Genetic Variations of Angiotensinogen, Angiotensin Converting Enzyme, and Angiotensin Type 1 Receptor with the Risk of Pulmonary Tuberculosis

Hamidreza Kouhpayeh[1], Mohammad Naderi[1], Zahra Mohammadghasemipour[1], Gholamreza Bahari[2], Nastaran Elahian[3], Mohsen Taheri[3,4], Mohammad Hashemi[3†]

[1] Infectious Diseases and Tropical Medicine Research Center, Zahedan University of Medical Sciences, Zahedan, Iran;
[2] Children and Adolescent Health Research Center, Zahedan University of Medical Sciences, Zahedan, Iran;
[3] Genetics of Non-Communicable Disease Research Center, Zahedan University of Medical Sciences, Zahedan, Iran;
[4] Department of Genetic, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran
[†] Deceased

Received September 4, 2023; Accepted January 30, 2024.

Key words: Tuberculosis – Angiotensin – Angiotensin converting enzyme – Angiotensin type 1 receptor – Polymorphism

Abstract: There is little data regarding the impact of renin-angiotensin system (RAS) gene polymorphisms on tuberculosis. The current study designed to survey the possible association between RAS polymorphisms and the risk of pulmonary tuberculosis (PTB) in a sample of the southeast Iranian population. This case-control study was done on 170 PTB patients and 170 healthy subjects. The AGT rs699 C>T, ACE rs4341 C>G and AT1R rs5186 C>A variants were genotyped using polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) and ACE rs4646994 (287bp I/D) variant by PCR method. Regarding AT1R rs5186 A>C polymorphism, the findings revealed that AC genotype and C allele significantly

This study was supported by a dissertation research grant (M.D. thesis of ZMG #8299) from Zahedan University of Medical Sciences.

Mailing Address: Prof. Mohsen Taheri, PhD., Department of Genetic, School of Medicine, Zahedan University of Medical Sciences, Khalije Fars Ave, Hesabi Square, Zahedan 9816743463, Iran; Phone: +98 541 333 721 16; e-mails: mohsen.taheri.gene@gmail.com, taheri@zaums.ac.ir

https://doi.org/10.14712/23362936.2024.1

decreased the risk of PTB (OR=0.39, 95% CI=0.22–0.67, p=0.001, and OR=0.53, 95% CI=0.25–0.72, p=0.002, C vs. A, respectively). The TC genotype and C allele of AGT rs699 T>C significantly associated with decreased the risk of PTB (OR=0.45, 95% CI=0.28–0.74, p=0.002, TC vs. TT and OR=0.51, 95% CI=0.32–0.80, p=0.005, C vs. T, respectively). The ID genotype of ACE 287bp I/D significantly increased the risk of PTB (OR=1.88, 95% CI=1.12–3.17, p=0.017). Our finding did not support an association between ACE rs4341 C>G variant and the risk of PTB. In summary, the findings revealed an association between AT1R rs5186 A>C, AGT rs699 T>C and ACE 287bp I/D polymorphisms and the risk of PTB in a sample of the southeast Iranian population. Further investigation with higher sample sizes and diverse ethnicities are required to confirm our findings.

Introduction

Tuberculosis (TB), an infectious disease caused by *Mycobacterium tuberculosis* (MTB) complex, is still a main public health problem globally and remains the top infectious killer in 2020 (World Health Organization, 2021). The *Mycobacterium tuberculosis* complex constitutes a genetically related group of bacteria that can cause tuberculosis in humans or in animals. The human pathogens are *Mycobacterium tuberculosis*, *Mycobacterium africanum*, and *Mycobacterium bovis*. Among them *Mycobacterium tuberculosis* is the most important human pathogen (Zhang et al., 2022). According to Global Tuberculosis Report 2021, there were expected 10.4 million new TB cases worldwide in 2016 (World Health Organization, 2021). Approximately one third of the world's population is infected with TB. Only about 5–10% infected cases will develop active TB (Taheri et al., 2020; Wu et al., 2020), which proposes a key role of genetic factors in host immunity. Until now, various genes have been recognized as TB candidate genes and variants in these genes have been proposed as risk factors for the disease (Naderi et al., 2014; Taheri et al., 2019; Li et al., 2022).

Renin-angiotensin system (RAS) is usually supposed as an endocrine system that regulates salt, water balance, and blood pressure. Current data have shown that renin and angiotensinogen genes and their products, well-known as local RAS, are also expressed locally at several tissue sites, where they function as major regulators of various physiological and pathophysiological processes (Su et al., 2021; Oosthuizen and Sturrock, 2022). Angiotensin II (AngII), the key effector of the RAS, mediates blood pressure-independent effects leading to target organ damage via diverse inflammatory processes, including activation of nuclear factor kappa B (NF-κB), mitogen-activated protein kinases (MAPK), and Janus-activated kinase-2 (JAK-2)/signal transducers and activators of transcription (STAT) (Kranzhofer et al., 1999; Seyedabadi et al., 2001; Cantero-Navarro et al., 2021). Activation of these signalling pathways may lead to overexpression of pro-inflammatory cytokines, chemokines, cell adhesion molecules, as well as elevation of reactive oxygen species

(ROS) (Hernandez-Presa et al., 1997; Kranzhofer et al., 1999; Seyedabadi et al., 2001; Esteban et al., 2004; Brasier, 2010).

Angiotensin converting enzyme (ACE) is an important component of the renin-angiotensin system (RAS). There are some studies indicating the raised serum levels of ACE in granulomatous diseases (Brice et al., 1995; Kwon et al., 2007; Lopez-Sublet et al., 2018). The cells in the macrophage-phagocytic system within the granulomas secret ACE into circulation (Lopez-Sublet et al., 2018). ACE polymorphism may influence the serum level of ACE. A functional insertion/deletion (I/D) polymorphism in the ACE gene has been recognized (Ristic et al., 2017). The ACE insertion/deletion (I/D) polymorphism is based on a 287bp Alu repeat sequence within intron 16 (Gong et al., 2012; Yigit et al., 2013). The ACE D/D genotype is associated with higher levels of serum ACE (Ay et al., 2007; Lopez-Sublet et al., 2018). Limited study investigated the impact of RAS polymorphisms and the risk of TB (Ogarkov et al., 2008; Zhang et al., 2014) and the findings were controversial. In the present study, we aimed to inspect the possible association between AGT rs699 C>T, ACE rs4341 C>G, ACE 287bp I/D, and AT1R rs5186 C>A variants and the risk of pulmonary tuberculosis (PTB) in as sample of the southeast Iranian population.

Material and Methods

Patients

The present case-control study was achieved on 170 PTB patients and 170 ages and sex matched healthy subjects. The enrolment procedure and the study design are described elsewhere (Kouhpayeh et al., 2012; Naderi et al., 2015, 2016a, b). Briefly, the cases were selected from PTB patients admitted to a university-affiliated hospital (Bou-Ali Hospital, Zahedan, referral center for TB). PTB was diagnosed according to the basis of clinical symptoms, acid-fast bacilli (AFB) smear-positive sputum, chest radiography, and culture positive for *M. tuberculosis*. The controls were unrelated adults chosen through the population without sign, symptom or history of TB. The project was approved by the local ethics committee of Zahedan University of Medical Sciences (IR.ZAUMS.REC.1396.073) and informed consent was taken from all participants. Extracting of genomic DNA from whole blood samples was done using salting out method.

Genotyping

Genotyping of the variants were performed using PCR-RFLP or PCR method. The primer sequences are shown in Table 1. In each 0.20 ml PCR reaction tube, 1 µl of genomic DNA (~100 ng/µl), 1 µl of each primer (10 µM), and 10 µl of 2X Prime Taq Premix (Genet Bio, Korea) and 7 µl ddH_2O were added.

Amplification was done with an initial denaturation step of 5 min at 95 °C followed by 30 cycles of 30 s at 95 °C, annealing at 68 °C for AGT rs699, 60 °C for AT1R

Table 1 – Primers sequences used for detection of the gene polymorphisms

Polymorphisms	Sequence (5'→3')	Restriction enzyme	Product size (bp)	Annealing temperature (°C)
AGT rs699	F: CCGTTTGTGCAGGGCCTGGCTCTCT R: CAGGGTGCTGTCCACACTGGACCCC	Tth111I	T allele: 165 C allele: 141+24	68
AT1R rs5186	F: AGAAGCCTGCACCATGTTTTGAG R: CCTGTTGCTCCTCTAACGATTTA	DdeI	A allele: 410bp C allele: 292+118	60
ACE rs4341 C>G	F: CGCCAATTTTATTCCAGCTC R: TCGGGTAAAACTGGAGGATG	BsmI	C allele: 200bp G allele: 123+77	58
ACE rs4646994 (287bp I/D)	F: GCCCTGCAGGTGTCTGCAGCATGT R: GGATGGCTCTCCCCGCCTTGTCTC	–	I allele: 599bp D allele: 312bp	66

rs5186, 58 °C for ACE rs4341 and 66 °C for ACE rs4646994 for 30 s and extension at 72 °C for 30 s, final extension was performed at 72 °C for 5 min.

For genotyping, 10 µl of PCR products was digested with appropriate restriction enzyme (Table 1) and then separated by electrophoresis in 2.5% agarose gels.

Statistical analysis

Statistical analysis was achieved using the SPSS 20.0 software. The analysis was done by chi-square test or independent sample *t*-test according to the data. The associations between genotypes and PTB were calculated by calculating the odds ratio (OR) and 95% confidence intervals (95% CI) from unconditional logistic regression analyses. P-value < 0.05 was considered statistically significant.

Results

A total of 340 subjects including 170 confirmed PTB patients (66 males, 104 females; ages 50.1 ± 20.3) and 170 unrelated healthy subjects (79 males, 91 females; ages 49.3 ± 14.8). There was no statistically significant difference between the groups regarding sex and age (P=0.188, and 0.703, respectively).

Genotypes and allele frequencies of AGT rs699 C>T, ACE rs4341 C>G, AT1R rs5186 C>A and ACE rs4646994 (289bp I/D) polymorphisms are shown in Table 2.

Regarding AT1R rs5186 A>C polymorphism, the findings revealed that AC genotype and C allele significantly decreased the risk of PTB (OR = 0.39, 95% CI = 0.22–0.67, p=0.001, AC vs. AA and OR = 0.43, 95% CI = 0.25–0.72, p=0.002, C vs. A, respectively). The TC genotype and C allele of AGT rs699 T>C significantly associated with decreased the risk of PTB (OR = 0.45, 95% CI = 0.28–0.74, p=0.002, TC vs. TT and OR = 0.51, 95% CI = 0.32–0.80, p=0.005, C vs. T, respectively). The ID genotype of ACE 287bp I/D significantly increased the risk of PTB (OR = 1.88, 95% CI = 1.12–3.17, p=0.017). Our finding did not support an association between ACE rs4341 C>G variant and the risk of PTB.

Discussion

A large number of tuberculosis susceptibility genes have been recognized and polymorphisms in these genes have been proposed as risk factors for TB (Bahari et al., 2013; Naderi et al., 2014; Hashemi et al., 2015; Kim et al., 2021; Li et al., 2022). The ACE gene, an important component of the RAS, is one of the candidate genes for TB (Kwon et al., 2007; Zhang et al., 2014). It has been proposed that ACE effect the potency of immunological response, and thus could play potential roles in the pathogenesis of TB (Ogarkov et al., 2008; Nakamura et al., 2018). Individuals with deterioration of the immune system have a much higher risk of falling ill from TB. We examined the possible association between AGT rs699 C>T, ACE rs4341

Table 2 – Frequency distribution of genotypes and allele frequencies of AT1R (rs5186), ACE (rs4341 and 289bp I/D) and AGT (rs699) polymorphisms in PTB and controls

Polymorphisms	Case n (%)	Control n (%)	OR (95% CI)	P
AT1R rs5186 A>C				
Genotype				
AA	148 (87.1)	123 (72.4)	1.00	–
AC	22 (12.9)	47 (27.6)	0.39 (0.22–0.67)	0.001
CC	0 (0.0)	0 (0.0)	–	–
Allele				
A	318 (93.5)	293 (86.2)	1.00	–
C	22 (6.5)	47 (13.8)	0.43 (0.25–0.72)	0.002
ACE 287bp I/D				
Genotype				
II	36 (21.2)	51 (30.0)	1.00	–
ID	101 (59.4)	76 (44.7)	1.88 (1.12–3.17)	0.017
DD	33 (19.4)	43 (25.3)	1.09 (0.58–2.03)	0.792
Allele				
I	173 (50.9)	178 (52.4)	1.00	–
D	167 (49.1)	162 (47.6)	1.06 (0.78–1.43)	0.759
ACE rs4341 C>G				
Genotype				
CC	54 (31.8)	48 (28.2)	1.00	–
CG	70 (41.2)	93 (54.7)	0.67 (0.41–1.10)	0.113
GG	46 (27.1)	29 (17.1)	1.41 (0.77–2.58)	0.266
Allele				
C	178 (52.4)	189 (55.6)	1.00	–
G	162 (47.6)	151 (44.4)	1.14 (0.85–1.53)	0.442
AGT rs699 T>C				
Genotype				
TT	137 (80.6)	111 (65.3)	1.00	–
TC	33 (19.4)	59 (34.7)	0.45 (0.28–0.74)	0.002
CC	0 (0.0)	0 (0.0)	–	–
Allele				
T	307 (90.3)	281 (82.6)	1.00	–
C	33 (9.7)	59 (17.4)	0.51 (0.32–0.80)	0.005

PTB – pulmonary tuberculosis; OR – odds ratio; CI – confidence intervals

C>G, ACE 287bp I/D, and AT1R rs5186 C>A polymorphisms and the risk of PTB in as sample of the southeast Iranian population. Our findings showed that AC genotype and C allele of AT1R rs5186 polymorphism significantly decreased the risk of PTB. We found a significant association between rs699 T>C variant and PTB. So that the TC genotype and C allele significantly decreased the risk of PTB. The ID genotype of ACE 287bp I/D significantly increased the risk of PTB. Our finding did not support an association between ACE rs4341 C>G variant and the risk of PTB.

To the best of our knowledge, there is only one report concerning the impact of RAS on TB. Zhang et al. (2014) performed a case-control study with the aim to assess the association between ACE 287bp I/D and PTB in Chinese population. In contrast to our findings, they reported that the I/D polymorphism was not associated with susceptibility to PTB.

ACE elevated production of ROS and the activation of redox-dependent signalling cascades are critically involved in AGT II activities (Touyz, 2003). AGT II binds to AT1R and triggers intracellular superoxide production (Griendling and Ushio-Fukai, 2000; Mollnau et al., 2002; Kimura et al., 2005). AGT II also increases nitric oxide (NO) generation (Pueyo et al., 1998), and since the reaction of NO with superoxide generates peroxynitrite, it can stimulate the production of ROS and reactive nitrogen species (RNS) and reduce NO availability (Pueyo et al., 1998; Mollnau et al., 2002). The serum levels of ACE were not significantly different between patients with active PTB and healthy control subjects. While, an inverse relationship between the diameter of the cutaneous reaction to tuberculin and serum ACE levels was found (Grange et al., 1984). This inverse association results may be due to competition for receptor sites for the related signal molecules on the macrophage cell surface (Grange et al., 1984).

There are some limitations in the study, one of which is relatively small sample sizes. Second limitation is that we did not determine the plasma levels of ACE. Despite the limitation, our results provide new data regarding the impact of AT1R, AGT, and ACE polymorphisms on PTB in a sample of the southeast Iranian population, which could be useful for futures studies.

In summary, our finding proposed that AT1R rs5186 A>C and AGT rs699 T>C significantly decreased and the ACE 287bp I/D polymorphism significantly increased the risk of PTB. Our findings require replication in a larger independent genetic association study.

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