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RESEARCH ARTICLE

Protective Effect of the T1212C Macrophage Mannose Receptor Gene Polymorphism on Pulmonary Tuberculosis

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Abstract

The interaction between the mannose receptor, which is encoded by the macrophage mannose receptor (MMR) gene, and the most virulent antigen (the mannose-capped lipoarabinomannan) cell wall of virulent strains of *Mycobacterium tuberculosis* trigger an innate and adaptive immune response. It also produces pro and anti-inflammatory cytokines, which play a role in the pathogenesis of tuberculosis (TB) infection. Therefore, MMR gene polymorphism is a risk factor associated with the prognosis for active pulmonary TB. This study aimed to determine the correlation between MMR gene polymorphism and active or latent pulmonary tuberculosis. In this phase, MMR gene polymorphism was analyzed using a case-control design consisting of 74 control group subjects (patients with latent TB) and 74 case groups (patients with active pulmonary TB). The subject's MMR gene DNA sequencing examination. The study was conducted at the Teaching Hospital, Faculty of Medicine, Universitas Padjadjaran Bandung, from February 2014 to January 2015. The statistical analysis used chi-square and odds ratio. The study's result has shown the MMR gene polymorphism factor that correlated to the incidence of active pulmonary TB was T1212C (OR=0.253; 95% CI=0.111–0.575; p=0.001). There was an MMR gene in one SNP in the control group (C1323T) only and five single nucleotide polymorphisms (SNPs) in both groups (C1303T, C1221, T1212C, G1186A, and G1195A). Therefore, it can be concluded that MMR gene polymorphism on the T1212C site correlated with the incidence of active pulmonary tuberculosis and was protective.

Keywords: Active pulmonary TB, latent TB, MMR gene, single nucleotide polymorphisms, T1212C

Introduction

Interaction between the host immune response and defense mechanism conducted by *Mycobacterium tuberculosis* (MTB) creates a balance of cytokine production and pro and anti-inflammation chemokine. It causes the pathogenesis of tuberculosis (TB) infection.[1–4] MTB's host immune response is started by recognizing microorganism antigen structures called pathogen-associated molecular patterns (PAMPs). Receptors specifically recognize PAMPs in a congenital immune system called pathogen recognition receptors (PRRs). PRRs are expressed on many effector cells such as macrophages, dendrites, and lymphocyte cells B.[1,4–6,8]

The basic pathogen-associated molecular patterns of TB infection are the lipid riched-MTB cell walls structure, such as mannose-capped lipoarabinomannan (Man-LAM), which has immunogenic effects as the most common important virulence factor of MTB. Some PRRS roles can recognize the interaction between PAMPs and MTB. They were the C-type lectins, toll-like receptors (TLRs), nucleotide oligomerization domain (NOD) like receptors (NLRs), dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN), and Dectin-1.[1,6]

C-type lectins are PRRS involved in recognizing pathogen's polysaccharide structure with one of the most important receptors, mannose receptor (MR), consisting of eight bond identifier domains with one cysteine-rich domain on one alveolar macrophage. MTB stimulation through MR creates a bridge between natural and congenital immunity that will be connected by setting the endosomal and phagosomal pathways and producing proinflammatory cytokines and

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chemokines. The most important of these is tumor necrosis factor α (TNF-α), a family of interleukin (IL)-1, namely (IL-1β, IL-18), IL-12, and INFg, as well as anti-inflammatory cytokines of which IL-10 and transforming growth factor-β (TGF-β).[1,4,6–8]

Based on the Qidwai et al.[9] study, it was estimated that about 275 single nucleotide polymorphisms (SNPs) located on 19 genes were involved in affecting protein structure and a person's vulnerability to being infected with TB. In addition, a study by Azad et al.[10] explained that more than 50 genes affect a person's susceptibility to TB disease.

The study in China found six single nucleotide polymorphisms (SNPs) MMR/MRC-1 encoding MR and located on chromosome 10p12 consisting of 30 exons. They are associated with the incidence of pulmonary tuberculosis (G1186A, G1195A, T1212C, C1221G, C1303T, and C1323T) in exon 7. The study used PCR and DNA sequencing methods on pulmonary TB patients and a control group of healthy people. Allelic G1186A frequency (rs34039386) of the MMR gene in the Chinese population was higher in pulmonary tuberculosis patients than in the healthy control group. There were significant differences between the frequency distribution of the two groups ($p=0.037$, OR=0.76, 95% CI=0.58–0.98). The genotypic analysis also showed that genotype AG in the Chinese population was significantly correlated with pulmonary tuberculosis ($p<0.01$, OR=0.57, 95% CI=0.37–0.87). This study first reported that the SNP in MMR genes might be associated with pulmonary tuberculosis in the Chinese population and reduce the risk.[11]

This study aimed to determine the picture of MMR gene mutations and polymorphism type in patients with active pulmonary TB and latent TB and to analyze the incidence of MMR gene polymorphism, a risk factor for active pulmonary tuberculosis. There has not yet been a study about the role of MMR gene SNPs in Indonesia, so it is expected that the study can be a basic addition mechanism of susceptibility to pulmonary TB disease in Indonesia.

Methods

This study used a case-control design with 148 subjects consisting of a control group (patients with latent TB) and a case group (patients with active pulmonary TB). Each group is 74 people. The study was conducted from February 2014 to January 2015 in the TB Research Clinic of the Teaching Hospital, Faculty of Medicine, Universitas Padjadjaran Bandung. Schematically, the flow of subject selection was in Figure 1.

The inclusion criteria for the case group were patients aged 15–55 years with clinical symptoms of pulmonary tuberculosis, sputum examination of positive acid-fast bacilli (AFB) with the Ziehl-Neelsen method by collecting samples during the early when at least two times positive and having positive smear culture. The inclusion criteria of the control group were latent TB patients aged 15–55 years who live together with people with TB but do not have any complaints and symptoms of TB, with the results of interferon-gamma release assay (IGRA) being positive. Exclusion criteria were subject to disease conditions that interfered with the immunological response, including diabetes mellitus, HIV/AIDS, or steroid treatment.

The first optimization of the research was to design the PCR primer for the MMR gene before sequencing the MMR gene DNA. The success of DNA sequencing is highly dependent on the success of the PCR process, and the success of the PCR process is highly dependent on the choice of primer design. The principle of PCR is to multiply exponentially specific nucleotide sequences in vitro. To identify the series to be duplicated, particular specific primers are needed. This area, known as a primer, will later be multiplied to thousands or millions of copies so that after electrophoresis, bands of the amplified DNA will be seen. The primer design was based on DNA sequences[11,12] with known protein-related sequences from the Genbank database.[13]

Based on previous research in China, a PCR primer for the MMR gene was found, later called primer I (20 bp length), as follows: forward primer 5'-TTG AGG CTG CAA TGA GAC AT-3' and reverse primer 5'-AGT GTA AGG TAG ACT GCT CT-3'. Then a new primer design was produced at the Biomolecular Clinical Pathology Laboratory, Dr. Hasan Sadikin General Hospital (hereinafter referred to as primer II) with a length of 20 bp, namely: forward primer 5'-CTA GTC AGT GGT GGC CGT AT-3' and reverse primer 5'-CAC ATT GTG GTC GCA TTT TCA GC-3'. Researchers took about 3 mL of venous blood from both groups to examine DNA isolation, PCR, and DNA sequencing.

DNA isolation used a DNA extraction kit (QIAamp DNA Blood Midi, Germany). Then, PCR primers (20 bp long) were used to detect

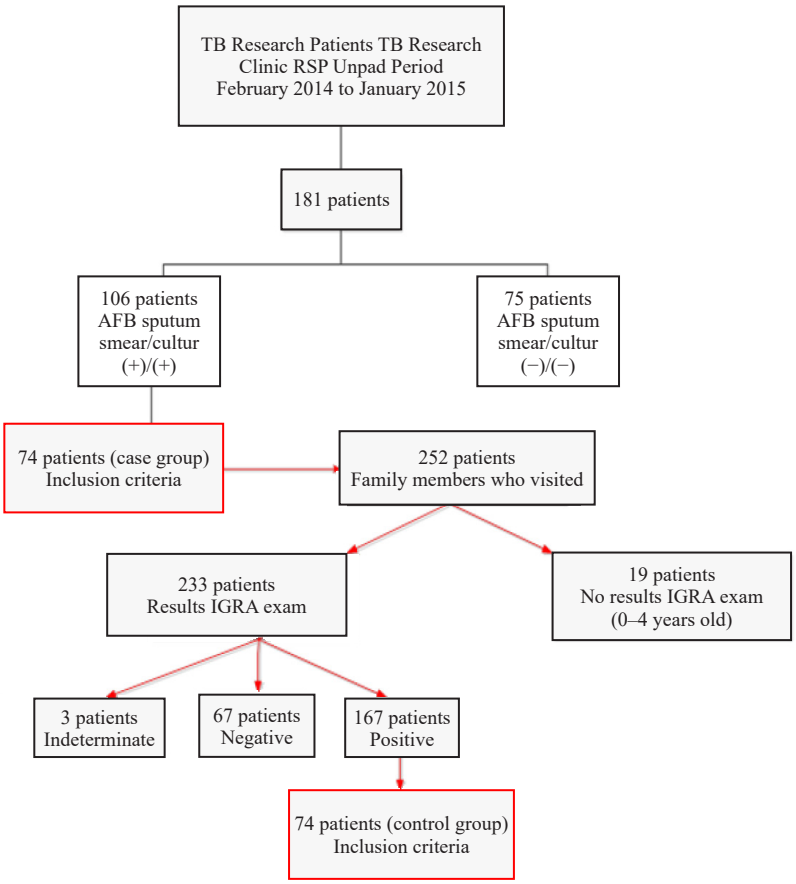

Figure 1 Flow of Subject Selection

the MMR gene DNA fragments using Primer3 software. Finally, confirmation was done using the NCBI Basic Local Alignment Search Tool (BLAST). We look at the possibility of primary mispriming with other areas on the MMR genes other than the region to be amplified.

MMR genes were detected using conventional PCR with DreamTaq master mix PCR reagent and gel-based PCR method. PCR products were then performed by PCR purification and clean-up kit (Geneaid), then DNA sequencing was completed with ABI 3130xl genetic analyzer tool. The exon 7 chromosome 10p MMR gene sequencing DNA examination was conducted at Eijkman Biomolecular Institute in Jakarta. Data of sequencing results were calculated in proportion to the type of mutation and analyzed by chi-square test to assess the odds ratio (OR) of each kind of mutation using R software.

The Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran, approved the study with letter number 344/UN6. C2.1.2/KEPK/PN/2014.

Results

The number of cases was 74, with 74 control. Characteristics of research subjects based on age, sex, and body mass index can be seen in Table 1.

Results of DNA sequencing genes MMR exon 7 were analyzed using DNA baser software. It was found six site mutations, namely G1186A (rs34039386, Gly396Ser), G1195A (rs71497223, Gly396-Ser), T1212C (rs71497224, Ile404Ile), C1221G (rs34284571, Leu407Phe), C1303T (Leu435 Phe), and C1323T (Asn441Asn) on both groups. The overview of MMR genes DNA sequencing in both groups, with baser DNA software as an example, can be seen in Figure 2.

The MMR gene mutations found MMR gene polymorphism confirmed in Asian populations using the genome browser HapMap software. On the G1186A site sequentially, the frequency of genotype A/A was 24% and 16%; the case group

Table 1 Characteristics of Research Subjects

Variables	Case Group n=74 (%)	Control Group n=74 (%)	Total n=148 (%)	p
Sex				
Male	34 (46)	33 (45)	67 (45)	0.869*
Female	40 (54)	41 (55)	81 (55)	
Age (year), median (JIK)	36 (17)	34 (19)	35 (19)	0.711#
Aged group (years old)				
<20	5 (7)	8 (11)	13 (9)	0.775*
20–29	16 (22)	18 (24)	34 (23)	
30–39	22 (30)	17 (23)	39 (26)	
40–49	24 (32)	22 (30)	46 (31)	
50–59	7 (9)	9 (12)	16 (11)	
BMI (kg/m^2), median (JIK)	17.83 (3.16)	23.73 (8.26)	19.46 (7.89)	<0.001#
BMI category (kg/m^2)				
Underweight (<18.5)	47 (64)	11 (15)	58 (39)	<0.001*
Normal (18.5–24.99)	25 (34)	28 (38)	53 (36)	
Overweight (≥25)	2 (3)	35 (47)	37 (25)	

Note: *chi-square test; #Mann-Whitney test; JIK: interquartil space; BMI: body mass index

Table 2 Distribution of SNP Exon 7 Gene MMR Genotype Frequency

SNP Site	Genotype	Case Group n=74 (%)	Control Group n=74 (%)	p	OR (95% CI)
G1186A	GG	24 (32)	21 (28)	-	Reference
	AA	18 (24)	12 (16)	0.569	1.313 (0.515–3.347)
	GA	32 (43)	41 (55)	0.316	0.683 (0.324–1.440)
G1195A	GG	71 (96)	71 (96)	-	Reference
	AA	0 (0)	0 (0)	1.000	1 (0.019–51.091)
	GA	3 (4)	3 (4)	1.000	1 (0.219–4.560)
T1212C	TT	63 (85)	43 (58)	-	Reference
	CC	1 (1)	4 (5)	0.161	0.171 (0.018–1.580)
	TC	10 (14)	27 (37)	0.001	0.253 (0.111–0.575)
C1221G	CC	72 (97)	72 (97)	-	Reference
	GG	0 (0)	0 (0)	1.000	1 (0.019–51.081)
	GC	2 (3)	2 (3)	1.000	1 (0.168–5.948)
C1303T	CC	72 (97)	70 (95)	-	Reference
	TT	0 (0)	0 (0)	1.000	1.028 (0.020–52.541)
	CT	2 (3)	4 (5)	0.681	1.851 (0.381–8.991)
C1323T	CC	74 (100)	72 (97)	-	Reference
	TT	0 (0)	0 (0)	1.000	1.028 (0.020–52.481)
	CT	0 (0)	2 (3)	0.681	1.850 (0.381–8.975)

Note: analysis of genotype difference between the case and control groups used the chi-square test if the assumption was fulfilled and used Fisher's exact if the chi-square premise not met

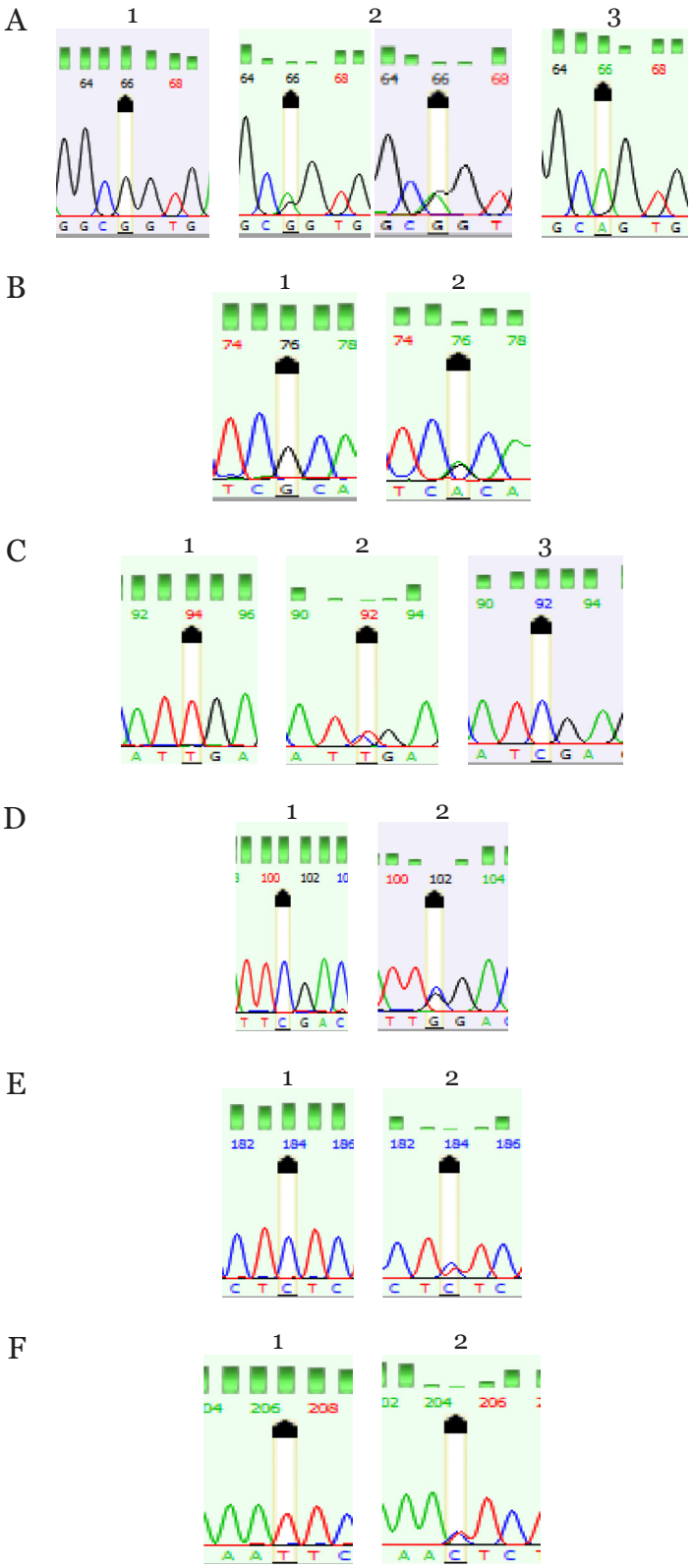

Figure 2 DNA Sequencing on Exon 7 MMR Gene

(A) G1186A; (**1**) Genotype G/G; (**2**) Genotype G/A; (**3**) Genotype A/A. **(B)** G1195A; (**1**) Genotype G/G; (**2**) Genotype G/A. **(C)** T1212C; (**1**) Genotype T/T; (**2**) Genotype T/C; (**3**) Genotype C/C. **(D)** C1221G; (**1**) Genotype C/C; (**2**) Genotype C/G. **(E)** C1303T; (**1**) Genotype C/C; (**2**) Genotype C/T. **(F)** T1323C; (**1**) Genotype T/T; (**2**) Genotype T/C

Table 3 Distribution of MMR Gene Exon 7 SNP Allele Frequency

SNP Site	Allele	Case Group		Control Group		p	OR (95% CI)
		n=148	Frequency	n=148	Frequency		
G1186A	G	80	0.541	83	0.561	-	1.00
	A	68	0.459	65	0.439	0.726	0.921 (0.583–1.457)
	HWE (p)	0.266		0.000			
G1195A	G	145	0.980	145	0.980	-	1.00
	A	3	0.020	3	0.020	1.000	1.00 (0.199–5.037)
	HWE (p)	0.859		1.000			
T1212C	T	136	0.919	113	0.764	-	1.00
	C	12	0.081	35	0.236	0.002	2.982 (1.484–5.993)
	HWE (p)	0.423		1.000			
C1221G	C	146	0.986	146	0.986	-	1.00
	G	2	0.014	2	0.014	1.000	1.00 (0.139–7.195)
	HWE (p)	0.906		1.000			
C1303T	C	146	0.986	144	0.973	-	1.00
	T	2	0.014	4	0.027	0.684	2.028 (0.366–11.244)
	HWE (p)	0.906		1.000			
C1323T	C	148	1.000	146	0.986	-	1.00
	T	0	0.000	2	0.014	0.498	5.068 (0.241–106.477)
	HWE (p)	0.000		1.000			

Note: all difference analysis between the case and control groups used the chi-square test if the assumption were met and used Fisher's exact if the chi-square hypothesis were not; HWE: Hardy-Weinberg equilibrium

was higher than the control group (OR=1.313, 95% CI=0.515–3.347, p=0.569). However, the frequency of genotype G/A was 43% and 55%; the case group was lower than the control group (OR=0.6833, 95% CI=0.324–1.440, p=0.316).

On T1212C sites sequentially, the C/C and T/C genotype frequency in the case group was lower than in the control group (OR=0.171, 95% CI=0.018–1.580, p=0.161 and OR=0.253, 95% CI=0.111–0.575, p=0.001). There was no significant difference in genotype frequency in both groups on G1195A, C1221G, C1303T, and C1323T sites (Table 2).

The frequency of the C allele at the T1212C site in the case group was lower than in the control group. The frequency was statistically significant (0.081 and 0.236) with OR=2.982, 95% CI=1.484–5.993, p=0.002). The frequency of alleles at the sites G1186A, G1195A, C1221G, C1303T, and C1323T were not significantly different between the two groups (Table 3).

Discussion

The characteristic of the study's subject in Table 1 from the case and the control group based on sex. There were 34 males (46%) in the case group and 33 males (45%) in the control group. While females were 40 (54%) in the case group and 41 females (55%) in the control group, this difference was not statistically significant. Suppose it was seen based on the age group. The median age was 36, with 19 interquartile distances in the case group. While in the control group, there was a median age of 34 with an interquartile distance of 19.

According to the body mass index (BMI) characteristic, the underweight condition was the most in the case group in 47 subjects (64%), while in the control group were 35 subjects (47%) that experience overweight BMI (≥25 kg/m^2). The results followed the previous study, which stated that BMI was related to nutrition status. One of the influential factors on host body resistance is defending against microorganisms attacking someone's body, such as TB. A low body mass index is one of the TB infection risk factors.[14–17] However, a good BMI did not guarantee someone was free of TB infection. It could see that most of the control group with IGRA(+) had good BMI status and were overweight.[11,18]

This study showed six SNPs in exon 7 of the MMR gene, G1186A (rs34039386, Gly396Ser), G1195A (rs71497223, Gly396Ser), T1212C

(rs71497224, Ile404Ile), C1221G (rs34284571, Leu407Phe), C1303T (Leu435Phe), and C1323T (Asn441Asn). In addition, was found two mutations: transitions and transversions. Transitions are mutation changes of the same base couple pain to purine (A becomes G or G becomes A) or pyrimidine to pyrimidine (C becomes T or T becomes C). It occurred on two sites G1186A, G1195A, T1212C, C1303T, and C1323T. Only one site that experienced transversion was nitrogen base changes, which caused several changes. The changes were purine to pyrimidine (G become C, G become T, A become C, or A become T) or pyrimidine to purine (C become G, C become A, T become A, or T become G). It occurred on the T1221C site.

In this study, polymorphisms of a gene can change the protein produced by the gene to lower its function. There was also polymorphism which was influenced by ethnicity and geography. Following the previous study in China, MR played an important role in congenital and adaptive immunity. This receptor-activated immune response recognizes extracellular carbohydrates that bond glycan from pathogen microbe structure and could play an important role in causing TB infection. Six SNPs in exon 7 from the MRC1 gene were analyzed. That study showed that genotype frequency (p=0.037, OR=0.76, 95% CI=0.58–0.98) and allele (p<0.01, OR=0.57, 95% CI=0.37–0.87) were statistically significant. OR genotype and allele value for G1186A were less than 1. It indicated that MMR gene polymorphism affected pulmonary TB development and could reduce the risk of pulmonary TB.[11]

G1186A site of MMR gene was a non-identical mutation that could change Gly amino acid into Ser. This site mutation could change MR function, influencing the MR protein bind of polysaccharide structure on the MTB surface. Therefore, it gave a contribution to anti-inflammation factor secretion. Different from the previous study in China.[11] It indicated five other SNPs of the MMR gene G1195A (rs71497223, Gly396Ser), T1212C (rs71497224, Ile404Ile), C1221G (rs34284571, Leu407Phe), C1303T (Leu435Phe), and C1323T (Asn441Asn) did not show a significant relationship with pulmonary TB (p>0.05). The study also showed that the polymorphism site was unrelated to pulmonary TB susceptibility. However, it was found that there was a significant difference between the case and control groups. T1212C (rs71497224, Ile404Ile), respectively genotype frequency T/T, C/C, and T/C in the case group, 85%, 1%, and 14%, while in the control group 58%, 5%, and 36%. T/C genotype frequency in the case group was lower than in the control group (OR=0.253, 95% CI=1.111–0.575, p=0.001).

It indicated that AA dominant mutation occurred more in pulmonary TB patients than in latent TB. However, this incident was not meant to be significant because of p>0.05. This condition indicated that G1186A played an essential role in pulmonary TB, appropriate with the previous research in China.[11]

Both groups' dominant and recessive mutation models on G1195A, C1221G, C1303T, and C1323T sites were not different from the previous study. Alter et al.[19] found that the frequency of allele SNP G1186A exon 7 of the MMR gene had significant differences between the leprosy patients as the case group and healthy people as a control group in the Vietnamese population (p=0.036, OR=0.76, 95% CI=0.60–0.96). Because OR value was less than 1, the results showed that the site had a significant protective role for leprosy and could reduce the risk of infection. Similarly, this study found that G1186A SNP allele frequency on leprosy as a case group was different from healthy people as a control group in the population of Brazil (p=0.016, OR=1.34; 95% CI=1.06–1.70). Odd ratio value of more than 1 indicated that the polymorphism was associated with the susceptibility to leprosy. Hattori et al.[20] reported that the frequency of the G1186A SNP allele in exon 7 of the MMR gene was not significantly associated with asthma in the Japanese population. Other studies explain that the role of the MMR gene can determine the diagnosis, susceptibility, and prognosis of TB, a biomarker for the progression of lung interstitial damage, specific glioma, and inflammatory bowel syndrome.[21–29]

It suggested that differences in genetics are a key factor in an individual's susceptibility to disease and gene polymorphism. From the result of previous studies could be concluded that the MMR gene polymorphism G1186A SNP was associated with TB and may have a protective function.[11,12,28,29]

There is no association between SNPs exon 7 on G1195A, C1221G, C1303T, and C1323T MMR gene and the incidence of pulmonary tuberculosis. Therefore, more samples require further research to analyze SNPs on MMR genes. Nevertheless, the

relationship of MMR gene SNP with the incidence of pulmonary tuberculosis in both groups could be statistically significant. However, more practical methods other than DNA sequencing are still needed, such as the PCR TaqMan method or DNA sequencing using restriction fragment length polymorphism. In addition, it is also proposed to analyze proinflammatory and anti-inflammatory cytokine levels that are affected by the expression of mannose receptors on the whole subject of study to clarify further the mechanism of the effect of genetic variation on cytokine products on the incidence of pulmonary tuberculosis.

Conclusions

The study concluded that there was 5 SNPs MMR gene (G1186A, G1195A, T1212C, C1221G, and C1303T) in both groups. In addition, MMR gene polymorphism on the T1212C site was associated with pulmonary tuberculosis and was protective.

Conflict of Interest

None declared.

Acknowledgment

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