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Brief communication (Original)

Human Leukocyte Antigen-G (HLA-G) 14-bp deletion polymorphism is associated with decreased risk of pulmonary fibrosis in Indonesian Javanese patients with multidrug-resistant tuberculosis

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Background: Human leukocyte antigen-G (HLA-G) is a nonclassical HLA class I antigen with immunomodulatory activity that usually inhibits immune responses. The role of the HLA-G polymorphism in multidrug-resistant tuberculosis (MDR-TB) is unknown.
Objectives: To analyze clinical data from Indonesian Javanese patients with MDR-TB to find an association between the HLA-G polymorphism and MDR-TB.
Methods: Fifty-seven Indonesian Javanese patients with MDR-TB were enrolled and monitored from May 2012 to Jan 2014. Non-TB individuals and non-MDR-TB individuals were recruited as controls. The HLA-G polymorphism status of each patient was determined by polymerase chain reaction. Patient clinical data were analyzed against polymorphism status. The presence of an association was estimated with an odds ratio (OR) and 95% confidence interval (CI) calculated via logistic regression.
Results: Nineteen (33.3%), 30 (52.6%), and 8 (14.1%) MDR-TB patient participants carried a homozygous deletion (D/D), heterozygous deletion (I/D), and homozygous insertion (I/I) genotypes, respectively. Among control participants, D/D genotype carriers less frequently had a history of TB infection (OR 0.4, 95% CI 0.179-0.981, $P = 0.043$). The deletion allele for MDR-TB patients was associated with a decreased likelihood of developing pulmonary fibrosis (adjusted OR 0.1, 95% CI 0.014-0.639, $P = 0.016$).
Conclusions: D/D genotype carriers are less susceptible to TB, and MDR-TB patients with a deletion allele are less likely to develop pulmonary fibrosis.

Keywords: HLA-G, Indonesia, MDR-TB, polymorphism, tuberculosis

Tuberculosis (TB) is a deadly human disease caused by *Mycobacterium tuberculosis* [1-4]. Approximately 9.0 million people suffer from TB, and 1.5 million died from the disease in 2013 [5]. The TB mortality rate has been reduced by 45% since 1990; however, the emergence of multidrug-resistant TB (MDR-TB) has become a serious health problem [3-8]. In 2013, an estimated 210,000 people died from MDR-TB, and there were approximately 480,000 new cases of MDR-TB worldwide [5].

Patients with MDR-TB require second-line drugs, which are much more expensive, cause more adverse

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events, and have lower cure rates [9-12]. Therapeutic responses among MDR-TB patients are not all the same. Independent of socioeconomic factors, malnutrition, and coinfection with other pathogens, genetic factors in MDR-TB patients exert significant influence [13, 14]. One of the individual genetic factors involved in the control of TB infection is a polymorphism in the gene coding for the major histocompatibility complex (MHC), also known as human leukocyte antigen (HLA) [15].

HLA-G is a nonclassical HLA class I antigen that exerts immunomodulatory activity by inhibiting the immune response and inflammatory processes, such as $CD8^+$ T cell and natural killer (NK) cell activities, $CD4^+$ T cell proliferation, antigen-presenting cell (APC) functions, B cell differentiation, and regulatory T cell induction [16-21]. In certain pathological conditions, HLA-G is expressed on APCs (antigen presenting cells including macrophages and dendritic cells [DCs]), thereby suppressing the host immune response necessary to control infection and malignancy [18, 22-25]. Given that macrophages are the main targets of *M. tuberculosis* infection [26], polymorphisms related to HLA-G expression may influence MDR-TB progression. Information regarding the association between HLA-G polymorphisms and MDR-TB is lacking. This study aimed to investigate the possible association between MDR-TB and HLA-G polymorphisms, particularly the 14-bp insertion/deletion (in/del) in exon 8 (the 3′-untranslated region) of the HLA-G gene.

Materials and methods

Study design

We enrolled 57 Indonesian Javanese patients with MDR-TB patients in this cohort study, TB-infected patients showing resistance to at least isoniazid and rifampisin, at Dr. Moewardi General Hospital, Central Java province, Indonesia, from May 2012 through January 2013. The patients came from various districts in Java island, mostly from Central Java province. There was no consecutive case observed, and none of the subjects were from the same family. Each patient was administered appropriate drugs (taking into account the patient's drug resistance status) and was monitored from the time of MDR-TB diagnosis until sputum conversion (when a bacterial microscopic test has a negative result) or until January 2014. As control groups, 34 healthy individuals without TB and 69 individuals with a history of TB infection, although not MDR-TB, who were cured during the study period were enrolled to assess a possible association between HLA-G polymorphism status and susceptibility to either TB or MDR-TB. Like the group of MDR-TB patients, the control groups consisted of Javanese people, predominantly from Central Java province.

Blood samples were obtained from all patients to examine their $CD4^+$ T cell counts and percentages, hematologic profiles (hemoglobin, hematocrit, erythrocytes, leukocytes, and thrombocytes), sodium (Na^+), potassium (K^+), interferon gamma (IFNg), and interleukin-10 (IL-10) levels. Patient sputum samples were evaluated initially at MDR-TB diagnosis and during routine follow-up.

Approval was obtained from the institutional ethical committee review boards of the Faculty of Medicine of Sebelas Maret University and Dr. Moewardi General Hospital, Central Java province, Indonesia (No: E.C. 129/VII/2009). Written informed consent was obtained from all study participants. All procedures were conducted according to the principles of the Declaration of Helsinki.

Detection of the HLA-G 14-bp in/del polymorphism

Genomic DNA from each patient was isolated from peripheral blood using a High Pure PCR Template Preparation Kit (Roche Diagnostics, Mannheim, Germany). For HLA-G 14-bp in/del polymorphism analysis, genomic samples were genotyped by polymerase chain reaction (PCR) using a FastStart HiFi PCR System dNTPack (Roche) with primer pairs that have been previously described [27]. The PCR products were electrophoresed in 3% agarose gels for 30 minutes at 100V and stained with ethidium bromide (EtBr). For the 14-bp insertion (+14bp), a PCR product of 214bp was obtained, while the deletion (–14bp) resulted in a PCR product of 200 bp. All samples were tested at least twice.

Statistical analysis

The chi-square (χ^2) test was used to assess whether the HLA-G 14-bp in/del genotype distributions in the study population were in Hardy–Weinberg equilibrium. The χ^2 test, Fisher's exact test, and the Kolmogorov–Smirnov test were used to analyze categorical variables. Logistic regression was performed to reveal associations between polymorphism status and TB/MDR-TB outcome and susceptibility. All data analyses used a 95% confidence interval (CI), and a two-tailed $P < 0.05$ was considered

statistically significant. All statistical analyses were performed with SPSS Statistics for Windows software, version 21 (IBM Corp, Armonk, NY, USA).

Results

Study participant population and patient clinical conditions

The group of MDR-TB patients consisted of 26 (46%) men and 31 (54%) women aged 19-62 years (mean: 41.1 ± 10.708). All patients suffered from intrapulmonary TB that was resistant to rifampicin and isoniazid. Other patients were also resistant to ethambutol (46%; 26/57) and streptomycin (54%; 31/57). In one patient, the resistance status to ethambutol and streptomycin was unknown. All patient bacterial cultures indicated the presence of *M. tuberculosis*. Data for patient body mass index (BMI) were obtained for 98% (56/57) of patients, with a mean BMI of 16.5 ± 2.82 kg/m^2. Of these, 41/56 (73%) patients were underweight (BMI < 18.5 kg/m^2), whereas 15/56 (27%) patients were normal weight (BMI = 18.5–24.9 kg/m^2). Sixteen (28%) patients smoked cigarettes, while other 41/57 (72%) patients did not. Patient blood samples were received from May 2012 until January 2014 and were sent for hematologic testing. Meanwhile, the control groups included 34 (33%) healthy participants without clinical symptom of TB and 69 (67%) participants with a history of TB, but not MDR-TB, who were cured during the study period. There was no difference between the group of MDR-TB patients and controls with respect to sex ($P = 0.90$), age ($P = 0.33$), and a history of smoking cigarettes ($P = 0.89$).

Evaluation of patient blood profiles was successfully conducted for 93% (53/57) of MDR-TB patients (**Table 1**). For the most part, subjects possessed normal CD4$^+$ T cell counts and percentages (74% [42/57] had CD4$^+$ T cell counts >500 cells/μL; 67% [38/57] had CD4$^+$ T cell percentages ≥29%). CD4$^+$ T cell counts of 200–500 and <200 cells/μL were observed in 25% (14/57) and 2% (1/57) of patients, respectively, while 33% (19/57) of patients had CD4$^+$ T cell percentages of 14%–28%. Among the total, 60% (34/57) and 98% (56/57) of patients demonstrated normal IFNγ and IL-10 levels (≤10pg/mL), respectively, while 40% (23/57) and 2% (1/57) of patients had excessive IFNγ and IL-10 levels (>10pg/mL), respectively.

Data for the thorax radiographical examination were obtained for 95% (54/57) of MDR-TB patients. Lung cavity infection was observed in 29/54 (54%) patients, infiltration in 48/54 (89%), nodules in 1/54 (2%), fibrosis in 15/54 (28%), pleural effusion in 3/54 (6%), atelectasis in 5/54 (9%), and consolidation in 1/54 (2%). None of the patients suffered fibrothorax.

During follow-up of MDR-TB patients, sputum conversion was observed mostly after two months of treatment (19/57, 33%). Other patients showed sputum conversion after three months (13/57, 23%), one month (11/57, 19%), four months (7/57, 12%), and five months (1/57, 2%) of treatment. Six (11%) patients died before sputum conversion.

HLA-G deletion polymorphism

In the total study population (n = 160; 57 MDR-TB patients, 69 controls with a history of TB infection, and 34 healthy controls), the D/D genotype was identified in 71 (44%) patients, I/D genotype in 68 (43%), and I/I genotype in 21 (13%) patients. The frequencies of the deletion (D) and insertion (I) alleles were 0.66 and 0.34, respectively. These frequencies complied with Hardy–Weinberg equilibrium ($P > 0.05$).

The number of MDR-TB patients with the D/D genotype was 19 (33%), I/D genotype was 30 (53%), and I/I genotype was 8 (14%), which resulted in D and I allele frequencies of 0.60 and 0.40, respectively. Among controls with a history of TB infection and healthy controls, the frequency of the D/D genotype was 30/69 (44%) vs 22/34 (65%), I/D genotype was 26/69 (38%) vs 12/34 (35%), and I/I genotype was 13/69 (19%) vs 0/34 (0%), respectively, with D and I allele frequencies of 0.62 vs 0.82 and 0.38 vs 0.18, respectively.

There was a difference in the proportions of the HLA-G 14-bp genotype between controls with a history of TB infection and healthy controls ($P = 0.014$); individuals carrying the D/D genotype less frequently had a history of TB infection (OR 0.4, 95% CI 0.179–0.981, $P = 0.043$), whereas the proportion of the HLA-G 14-bp genotype between controls with a TB history and the MDR-TB group was not different ($P = 0.243$).

Implication of the HLA-G deletion polymorphism in MDR-TB patients

The frequency of the HLA-G genotype was not different in terms of hematocrit, erythrocytes, leukocytes, thrombocytes, Na$^+$, K$^+$, or IFNγ levels (**Table 1**). Similarly, the HLA-G genotypic status proportion did not differ when taking into consideration patient drug resistance status (**Table 2**) and time to sputum conversion ($P > 0.05$).

The numbers of cured and uncured patients did not differ based on HLA-G genotype status ($P > 0.05$). Interestingly, the distribution frequency of pulmonary fibrosis was different when considering patient HLA-G genotype ($P = 0.02$) and was associated with the HLA-G 14-bp deletion allele (adjusted OR 0.1, 95% CI 0.014–0.639, $P = 0.016$). Moreover, patients with pulmonary fibrosis were less likely to be cured (adjusted OR 0.1, 95% CI 0.014–0.514, $P = 0.007$).

Table 1. Distribution of the HLA-G 14-bp in/del polymorphism in the context of hematologic profiles of MDR-TB patients.

	Genotypes (n,%)			*P*
	D/D (n = 19)	**I/D (n = 30)**	**I/I (n = 8)**	
Hemoglobin (g/dL)*				–
<13.3♂ or <11.8♀	9 (47)	16 (53)	4 (50)	
13.3-16.7♂ or 11.8-14.8♀	9 (47)	11 (37)	3 (38)	
>16.7♂ or >14.8♀	0 (0)	1 (3)	0 (0)	
Erythrocytes ($\times 10^6$/µL)*				0.999[b], 0.999[b],
<4.37♂ or <3.88♀	5 (26)	5 (17)	1 (13)	0.56[b], respectively
4.37-5.66♂ or 3.88-4.99♀	11 (58)	20 (67)	3 (38)	
>5.66♂ or >4.99♀	2 (11)	3 (10)	3 (38)	
Leukocytes ($\times 10^6$/µL)*				0.45[a]
3.9-11.1♂ or 3.7-9.5♀	12 (63)	22 (73)	4 (50)	
>11.1♂ or >9.5♀	6 (32)	6 (20)	3 (38)	
Thrombocytes ($\times 10^5$/µL)*				0.64[a], 0.17[a],
1.5-4.0	12 (63)	15 (50)	6 (75)	0.23[c], respectively
>4.0	6 (32)	13 (43)	1 (13)	
Hematocrit (%)*				0.999[b], 0.999[b],
<33	4 (21)	5 (17)	2 (25)	0.999[b], respectively
33-45	13 (68)	19 (63)	5 (63)	
>45	1 (5)	4 (13)	0 (0)	
Na^+ (mEq/L)*				0.37[a], 0.13[a],
<135	4 (21)	11 (37)	1 (13)	0.66[c], respectively
135-145	14 (74)	17 (57)	6 (75)	
K^+ (mEq/L)*				0.88[a], 0.63[a],
<3.7	5 (26)	7 (23)	1 (13)	0.92[b], respectively
3.7-5.2	6 (32)	12 (40)	2 (25)	
>5.2	7 (37)	9 (30)	4 (50)	
$CD4^+$ T cell count (cells/µL)				–
<200	1 (5)	0 (0)	0 (0)	
200-500	3 (16)	7 (23)	4 (50)	
>500	15 (79)	23 (77)	4 (50)	
% $CD4^+$ T cells				0.96[a]
14-28	6 (32)	10 (33)	3 (38)	
≥29	13 (68)	20 (67)	5 (63)	
IFNa (pg/mL)				0.34[a], 0.55[a],
≤10	13 (68)	19 (63)	2 (25)	0.05[c], respectively
>10	6 (32)	11 (37)	6 (75)	
IL-10 (pg/mL)				
≤10	18 (95)	30 (100)	8 (100)	–
>10	1 (5)	0 (0)	0 (0)	

Data presented as n (%), [a]*P* from Chi-square test, [b]*P* from Kolmogorov–Smirnov test, [c]*P* from Fisher's exact test, ♂ for men, ♀ for women, *some data were missing. IFNγ = interferon-gamma; IL-10 = interleukin-10

Table 2. Distribution of the HLA-G 14-bp in/del polymorphism in the context of MDR-TB patient drug resistance status and the results of the thorax radiographical imaging.

	Genotypes (n, %)			*P*
	D/D (n = 19)	I/D (n = 30)	I/I (n = 8)	
Drug Resistances*				
Ethambutol				0.18[a],0.27[a], 0.999[c], respectively
Sensitive	12 (63)	14 (47)	4 (50)	
Resistant	6 (32)	16 (53)	4 (50)	
Streptomicin				0.26[a], 0.45[a], 0.72[c], respectively
Sensitive	10 (53)	12 (40)	3 (38)	
Resistant	8 (42)	18 (60)	5 (63)	
Rontgen of thorax*				
Cavity				0.70[a], 0.82[a], 0.999[c], respectively
Negative	9 (47)	13 (43)	3 (38)	
Positive	9 (47)	16 (53)	4 (50)	
Infiltration				–
Negative	2 (11)	3 (10)	1 (13)	
Positive	16 (84)	26 (87)	6 (75)	
Nodule				–
Negative	18 (95)	29 (97)	6 (75)	
Positive	0 (0)	0 (0)	1 (13)	
Fibrosis				0.02[a]
Negative	14 (74)	23 (77)	2 (25)	
Positive	4 (21)	6 (20)	5 (63)	
Consolidation				–
Negative	17 (90)	29 (97)	7 (88)	
Positive	1 (5)	0 (0)	0 (0)	
Pleural effusion				–
Negative	17 (90)	28 (93)	6 (75)	
Positive	1 (5)	1 (3)	1 (13)	

Data presented as n (%), [a]*P* from Chi-square test, [c]*P* from Fisher's exact test,*some data were missing.

Discussion

In some pathological conditions, such as in cytomegalovirus and human immunodeficiency virus infections, lung carcinoma, psoriasis, multiple sclerosis, breast cancer, and nontumorous pulmonary disease, HLA-G is expressed in macrophages [28, 29]. Because macrophages are the main immune cell type involved in the pathogenesis of *M. tuberculosis* infection and express HLA-G receptors (leukocyte immunoglobulin-like receptor or immunoglobulin-like transcript (ILT) 2 and ILT4) [20, 29], host genetic factors influencing HLA-G expression potentially playing critical roles in MDR-TB.

The HLA-G 14-bp in/del polymorphism has been suggested to be associated with HLA-G mRNA stability and HLA-G expression [30-33]; however, data regarding the impact of this polymorphism on MDR-TB are lacking. In this study, the HLA-G 14-bp polymorphism did not influence drug resistance status, time to sputum conversion, treatment results, or IFNγ and IL-10 levels of Indonesian Javanese patients with MDR-TB. Notably, an association was identified between pulmonary fibrosis and the HLA-G 14-bp deletion allele; MDR-TB patients carrying the deletion allele were less likely to develop pulmonary fibrosis, suggesting a possible role for the HLA-G polymorphism in MDR-TB pathogenesis that will need to be characterized in further studies. The results of this study also showed that patients with pulmonary fibrosis were less likely to be cured; thus, clinicians must be more concerned by this manifestation.

This study identified a difference in the proportion of the HLA-G genotype distribution between healthy people and people with a history of TB infection ($P = 0.014$), but not between people with a history of TB infection and MDR-TB patients ($P = 0.24$).

Notably, D/D genotype carriers were less susceptible to TB infection (OR 0.4, 95% CI 0.179-0.981, $P = 0.043$). Moreover, the frequency of the deletion allele in healthy controls without a history of TB infection was higher than that in either MDR-TB subjects or controls with TB history (0.82 vs 0.60, 0.62, respectively). These results indicate that the deletion allele may be beneficial and protective against TB.

This study provides information about the frequencies of the HLA-G 14-bp polymorphism among Indonesian Javanese; most Indonesian participants in the study carried the D/D genotype (44%), followed by the I/D (43%), and I/I genotypes (13%). The frequencies of the deletion and insertion alleles were 0.66 and 0.34, respectively. These early data contribute to our knowledge of the status of the HLA-G polymorphism in the Indonesian Javanese population, which is currently limited.

This study has several limitations, such as the limited number of participants and missing data from a number of participants. The results of this study require confirmation in studies using larger sample sizes and different populations.

Conclusion

The results of this study indicated that D/D genotype carriers are less susceptible to TB. Furthermore, the absence of the HLA-G 14-bp deletion allele may be a biomarker for the development of lung fibrosis in patients with MDR-TB.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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