------|------------------------|------|-------|-----|-------|-------|-------|
|            |            |            |                        | LTBI |       | HCS |       | LTBI  | HCS   |
| rs1048290  | 19         | 10,600,442 | Synon_exon4            | G    | 0.472 | G   | 0.48  | 0.197 | 0.363 |
| rs11545829 | 19         | 10,599,965 | Synon_exon5            | A    | 0.298 | A   | 0.311 | 0.347 | 0.298 |
| rs11668429 | 19         | 10,616,303 | /                      | T    | 0.49  | T   | 0.485 | 0.371 | 0.958 |

**Abbreviations:** SNP, single nucleotide polymorphism; LTBI, latent tuberculosis infection; HCS, healthy controls; MA, minor allele; MAF, minor allele frequency; HWE, Hardy Weinberg equilibrium.

**Table 3** Association Between KEAPI Genotypic/Allelic Frequencies and LTBI/PTB

| SNPs            |           | PTB (%), N=209 | LTBI (%), N=201 | HCS (%), N=204 | PTB vs LTBI    |                          | LTBI vs HCS    |                          | PTB vs HCS     |                          |
|-----------------|-----------|----------------|-----------------|----------------|----------------|--------------------------|----------------|--------------------------|----------------|--------------------------|
|                 |           |                |                 |                | P <sup>#</sup> | OR (95% CI) <sup>#</sup> | P <sup>#</sup> | OR (95% CI) <sup>#</sup> | P <sup>#</sup> | OR (95% CI) <sup>#</sup> |
| rs1048290(C>G)  | Genotype  |                |                 |                |                |                          |                |                          |                |                          |
|                 | CC        | 54(25.8)       | 62(31)          | 50(24.5)       |                |                          |                |                          |                |                          |
|                 | GC        | 46(22.0)       | 87(43.5)        | 112(54.9)      | 0.051          | 1.62(0.99–2.63)          | 0.043          | 0.62(0.39–0.98)          | 0.768          | 1.03(0.85–1.25)          |
|                 | GG        | 109(52.2)      | 51(25.5)        | 42(20.6)       | 0.383          | 1.30(0.72–2.35)          | 0.855          | 0.95(0.54–1.66)          | 0.795          | 0.98(0.84–1.14)          |
|                 | Alleles   |                |                 |                |                |                          |                |                          |                |                          |
|                 | C         | 217(51.9)      | 211(52.8)       | 212(52)        |                |                          |                |                          |                |                          |
| Genetic model   | G         | 201(48.1)      | 189(47.2)       | 196(48)        | 0.381          | 1.14(0.85–1.52)          | 0.727          | 0.95(0.72–1.26)          | 0.834          | 1.03(0.78–1.36)          |
|                 | Dominant  |                |                 |                | 0.081          | 1.50(0.95–2.37)          | 0.119          | 0.70(0.45–1.10)          | 0.984          | 0.99(0.63–1.58)          |
|                 | Recessive |                |                 |                | 0.689          | 0.91(0.56–1.47)          | 0.282          | 1.29(0.81–2.07)          | 0.702          | 1.10(0.68–1.78)          |
| rs11545829(G>A) | Genotype  |                |                 |                |                |                          |                |                          |                |                          |
|                 | GG        | 116(55.5)      | 103(51.5)       | 92(45.1)       |                |                          |                |                          |                |                          |
|                 | GA        | 80(38.3)       | 75(37.5)        | 97(47.5)       | 0.205          | 0.75(0.48–1.70)          | 0.092          | 0.70(0.46–1.06)          | 0.062          | 0.79(0.611–1.01)         |
|                 | AA        | 13(6.2)        | 22(11)          | 15(15)         | 0.050          | 0.46(0.21–0.99)          | 0.430          | 1.34(0.65–2.78)          | 0.017          | 0.84(0.73–0.97)          |
|                 | Alleles   |                |                 |                |                |                          |                |                          |                |                          |
|                 | G         | 312(74.6)      | 281(70.3)       | 281(68.9)      |                |                          |                |                          |                |                          |
| Genetic model   | A         | 106(25.4)      | 119(29.8)       | 127(31.1)      | 0.034          | 0.70(0.51–0.97)          | 0.685          | 0.94(0.69–1.27)          | 0.031          | 0.71(0.52–0.97)          |
|                 | Dominant  |                |                 |                | 0.084          | 0.69(0.46–1.05)          | 0.210          | 0.78(0.52–1.15)          | 0.013          | 0.60(0.40–0.90)          |
|                 | Recessive |                |                 |                | 0.088          | 0.52(0.25–1.10)          | 0.217          | 1.55(0.77–3.09)          | 0.604          | 0.81(0.37–1.79)          |
| rs11668429(G>T) | Genotypes |                |                 |                |                |                          |                |                          |                |                          |
|                 | TT        | 49(23.4)       | 53(26.5)        | 47(23)         |                |                          |                |                          |                |                          |
|                 | GT        | 113(54.1)      | 90(45)          | 104(51)        | 0.041          | 1.68(1.02–2.77)          | 0.395          | 0.82(0.51–1.31)          | 0.708          | 1.04(0.86–1.25)          |
|                 | GG        | 47(22.5)       | 57(28.5)        | 53(26)         | 0.319          | 1.36(0.74–2.50)          | 0.920          | 1.03(0.59–1.78)          | 0.272          | 1.01(0.94–1.27)          |
|                 | Alleles   |                |                 |                |                |                          |                |                          |                |                          |
|                 | T         | 211(50.5)      | 196(49)         | 198(48.5)      |                |                          |                |                          |                |                          |
| Genetic model   | G         | 207(49.5)      | 204(51)         | 210(51.5)      | 0.355          | 1.15(0.86–1.53)          | 0.927          | 1.01(0.77–1.34)          | 0.546          | 1.09(0.82–1.44)          |
|                 | Dominant  |                |                 |                | 0.066          | 1.56(0.97–2.50)          | 0.586          | 0.89(0.57–1.38)          | 0.286          | 1.29(0.81–2.06)          |
|                 | Recessive |                |                 |                | 0.728          | 0.92(0.57–1.48)          | 0.477          | 1.18(0.75–1.86)          | 0.946          | 0.98(0.62–1.57)          |

**Notes:** <sup>#</sup>Adjusted by age and sex status. Dominant model: relatively low frequency homozygous genotype combined with heterozygous vs relatively high frequency homozygous genotype. Recessive model: relatively low frequency homozygous genotype vs relatively high frequency homozygous genotype combined with heterozygous.

**Abbreviations:** SNPs, single nucleotide polymorphisms; CI, confidence interval; OR, odds ratio; PTB, pulmonary tuberculosis; LTBI, latent tuberculosis infection; HCS, healthy control subject.

differences in alleles and genotypes of KEAP1 between PTB and HCS. We found that rs11545829 AA ( $P = 0.017$ , OR = 0.84, 95% CI: 0.73–0.97) genotype and A ( $P = 0.031$ , OR = 0.71, 95% CI: 0.52–0.97) allele were associated with PTB.

## LD Patterns and Haplotype Analysis

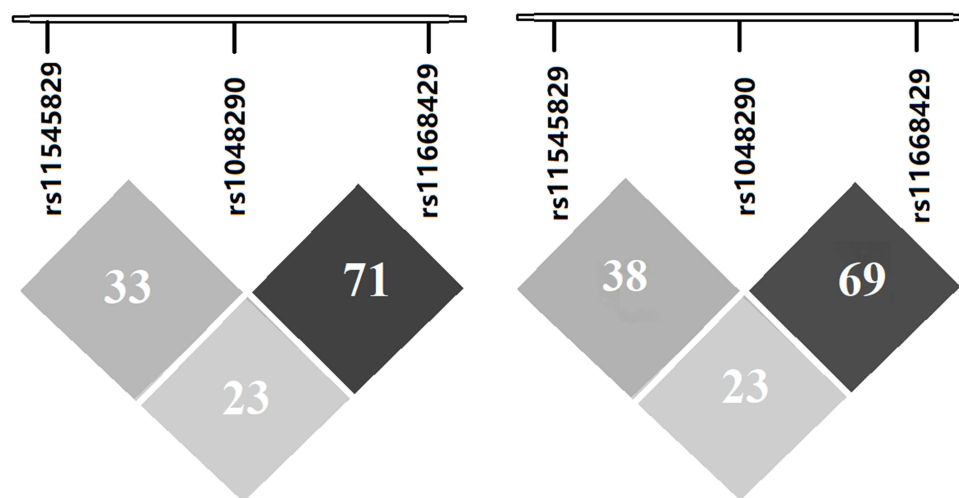
Pair-wise linkage disequilibrium ( $r^2$ ) analysis was conducted among the 3 SNPs of KEAP1. Haplotype blocks were built based on the  $r^2$  values ( $>0.7$ ) (Figure 1). rs11545829 and rs11668429 were found in strong LD in the PTB and LTBI groups. No haplotypes were significantly associated with PTB or LTBI (Table 4).

## Discussion

Most previous genetic studies on TB have used associations between TB and genetic polymorphisms, with controls including LTBI and uninfected individuals. However, few scholars have studied the association between LTBI and gene polymorphism. We designed three groups, including PTB, LTBI, and HCS, to identify candidate genes for PTB and LTBI to find genetic markers at different stages of TB development. This study is the first to find that KEAP1 gene polymorphisms were associated with PTB and LTBI.

The past studies based on immunocompromised population, twin comparisons, candidate genes, and the genome-wide association study show that host genetic factors affect the progress of TB.<sup>16–19</sup> Oxidative stress plays an important role in the susceptibility to TB according to literature.<sup>7</sup> Some key factors related to TB have been identified, but further study of the fine-tuning of oxidative stress is necessary so as to further understand the role of antioxidant balance in TB treatment. The oxidative stress signaling pathway involved in KEAP1 was associated with a variety of diseases, such as insulin resistance,<sup>20</sup> tumor,<sup>21</sup> and neuronal apoptosis.<sup>22</sup> Some studies have also shown that it is involved in respiratory diseases, like respiratory infections.<sup>23</sup> Meanwhile, MTB is able to reduce the KEAP1 gene expression level.<sup>24</sup> It has also been shown that rs1048290 and rs11545829 gene polymorphisms are associated with KEAP1 gene expression.<sup>25</sup> Therefore, based on the association of KEAP1 with multiple respiratory diseases and the effect of MTB on KEAP1 expression, we hypothesized that KEAP1 polymorphisms plays a role in PTB.

The association between KEAP1 polymorphisms and TB has not been studied, and this study was the first to explore the relationship between KEAP1 polymorphisms and PTB. Previously published studies have shown that KEAP1 gene polymorphisms were associated with the risk of various respiratory diseases. For example, KEAP1 rs11085735 and rs1048287 were associated with chronic obstructive pulmonary disease (COPD) and asthma.<sup>26</sup> They also found that KEAP1 rs9676881 was closely related to COPD. Ungvári et al demonstrated that KEAP1 polymorphisms are associated with asthma.<sup>26</sup> However, the association of KEAP1 gene polymorphisms with TB has not been clearly established.



**Figure 1** LD of KEAP1 gene polymorphisms in the both PTB vs LTBI (left) and PTB vs HCS (right) populations LD  $r^2$  values (range from 0 to 1) for all pairs of SNPs are presented as percentages. Shading from white to black indicates LD measured as  $r^2$  (range from 0 to 1).

**Table 4** Haplotypes of the KEAP1 Genes and Their Distributions in the Three Groups

| Haplotype     | LTBI vs PTB     |                    |       |                 | HCS vs LTBI     |                    |       |                 |
|---------------|-----------------|--------------------|-------|-----------------|-----------------|--------------------|-------|-----------------|
|               | Case (%), N=418 | Control (%), N=400 | P     | OR (95% CI)     | Case (%), N=400 | Control (%), N=408 | P     | OR (95% CI)     |
| ACG           | 96.86(23.2)     | 105.14(26.3)       | 0.306 | 0.85(0.62–1.2)  | 105.14(26.3)    | 110.69(27.1)       | 0.919 | 0.98(0.72–1.35) |
| ACT           | 9.14(2.2)       | 12.59(3.1)         | 0.394 | 0.69(0.29–1.63) | 12.59(3.1)      | 16.30(4)           | 0.553 | 0.80(0.38–1.69) |
| GCG           | 100.67(24.1)    | 85.24(21.3)        | 0.336 | 1.18(0.85–1.63) | 85.24(21.3)     | 83.51(20.5)        | 0.660 | 1.08(0.77–1.52) |
| GGG           | 9.47(2.3)       | 13.61(3.4)         | 0.328 | 0.66(0.28–1.53) | 13.61(3.4)      | 15.79(3.9)         | 0.764 | 0.89(0.43–1.87) |
| GGT           | 191.5(45.8)     | 174.13(43.5)       | 0.493 | 1.10(0.83–1.46) | 174.13(43.5)    | 180.21(44.2)       | 0.947 | 1.01(0.76–1.34) |
| Other pooled* | 10.34(2.5)      | 9.28(2.3)          |       |                 | 9.28(2.3)       | 1.49(0.4)          |       |                 |

**Note:** \*Total subjects which lowest frequency both in case and control less than 0.03.

**Abbreviations:** CI, confidence interval; OR, odds ratio; PTB, pulmonary tuberculosis; LTBI, latent tuberculosis infection; HCS, healthy control subject.

In a cohort of study in a Russian population, the rs1048290 polymorphism was reported to be associated with COPD, with a particularly significant association in the additive model. In their study, the C allele frequency was lower in the COPD group.<sup>12</sup> Another study showed that the rs1048290 gene polymorphism was a susceptibility factor for rectal cancer. Among them, the CC genotype and the C allele increase the risk of colorectal cancer.<sup>25</sup> Meanwhile, rs1048290 was associated with KEAP1 mRNA expression level, and KEAP1 expression level was relatively decreased in CC genotype. In our study, rs1048290 GC genotype compared with CC was a protective factor for LTBI compare with HCS. rs11545829 was in the fifth exon in KEAP1. There were few studies on the rs11545829 gene polymorphisms, and a study in Chinese population showed that the rs11545829 AA genotype has a protective effect on type 2 diabetes mellitus.<sup>27</sup> Another study showed that the rs1048290-rs11545829 GT haplotype was a low risk factor for colorectal cancer.<sup>25</sup> In the current study, we found that the rs11545829 A allele was a protective factor for PTB. There is only one study on the rs11668429 polymorphism so far.<sup>26</sup> Ungvári et al explored the association of rs11668429 with childhood asthma, but they found no association between them. In the present study, the rs11668429 polymorphism was associated with PTB, and GT genotype was a risk factor for PTB. More researches are needed to validate our results.

There are still some deficiencies in this study. First, the included SNPs loci lack functional validation. Therefore, the relationship between the KEAP1 gene and PTB is still unknown. Second, the results of this study have not been validated in an independent population and therefore may lead to type I errors. Finally, the association of clinical information and KEAP1 polymorphisms was not analyzed due to the incomplete collection of clinical data.

## Conclusion

In conclusion, our study suggested that KEAP1 polymorphisms were significantly related to susceptibility to PTB and LTBI subjects. This study may reflect the role of gene polymorphisms in different stages of TB progression, potential to help detect and treat TB early, but more studies are needed to verify the results.

## Data Sharing Statement

Please contact corresponding author for original data.

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## Disclosure

The authors report no conflicts of interest in this work.

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