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Association of *monocyte chemoattractant protein-1* rs1024611 and *telomerase* rs2736100 polymorphisms with susceptibility to pulmonary tuberculosis in Han Chinese population

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ABSTRACT. Pulmonary tuberculosis (PTB) is caused by *Mycobacterium tuberculosis* infection and accumulated evidence reveals the genetic context of its infection phenotypes. *Monocyte chemoattractant protein-1* (*MCP-1*) rs1024611 variant is shown to be associated with PTB susceptibility in some studies, but

significant disparities exist. In addition, telomerase plays a key role in immunocompetence, and the *telomerase reverse transcriptase* (*TERT*) polymorphism is associated with susceptibility to different diseases. We, thus, determined the relationship between *MCP-1* rs1024611 and *TERT* rs2736100 variants and PTB susceptibility by genotyping 183 Han Chinese patients with active PTB and 210 ethnicity/age/sex-matched healthy controls. The rs1024611_GG genotype was found at a higher frequency in controls than in patients with PTB. The GA genotype exhibited significantly reduced risk of PTB (P = 0.03). When GA and AA genotypes were grouped together, the GG variant remained at a significantly higher risk for PTB (P = 0.042). Further analyses revealed that the risk occurred in males, but not females (P = 0.037). There was no difference in *TERT* rs2736100 genotypes between controls and patients, suggesting the lack of association of this genetic variant with PTB risk. Taken together, Han Chinese male rs1024611_GG-carriers exhibit a significantly higher susceptibility to active PTB.

Key words: MCP-1; Telomerase; TERT; Pulmonary tuberculosis; Single nucleotide polymorphisms

INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* infection, remains a huge global health concern, contributing to 1.5 million deaths and 9 million new cases annually worldwide (Cudahy and Shenoi, 2016). Enormous evolutionary pressures on the interactions between host and pathogen genomes have been suggested due to widespread *M. tuberculosis* infection in the human race over a prolonged duration (Azad et al., 2012). Indeed, genetic epidemiological studies have suggested the host-genetic background of susceptibility to TB; (Azad et al., 2012) moreover, recent genome-wide association study further identified a panel of single nucleotide polymorphisms (SNPs) associated with TB susceptibility. Because the host immune system, responsible for both innate and adaptive immunity, plays a key role in controlling TB infection, along with the involvement of several different cell types, including dendritic cells, macrophages, natural killer (NK) cells, T cells, B cells, and neutrophils, its association with genetic variants of immune response factors has been extensively studied (Azad et al., 2012; Fol et al., 2015). Until now, variations in genes encoding IL-23 receptor, CD14, CD209, CD206, FOXO3, Toll-like receptors, TNF-α, HLAs, IFNγ, CTLA4, etc. have been found to affect TB susceptibility (Banoei et al., 2010; Azad et al., 2012; Chen et al., 2015; Fol et al., 2015; Wu et al., 2015; Kuai et al., 2016; Lv et al., 2016).

Monocyte chemoattractant protein-1 (MCP-1) (also known as CCL2) is a small molecular weight protein belonging to the C-C chemokine family, and has strong chemotactic behavior towards monocytes, NK cells, and CD4+ T cells; during inflammation caused by injury or infection, MCP-1 recruits these cells to the inflammatory sites (Fol et al., 2015; Vásquez-Loarte et al., 2015). In TB infection, the presence of sufficient MCP-1 is required for granuloma formation and *M. tuberculosis* clearance, (Flores-Villanueva et al., 2005; Vásquez-Loarte et al., 2015) while the SNP A2518G in the MCP-1 promoter (rs1024611) substantially influences its expression (Flores-Villanueva et al., 2005). In a previous study on Mexican

and Korean subjects, Flores-Villanueva et al. observed that the MCP-1 rs1024611 G allele was significantly associated with susceptibility to PTB (Flores-Villanueva et al., 2005). However, recent analyses of PTB from South Africa, the USA, Argentina, and Iran failed to show this association (Alagarasu et al., 2009; Ganachari et al., 2010; Ben-Selma et al., 2011; Hussain et al., 2011; Naderi et al., 2011; Arji et al., 2012; Feng et al., 2012; Mishra et al., 2012; Velez Edwards et al., 2012; Gong et al., 2013; Vásquez-Loarte et al., 2015). Intriguingly, in case of the Han Chinese ethnic group, the obtained results differed between subjects from Hong Kong and Mainland China (Chu et al., 2007; Xu et al., 2009; Yang et al., 2009). Therefore, it is absolutely necessary to further define the relationship between the *MCP-1* rs1024611 SNPs and PTB.

Telomerase, an RNA-dependent DNA polymerase, plays important roles in regulating cellular life-span, and its activation, which is required for their sustained proliferation and functionality, is a characteristic of activated immune cells (Ge et al., 2006; Calado and Young, 2009; Daniel et al., 2012; Kong et al., 2014). In contrast, impaired telomerase activation is associated with immune system senescence and lower activity against pathogens (Ge et al., 2006; Calado and Young, 2009; Fujii et al., 2009; Cohen et al., 2013). Telomerase reverse transcriptase (TERT) is the rate-limiting catalytic component of telomerase, (Daniel et al., 2012; Kong et al., 2014) and there are multiple SNPs in the *TERT* locus, among which rs2736100 is the most studied (Mocellin et al., 2012; Yuan et al., 2016). The rs2736100 variant has been shown to be associated with several disorders (Shete et al., 2009; Turnbull et al., 2010; Chen et al., 2012; Mocellin et al., 2012; Feng et al., 2014; Wei et al., 2015, 2016; Yuan et al., 2016). Biologically, rs2736100_CC stimulates *TERT* transcription, thereby enhancing telomerase activity (Wei et al., 2015). Considering a key role of telomere and telomerase or TERT in the immune cells, it is interesting to determine whether the rs2736100 genotype modifies the susceptibility to PTB.

In the present study, we, thus, elucidated a potential association between the *MCP-1* rs1024611 and *TERT* rs2736100 genotypes and PTB risk.

MATERIAL AND METHODS

Study populations

The study includes 393 unrelated Han Chinese adults consisting of 183 patients with active PTB (cases) and 210 healthy adults as controls. All 183 patients with PTB were recruited from the Shandong Provincial Chest Hospital and Central Hospital Affiliated to Shandong University between January 2014 and December 2015. Active PTB was diagnosed by chest radiographical alterations and a positive sputum acid-fast smear and culture confirmed *M. tuberculosis*. All 210 healthy adults with age- and sex-matched to cases were recruited from Physical Examination Center, Shandong University Second Hospital. The study was approved by the Ethics Review Committee of Shandong University Second Hospital.

DNA extraction and genotyping

Genomic DNA was extracted using peripheral white blood cells derived from patients with TB and healthy controls by QIAGEN DNA extraction kits (QIAGEN, Hilden, Germany). The *MCP-1* rs1024611 (AG) and *TERT* rs2736100 (AC) genotyping was carried out using pre-designed TaqMan SNP genotyping assay kits on an ABI PRISM 7900 HT Sequence

Detection System (Applied Biosystems), according to manufacturer's instructions (Wei et al., 2015; Yuan et al., 2016). Both positive and negative controls were included in all the assays and the reaction conditions were as follows: 95°C for 10 min, followed by 40 cycles of 92°C for 15 s and 60°C for 1 min.

Statistical analyses

All the statistical tests were performed using SigmaStat3.1® software (Systat Software, Inc., Richmond, CA). P values of 0.05 were considered statistically significant. The difference in age and gender between patients and healthy controls was assessed using the Mann-Whitney U-test and Chi-square (χ^2) test, respectively. The evaluation of distribution differences in selected variables and genotypes between patients and healthy controls was done using χ^2 test. Hardy-Weinberg equilibrium of the genotype distribution among the controls was tested by a goodness-of-fit χ^2 test. Unconditional univariate and multivariate logistic regression analyses were used to estimate odds ratios (ORs) for risk of PTB and their 95% confidence intervals (CIs).

Ethics approval

The study was approved by the Ethics Review Committee of Shandong University Second Hospital and written informed consent was obtained from the participants. All experiments were performed in accordance with the principles expressed in the Declaration of Helsinki.

RESULTS

Demographical and/or clinical characteristics of study subjects

A total of 183 patients with active PTB were genotyped for *MCP-1* rs1024611 and *TERT* rs2736100 variants. Patient age was 42.2 ± 20.1 years (mean ± SD) and sex ratio was 125/58 = 2.16 (M/F). Healthy adults recruited as controls were largely age- (42.8 ± 14.1) and sex-matched (140/70 = 2.0). Both cases and controls belonged to the Han Chinese ethnic group living in the Jinan area (East China).

Association of *MCP-1*_GG with PTB susceptibility

The *MCP-1* rs1024611 genotyping was performed using DNA from 210 controls and 183 patients with active PTB. As shown in Table 1, among 210 controls, 97 had GG (46.2%), 82 had GA (39.0%), and 31 had AA (14.8%) genotype, while there were 66 GG (36.1%), 90 GA (49.2%), and 27 AA (14.7%) genotypes among 183 cases. Clearly, the GG genotype was found at a higher frequency in healthy controls than in patients with PTB. The GA genotype exhibited significantly reduced risk of PTB (GG *vs* GA: OR, 0.620; 95%CI, 0.427-1.428, P = 0.03). There was no difference in the AA genotype alone between cases and controls, however, when GA and AA genotypes were grouped together, the GG variant was exhibited at a significantly higher susceptibility to PTB (GG *vs* GA + AA: OR, 0.657; 95%CI, 0.438-0.986; P = 0.042). The A allele tended to have a lower PTB risk than the G allele did; however, the difference was not statistically significant (P = 0.142) (Table 1).

Table 1. *MCP-1* rs1024611 and *TERT* rs2736100 genotypes in healthy adults and patients with PTB.

	HA	TB	Odds ratio (95%CI)	P value
N	210	183		
Genotype				
rs1024611 (N)	210 (100%)	183 (100%)		
GG	97 (46.2%)	66 (36.1%)	1.0 (ref.)	
GA	82 (39.0%)	90 (49.2%)	0.620 (0.402-0.956)	**0.03**
AA	31 (14.8%)	27 (14.7%)	0.781 (0.427-1.428)	0.422
GA + AA	113	117	0.657 (0.438-0.986)	**0.042**
G	276 (65.7%)	222 (60.7%)	1.0 (ref.)	
A	144 (34.3%)	144 (39.3%)	0.804 (0.601-1.076)	0.142
rs2736100 (N)	210 (100%)	183 (100%)		
AA	81 (38.6%)	61 (33.3%)	1.0 (ref.)	
AC	93 (44.3%)	92 (50.3%)	0.761 (0.490-1.182)	0.224
CC	36 (17.1%)	30 (16.4%)	0.904 (0.502-1.626)	0.735
AC + CC	129	122	0.796 (0.526-1.205)	0.281
A	255 (60.7%)	214 (58.5%)	1.0 (ref.)	
C	165 (39.3%)	152 (41.5%)	0.911 (0.685-1.212)	0.522

CI, confidence interval; Ref., reference; HA, healthy adults; PTB, pulmonary tuberculosis. Bolded P values: with statistically significant difference.

Further, the rs1024611 genotype distribution was compared in male and female individuals separately. A significant difference in the genotype distribution between healthy males and females (P = 0.156) was not observed. The GG genotype was observed at a lower frequency in male cases (35.2%) than in male controls (47.9%) and the risk was at a borderline significance as compared to the GA genotype (Table 2) (GG *vs* GA: OR, 0.604; 95%CI = 0.358-.019; P = 0.058). The cases with combined GA and AA genotypes exhibited significantly decreased PTB risk as compared to that exhibited by the GG variant carriers (Table 2) (GG *vs* GA + AA: OR, 0.592; 95%CI = 0.361-0.971; P = 0.037). In contrast, differences in the genotype distribution were not significant between female controls and cases (controls *vs* cases in female, P > 0.05 in all the comparisons) (Table 2).

Table 2. Difference in the association between *MCP-1* rs1024611 variants and PTB depending on the sex.

	Male		Odds ratio (95%CI)	P value
	HA	TB		
Genotype (N)	140 (100%)	125 (100%)		
GG	67 (47.9%)	44 (35.2%)	1.0 (ref.)	
GA	57 (40.7%)	62 (49.6%)	0.604 (0.358-1.019)	**0.058**
AA	16 (11.4%)	19 (15.2%)	0.553 (0.257-1.190)	0.127
GA + AA	73	81	0.592 (0.361-0.971)	**0.037**
	Female			
	HA	TB		
Genotype (N)	70 (100%)	58 (100%)		
GG	30 (42.9%)	22 (37.9%)	1.0 (ref.)	
GA	25 (35.7%)	28 (48.3%)	0.655 (0.303-1.415)	0.280
AA	15 (21.4%)	8 (13.8%)	1.375 (0.496-3.810)	0.540
GA + AA	40	36	0.815 (0.400-1.659)	0.572

CI, confidence interval; Ref., reference; HA, healthy adults; TB, pulmonary tuberculosis. Bolded P values: with statistically significant difference or at board-line difference.

TERT rs2736100 variant and PTB risk

The *TERT* rs2736100 genotyping was performed using DNA from the same individuals, and the genotype frequency was summarized in Table 1. The genotype distributions were 38.6, 44.3, and 17.1% for AA, AC, and CC, respectively, in healthy adults, while 33.3, 50.3,

and 16.4% for AA, AC, and CC, respectively, in patients with PTB (Table 1). There was no significant difference in the rs2736100 genotype frequency between healthy controls and patients with PTB. Moreover, the A and C allele distribution was comparable between cases and controls (Table 1). The result collectively indicates the lack of association between rs2736100 variant and PTB susceptibility.

DISCUSSION

In the present study, we evaluated the association of *MCP-1* rs1024611 and *TERT* rs2736100 variants with PTB in Han Chinese population from the Jinan area (East China). Our results indicated that males with rs1024611_GA and AA variants had significantly lower PTB risk than the GG carriers did. There was no association between the *TERT* rs2736100 SNPs and PTB susceptibility. Thus, the findings in our study support the association between the *MCP-1* rs1024611_GG variant and PTB risk in the Han Chinese population.

MCP-1 is a member of the C-C chemokine sub-family and plays a key role in the granulomatous reaction and *M. tuberculosis* clearance (Flores-Villanueva et al., 2005; Feng et al., 2012). Earlier linkage analyses identified the 17q11-q21 chromosomal region encompassing MCP-1 as a candidate for TB susceptibility, and later the study by Flores Villanueva et al. further revealed that the *MCP-1* rs1024611_GG genotype contributed to significantly higher risk of developing PTB in Mexican and Korean populations (Flores-Villanueva et al., 2005). They found that carriers of the rs1024611_GG genotype produced high levels of MCP-1, which inhibits IL-12 production in response to *M. tuberculosis*, thereby promoting active PTB. Since then, the relationship between rs1024611 genotype and PTB risk has been extensively explored; however, inconsistent results were obtained depending on the ethnicities (Chu et al., 2007; Alagarasu et al., 2009; Xu et al., 2009; Yang et al., 2009; Ganachari et al., 2010; Ben-Selma et al., 2011; Hussain et al., 2011; Naderi et al., 2011; Arji et al., 2012; Feng et al., 2012; Mishra et al., 2012; Velez Edwards et al., 2012; Gong et al., 2013; Vásquez-Loarte et al., 2015). A significant association between *MCP-1* rs1024611 polymorphisms and PTB susceptibility was found only in the East Asian and Latin American ethnic groups, while it was not found in the ethnicities from India, Iran, Persia, Gambia, Guinea-Bissau, European ancestry from the USA and Argentina, and the South African or African-American ethnic groups. Moreover, even in case of the Han Chinese ethnic group, the obtained results were different between subjects from Hong Kong and Inland China (Chu et al., 2007; Xu et al., 2009; Yang et al., 2009). Taken together, all the above data reflect complexities regarding the effect of the *MCP-1* genetic variation on PTB risk. Further studies are apparently needed to define the role of the *MCP-1* rs1024611 variant in PTB susceptibility by comparing its polymorphism frequencies between cases and controls in different ethnic populations.

Intriguingly, we observed that the association between the rs1024611_GG genotype and PTB risk was only limited to males, which has not yet been documented. Therefore, it may be necessary to re-analyze previous results by separating males from females. The *MCP-1* rs1024611 SNP has also been associated with modulation of risk for spina bifida, coronary artery disease, rheumatoid arthritis, lupus nephritis, multiple sclerosis, insulin-resistant diabetes, HIV-1, etc. (Mihret et al., 2014; Cai et al., 2015). It is currently unclear whether the sex modifies the effect of the rs1024611 SNPs on these diseases, which should be taken into consideration in future studies.

Telomerase or TERT and telomeres have long been recognized to play roles in the

immune system (Calado and Young, 2009). It was previously shown that longer leukocyte telomere was associated with increased resistance to experimentally induced acute upper respiratory infection and clinical illness in adults (Cohen et al., 2013). Mechanistically, shorter telomeres in leukocytes limit their proliferation potentials and compromise immune response to pathogens, thereby increasing susceptibility to infection. The rs2736100_CC carriers were reported to have longer telomere in their leukocytes, as C allele-containing sequences exhibited a higher *TERT* mRNA expression and telomerase activity than that exhibited by A allele-carrying fragments (Turnbull et al., 2010; Atzmon et al., 2010; Wei et al., 2015). However, the present finding showed lack of association between the rs2736100 variants and PTB susceptibility, despite several studies revealing significant effects of this genetic variant on susceptibility to cancer, atherosclerosis, idiopathic pulmonary fibrosis, depression, etc. (Shete et al., 2009; Turnbull et al., 2010; Chen et al., 2012; Mocellin et al., 2012; Feng et al., 2014; Wei et al., 2015; Yuan et al., 2016).

In summary, this study showed that PTB susceptibility is associated with the *MCP-1* rs1024611 variant, but not with *TERT* rs2736100 SNPs. However, it should be pointed out that the association between rs1024611_GG and PTB risk is weak and only limited to males. Given the complexity of this relationship, as shown in previous studies, further studies are definitely required to define the role of rs1024611 variants in PTB pathogenesis by recruiting a large cohort of patients and controls belonging to various ethnic backgrounds.

Conflicts of interest

The authors declare no conflict of interest.

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