Genetic polymorphisms of rs12437118 in ESRRB locus associated with tuberculosis susceptibility in a Chinese Han population

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Abstract

ESRRB (Estrogen Related Receptor Beta) plays a crucial role in stem cells self-renewal, naïve pluripotency, and early development of the embryo via participating in regulation of chromatin remodeling. The objective was to investigate whether rs12437118 in ESRRB locus was associated with tuberculosis susceptibility in a Chinese Han cohort. A total of 607 TB patients and 660 healthcare workers were enrolled for this study. ESRRB rs12437118 polymorphisms genotyping was performed by competitive allele-specific PCR (KASP) assay. ESRRB plasma expression level was detected by enzyme linked immunosorbent assay (ELISA). Logistic regression was used to calculated odds ratios (ORs) and 95% confidence intervals (CIs). Genotype GA showed a decreased risk of TB (P = 0.014, OR = 0.745, 95%CI: 0.59–0.94). No association with TB risk was found for other genotypes and any genetic model. ESRRB expression lower in TB patients than in healthy controls, but no association was found between ESRRB expression level in plasma and different genotypes of rs12437118. Our results demonstrated that genotype GA of rs12437118 decreased risk of TB in a Han cohort in North of China.

1 Introduction

Tuberculosis (TB) disease caused by *Mycobacterium tuberculosis*(MTB)infection is still a worldwide public health problem, and remains the top infectious killer worldwide with nearly 9.9 million new TB cases and 1.5 million deaths in 2021(Organization., 2019). Approximate one third of the world's population is thought to have latent TB infection (LTBI), and 5–10% of the LTBI population has a lifetime risk of developing active TB disease(Mushtaq, 2020). Not all individuals with MTB exposure history will become infected or developed active TB disease. It’s incontestable that human genetic factors play a major role in TB pathogenesis and resistance mechanism(Moller et al., 2018; Moller and Kinnear, 2020; Aravindan, 2019).

Accumulating evidences from Genome-Wide Association Studies(GWAS)(Miao et al., 2018; Zheng et al., 2018; Queiros et al., 2018; Grant et al., 2016; Png et al., 2012), candidate gene studies(Wu et al., 2019; Tang et al., 2009; Ghamari et al., 2016; Liu et al., 2020) and meta-analysis studies(Zhou and Zhang, 2019; Xu and Shen, 2019; Alshammari et al., 2016; Chen and Ma, 2020; Yu et al., 2019; Tong et al., 2019), discovered many contributing genes and variants associated with TB susceptibility. A noncoding variant rs557011 located in intergenic region between *HLA-DQA1* and *HLA-DRB1* was associated with *MTB* infection and TB disease progression, while another variant rs9271378 located in the same region does not associate with *MTB* infection but protects against development of TB disease in those infected individuals(Sveinbjornsson et al., 2016). Besides, numerous evidences provide an association between host genetic polymorphisms and TB susceptibility including Vitamin D receptor, interferon gamma (IFNG) and IFNG receptor 1, IRGMI, interleukin (IL) 8, toll-like receptor (TLR), and nucleotide-binding oligomerization domain-containing protein 2 (NOD 2) genes(Xu and Shen, 2019; Wu et al., 2019).

Estrogen-related receptor beta (ESRRB) is a member of estrogen-related receptors (ERRs) belonging to the NR3B subgroup of nuclear receptors(Tremblay and Giguere, 2007). ESRRB majorly participates in

chromosome reprogramming involved in controlling of energy homeostasis, cell development and differentiation(Festuccia et al., 2018). In a GWAS study reported in 2018, rs12437118 (at 14q24.3) was identified as a TB susceptibility SNP, and located in an intergenic region approximately 16 kb downstream of *ESRRB* gene. In the previous GWAS study, volunteers recruitment mainly from southern cities of China, while the frequencies for risk allele A of rs12437118 ranged from 0.261 to 0.288(Zheng et al., 2018), which was a slightly lower than that in northern China where the frequencies for allele A of rs12437118 was 0.31(Hunt et al., 2018).

To date, fewer studies have been conducted to investigate the relationship between ESRRB polymorphisms and TB risk. Therefore, we carried out a case control study to validate the correlation between rs12437118 polymorphisms and TB risk in a north Chinese Han cohort.

2 Materials And Methods

2.1 Ethics

The study was conducted according to the Declaration of Helsinki principles. The protocol was approved by the local ethics committee of Beijing Chest Hospital Affiliated to Capital Medical University (permit number: 2018-41-01).

2.2 Participants

TB patients above 18 years old were recruited from Beijing Chest Hospital Affiliated to Capital Medical University. Diagnostic criteria for TB was according to the following criteria: sputum culture for MTB, acid-fast stain test of sputum smear, radiological signs (such as X-ray or computed tomography scan) combined with clinical symptoms. Heathy controls were recruited from employees working for more than 2 years in Beijing Chest Hospital Affiliated to Capital Medical University. Those who with a history of prior anti-TB treatment were excluded. Those participants diagnosed as diabetes mellitus, human immunodeficiency virus (HIV) co-infection, or in receipt of immunosuppressive therapy were also excluded.

2.3 Genomic DNA extraction

Total of 2 ml blood samples were collected from the participants in this study. No Genomic DNA extraction were conducted using Whole Blood DNA Extraction Kit (Bio Teke, Wuxi, China) according to the manufacturer's instructions. The extracted genome DNA was diluted to working concentration of 50 ng/μL for genotyping analysis.

2.4 Genotyping

Genotyping was performed by using KASP assay a fluorescence-based competitive allele-specific PCR (LGC Genomics, Hoddesdon, UK) (Wang et al., 2018; Alshammari et al., 2016). Primers used in this study were summarized as Supplementary Table S1. For quality control, we repeatedly genotyped 3% of the

total samples by sanger sequencing (Sangon Biotech, Shanghai, China). The concordance rate of the repeated cases reached 100%, which verified that the genotyping results were reliable.

2.5 ELISA assay for ESRRB

Plasma was separated from blood samples by centrifugation and then stored at − 80°C until analysis. ESRRB expression levels in plasma were determined by using a Human ESRRB ELISA kit (Beijing FreeMore Bioscience, Co., LTD) according to the manufacturer's instructions.

2.6 Statistical Analysis

The Hardy-Weinberg Equilibrium (HWE) for ESRRB polymorphisms distribution was analyzed respectively in cases and controls by using Pearson chi-square test(Wigginton et al., 2005). The allelic and genotypic frequencies of rs12437118 between cases and controls were compared using the IBM SPSS Statistics 22.0 software (SPSS, Inc., Chicago, IL, USA). The plasma ESRRB expression data among different genotypes was calculated with Graph-Pad Prism 9.0 software (GraphPad, San Diego, CA, USA). Mann-Whitney U test was used to analyze the difference of ESRRB expression between TB cases and controls. One-way ANOVA followed by Bonferroni post hoc test was conducted to analyze genetic effect on ESRRB expression. The unconditional logistic regression adjusted by gender and age were performed to calculate the odd ratios (ORs), 95% confidence intervals (CIs) and corresponding *p* values under three alternative models (additive, dominant and recessive). *p* values less than 0.05 were considered to indicate statistical significance, and the number of asterisks represents the degree of significance with regarding to the *p* values.

3 Results

3.1 Clinical characteristics of study subjects

The basic information of study subjects is listed in Table 1. A total of 607 patients with TB and 660 healthcare workers were enrolled in the study. The mean age was 37.74 ± 10.14 years for the PTB group and 39.56 ± 10.20 years for the control group. There were no significant differences in the distribution of gender and age between PTB cases and controls ($p > 0.05$).

Table 1
General characteristics of study subjects.

characteristics	cases (*n* = 607)	controls (n = 660)	*P*-value	OR (95% CI)
Gender				
Male, n (%)	310 (51.07%)	309 (46.81%)	0.130	1.186(0.951–1.478)
Female, n (%)	297 (48.93%)	351 (53.19%)		
Age,(years)				
18–49	450	495	0.084	1.239(0.957–1.605)
50–70	157	165		
Abbreviations: OR, odds ratio.				

3.2 Allele and genotype frequencies of ESRRB gene

The genotypic and allelic frequencies of ESRRB rs12437118 gene polymorphism in cases and controls are presented in Table 2. The GG, GA and AA genotypic frequencies of rs12437118 were 50.7%, 38.1%, and 11.7% in cases, 44.8%, 45.7%, and 9.5% in healthy controls, respectively. However, it showed that there was no significant difference in allelic frequencies between tuberculosis patients and controls. GA genotype is a is associated with decreasing TB risk and the estimated OR of 0.75, ranging from 0.59 to 0.95 (*P*-value of 0.014 after adjusting for age and gender). Obtained genotypic frequencies for the SNP did not significantly deviate from Hardy-Weinberg equilibrium expectations in control group (*P*-value is 0.28 > 0.05).

Table 2
Genotypic and allelic frequencies distributions in TB cases and healthy controls.

SNP		cases, n (%)	Controls, n (%)	*P*-value*	OR (95%CI) *
rs12437118	Genotypes				
G > A	GG	305(50.7%)	296(44.8%)		
	GA	231(38.1%)	301(45.7%)	**0.014**	0.75 (0.59, 0.95)
	AA	71(11.7%)	63(9.5%)	0.640	1.09 (0.75, 1.59)
	Alleles				
	G	841(69.3%)	893(67.7%)		
	A	373(30.7%)	427(32.3%)	0.380	1.08 (0.91, 1.28)
Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio. Bold indicates statistically significant value. *Adjusted by age, gender.					

3.3 Associations between the *ESRRB* gene polymorphism and TB risk

We assessed the associations of the *ESRRB* rs12437118 polymorphism with TB in different genetic models, including dominant and recessive models (Table 3). The rs12437118 polymorphism failed to show significant association in both dominant (*P*-value is 0.214) and recessive (*P*-value is 0.055) genetic models.

Table 3
Association between rs12437118 SNP and risk of TB under different genetic models.

Model	Genotype	Cases (*n* = 607)	Controls (n = 660)	OR(95%CI)	*P*-value*
Dominant (AA + GA vs. GG)	AA	71	63	1.255(0.887–1.797)	0.214
	GG + GA	536	597		
Recessive (GG vs. AA + GA)	GG	305	296	1.242(0.996–1.549)	0.055
	AA + GA	302	364		
Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio. *Adjusted by age, gender.					

3.4 Association of ESRRB levels in plasma with TB

To evaluate the potential biological function of rs12437118, we detect the ESRRB expression in plasma from 141 TB patients and 147 healthy controls carrying different genotypes using an ESRRB ELISA assay kit. The results show that the ESRRB level in TB patients were significantly lower than in healthy controls (*P*- value is 0.000) (Fig. 1a), which further indicated that the plasma ESRRB may play an important role in TB progression. In TB group, G allele carriers had significantly lower ESRRB expression in plasma than A allele, no statistical difference was found in ESRRB expression among different genotypes in health control group (Fig. 1b).

4 Discussion

ESRRB is a member of the orphan nuclear receptor play a vital role of pluripotency network in embryonic stem cells (ESCs)(Festuccia et al., 2018), and involved in early development and reprogramming(Adachi et al., 2018; Festuccia et al., 2018). ESRRB gene variations were associated with rotator cuff injury(Longo et al., 2019), hearing loss (Noman et al., 2019) and dental caries(Weber et al., 2014). To date, few studies were reported about ESRRB and tuberculosis. ESRRB is a pivotal target of the Wnt signaling pathway(Papp and Plath, 2012). Remarkably, Wnt signaling pathway plays a key role at different stages

of TB prognosis, including *M. tuberculosis* survival in the macrophages, modulation of the inflammatory response, and later on granuloma formation and to control the adaptive immune response(Villasenor et al., 2017; Gao et al., 2019). A transcriptome analysis result referred that ESRRB is one of the key transcriptional regulatory factors involved in the regulation of the ratio of monocytes and lymphocytes (ML ratio) through regulating genes involved in type-I and -II interferon signal pathways, and the elevated peripheral blood ML ratio is associated with risk of TB disease in adults, infants, and pregnant women(Naranbhai et al., 2015), while further specific mechanisms remain to be investigated. According to a three-stage GWAS carried out in the Han Chinese population (2949 pulmonary TB patients and 5090 healthy controls), two risk loci were identified, the one was intergenic rs12437118 of ESRRB loci on chromosome 14q24.3 [odds ratio (OR) 1.28, 95% confidence interval (CI) 1.19–1.37], but no difference was detected between rs12437118 and ESRRB mRNA in PBMCs(Zheng et al., 2018). In our study, the results show that people with GA genotype have a decreased risk of TB [OR 0.75, 95%CI (0.59, 0.95)]. The A allele does not increase the risk of tuberculosis in this cohort [OR 1.08, 95%CI (0.91, 1.28)]. While from a precious study, it was found that A allele of rs12437118 increase TB risk in Chinese Han cohort from south of China(Zheng et al., 2018). To explore the reasons for the inconsistent results between these two studies. Firstly, participants in our study are recruited from Beijing located in the north of China. According to the ensemble database the frequencies for allele A in south of China is 0.27, while in Beijing is 0.31 little higher than south of China (Hunt et al., 2018). Secondly, it's possibly be associated with the inclusion criteria of the heathy control participants. In our study, all healthy control participants are working in TB high-risk environment for more than 2 years, while TB contact history was not described in the precious study. Tuberculosis contact history of health participants makes the data acquired from our study more reliable.

Furthermore, we found that plasma ESRRB expression level is significantly lower in TB patients than heath controls, but there is no statistical difference among different rs12437118 genotypes. This result show that rs12437118 polymorphisms is not the key regulator involved in ESRRB expression during the disease process of TB. The molecular mechanism Further studies warrants additional studies.

Our study reports the first data describing the association between ESRRB rs12437118 polymorphisms and TB in Northern Han Chinese population. The results indicate that GA genotype maybe a protective factor of TB. Till now, the function and molecular mechanism of ESRRB in TB infection still need further research. However, whether this intronic SNP regulates gene expression via modulating suppressor activity warrants further investigation.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Lingjuan Zhao, Yong Sun. ELISA test was carried out by Weicong Ren and Xuxia Zhang. The first draft of the manuscript was written by Wei Wang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The data used to support the findings of this study are included within the article.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local ethics committee of Beijing Chest Hospital Affiliated to Capital Medical University (permit number: 2018-41-01).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

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Figures

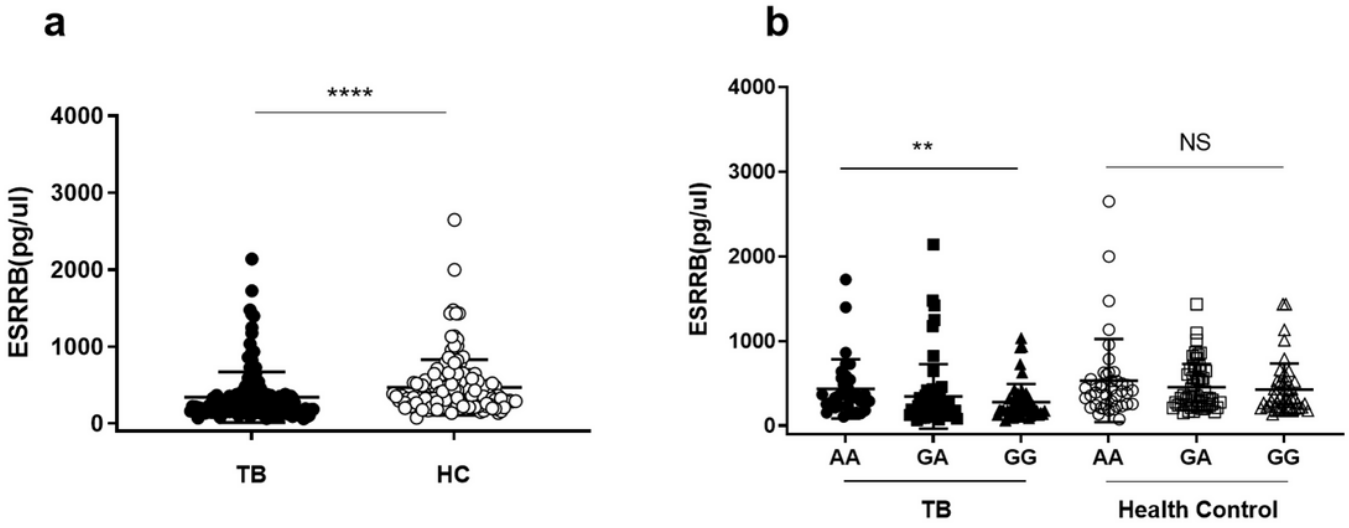

Figure 1

Association of SNP rs12437118 with ESRRB expression in plasma.

Plasma was isolated from 141 TB patients (TB) and 147 healthy individuals (HC). ESRRB expression was measured via ELISA test. a. ESRRB expression in TB and HC respectively. b. The association between ESRRB expression and rs12437118 genotype. Each symbol represents an individual. Data are representative of one independent experiments. Data shown were mean ± SD and statistical significance was determined via linear regression, ****, $P < 0.0001$; ** $P < 0.001$; NS, not significant.