

The effects of *SP110*'s associated genes on fresh cavitory pulmonary tuberculosis in Han Chinese population

Shi-Yao Jiang · Lin-Lin Li · Jun Yue ·
Wen-zhong Chen · Chao Yang · Chun-Ling Wan ·
Lin He · Lei Cai · Shao-Li Deng

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Abstract *SP110* is a promising anti-*Mycobacterium tuberculosis* (*MTB*) gene. To investigate the effects of *SP110* and its associated genes, i.e., *MYBBP1A* and *RELA*, on pathological progression of *MTB* infection, an association study with 424 patients of fresh pulmonary tuberculosis (PTB) and 424 healthy controls was performed. Moreover, classification and regression tree and multifactor dimensionality reduction were employed to explore the effects of gene–gene interactions on cavitory PTB. The results indicated that both the heterozygous genotype GC and homozygous genotype CC in rs3809849 had significant effects on the risk of PTB (OR 1.42, 95 % CI 1.06–1.92, p 0.019; OR 1.55, 95 % CI 1.04–2.33, p = 0.033, respectively), and heterozygous genotype CT in rs9061 also had similar effects (OR 1.43, 95 % CI 1.07–1.90, p = 0.014). The rs3809849 and rs9905742 in *MYBBP1A* were also

significantly associated with cavitory PTB (p = 0.00046 and 0.039, respectively), while rs9061 in *SP110* had no such association (p = 0.06931) except its significant association with non-cavitory PTB (p = 0.0093). The interaction of *MYBBP1A* and *RELA* had significant effect on cavitory PTB (OR 4.24, 95 % CI 1.44–12.49, p = 0.005). These suggest that *MYBBP1A* instead of *SP110* may be a genetic risk factor for cavitory PTB and play important effects on its whole progress.

Keywords Tuberculosis · *SP110* · *MYBBP1A* · MDR · CART

Abbreviations

MTB	<i>Mycobacterium tuberculosis</i>
MYBBP1A	MYB-binding protein
MDR	Multifactor dimensionality reduction
CART	Classification and regression tree
LR	Logistic regression

Shi-Yao Jiang and Lin-Lin Li have contributed equally to this work.

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S.-Y. Jiang · C.-L. Wan · L. He · L. Cai (✉)
Bio-X Institutes, Key Laboratory for the Genetics of
Developmental and Neuropsychiatric Disorders (Ministry of
Education), Shanghai Jiaotong University, 55 Guangyuanxi
Road, Shanghai 200030, China
e-mail: cailei2010@126.com

L. He
e-mail: helinhelin@gmail.com

S.-Y. Jiang · S.-L. Deng (✉)
Department of Laboratory Medicine, Institute of Surgery
Research, Daping Hospital, The Third Military Medical
University, 10 Changjiangzhuilu, Daping, Chongqing 400022,
China
e-mail: shaoli.deng@yahoo.com

L.-L. Li · C. Yang
College of Life Science, Anhui Normal University,
Wuhu 241000, Anhui, China

J. Yue
Shanghai Key Laboratory of Mycobacterium Tuberculosis,
Shanghai Pulmonary Hospital, Tongji University School of
Medicine, Shanghai, China

W. Chen
Department of Infectious Diseases, Shanghai Mental Health
Center, Shanghai Jiaotong University, Shanghai, China

Introduction

With an estimated 8–9 million new cases occurring annually around the world, tuberculosis (TB) is still one of the major health issues worldwide [1]. *Mycobacterium tuberculosis* (*MTB*), responsible for developing clinical tuberculosis, can cause caseous necrosis in the host lung, which goes further into lung cavities through liquefaction. Pulmonary cavitation, the severe pathological consequence of pulmonary tuberculosis (PTB), is important clinical feature of high-level replicating or destructive *MTB* infection [2]. And lung cavities are known to serve as an excellent growth place for *MTB*. Therefore, the identification of host inner genetic factors for cavitory PTB is necessary for unveiling the progression and pathogenesis of tuberculosis in humans.

The *SP110* gene has been shown in mice to have the ability to control *MTB* growth in macrophages and induce infected macrophage cells apoptosis [3]. The human *SP110* gene is postulated to play roles in the development of clinical TB [4]. And current meta-analysis result supports that the *SP110* rs9061 T allele may confer significant risk of PTB in East Asian populations [5]. However, *SP110*'s effects on progression to lung cavitation are unknown yet. Studying *SP110*'s effects on cavitory PTB is of help to know gene effects on the pathological progression of *MTB* infection.

In the present study, the effects of main single nucleotide polymorphisms (SNPs) in *SP110* on cavitory PTB are examined. Furthermore, *MYBBP1A* and *RELA*, which are known to be *SP110*'s interacting proteins and be involved in *SP110*'s induction of macrophage apoptosis, are also studied [6, 7]. Since the sub-phenotype of complex disease may usually result from interactions of multiple genetic factors, multiple methods of classification and regression tree (CART) construction and multifactor dimensionality reduction (MDR) analysis are employed to detect the effects of gene–gene interactions on the cavitory PTB.

Materials and methods

Subjects

A total of 424 patients with pulmonary TB without previous episodes of TB were recruited from the Chongqing Daping Hospital and Shanghai Pulmonary Hospital in southern China from September 2010 to June 2013. All patients were HIV negative, and none presented with other infectious diseases or immunosuppressive conditions, and diagnosis of TB rested on chest radiographs and was confirmed by sputum smears and *MTB* culture. Severe form of TB was identified based on the appearance of cavities

revealed by chest radiographs, denoting clinically destructive TB. Among the patients, 299 were men and 125 women; the mean age (\pm SD) was 40.08 ± 14.64 years. And among these patients, 159 had lung cavities and 265 had no lung cavities.

A total of 424 blood donors matched with cases were recruited as healthy controls described in the previous study [5], among whom, 284 were men and 140 women; the mean age (\pm SD) was 41.17 ± 17.68 years. There were no significant differences between PTB patients and healthy controls with regard to gender or age ($p = 0.266$ and 0.329 , respectively). Healthy control subjects had negative tuberculin skin tests with indurations of <5 mm on the fourth day after inoculation, no history of TB and no evidence of prior TB noted in chest radiographies. This study was approved by the Ethics Committees of the Hospitals. And oral or written informed consent was provided by all subjects.

Genotyping analysis

Three tagging SNPs (rs3809849, rs10852863, rs9905742) in *MYBBP1A*, two tagging SNPs (rs9061, rs1135791) in *SP110* and one tagging SNP (rs11820062) in *RELA* genes were selected as the first five SNPs and were found to be significantly associated with TB [5], and the last tagging SNP was located in the link disequilibrium region including whole *RELA* gene. All these SNPs were genotyped as previously described [5]. Briefly, all SNPs except rs9061 were genotyped using MASSarray platform (Sequenom; CA). The rs9061 and another SNP rs1135791 as an evaluator for the above genotyping method were tested using the SNaPshot Kit (Applied Biosystems; CA). For MASSarray, multiplex PCR was performed, and purified extension reaction products were spotted onto spectroCHIPS and determined by matrix-assisted laser desorption–ionization time-of-flight (MALDI-TOF) mass spectrometry. For SNaPshot method, PCR was firstly performed, and then, the products were then processed as templates for a mini-sequencing extension reaction using SNaPshot Kit. Finally, purified products were sequenced by capillary electrophoresis on an ABI3730xl DNA analyzer (Applied Biosystems; CA).

Statistical analysis

A Chi-squared test and *t* test were used to test the difference of gender or age between patients and controls. Fisher's exact test was used to test Hardy–Weinberg equilibrium (HWE) for each SNP in control subjects. Odd ratios (ORs) and 95 % confidence intervals (CIs) for the heterozygous and homozygous carriers of the minor allele were calculated using the homozygous carrier of the major

allele as the reference. The association between the genotypes of individual SNPs and PTB was determined using a Cochran–Armitage trend test. The data analysis was performed using the Stata 12.0 software (Stata Co., College Station, TX).

High-order gene–gene interactions were explored using CART analysis with CART 6.0 software (Salford Systems, USA). CART uses recursive partitioning to build a decision tree that enables the identification of subgroups of individuals at different levels of risks and with specific genotype interactions. Subgroups of individuals having different risk associations with TB were identified in the different terminal nodes of the tree, indicating the potential presence of interactions. Finally, the risk of these subgroups was evaluated by using logistic regression (LR) analysis. ORs and 95 % CIs were calculated with the least percentage of cases as the reference.

The free MDR software (<http://www.multifactor-dimensionalityreduction.org/>) was used to identify possible locus–locus and gene–gene interaction models, which were associated with cavitory PTB risk. The MDR is a non-parametric, model-free method for the detection and characterization of gene–gene interactions in small sample sizes [8]. Through dividing genotype factors into high and low risk level, MDR can effectively reduce the multifactor classification and prediction from high dimension to one dimension. In this study, Tuned ReliefF (TuRF) filter algorithm was applied to discard noisy SNPs and avoid overfitting. The best candidate interaction models for each locus were selected with the maximal testing balance accuracy (TBA) and the cross-validation consistency (CVC). The best interaction model was determined using 1,000-fold permutation testing, whose result was viewed statistically significant at the 0.05 level.

To visualize the MDR results, interaction entropy graphs containing nodes for corresponding SNPs and pairwise connections were constructed [9]. In the interaction entropy graphs based on information theory, synergy means positive interactions, while redundancy means negative interactions. Nodes for individual SNPs are connected in a pairwise way. The percentage of entropy removed by each SNP/pairwise connection is visualized for each node/line. And the red color represents a high degree of synergy with more entropy percentage, orange a lesser degree, and gold represents independence or a midway point between synergy and redundancy.

Results

Before testing the effects of each SNP on cavitory PTB, we tested the susceptibility to *MTB* infection of each SNP. Both the heterozygous genotype GC and homozygous

genotype CC in rs3809849 were associated with increased risk of PTB (OR 1.42, 95 % CI 1.06–1.92, $p = 0.019$; OR 1.55, 95 % CI 1.04–2.33, $p = 0.033$, respectively), and heterozygous genotype CT in rs9061 (OR 1.43, 95 % CI 1.07–1.90, $p = 0.014$) was associated with increased risk of PTB (Supplementary Table 1).

Genotype distributions of rs3809849 and rs9905742 in the *MYBBP1A* gene were significantly associated with cavitory PTB ($p = 0.00046$ and 0.039 , respectively), and *SP110* rs9061 polymorphism was found to be associated with non-cavitory PTB ($p = 0.0093$; Supplementary Table 2). After the p value was adjusted using Bonferroni's method, the heterozygous genotypes GC at rs3809849 and TA at rs9905742 were associated with increased risk of cavitory PTB (OR 1.9, 95 % CI 1.29–2.82, $p = 0.006$; OR 2.47, 95 % CI 1.37–4.46, $p = 0.018$, respectively (Table 1). Both the rs3809849 and rs9905742 polymorphisms were associated with increased risk to cavitory PTB in both the recessive and multiplicative genetic models (Supplementary Table 3).

Furthermore, with patients with cavitory PTB compared to the patients with non-cavitory PTB, the heterozygous genotypes GC at rs3809849 was associated with increased risk of lung cavitation during PTB (OR 1.69, 95 % CI 1.11–2.58, $p = 0.015$). However, after the p value was adjusted using Bonferroni's method, no genotype of each SNP was found to be significantly associated with lung cavitation formation (Table 2).

The up to four orders of best interaction models from MDR analysis were shown in Table 3, along with their CVCs and TBAs for data sets of cavitory TB. The best one-factor model for predicting cavitory PTB risk was rs3809849 (CVC = 10/10, TBA = 0.5782, $p = 0.027$). The best model turned out to be the three-locus model comprising of rs3809849, rs1135791 and rs11820062 with a CVC of 10/10 and TBA equals to 0.6344 ($p < 0.001$). While the two-locus model had lower TBA (56.76 %), and four-locus models had lower CVC (9/10) than the three-locus model.

Consistent with the MDR best one-factor model, the initial split of the root node was rs3809849 (Fig. 1), suggesting that this SNP was the strongest risk factor for cavitory PTB among the examined SNPs. Using terminal node two with the least percentage of cases as the reference, among individuals carrying the rs3809849 C allele, the maximum risk was observed for terminal node 4 with the rs11820062 CT or TT genotypes (OR 4.24, 95 % CI 1.44–12.49, $p = 0.0050$).

Interaction entropy graphs were constructed using the MDR results obtained from the analysis of cavitory PTB data set. In cavitory PTB, rs3809849 tended to have a strong independent effect because the entropy removing this individual SNP was 1.55 % in a high degree, and a

Table 1 Genotype frequencies of SNPs within *Mybbp1a*, *SP110* and *RelA* genes in cavitary pulmonary TB patients and control subjects

SNP	Genotypes	Phenotype	Con (%)	Cavitary PTB (%)	OR (95 % CI) ^a	<i>p</i> value	<i>p</i> value ^b
rs3809849	GG	Glu8Glu	301 (70.99)	88 (55.35)	Ref		
	GC	Glu8Gln	114 (26.89)	65 (40.88)	1.9 (1.29–2.82)	0.001	0.006
	CC	Gln8Gln	9 (2.12)	6 (3.77)	1.65 (0.96–2.83)	0.068	0.41
rs10852863	AA	Non-coding	116 (27.36)	57 (35.85)	Ref		
	AG	Non-coding	216 (50.94)	68 (42.77)	0.63 (0.41–0.95)	0.03	0.18
	GG	Non-coding	92 (21.7)	34 (21.38)	0.88 (0.68–1.14)	0.34	1
rs9905742	TT	Leu1208Leu	395 (93.16)	139 (87.42)	Ref		
	TA	Leu1208Met	28 (6.6)	20 (12.58)	2.47 (1.37–4.46)	0.003	0.018
	AA	Met1208Met	1 (0.24)	0 (0)			
rs9061	CC	Glu207 Glu	276 (65.09)	88 (55.35)	Ref		
	CT	Glu207Lys	139 (32.78)	69 (43.4)	1.53 (1.04–2.24)	0.029	0.17
	TT	Lys 207Lys	9 (2.12)	2 (1.26)	0.77 (0.35–1.69)	0.51	1
rs1135791	TT	Met523 Met	280 (66.04)	109 (68.55)	Ref		
	TC	Met523Thr	125 (29.48)	46 (28.93)	0.98 (0.65–1.48)	0.94	1
	CC	Thr 523Thr	19 (4.48)	4 (2.52)	0.73 (0.42–1.28)	0.27	1
rs11820062	CC	Non-coding	166 (39.15)	48 (30.19)	Ref		
	CT	Non-coding	186 (43.87)	82 (51.57)	1.55 (1.02–2.36)	0.04	0.24
	TT	Non-coding	72 (16.98)	29 (18.24)	1.32 (0.99–1.76)	0.055	0.33

SNP single-nucleotide polymorphism, Con control, PTB pulmonary tuberculosis, Ref reference, OR odds ratio, CI confidence interval

^a Adjusted for age and gender

^b *p* values were corrected with Bonferroni method

strong synergistic interaction was found between rs1135791 and rs11820062 as the combination had the highest entropy of 2.72 % among the entropy for SNPs or connections (Supplementary Fig. 1).

Discussion

TB, usually caused by *MTB*, is a re-emerging disease epidemic in many parts of the world. Pulmonary cavitation, which is an ideal place for high-level replicating or destructive *MTB* infection, is the severe pathological phenotype of PTB [2]. The *SP110* gene is emerging as a promising candidate for controlling *MTB* infections in mice model [3]. The meta-analysis result suggests that the *SP110* rs9061 T allele may confer risk of PTB in East Asian populations [5]. The previous study results also demonstrate that both *Mybbp1A* and *sp110* may be a susceptible gene for PTB [5]. However, in that study, the patients with previous episodes of TB might be included, which could not sufficiently explain the genetic factors determining the susceptibility of fresh *MTB* infection. Moreover, *SP110* and its associated genes' effects on progression to lung cavitation are unknown yet. Thus, we examined the effect of each SNP and the interaction of gene–gene on cavitary PTB.

In the present study, it was found that the presence of the genotypes CT at rs9061 in *SP110*, and GC and CC at

rs3809848 in *MYBBP1A* independently conferred susceptibility to PTB. It suggested that *MYBBP1A* not *SP110* tended to play an important role in elevating the risk of developing cavitary PTB. *MTB*, an ancient microbiology, has sophisticated strategies to cope with host monocytic cells. After entering a host organism, *MTB* can actively induce lung epithelioid cell granulomas and subsequently necrosis or stay in macrophages as dormant bacteria. The morphological hallmark of necrosis is the appearance of a cheese-like material termed caseous necrosis. Caseation may lead to extensive tissue damage, such as liquefaction and formation of cavities. Within the cavities, *MTB* can proliferate extracellularly in a larger scale and prepare to spread throughout the body or release in aerosols [10]. In human, following induction by interferon- α or interferon- γ , *SP110* becomes manifest as a leukocyte-specific component of the nuclear body, which has been reported to inhibit virus replication [11, 12]. The *SP110*'s homologue in mice has been proved to have the ability to control *MTB* growth in macrophages and induce infected macrophage cells apoptosis [3]. In current study, *SP110* gene has been found to be associated with the PTB, while not to be associated with the presence of pulmonary cavities. It is reasonable to speculate that during TB active infection, *SP110* is induced and plays important roles to intracellularly resist TB through inducing apoptosis of infected macrophages. Usually, the apoptosis of macrophages means fewer cells

Table 2 Genotype frequencies of SNPs within Mybbp1a, SP110 and RelA genes in cavitory and non-cavitory pulmonary TB patients

SNP	Genotypes	Non-cavitory TB (%)	Cavitory PTB (%)	OR (95 % CI) ^a	<i>p</i> value	<i>p</i> value ^b	<i>p</i> value ^c
rs3809849	GG	175 (66.04)	88 (55.35)	Ref			
	GC	77 (29.06)	65 (40.88)	1.69 (1.11–2.58)	0.015	0.09	
	CC	13 (4.91)	6 (3.77)	0.98 (0.59–1.61)	0.925	1	0.10
rs10852863	AA	84 (31.7)	57 (35.85)	Ref			
	AG	132 (49.81)	68 (42.77)	0.77 (0.49–1.21)	0.26	1	
	GG	49 (18.49)	34 (21.38)	1.01 (0.77–1.34)	0.919	1	0.86
rs9905742	TT	242 (91.32)	139 (87.42)	Ref			
	TA	23 (8.68)	20 (12.58)	1.53 (0.81–2.89)	0.193	1	0.19
	AA	0 (0)	0 (0)				
rs9061	CC	150 (56.6)	88 (55.35)	Ref			
	CT	102 (38.49)	69 (43.4)	1.16 (0.77–1.75)	0.476	1	
	TT	13 (4.91)	2 (1.26)	0.51 (0.24–1.1)	0.086	0.516	0.63
rs1135791	TT	190 (71.7)	109 (68.55)	Ref			
	TC	69 (26.04)	46 (28.93)	1.16 (0.75–1.81)	0.502	1	
	CC	6 (2.26)	4 (2.52)	1.07 (0.56–2.03)	0.841	1	0.51
rs11820062	CC	99 (37.36)	48 (30.19)	Ref			
	CT	119 (44.91)	82 (51.57)	1.47 (0.93–2.3)	0.096	0.576	
	TT	47 (17.74)	29 (18.24)	1.12 (0.84–1.51)	0.414	1	0.28

SNP single-nucleotide polymorphism, *Con* control, *PTB* pulmonary tuberculosis, *Ref* reference, *OR* odds ratio, *CI* confidence interval

^a Adjusted for age and gender

^b *p* values were corrected with Bonferroni method

^c *p* values were calculated by the Cochran-Armitage's trend test

Table 3 Interaction models by MDR analysis

No. of locus	Model	<i>p</i> value ^a	TBA	CVC	<i>p</i> value ^b
Cavitory TB					
First order	rs3809849	0.0007	0.5782	10	0.027
Second order	rs3809849, rs11820062	<0.0001	0.5676	4	0.073
Third order ^c	rs3809849, rs1135791, rs11820062	<0.0001	0.6344	10	<0.001
Fourth order	rs3809849, rs9061, rs1135791, rs11820062	<0.0001	0.6482	9	<0.001

^a *p* values were calculated using the Chi-square test

^b *p* values were calculated based on 1,000-fold permutation test

^c Best models are selected with maximum cross-validation consistency (CVC) and maximum testing balance accuracy (TBA)

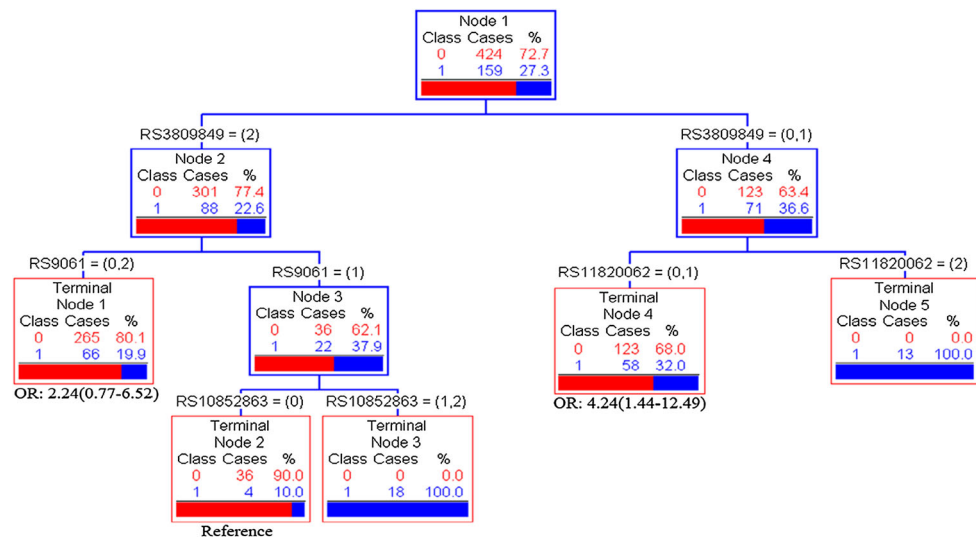
acting as protected *MTB* sanctuaries. However, sometimes, the apoptosis of macrophages is of help for *MTB* to elude immune system surveillance and spread surviving bacilli [13]. Thus, the association between the *SP110* and PTB might be due to decreased replication of the bacilli in the macrophage rather than to extracellular spread of surviving bacilli and lung cavitation.

It should be noted that genotype distribution of each SNP is not found to be significantly different between cavitory PTB patients and non-cavitory PTB ones. Although the heterozygous genotype GC in rs3809849 is associated with lung cavity formation ($p = 0.015$), after adjustment using Bonferroni's method, no genotype of

each SNP was found to be significantly associated with lung cavitation formation. Thus, the *MYBBP1A* interpreted as a predisposed risk factor to cavitory PTB might be not via the effects on the lung cavitation formation. However, given the possibility of most non-cavitory PTB patients with other severe features, genetic analyses between patients with and without cavitory PTB would not obtain real results. And thus, the comparison between patients with cavitory PTB and healthy controls is proper.

Furthermore, we performed multiple methods including MDR and CART, which could identify many genes interactions based on genetic data. Compared with traditional parametric statistical methods, such as logistic regression

Fig. 1 Classification and regression tree (CART) analysis of *MYBBP1A*, *SP110* and *RELA* gene polymorphism in case of cavitory PTB. Class 0 refers to the healthy controls corresponding to the red bar, and class 1 refers to the TB patients corresponding to the blue bar (color figure online)



analysis, MDR analysis, which uses a nonparametric/model-free approach to detect nonlinear interactions among discrete genetic factors, can more easily characterize the complex multifactor interactions with the sparseness of the data in certain dimensions and of the insufficient power. The results reflect that rs3809849 in *MYBBP1A* has strong association with cavitory PTB as being the only one factor in the best MDR model and the first split in CART. Both CART and MDR results suggest there is the interaction between the rs3809849 polymorphism in *MYBBP1A* with rs11820062 polymorphism in *RELA*. *MYBBP1A* is a transcription factor critical for hematopoietic cell proliferation and differentiation. This finding is consistent with that *MYBBP1A* can bind to *RELA* in Jurkat T cells [7]. *RELA* is a member of the NF- κ B family of structurally related inducible transcription factors [14]. NF- κ B, which is known to interact with IFN- γ during TB development, regulates the expression of a wide variety of human genes, including factors regulating apoptosis [15, 16]. This interaction might be a potential risk factor for cavitory PTB.

There may be some limits to the current study. The sample size of current study is not large. However, based on the effect size of 0.15, the minimum total sample size needed is 732 at 5 % level of significance with a power value of 90 %. A total of 848 samples in the present study can meet this criterion. And the environment risk factors, such as smoking, are not studied. Smoking is well known to exacerbate most lung diseases, and the present study provides only genetic information about the genes involved in cavitory PTB.

The percentage of pulmonary TB cases suffer from cavitory disease varies significantly by age and other risk factors from 50 to 80 % [1]. However, PTB patients with cavitory disease are more contagious than those without

and have increased risk of relapse. The current study suggests that *MYBBP1A* may be a genetic risk factor for cavitory PTB, and hints that when treating patients with cavitory PTB, physicians may need pay extra attention on the genetic factors and provide individual therapy.

Conclusion

In conclusion, *MYBBP1A* and *SP110* may be genetic risk factors for TB in the Han Chinese population. *MYBBP1A* rather than *SP110* may play important roles in predisposing risk to cavitory PTB.

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Conflict of interest None.

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