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), 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 AMAP1 or DDEF1. It encodes ASAP1, a member of ADP-ribosylation...

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].

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factor GTPase-activating proteins (Arf-GAPs), which is a multifunctional scaffold protein [9, 15]. The expression of ASAP1 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 genomewide association studies (GWAS) [21] have identified ASAP1 as a novel gene associated with the susceptibility to TB. Two SNPs (rs4733781 and rs10956514) in the ASAP1 gene are significantly associated with susceptibility to TB in a Russian population [5]. Moreover, ASAP1 expression is markedly decreased in Mtb-infected dendritic cells, which may result in impaired dendritic cell migration and indicate a potential mechanism of ASAP1 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 ASAP1 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 ASAP1 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 ASAP1 were chosen for subsequent genotyping. Blood samples were collected from the cases and controls in EDTA-coated tubes and stored at −80°C. Genomic DNA was isolated from a 200 μL 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® spectro-photometer (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 ASAP1 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 χ² 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 ± 15.62 years) and 217 healthy controls (114 males and 103 females; mean age: 44.95 ± 15.73 years) were included in this study. There were significant differences between the two groups in sex and education...
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
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 2: Distribution frequency of SNPs of ASAP1 and SP110 gene in TB and healthy population.

| Gene | SNP | Genotypes | TB (n = 197) | Control (n = 217) | $\chi^2$ | p value | Univariate logistic model | p value |
|------|-----|------------|--------------|-------------------|---------|---------|--------------------------|---------|
| ASAP1 | rs10956514 | GG | 59 (29.9) | 61 (28.1) | 0.234 | 0.889 | 1.00 (ref) | 
| | | GA | 107 (54.3) | 119 (54.8) | 0.87 (0.48, 1.57) | 0.637 |
| | | AA | 31 (15.7) | 37 (17.1) | 0.432 | 0.806 | 1.00 (ref) | 
| rs4733781 | CC | 61 (31.0) | 61 (29.5) | 0.88 (0.57, 1.37) | 0.576 |
| | CA | 104 (52.8) | 118 (55.8) | 0.88 (0.57, 1.37) | 0.576 |
| | AA | 61 (31.0) | 61 (29.5) | 0.88 (0.57, 1.37) | 0.576 |
| rs2033059 | TT | 61 (31.0) | 61 (28.1) | 0.88 (0.57, 1.37) | 0.576 |
| | 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 |
| SP110 | rs12680942 | GG | 62 (31.5) | 61 (28.1) | 0.636 | 0.727 | 1.00 (ref) | 
| | GA | 104 (52.8) | 118 (54.4) | 0.88 (0.57, 1.37) | 0.576 |
| | AA | 60 (30.5) | 60 (27.6) | 0.88 (0.57, 1.37) | 0.576 |
| rs1469288 | AA | 60 (30.5) | 60 (27.6) | 0.88 (0.57, 1.37) | 0.576 |
| | AG | 106 (53.8) | 119 (54.9) | 0.88 (0.57, 1.37) | 0.576 |
| | GG | 31 (15.7) | 38 (17.5) | 0.88 (0.57, 1.37) | 0.576 |
| rs17285138 | AA | 62 (31.5) | 61 (28.1) | 0.84 (0.47, 1.52) | 0.568 |
| | AT | 104 (52.8) | 118 (54.4) | 0.84 (0.47, 1.52) | 0.568 |
| | TT | 31 (15.7) | 38 (17.5) | 0.84 (0.47, 1.52) | 0.568 |
| rs1135791 | AA | 137 (69.5) | 156 (71.9) | 1.696 | 0.428 | 1.0 (ref) | 
| | 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 | 1.0 (ref) | 
| | 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 | 1.0 (ref) | 
| | CT | 106 (53.8) | 93 (42.9) | 1.78 (1.16, 2.72) | 0.008 |
| | 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) | 1.0 (ref) | 
| | AA | 0 | 0 | NA | 
| rs11679983 | GG | 181 (91.9) | 195 (89.9) | 0.504 | 0.296 | 1.0 (ref) | 
| | 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 | 1.0 (ref) | 
| | 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 | 1.0 (ref) | 
| | 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.
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 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

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

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.
### Table 4: Analysis of the inheritance models of ASAPI and SP110 polymorphism associated with tuberculosis.

| Gene | SNP | Model   | Genotype | TB, N (%) | Control, N (%) | Univariate logistic model OR (95 CI) | p value |
|------|-----|---------|----------|-----------|----------------|-------------------------------------|---------|
|      |     |         |          |           |                |                                     |         |
|      |     | 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)    | 0.91 (0.54, 1.53)                  | 0.718   |
|      |     |         | A/A      | 31 (15.7) | 37 (17.1)     |                                     |         |
|      |     | Additive| C/C      | 59 (29.9) | 61 (28.1)     | 0.87 (0.48, 1.57)                  | 0.637   |
|      |     |         | A/A      | 31 (15.7) | 37 (17.1)     |                                     |         |
|      |     | Dominant| A/C-A/A  | 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)    | 0.91 (0.55, 1.53)                  | 0.731   |
|      |     |         | A/A      | 32 (16.2) | 38 (17.5)     |                                     |         |
|      |     | Additive| C/C      | 61 (31.0) | 61 (28.1)     | 0.84 (0.47, 1.52)                  | 0.568   |
|      |     |         | A/A      | 32 (16.2) | 38 (17.5)     |                                     |         |
|      |     | Dominant| T/T-C/T  | 61 (31.0) | 61 (28.1)     | 0.87 (0.57, 1.33)                  | 0.525   |
|      |     |         | C/T-C/T  | 136 (69.0)| 156 (71.9)    |                                     |         |
|      |     | Recessive| T/T-C/T  | 165 (83.8)| 179 (82.5)    | 0.91 (0.55, 1.53)                  | 0.731   |
|      |     |         | C/C      | 32 (16.2) | 38 (17.5)     |                                     |         |
|      |     | Additive| T/T      | 61 (31.0) | 61 (28.1)     | 0.84 (0.47, 1.52)                  | 0.568   |
|      |     |         | C/C      | 32 (16.2) | 38 (17.5)     |                                     |         |
|      |     | Dominant| A/A      | 62 (31.5) | 61 (28.1)     | 0.85 (0.56, 1.30)                  | 0.455   |
|      |     |         | G/A-G/A  | 135 (68.5)| 156 (71.9)    |                                     |         |
|      |     | Recessive| G/A-G/A  | 166 (84.3)| 179 (82.5)    | 0.88 (0.52, 1.48)                  | 0.628   |
|      |     |         | A/A      | 31 (15.7) | 38 (17.5)     |                                     |         |
|      |     | Additive| G/G      | 62 (31.5) | 61 (28.1)     | 0.80 (0.44, 1.45)                  | 0.466   |
|      |     |         | A/A      | 31 (15.7) | 38 (17.5)     |                                     |         |
|      |     | 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)    |                                     |         |
|      |     |         | A/A      | 31 (15.7) | 38 (17.5)     |                                     |         |
|      |     | Recessive| A/A-G/A  | 166 (84.3)| 179 (82.5)    | 0.88 (0.52, 1.48)                  | 0.628   |
|      |     |         | A/A      | 31 (15.7) | 38 (17.5)     |                                     |         |
|      |     | Additive| A/A      | 60 (30.5) | 60 (27.6)     | 0.82 (0.45, 1.48)                  | 0.502   |
|      |     |         | G/G      | 31 (15.7) | 38 (17.5)     |                                     |         |
|      |     | 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)    | 0.88 (0.52, 1.48)                  | 0.628   |
|      |     |         | T/T      | 31 (15.7) | 38 (17.5)     |                                     |         |
|      |     | Additive| A/A      | 62 (31.5) | 61 (28.1)     | 0.80 (0.44, 1.45)                  | 0.466   |
|      |     |         | T/T      | 31 (15.7) | 38 (17.5)     |                                     |         |
|      |     | Dominant| A/A      | 137 (69.5)| 156 (71.9)    | 1.12 (0.73, 1.71)                  | 0.600   |
|      |     |         | G/A-G/G  | 60 (30.5) | 61 (28.1)     |                                     |         |
|      |     | Recessive| A/A-A/G  | 192 (97.5)| 215 (99.1)    | 2.80 (0.54, 14.60)                 | 0.222   |
|      |     |         | G/G      | 5 (2.5)   | 2 (0.9)       |                                     |         |
|      |     | Additive| A/A      | 137 (69.5)| 156 (71.9)    | 2.85 (0.54, 14.91)                 | 0.216   |
|      |     |         | G/G      | 5 (2.5)   | 2 (0.9)       |                                     |         |
|      |     | 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)    | 0.73 (0.20, 2.62)                  | 0.628   |
|      |     |         | T/T      | 4 (2.0)   | 6 (2.8)       |                                     |         |
|      |     | Additive| C/C      | 135 (68.5)| 139 (64.1)    | 0.69 (0.19, 2.49)                  | 0.567   |
|      |     |         | C/T      | 4 (2.0)   | 6 (2.8)       |                                     |         |
|      |     | Dominant| C/C      | 61 (31.0) | 95 (43.8)     | 1.74 (1.16, 2.60)                  | 0.007   |
|      |     |         | C/T-T/T  | 136 (69.0)| 122 (56.2)    |                                     |         |
|      |     | Recessive| C/C-C/T  | 167 (84.8)| 188 (86.6)    | 1.16 (0.67, 2.02)                  | 0.588   |
|      |     |         | T/T      | 30 (15.2) | 29 (13.4)     |                                     |         |
necrosis to apoptosis in infected macrophages [25]. It also regulates NF-κB-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 rs72255 SNP in the SP110 gene is a risk factor for pulmonary TB.

| Gene   | SNP       | Model | Genotype | TB, N (%) | Control, N (%) | Univariate logistic model OR (95 CI) | p value |
|--------|-----------|-------|----------|-----------|----------------|--------------------------------------|---------|
|        | rs11679983| Recessive | G/G-G/A | 197 (100.0) | 217 (100.0) | NA |                                  |
|        | rs1365776 | Recessive | T/T-C/T | 196 (99.5) | 214 (98.6) | 0.36 (0.04, 3.53) | 0.383 |
|        | rs11556887| Recessive | G/G-GA | 197 (100.0) | 217 (100.0) | NA |                                  |
|        | rs1469288 | Additive | G/G     | 181 (91.9) | 195 (89.9) | 0.78 (0.40, 1.54) | 0.479 |
|        | rs1017281 | Additive | G/G     | 181 (91.9) | 195 (89.9) | 0.78 (0.40, 1.54) | 0.479 |
|        | rs10956514| Additive | G/G     | 181 (91.9) | 195 (89.9) | 0.78 (0.40, 1.54) | 0.479 |
|        | rs12680942| Additive | G/G     | 181 (91.9) | 195 (89.9) | 0.78 (0.40, 1.54) | 0.479 |
|        | rs2033059 | Additive | G/G     | 181 (91.9) | 195 (89.9) | 0.78 (0.40, 1.54) | 0.479 |
|        | rs4733781 | Additive | G/G     | 181 (91.9) | 195 (89.9) | 0.78 (0.40, 1.54) | 0.479 |
|        | rs17285138| Additive | G/G     | 181 (91.9) | 195 (89.9) | 0.78 (0.40, 1.54) | 0.479 |
|        | rs1135791 | Additive | G/G     | 181 (91.9) | 195 (89.9) | 0.78 (0.40, 1.54) | 0.479 |

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.
susceptibility in the Mongolian population in China. SNPs in ASAP1 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 rs7222555 SNP in SP110 is a risk factor for TB susceptibility in the Mongolian population. In contrast, SNPs in ASAP1 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 ASAP1 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
ASAP1: 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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Table 5: The haplotypes analysis of ASAP1 and SP110 gene and TB in Mongolian population.

| Gene     | SNPs                     | Group               | Haplotype | TB case_F | Healthy control_F | OR    | 95% CI  | p value |
|----------|--------------------------|---------------------|-----------|-----------|-------------------|-------|---------|---------|
| ASAP1    | rs1469288                | Active tuberculosis vs. heath controls | AGGTCA    | 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               |                     |           |           |                   |       |         |         |
|          | rs2033059                |                     |           |           |                   |       |         |         |
|          | rs4733781                |                     |           |           |                   |       |         |         |
|          | rs17285138               |                     |           |           |                   |       |         |         |
| SP110    | rs7222555                | Active tuberculosis vs. heath controls | CA        | 113 (0.572) | 141 (0.649)     | 1.38  | 0.93-2.05 | 0.112   |
|          | rs1135791                |                     | TA        | 52 (0.263)  | 45 (0.206)      | 0.73  | 0.46-1.15 | 0.175   |
|          | rs9061                   | Active tuberculosis vs. heath controls | TG        | 31 (0.159)  | 31 (0.142)      | 0.89  | 0.52-1.53 | 0.680   |
|          | rs11556887               |                     | CG        | 164 (0.832) | 175 (0.806)    | 0.84  | 0.51-1.39 | 0.492   |
|          |                         |                     | TG        | 17 (0.089)  | 27 (0.127)     | 1.50  | 0.79-2.85 | 0.211   |
|          |                         |                     | TA        | 16 (0.079)  | 15 (0.067)     | 0.84  | 0.40-1.75 | 0.641   |

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