

## Research Article

# Polymorphisms in the *ASAP1* and *SP110* Genes and Its Association with the Susceptibility to Pulmonary Tuberculosis in a Mongolian Population

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Tuberculosis (TB) remains one of the deadliest infectious diseases in the world. Previous genome-wide association studies suggested that single-nucleotide polymorphisms (SNPs) in some genes could indicate the susceptibility to TB in some populations. Herein, we studied the association of SNPs in the immunity-related genes, i.e., *ASAP1* and *SP110* genes with the susceptibility to TB in a Mongolian population in China. A case-control study was performed with 197 TB patients and 217 healthy controls. Six SNPs in *ASAP1* and six SNPs in *SP110* were selected for genotyping test by second-generation sequencing technique. A SNP in *SP110* gene (rs722555) was identified to be associated with susceptibility to TB in the Mongolian population ( $p < 0.05$ ). The T allele of rs722555 in *SP110* gene was associated with a 36% increase of risk at TB (OR 1.36, 95% CI 1.03–1.81), and the CT+TT genotype of rs722555 was associated with a 74% increase of risk at TB (OR 1.74, 95% CI 1.16–2.60) in the dominant genetic model. None of SNPs in *ASAP1* gene tested in this study were significantly associated with TB susceptibility, while some individuals with SNPs (rs10956514, rs4733781, rs2033059, rs12680942, rs1017281, rs1469288, and rs17285138) in the *ASAP1* gene tended to have a reduced risk at TB. In conclusion, this study suggested that the rs722555 SNP in *SP110* gene might be a risk factor for TB in a Mongolian population.

## 1. Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* bacillus (Mtb), is one of the oldest infectious diseases. According to the newest data from World Health Organization (WHO), around 9.9 million (range: 9–11 million) people became newly sick with TB in 2021, 86% of which (about 7–8 million) resided in 30 high-burden countries [1]. However, only 4–6 million were officially diagnosed. Between 1 and 3 million people are estimated to die from TB each year [1]. Previous epidemiological studies have reported that almost 25% of the population are latently infected with Mtb, but only 5%

of these individuals might develop into the active disease during their lifetime [2], indicating that TB is a multifactorial disease and its development is affected by many factors [3, 4].

Genetic factors, in addition to malnutrition, human immunodeficiency, virus infection, and environmental factors, have been documented to influence the risk of TB [3, 4]. For genetic factors, a large number of studies have investigated the association between genetic polymorphisms and the risk of TB, in which the genes encoding Arf-GAP with SH3 domain, ankyrin repeat, and PH domain 1 (*ASAP1*) and Speckled 110 (*SP110*) are the most striking [3–14]. *ASAP1* is also known as *AMAPI* or *DDEF1*. It encodes *ASAP1*, a member of ADP-ribosylation

factor GTPase-activating proteins (Arf-GAPs), which is a multifunctional scaffold protein [9, 15]. The expression of *ASAPI* regulates the cell motility and invasion and also affects the progression and metastasis of tumor cells including ovary cancer [16], prostate cancer [17], and breast cancer [18, 19]. To screen the genes that exert the largest impact on susceptibility to a multifactorial disease at a population level [20], the genome-wide association studies (GWAS) [21] have identified *ASAPI* as a novel gene associated with the susceptibility to TB. Two SNPs (rs4733781 and rs10956514) in the *ASAPI* gene are significantly associated with susceptibility to TB in a Russian population [5]. Moreover, *ASAPI* expression is markedly decreased in Mtb-infected dendritic cells, which may result in impaired dendritic cell migration and indicate a potential mechanism of *ASAPI* polymorphisms to predispose individuals to TB.

*SP110* gene could also affect the susceptibility to TB. *SP110* is the human homolog of the intracellular pathogen resistance-1 (*Ipr1*) gene in mice. *Ipr1* is located on chromosome 1 at the supersusceptibility to tuberculosis 1 (*sst1*) locus and associated with resistance to pulmonary TB in a murine model [7]. *SP110*-encoded protein is a component of nuclear bodies [4]. This protein can mediate interactions between hosts and pathogens by participating in the activation of the response to intracellular pathogens in macrophages at the transcriptional level. In 2006, Tosh et al. first reported that *SP110* was related to TB in a West African population using a family-based experimental design. Subsequently, more studies with various study designs were conducted and demonstrated the associations of polymorphisms in *SP110* with LTBI susceptibility [4, 5, 7, 8, 10–13].

To understand if the population diversity and genetic heredity could influence the association of SNPs in *ASAPI* and *SP110* with the susceptibility of TB, we selected a set of SNPs and focused on genetic polymorphisms relating to pulmonary TB in a minority Mongolian population in China. The clinical relevance of SNPs in these two genes to the development of pulmonary TB was explored.

## 2. Materials and Methods

**2.1. Study Population and Sample Collection.** A total of 414 participants were involved in this study, consisting of 197 active TB patients as the cases and 217 healthy volunteers as the controls. The cases were diagnosed with TB for the first time and recruited from the Second People's Hospital of Hulunbuir city, Heilongjiang province, China, where the Mongolian people lived for several generations. Pulmonary tuberculosis (PTB) patients were diagnosed based on the clinical information including positive Mtb sputum culture, sputum smear analysis with acid-fast bacillus microscopy, clinical symptoms, and X-ray or CT scanning and histological pathology. The volunteers were healthy blood donors who had negative results for the TB-interferon gamma release assay (TB-IGRA), no history of TB infection, and were normal in physical examinations. In this study, all individuals were from the minority Mongolian population. The demographic and primary clinical data were obtained by interviewing the participants and/or retrieved from their hospital medical records with permission.

This research involving human subjects complied with all relevant national regulations and institutional policies and was in accordance with the tenets of the Helsinki Declaration (revised in 2013). This study was approved by the Research Ethics Committee of Baotou Medical College, Inner Mongolia University of Science and Technology (no. 2018002).

**2.2. Selection of SNPs and Genotyping.** Genetic variation data for candidate SNPs in *ASAPI* and *SP110* were obtained via a thorough scan of the dbSNP database (<https://www.ncbi.nlm.nih.gov/snp/>). The SNPs within potentially functional regions (i.e., exon, promoter, or untranslated regions) were selected. In addition, rs4733781 and rs10956514 were included in our study because of their potential roles in conferring predisposition to TB. Finally, six SNPs in *SP110* and six SNPs in *ASAPI* were chosen for subsequent genotyping. Blood samples were collected from the cases and controls in EDTA-coated tubes and stored at  $-80^{\circ}\text{C}$ . Genomic DNA was isolated from a  $200\ \mu\text{L}$  aliquot of each blood sample using TIANamp Genomic DNA Kits (TIANGEN, Beijing, China). DNA degradation and contamination were monitored using 1% agarose gels, and DNA purity was checked using a NanoPhotometer<sup>®</sup> spectrophotometer (Implen, Westlake Village, CA, USA). The genotypes of polymorphic loci were detected using next-generation sequencing with the primers shown in Table S1. The SNP genotyping in the validation cohort was conducted by Sangon Biotech Co., Ltd. (Shanghai, China). High-throughput sequencing (Illumina Hi-seq 2000, San Diego, CA, USA) was performed for SNP genotyping of the candidate SNPs in *ASAPI* and *SP110*.

**2.3. Statistical Analysis.** EpiData 3.1 (EpiData Association, Odense, Denmark) and SPSS 20.0 (SPSS Inc., Chicago, IL, USA) software packages were used for statistical analysis. Categorical and continuous variables were compared using the  $\chi^2$  test. Testing of the Hardy-Weinberg equilibrium (HWE) was used to determine whether the two groups were in genetic equilibrium. Logistic regression analysis was conducted to test the association between SNPs and TB. The distribution of allele frequencies, genotypes, the genetic dominant model, and the recessive model for each polymorphism were compared. Comparisons of frequencies between groups were presented as odds ratios (ORs) and 95% confidence intervals (CIs). We also used unconditional logistic regression analyses to calculate ORs and 95% CIs adjusted for sex and education level. Moreover, linkage disequilibrium (LD) analysis was conducted using Haploview 4.2 (Broad Institute, Cambridge, MA, USA). Statistical significance was set at the level of  $p < 0.05$ .

## 3. Results

**3.1. Participant Characteristics.** The demographic characteristics of all case and control participants are presented in Table 1. In total, 197 pulmonary TB patients (135 males and 62 females; mean age:  $44.36 \pm 15.62$  years) and 217 healthy controls (114 males and 103 females; mean age:  $44.95 \pm 15.73$  years) were included in this study. There were significant differences between the two groups in sex and education

TABLE 1: Sociodemographic characterization among 197 tuberculosis patients and 217 healthy controls from Mongolian population.

| Characteristics                     | Total <sup>a</sup> , <i>n</i> (%) | TB patients, <i>n</i> (%) | Healthy controls, <i>n</i> (%) | <i>p</i> value <sup>c</sup> |
|-------------------------------------|-----------------------------------|---------------------------|--------------------------------|-----------------------------|
| Age, mean ± SD (years) <sup>b</sup> | 44.68 ± 15.67                     | 44.36 ± 15.62             | 44.95 ± 15.73                  | 0.156                       |
| <i>Sex</i>                          |                                   |                           |                                |                             |
| Male                                | 240 (59.3)                        | 126 (67.0)                | 114 (52.5)                     | 0.003                       |
| Female                              | 165 (40.7)                        | 62 (33.0)                 | 103 (47.5)                     |                             |
| <i>Smoking</i>                      |                                   |                           |                                |                             |
| Yes                                 | 116 (29.3)                        | 60 (33.5)                 | 56 (25.8)                      | 0.097                       |
| No                                  | 280 (70.7)                        | 119 (66.5)                | 161 (74.2)                     |                             |
| <i>Drinking</i>                     |                                   |                           |                                |                             |
| Yes                                 | 141 (35.6)                        | 75 (41.9)                 | 66 (30.4)                      | 0.020                       |
| No                                  | 255 (64.4)                        | 104 (58.1)                | 151 (69.6)                     |                             |
| <i>Education level</i>              |                                   |                           |                                |                             |
| Primary school or lower             | 104 (26.2)                        | 60 (33.3)                 | 44 (20.3)                      | 0.004                       |
| Junior school                       | 195 (49.1)                        | 74 (41.1)                 | 121 (55.7)                     |                             |
| Senior high school and higher       | 98 (24.7)                         | 46 (25.6)                 | 52 (24.0)                      |                             |
| <i>Marital status</i>               |                                   |                           |                                |                             |
| Married                             | 313 (79.0)                        | 145 (79.7)                | 168 (78.5)                     | 0.805                       |
| Unmarried/divorced/widowed          | 83 (21.0)                         | 37 (20.3)                 | 46 (21.5)                      |                             |

<sup>a</sup>Tuberculosis patients; <sup>b</sup>healthy controls.

level ( $p = 0.003$  and  $0.005$ , respectively), but not for age, habitats (smoking and drinking), or marital status ( $p = 0.156$ ,  $0.093$ ,  $0.063$ , and  $0.192$ , respectively).

**3.2. HWE Test.** In this study, six SNPs in *SP110* and six SNPs in *ASAP1* were selected for the HWE test.

The genotypic distributions of rs10956514, rs4733781, rs2033059, rs12680942, rs1017281, rs1469288, and rs17285138 in *ASAP1* were in accordance with the HWE among the study participants (Table S2).

The genotypic distributions of rs113579, rs9061, rs722555, rs3948464, rs11679983, rs1365576, and rs11556887 in *SP110* were also in accordance with the HWE among the pulmonary TB patients and healthy controls (Table S2).

**3.3. Single SNP Associations.** The genotypes and distributions of alleles are summarized in Tables 2 and 3. The impact of SNPs on susceptibility to TB was investigated using a case-control experimental design. All of the investigated SNPs were in agreement with the HWE in the study population. Among 12 SNPs that were successfully genotyped in *ASAP1* and *SP110*, only one SNP in the *SP110* gene (rs722555) was significantly associated with susceptibility to TB in the Mongolian population (Table 2).

The genotypes and allele frequencies of the six SNPs in *ASAP1* are summarized in Tables 2 and 3. Logistic regression analysis did not detect a significant association between *ASAP1* rs10956514 and the risk of TB ( $p = 0.889$ ; allele OR = 1.07, 95% CI: 0.81–1.40). Similarly, no significant associations were observed for rs11774633, rs4733781, rs2033059, rs12680942, rs1469288, or rs17285138 in *ASAP1* ( $p > 0.05$ ), whereas a trend of decreased risk of TB was observed for all of these variants.

For the *SP110* gene, we found an association between one SNP rs722555 and TB susceptibility. The T allele in rs722555 was significantly higher in TB patients compared with healthy individuals (OR 1.36, 95% CI 1.03–1.81,  $p = 0.03$ ). Moreover, the CT genotype in rs722555 conferred a significantly increased risk, by 78%, compared with the wild-type CC genotype (OR 1.78, 95% CI 1.16–2.72,  $p = 0.008$ ). Although the TT genotype in rs722555 appeared to indicate an increased risk of TB, this result was not statistically significant (OR 1.61, 95% CI 0.88–2.95,  $p = 0.121$ ), which might be due to the limited sample size. There were no significant differences in distribution between the other alleles or genotypes and TB risk.

**3.4. Associations between the Risk of TB and Genetic Models of SNPs.** Additive, dominant, and recessive models of *ASAP1* and *SP110* gene polymorphisms were built to find the optimal genetic model.

As shown in Table 4, the rs722555 site in *SP110* was detected to confer an increased risk of TB in the dominant model (CT+TT vs. CC: OR, 1.74; 95% CI: 1.16–2.60;  $p = 0.007$ ). We also found similar patterns in the recessive (CT+TT vs. CC: OR 1.16, 95% CI 0.67–2.02,  $p = 0.588$ ) and additive (CT+TT vs. CC: OR 1.61, 95% CI 0.88–2.95,  $p = 0.121$ ) models, albeit with no statistical significance. However, we did not observe any significant associations for the other selected SNPs in *ASAP1* and *SP110* in these models.

**3.5. LD and Haplotype Analyses.** The LD was estimated by calculating the pairwise  $r^2$  coefficient. Figure 1 shows the LD patterns for the cluster of six SNPs in *ASAP1* and six SNPs in *SP110* genotyped in the Mongolian population in China.

The LD patterns of SNPs in *ASAP1* are shown in Figure 1. Using a pairwise  $r^2 > 0.8$  as the threshold for strong LD, the six

TABLE 2: Distribution frequency of SNPs of *ASAP1* and *SP110* gene in TB and healthy population.

| Gene         | SNP        | Genotypes  | TB ( <i>n</i> = 197) | Control ( <i>n</i> = 217) | $\chi^2$ | <i>p</i> value   | Univariate logistic model |                |
|--------------|------------|------------|----------------------|---------------------------|----------|------------------|---------------------------|----------------|
|              |            |            |                      |                           |          |                  | OR (95 CI)                | <i>p</i> value |
| <i>ASAP1</i> | rs10956514 | GG         | 59 (29.9)            | 61 (28.1)                 | 0.234    | 0.889            | <b>1.00 (ref)</b>         |                |
|              |            | GA         | 107 (54.3)           | 119 (54.8)                |          |                  | 0.93 (0.60, 1.45)         | 0.747          |
|              |            | AA         | 31 (15.7)            | 37 (17.1)                 |          |                  | 0.87 (0.48, 1.57)         | 0.637          |
|              | rs4733781  | CC         | 61 (31.0)            | 61 (29.5)                 | 0.432    | 0.806            | <b>1.00 (ref)</b>         |                |
|              |            | CA         | 104 (52.8)           | 118 (55.8)                |          |                  | 0.88 (0.57, 1.37)         | 0.576          |
|              |            | AA         | 61 (31.0)            | 61 (29.5)                 |          |                  | 0.84 (0.47, 1.52)         | 0.568          |
|              | rs2033059  | TT         | 61 (31.0)            | 61 (28.1)                 | 0.432    | 0.806            | <b>1.0 (ref)</b>          |                |
|              |            | TC         | 104 (52.8)           | 118 (54.4)                |          |                  | 0.88 (0.57, 1.37)         | 0.576          |
|              |            | CC         | 32 (16.2)            | 38 (17.5)                 |          |                  | 0.84 (0.47, 1.52)         | 0.568          |
|              | rs12680942 | GG         | 62 (31.5)            | 61 (28.1)                 | 0.636    | 0.727            | <b>1.0 (ref)</b>          |                |
|              |            | GA         | 104 (52.8)           | 118 (54.4)                |          |                  | 0.87 (0.56, 1.35)         | 0.526          |
|              |            | AA         | 31 (15.7)            | 38 (17.5)                 |          |                  | 0.8 (0.44, 1.45)          | 0.466          |
|              | rs1469288  | AA         | 60 (30.5)            | 60 (27.6)                 | 0.496    | 0.780            | <b>1.0 (ref)</b>          |                |
|              |            | AG         | 106 (53.8)           | 119 (54.9)                |          |                  | 0.89 (0.57, 1.39)         | 0.609          |
|              |            | GG         | 31 (15.7)            | 38 (17.5)                 |          |                  | 0.82 (0.45, 1.48)         | 0.502          |
|              | rs17285138 | AA         | 62 (31.5)            | 61 (28.1)                 | 0.636    | 0.727            | <b>1.0 (ref)</b>          |                |
|              |            | AT         | 104 (52.8)           | 118 (54.4)                |          |                  | 0.87 (0.56, 1.35)         | 0.526          |
|              |            | TT         | 31 (15.7)            | 38 (17.5)                 |          |                  | 0.8 (0.44, 1.45)          | 0.466          |
| <i>SP110</i> | rs1135791  | AA         | 137 (69.5)           | 156 (71.9)                | 1.696    | 0.428            | <b>1.0 (ref)</b>          |                |
|              |            | AG         | 55 (27.9)            | 59 (27.2)                 |          |                  | 1.06 (0.69, 1.64)         | 0.787          |
|              |            | GG         | 5 (2.5)              | 2 (0.9)                   |          |                  | 2.85 (0.54, 14.91)        | 0.216          |
|              | rs9061     | CC         | 135 (68.5)           | 139 (64.1)                | 1.002    | 0.606            | <b>1.0 (ref)</b>          |                |
|              |            | CT         | 58 (29.4)            | 72 (33.2)                 |          |                  | 0.83 (0.55, 1.26)         | 0.382          |
|              |            | TT         | 4 (2.0)              | 6 (2.8)                   |          |                  | 0.69 (0.19, 2.49)         | 0.567          |
|              | rs722555   | CC         | 61 (31)              | 95 (43.8)                 | 7.327    | 0.026            | <b>1.0 (ref)</b>          |                |
|              |            | CT         | 106 (53.8)           | 93 (42.9)                 |          |                  | <b>1.78 (1.16, 2.72)</b>  | <b>0.008</b>   |
|              |            | TT         | 30 (15.2)            | 29 (13.4)                 |          |                  | 1.61 (0.88, 2.95)         | 0.121          |
|              | rs3948464  | GG         | 197 (100)            | 213 (98.2)                | 3.667    | 0.074            | NA                        |                |
|              |            | GA         | 0                    | 4 (1.8)                   |          |                  | <b>1.0 (ref)</b>          |                |
|              |            | AA         | 0                    | 0                         |          |                  | 0                         | 0              |
|              | rs11679983 | GG         | 181 (91.9)           | 195 (89.9)                | 0.504    | 0.296            | <b>1.0 (ref)</b>          |                |
|              |            | GA         | 16 (8.1)             | 22 (10.1)                 |          |                  | 0.78 (0.4, 1.54)          | 0.479          |
|              |            | AA         | 0                    | 0                         |          |                  | NA                        |                |
|              | rs1365776  | TT         | 150 (76.1)           | 167 (77)                  | 0.985    | 0.619            | <b>1.0 (ref)</b>          |                |
|              |            | TC         | 46 (23.4)            | 47 (21.7)                 |          |                  | 2.94 (0.29, 29.27)        | 0.359          |
|              |            | CC         | 1 (0.5)              | 3 (1.4)                   |          |                  | 2.69 (0.28, 26.18)        | 0.393          |
| rs11556887   | GG         | 166 (84.3) | 188 (86.6)           | 0.469                     | 0.293    | <b>1.0 (ref)</b> |                           |                |
|              | GA         | 31 (15.7)  | 29 (13.4)            |                           |          | 1.21 (0.7, 2.09) | 0.494                     |                |
|              | AA         | 0          | 0                    |                           |          | NA               |                           |                |

Data are presented as *n* (%). SNP: single-nucleotide polymorphism; TB: tuberculosis; OR: odds ratio; CI: confidence intervals; ref: reference; NA: not applicable. *p* values below 0.05 are highlighted in bold.

polymorphisms of *ASAP1* (rs1469288, rs10956514, rs12680942, rs2033059, rs4733781, and rs17285138) were in strong LD with one another, which suggests a strong recombination block. Haplotype analysis identified two haplotypes in this recombination block: AGGTCA and GAACAT (Table 5). When comparing the frequencies between cases and controls, there was no significant LD observed for these haplotypes (Table 5).

For *SP110*, we discovered two haplotype blocks (Figure 1), including four SNPs (block 1: rs722555 and rs1135791; block 2: rs9061 and rs11556887). As shown in Table 5, there were three haplotypes (CA, TA, and TG) in block 1, and three haplotypes (CG, TG, and TA) in block 2. However, when comparing the frequencies between cases and controls, there was no significant LD for these haplotypes.

TABLE 3: The distribution of alleles of SNPs in the *ASAP1* and *SP110* genes in TB and healthy control population.

| Gene         | SNP        | Alleles    | TB, N (%)  | Control, N (%)   | Univariate logistic model |                |
|--------------|------------|------------|------------|------------------|---------------------------|----------------|
|              |            |            |            |                  | OR (95 CI)                | <i>p</i> value |
| <i>ASAP1</i> | rs10956514 | G          | 225 (57.1) | 241 (55.5)       | 1.0 (ref)                 | 0.648          |
|              |            | A          | 169 (42.9) | 193 (44.5)       | 0.94 (0.71, 1.23)         |                |
|              | rs4733781  | C          | 226 (57.4) | 240 (55.3)       | 1.0 (ref)                 | 0.551          |
|              |            | A          | 168 (42.6) | 194 (44.7)       | 0.92 (0.7, 1.21)          |                |
|              | rs2033059  | T          | 226 (57.4) | 240 (55.3)       | 1.0 (ref)                 | 0.551          |
|              |            | C          | 168 (42.6) | 194 (44.7)       | 0.92 (0.7, 1.21)          |                |
|              | rs12680942 | G          | 228 (57.9) | 240 (55.3)       | 1.0 (ref)                 | 0.457          |
|              |            | A          | 166 (42.1) | 194 (44.7)       | 0.9 (0.68, 1.19)          |                |
|              | rs1469288  | A          | 226 (57.4) | 239 (55.1)       | 1.0 (ref)                 | 0.507          |
|              |            | G          | 168 (42.6) | 195 (44.9)       | 0.91 (0.69, 1.2)          |                |
| rs17285138   | A          | 228 (57.9) | 240 (55.3) | 1.0 (ref)        | 0.457                     |                |
|              | T          | 166 (42.1) | 194 (44.7) | 0.9 (0.68, 1.19) |                           |                |
| <i>SP110</i> | rs1135791  | A          | 329 (83.5) | 371 (85.5)       | 1.0 (ref)                 | 0.431          |
|              |            | G          | 65 (16.5)  | 63 (14.5)        | 1.16 (0.8, 1.7)           |                |
|              | rs9061     | C          | 328 (83.2) | 350 (80.6)       | 1.0 (ref)                 | 0.332          |
|              |            | T          | 66 (16.8)  | 84 (19.4)        | 0.84 (0.59, 1.2)          |                |
|              | rs722555   | C          | 228 (57.9) | 283 (65.2)       | 1.0 (ref)                 | <b>0.030</b>   |
|              |            | T          | 166 (42.1) | 151 (34.8)       | <b>1.36 (1.03, 1.81)</b>  |                |
|              | rs3948464  | G          | 394 (100)  | 430 (99.1)       | 1.0 (ref)                 | NA             |
|              |            | A          | 0 (0)      | 4 (0.9)          | NA                        |                |
|              | rs11679983 | G          | 378 (95.9) | 412 (94.9)       | 1.0 (ref)                 | 0.490          |
|              |            | A          | 16 (4.1)   | 22 (5.1)         | 0.79 (0.41, 1.53)         |                |
|              | rs1365776  | T          | 346 (87.8) | 381 (87.8)       | 1.0 (ref)                 | 0.990          |
|              |            | C          | 48 (12.2)  | 53 (12.2)        | 1 (0.66, 1.51)            |                |
|              | rs11556887 | G          | 363 (92.1) | 405 (93.3)       | 1.0 (ref)                 | 0.511          |
| A            |            | 31 (7.9)   | 29 (6.7)   | 1.19 (0.7, 2.02) |                           |                |

Data are presented as *n* (%). SNP: single-nucleotide polymorphism; TB: tuberculosis; OR: odds ratio; CI: confidence intervals; NA: not applicable. *p* values below 0.05 are highlighted in bold.

#### 4. Discussion

The association between *ASAP1* or *SP110* and susceptibility to TB has been investigated in various populations. The results from these studies are generally controversial [4, 6, 10–13, 22]. To further clarify the inconsistency, our study focused on a Mongolian population in China and revealed that one SNP in *SP110* (rs722555) rather than in *ASAP1* was associated with the risk of TB. Individuals with the CT and TT genotypes of rs722555 in *SP110* have an increased risk of pulmonary TB.

*ASAP1* gene encoding ASAP1 protein is a key regulator of membrane trafficking and the actin cytoskeleton [9, 23]; therefore, it plays important roles in many cellular functions including adhesion and motility, bone resorption, neurite outgrowth, and pathogen internalization by immune cells [15, 24]. The SNPs in *ASAP1* had been shown to be significantly associated with TB in a Russian population [5], or Han Chinese population [9], or Xinjiang Muslim population [14]. However, these SNPs seem not to be associated with pulmonary TB in a Mongolian population in our study, suggesting the potential effects of genetic diversity of human population.

In our study, the rs722555 SNP in the *SP110* gene was particularly notable, in which the CT genotype increased the risk of TB infection, with a 78% increase compared with the CC genotype (Table 2). Furthermore, individuals with T alleles were observed to be more susceptible to pulmonary TB than individuals with C alleles. These results are consistent with a previous study showing that rs722555 variation was associated with TB susceptibility in a Chongqing Han population [2], but in contrast to the results of studies which performed with a southern Chinese population [3] or the TB patients in Russia, which demonstrated that rs722555 was not significantly associated with TB (OR = 1.03, *p* = 0.46) [4]. The reasons for these discrepancies have yet to be investigated. There are likely individual differences in TB susceptibility between different populations. In the dominant model, similar trends were detected in regard to the increased risk of TB. We also found similar trends in the recessive model and the additive model, albeit with no statistical significance. Results of the LD analysis revealed that rs722555/rs1135791 and rs9061/rs11556887 were genetically linked.

*SP110*-encoded protein can inhibit the growth of intracellular pathogens by switching a cell death pathway from

TABLE 4: Analysis of the inheritance models of *ASAP1* and *SP110* polymorphism associated with tuberculosis.

| Gene         | SNP        | Model     | Genotype   | TB, N (%)  | Control, N (%)           | Univariate logistic model<br>OR (95 CI) | <i>p</i> value |
|--------------|------------|-----------|------------|------------|--------------------------|---|----------------|
| <i>ASAP1</i> | rs10956514 | Dominant  | G/G        | 59 (29.9)  | 61 (28.1)                | 0.91 (0.60, 1.40)                       | 0.681          |
|              |            |           | G/A-A/A    | 138 (70.1) | 156 (71.9)               |   |                |
|              |            | Recessive | G/G-G/A    | 166 (84.3) | 180 (82.9)               |   |                |
|              |            |           | A/A        | 31 (15.7)  | 37 (17.1)                |   |                |
|              |            | Additive  | G/G        | 59 (29.9)  | 61 (28.1)                |   |                |
|              |            |           | A/A        | 31 (15.7)  | 37 (17.1)                |   |                |
|              | rs4733781  | Dominant  | C/C        | 61 (31.0)  | 61 (28.1)                | 0.87 (0.57, 1.33)                       | 0.525          |
|              |            |           | A/C-A/A    | 136 (69.0) | 156 (71.9)               |   |                |
|              |            | Recessive | C/C-A/C    | 165 (83.8) | 179 (82.5)               |   |                |
|              |            |           | A/A        | 32 (16.2)  | 38 (17.5)                |   |                |
|              |            | Additive  | C/C        | 61 (31.0)  | 61 (28.1)                |   |                |
|              |            |           | A/A        | 32 (16.2)  | 38 (17.5)                |   |                |
|              | rs2033059  | Dominant  | T/T        | 61 (31.0)  | 61 (28.1)                | 0.87 (0.57, 1.33)                       | 0.525          |
|              |            |           | C/T-C/C    | 136 (69.0) | 156 (71.9)               |   |                |
|              |            | Recessive | T/T-C/T    | 165 (83.8) | 179 (82.5)               |   |                |
|              |            |           | C/C        | 32 (16.2)  | 38 (17.5)                |   |                |
|              |            | Additive  | T/T        | 61 (31.0)  | 61 (28.1)                |   |                |
|              |            |           | C/C        | 32 (16.2)  | 38 (17.5)                |   |                |
|              | rs12680942 | Dominant  | G/G        | 62 (31.5)  | 61 (28.1)                | 0.85 (0.56, 1.30)                       | 0.455          |
|              |            |           | A/G-A/A    | 135 (68.5) | 156 (71.9)               |   |                |
|              |            | Recessive | G/G-A/G    | 166 (84.3) | 179 (82.5)               |   |                |
|              |            |           | A/A        | 31 (15.7)  | 38 (17.5)                |   |                |
|              |            | Additive  | G/G        | 62 (31.5)  | 61 (28.1)                |   |                |
|              |            |           | A/A        | 31 (15.7)  | 38 (17.5)                |   |                |
| rs1469288    | Dominant   | A/A       | 60 (30.5)  | 60 (27.6)  | 0.87 (0.57, 1.33)        | 0.530                                   |                |
|              |            | G/A-G/G   | 137 (69.5) | 157 (72.4) |                          |   |                |
|              | Recessive  | A/A-G/A   | 166 (84.3) | 179 (82.5) |                          |   |                |
|              |            | G/G       | 31 (15.7)  | 38 (17.5)  |                          |   |                |
|              | Additive   | A/A       | 60 (30.5)  | 60 (27.6)  |                          |   |                |
|              |            | G/G       | 31 (15.7)  | 38 (17.5)  |                          |   |                |
| rs17285138   | Dominant   | A/A       | 62 (31.5)  | 61 (28.1)  | 0.85 (0.56, 1.30)        | 0.455                                   |                |
|              |            | T/A-T/T   | 135 (68.5) | 156 (71.9) |                          |   |                |
|              | Recessive  | A/A-T/A   | 166 (84.3) | 179 (82.5) |                          |   |                |
|              |            | T/T       | 31 (15.7)  | 38 (17.5)  |                          |   |                |
|              | Additive   | A/A       | 62 (31.5)  | 61 (28.1)  |                          |   |                |
|              |            | T/T       | 31 (15.7)  | 38 (17.5)  |                          |   |                |
| <i>SP110</i> | rs1135791  | Dominant  | A/A        | 137 (69.5) | 156 (71.9)               | 1.12 (0.73, 1.71)                       | 0.600          |
|              |            |           | A/G-G/G    | 60 (30.5)  | 61 (28.1)                |   |                |
|              |            | Recessive | A/A-A/G    | 192 (97.5) | 215 (99.1)               |   |                |
|              |            |           | G/G        | 5 (2.5)    | 2 (0.9)                  |   |                |
|              |            | Additive  | A/A        | 137 (69.5) | 156 (71.9)               |   |                |
|              |            |           | G/G        | 5 (2.5)    | 2 (0.9)                  |   |                |
|              | rs9061     | Dominant  | C/C        | 135 (68.5) | 139 (64.1)               | 0.82 (0.54, 1.23)                       | 0.337          |
|              |            |           | C/T-T/T    | 62 (31.5)  | 78 (35.9)                |   |                |
|              |            | Recessive | C/C-C/T    | 193 (98.0) | 211 (97.2)               |   |                |
|              |            |           | T/T        | 4 (2.0)    | 6 (2.8)                  |   |                |
|              |            | Additive  | C/C        | 135 (68.5) | 139 (64.1)               |   |                |
|              |            |           | T/T        | 4 (2.0)    | 6 (2.8)                  |   |                |
| rs722555     | Dominant   | C/C       | 61 (31.0)  | 95 (43.8)  | <b>1.74 (1.16, 2.60)</b> | <b>0.007</b>                            |                |
|              |            | C/T-T/T   | 136 (69.0) | 122 (56.2) |                          |   |                |
|              | Recessive  | C/C-C/T   | 167 (84.8) | 188 (86.6) |                          |   |                |
|              |            | T/T       | 30 (15.2)  | 29 (13.4)  |                          |   |                |

TABLE 4: Continued.

| Gene       | SNP       | Model | Genotype   | TB, N (%)   | Control, N (%) | Univariate logistic model<br>OR (95 CI) | <i>p</i> value |
|------------|-----------|-------|------------|-------------|----------------|---|----------------|
| rs3948464  | Additive  |       | C/C        | 61 (31.0)   | 95 (43.8)      | 1.61 (0.88, 2.95)                       | 0.121          |
|            |           |       | T/T        | 30 (15.2)   | 29 (13.4)      |   |                |
|            | Dominant  |       | G/G        | 197 (100.0) | 213 (98.2)     | NA                                      |                |
|            |           |       | G/A-AA     | 0 (0.0)     | 4 (1.8)        |   |                |
|            | Recessive |       | G/G-G/A    | 197 (100.0) | 217 (100.0)    | NA                                      |                |
|            |           |       | AA         | 0 (0.0)     | 0 (0.0)        |   |                |
| rs11679983 | Additive  |       | G/G        | 197 (100.0) | 213 (98.2)     | NA                                      |                |
|            |           |       | AA         | 0 (0.0)     | 0 (0.0)        |   |                |
|            | Dominant  |       | G/G        | 181 (91.9)  | 195 (89.9)     | 0.78 (0.40, 1.54)                       |                |
|            |           |       | G/A-AA     | 16 (8.1)    | 22 (10.1)      |   |                |
|            | Recessive |       | G/G-G/A    | 197 (100.0) | 217 (100.0)    | NA                                      |                |
|            |           |       | AA         | 0 (0.0)     | 0 (0.0)        |   |                |
| rs1365776  | Additive  |       | G/G        | 181 (91.9)  | 195 (89.9)     | NA                                      |                |
|            |           |       | AA         | 0 (0.0)     | 0 (0.0)        |   |                |
|            | Dominant  |       | T/T        | 150 (76.1)  | 167 (77.0)     | 1.05 (0.66, 1.65)                       |                |
|            |           |       | C/T-C/C    | 47 (23.9)   | 50 (23.0)      |   |                |
|            | Recessive |       | T/T-C/T    | 196 (99.5)  | 214 (98.6)     | 0.36 (0.04, 3.53)                       |                |
|            |           |       | C/C        | 1 (0.5)     | 3 (1.4)        |   |                |
| rs11556887 | Additive  |       | T/T        | 150 (76.1)  | 167 (77.0)     | 0.37 (0.04, 3.61)                       |                |
|            |           |       | C/C        | 1 (0.5)     | 3 (1.4)        |   |                |
|            | Dominant  |       | GG         | 166 (84.3)  | 188 (86.6)     | 1.21 (0.70, 2.09)                       |                |
|            |           |       | GA-AA      | 31 (15.7)   | 29 (13.4)      |   |                |
|            | Recessive |       | G/G-GA     | 197 (100.0) | 217 (100.0)    | NA                                      |                |
|            |           |       | A/A        | 0 (0.0)     | 0 (0.0)        |   |                |
| Additive   |           | GG    | 166 (84.3) | 188 (86.6)  | NA             |   |                |
|            |           | A/A   | 0 (0.0)    | 0 (0.0)     |                |   |                |

Data are presented as *n* (%). SNP: single-nucleotide polymorphism; TB: tuberculosis; OR: odds ratio; CI: confidence intervals; NA: not applicable. *p* values below 0.05 are highlighted in bold.

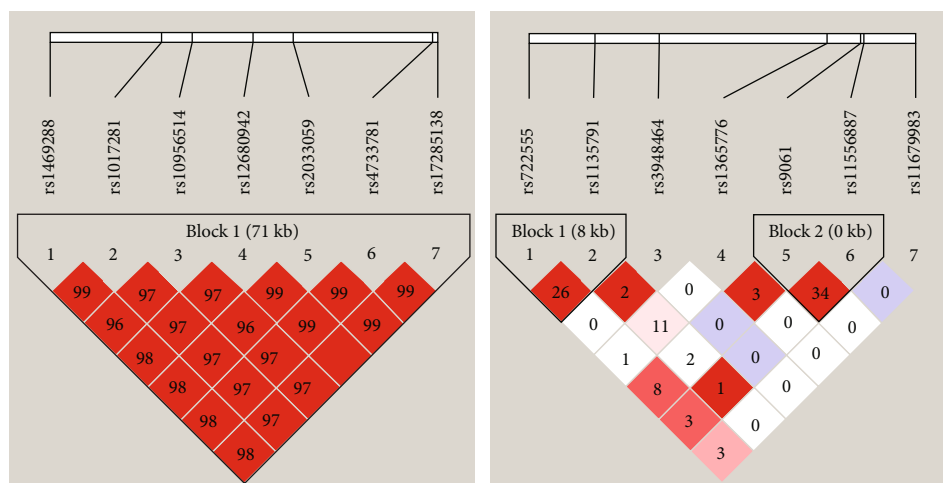


FIGURE 1: Linkage disequilibrium analysis of SNPs of *ASAP1* and *SP110* in the Mongolian population.

necrosis to apoptosis in infected macrophages [25]. It also regulates NF- $\kappa$ B-mediated transcription [26], which is involved in immune responses, apoptosis, defense responses, and inflammatory responses [25]. Collectively, all these observations suggest that *SP110* may play potential roles in

the TB susceptibility. However, how the SNPs in *SP110* affects the susceptibility to TB in the Mongolian population remains to be explored.

The results in this report demonstrate that the rs722555 SNP in the *SP110* gene is a risk factor for pulmonary TB

TABLE 5: The haplotypes analysis of *ASAPI* and *SP110* gene and TB in Mongolian population.

| Gene         | SNPs       | Group                                   | Haplotype                               | TB case_F                               | Healthy control_F | OR          | 95% CI      | p value   |           |       |
|--------------|------------|---|---|---|-------------------|-------------|-------------|-----------|-----------|-------|
| <i>ASAPI</i> | rs1469288  | Active tuberculosis vs. health controls | AGGTC                                   | 111 (0.563)                             | 119 (0.551)       | 0.94        | 0.64-1.39   | 0.758     |           |       |
|              | rs10956514 |   | GAACAT                                  | 83 (0.419)                              | 97 (0.445)        | 1.11        | 0.75-1.64   | 0.599     |           |       |
|              | rs12680942 |   |   | Active tuberculosis vs. health controls | CA                | 113 (0.572) | 141 (0.649) | 1.38      | 0.93-2.05 | 0.112 |
|              | rs2033059  |   |   |   | TA                | 52 (0.263)  | 45 (0.206)  | 0.73      | 0.46-1.15 | 0.175 |
|              | rs4733781  |   |   |   | TG                | 31 (0.159)  | 31 (0.142)  | 0.89      | 0.52-1.53 | 0.680 |
| rs17285138   | CG         | 164 (0.832)                             | 175 (0.806)                             | 0.84                                    | 0.51-1.39         | 0.492       |             |           |           |       |
| <i>SP110</i> | rs7222555  | Active tuberculosis vs. health controls | TG                                      | 17 (0.089)                              | 27 (0.127)        | 1.50        | 0.79-2.85   | 0.211     |           |       |
|              | rs1135791  |   | TA                                      | 16 (0.079)                              | 15 (0.067)        | 0.84        | 0.40-1.75   | 0.641     |           |       |
|              | rs9061     |   | Active tuberculosis vs. health controls | CA                                      | 113 (0.572)       | 141 (0.649) | 1.38        | 0.93-2.05 | 0.112     |       |
|              | rs11556887 |   |   | TA                                      | 52 (0.263)        | 45 (0.206)  | 0.73        | 0.46-1.15 | 0.175     |       |
|              |            |   |   | TG                                      | 31 (0.159)        | 31 (0.142)  | 0.89        | 0.52-1.53 | 0.680     |       |

Note: SNP: single-nucleotide polymorphism; TB: tuberculosis; OR: odds ratio; CI: confidence intervals; vs., versus.

susceptibility in the Mongolian population in China. SNPs in *ASAPI* had no association with TB susceptibility in this Mongolian population, although these SNPs may be associated with a reduced risk of TB in other populations. In conclusion, this study provides a new piece of evidence to support the importance of genetic variability of hosts in the pathogenesis of TB and may help to improve patient-specific clinical TB diagnosis or favor more suitable precautions against TB among high-risk individuals.

## 5. Conclusion

In conclusion, this study provides evidence to support the idea that genetic variability in the host could affect the susceptibility to TB. Our results indicate that the rs722555 SNP in *SP110* is a risk factor for TB susceptibility in the Mongolian population. In contrast, SNPs in *ASAPI* had no association with TB susceptibility in our Mongolian population, although these SNPs may be associated with a reduced risk of TB in this population. A large-scale GWAS therefore should be performed to obtain more solid evidence of whether these *ASAPI* SNPs are associated with TB in this ethnic minority. The results from our study may be beneficial for the assessment of genetic susceptibility factors and to improve the possible outcomes of TB infection in the Mongolian population.

## Abbreviations

Mtb: Mycobacterium tuberculosis  
 TB: Tuberculosis  
 SNP: Single-nucleotide polymorphisms  
*ASAPI*: Ankyrin repeat and PH domain 1  
*SP110*: Speckled 110  
 OR: Odds ratios  
 CI: Confidence intervals  
 LPS: Lipopolysaccharide  
 PTB: Pulmonary tuberculosis  
 HWE: Hardy-Weinberg equilibrium  
 LD: Linkage disequilibrium

LTBI: Latent tuberculosis infection.

## Data Availability

All relevant data are available within the manuscript and its supporting information files.

## Conflicts of Interest

The authors declare that they have no competing interests.

## Authors' Contributions

XC, TY, and YL performed the data analysis and wrote the manuscript. PN, JH, and LD collected the data. XC, TY, FL, MH, and CW participated in the experimental design and helped interpret the results. XC, YL, JF, LD, LX, and CW conceived and designed the experiments and wrote the manuscript. Xiaogang Cui, Tianqi Yuan, and Pengyuan Ning contributed equally to this work.

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## Supplementary Materials

*Supplementary 1.* Supplementary Table 1: primers for SNPs in *ASAP1* and *SP110*.

*Supplementary 2.* Supplementary Table 2: analysis of SNP of TB acceptability associated genes using H-WE.

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