RESEARCH COMMUNICATION

Association Between HLA-DQ Genotypes and Haplotypes vs *Helicobacter pylori* Infection in an Indonesian Population

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Abstract

Background: *Helicobacter pylori* is an important gastrointestinal pathogen related to the development of not only atrophic gastritis and peptic ulcer, but also gastric cancer. Human leukocyte antigens (HLA) may play particular roles in host immune responses to bacterial antigens. This study aimed to investigate the association between HLA-DQA1 and DQB1 genotypes and haplotypes vs *H. pylori* infection in an Indonesian population. Methods: We selected 294 healthy participants in Mataram, Lombok Island, Indonesia. *H. pylori* infection was determined by urea breath test (UBT). We analyzed HLA-DQA1 and DQB1 genotypes by PCR-RFLP and constructed haplotypes of HLA-DQA1 and DQB1 genes. Multiple comparisons were conducted according to the Bonferroni method. Results: The *H. pylori* infection rate was 11.2% in this Indonesian population. The DQB1*0401 genotype was noted to be associated with a high risk of *H. pylori* infection, compared with the DQB1*0301 genotype. None of the HLA-DQA1 or DQB1 haplotypes were related to the risk of *H. pylori* infection. Conclusions: The study suggests that HLADQB1 genes play important roles in *H. pylori* infection, but there was no statistically significant association between HLA-DQA1 or DQB1 haplotypes and *H.pylori* infection in our Lombok Indonesian population.

Keywords: HLA - DQA1 - HLA - DQB1 - haplotype - *H. pylori* - infection - association

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Introduction

More than 50% of the world's population is infected with *Helicobacter pylori (H. pylori)* in the pylorus of the stomach (Brown, 2000). In particular, *H. pylori* infection is more prevalent in developing countries, varying with the geographic area, age, socioeconomic status, race, and ethnicity. The precise transmission route is unknown, but most individuals may become infected in childhood (Klein et al., 1991). *H. pylori* is an important gastrointestinal pathogen associated with chronic gastritis, gastric or duodenal ulcers, and gastric cancer (Asaka et al., 1994; Honda et al., 1998; Peek et al., 2000). Although the majority of *H. pylori*-infected patients develop asymptomatic gastritis, gastric or duodenal ulcers, only a small proportion of them suffer from gastric cancer. The different outcomes of *H. pylori* infection seem to be due to bacterial genotypes and strain diversities, duration of infection, or factors involving the host and environment. Host individual differences in immune response also have appeared to play a key role in the establishment and progression of *H. pylori* infection.

In Asia, infection rates of *H. pylori* are high in Japan (Tokudome et al., 2005), Korea (Lee et al., 2008), China (Brown et al., 2002) and Vietnam (Nguyen et al., 2006) and the incidence rates of gastric cancer are generally high in the areas with a higher prevalence of *H. pylori* infection. In Indonesia, on the other hand, not only urea breath testing (UBT) but also IgG antibodies to *H. pylori* were found to be low in men and women, significantly lower than the 62% and 57%, respectively, in Japan. For example gastric cancer incidence in Yogyakarta and Semarang, Indonesia appeared exceedingly low, only approximately 1% of that in Japan (Tokudome et al., 2005; Tokudome et al., 2005).

Human leukocyte antigen (HLA) class II molecules are α-β heterodimeric membrane glycoproteins that are expressed on the surface of antigen-presenting cells such as macrophages, dendritic cells and B lymphocytes (Kaufman et al., 1984). Only helper T cells can recognize peptides derived from extracellular antigens which are associated with HLA class II molecules. The interaction

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of T cell receptors, peptides and HLA class II molecules determines T cell activation and an immune response to various antigens (Sette et al., 1987; Peace et al., 1991; Topalian et al., 1994). HLA polymorphism is responsible for variation in the immune response of different individuals to various antigens, and contributes to the susceptibility or resistance to infections and autoimmune diseases (Amar et al., 1984; Payami et al., 1986; Todd et al., 1987; 1988; Hill et al., 1991). Previous studies have shown that adhesion of *H. pylori* to gastric epithelial cells transferred with HLA genes leads to different degrees of apoptosis (Fan et al., 1998). The HLA-D region accounts for over 50% of the heritability in hosts (Azuma et al., 1995), and it was also reported that there is an association of HLA-DQA1 and DQB1 genotypes with gastric disease (Rotter et al. 1984; Etoglu et al., 1992; Ohmori et al., 1997). The present study was conducted in order to investigate the association of HLA-DQA1 and DQB1 genetic diversity in individuals infected with *H. pylori* in an Indonesian population.

Materials and Methods

Study Population

Since 2004, international collaborative epidemiologic studies on host and environmental factors for stomach cancer have been conducted in several Southeast Asian countries, including Thailand, Vietnam and Indonesia. In March 2007, we conducted an epidemiologic study on 107 male and 187 female participants from the general population in the city of Mataram, Lombok Island, Indonesia. Their age ranged from 6 to 74 years with a mean age of 34.0 (±14.4) (±SD). Informed consent was obtained from all subjects for the examination of *H. pylori* infection and the analysis of host factors, including HLA-DQ antigen genotypes. The protocol was approved by the Ethics Committee of the Nagoya City University Graduate School of Medical Sciences.

Urea Breath Test

H. pylori infection was determined by UBT, UBiT-IR300 kits (Otsuka Pharmaceutical Co., Tokyo, Japan) with ≥2.5‰ as positive. All subjects were classified as *H. pylori* -positive (+) or -negative (-) in this study (Tokudome et al., 2005).

Genotyping of DQA1 and DQB1

Template of genomic DNA was isolated from 100 μl of peripheral blood leukocytes by the Nucleic Acid Purification System (MagExtractor MFX-6000 TOYOBO Japan). The primer pair used to amplify DQA1 consisted of DQA1-5' (5'-CAC GGA TCC GGT AGC AGC GGT AGA GTT G-3') and DQA1-3' (5'-ATG GTG TAA ACT TGA ACC AGT-3') (Maeda et al., 1989; Steck et al., 1995). DQA1 PCR products were digested with FokI, HaeIII, DdeI, ScrFI and RsaI (Ota et al., 1991; Teutsch et al., 1996) . The exon of DQB1 with DQw1 specificity was amplified using PCR primers GH28NL and QB202 (DQB1 202 primer 1: 5'-CTC GGA TCC GCA TGT GCA ACT TCA CCA ACG, primer 2 5'-CAC CTG CAG ATC CCG CGG TAC GCC ACC TC). The DQB1 (DQw1) PCR products were digested with FokI, ApaI, HaeII, BssHII, HphI and HhaI. The exon of DQB1 with DQw2, 3 or 4 specificities was amplified using PCR primers GH28NL and DQ204 (DQB1204 primer 1:5'-CTC GGA TCC GCA TGT GCT ACT TCA CCA ACG, primer2: 5'-CAC CTG CAG TGC GGA GCT CCA ACT GGT A) (Uryu et al., 1990; Wang et al., 2004). The DQB1 (DQw2, 3, 4) PCR products were digested with FokI, BglI, SacI, BsaHI and MspI. Samples of the restriction enzyme-cleaved amplified DNAs were usually subjected to electrophoresis in 5% agarose gel (Lonza USA) in a horizontal minigel apparatus. When digested with restriction enzyme, 5% agarose gel was used. Cleavage or no cleavage of amplified fragments was detected by staining with ethidium bromide (Nomura et al., 1991; Teutsch et al., 1996).

Statistical Analyses

Differences in the distribution by age according to prevalence of *H. pylori* infection were examined by t-test. Differences in the distribution by sex and genotype were assessed with Chi-square test. Hardy-Weinberg equilibrium was examined for HLA-DQA1 and DQB1 allele polymorphisms. Multi-comparisons for HLA-DQA1 and DQB1 alleles and haplotypes were made according to the Bonferroni method. Associations of the HLA genotypes and haplotypes with *H. pylori* infection were examined by odds ratio (OR) and 95% CI (confidence interval) using unconditional logistic regression analysis. Statistical significance was determined as $p<0.05$. All the statistical analyses were performed using SAS software package (version 9.1).

Results

The positive *H. pylori* infection rate as a whole was 11.2% in Mataram (Table 1). No obvious differences were noted for *H. pylori* infection rates by sex or age. DQA1*0601, DQB1*0501, and DQB1*0301, DQB1*0302 were frequent. Individuals carrying DQB1*0401 genotypes were noted to be at higher risk of *H. pylori* infection, compared with those carrying DQB1*0301 (OR=5.24, 95% CI=1.25-21.91) (Table 2). None of haplotypes DQA1 or DQB1 were related to *H. pylori* infection (Table 3).

Table 1. Age and Prevalence of *H. pylori* infection (%) by Sex and Age in the People of Mataram, Lombok island, Indonesia.

		H. pylori (+)	*H. pylori* (-)
Sex:	Male	9 (8.4)	98
	Female	24 (12.8)	163
		33 (11.2)	261
Age:	30	12 (9.6)	113
	31- 40	9 (11.5)	69
	41 - 50	7 (14.6)	41
	51- 60	3 (10.3)	29
	>60	2 (18.2)	9
		33 (11.2)	261
Mean age		36.3±14.6 (SD)	33.7±14.4 (SD)

Table 2. Association between HLA-DQA1 and DQB1 Genotypes vs *H. pylori* infection in Mataram, Lombok island, Indonesia.

Genotype		*H. pylori* (+) n=33	*H. pylori* (-) n=261	OR*	95% CI*
DQA1:	0601	10 (30.3)	93 (35.6)	1.00(Ref)	
	0101[a]	9 (27.3)	86 (33.0)	0.97	0.37-2.50
	0103	3 (9.1)	24 (9.2)	1.09	0.28-4.31
	0201	4 (12.1)	15 (5.8)	2.39	0.65-8.74
	0301	3 (9.1)	16 (6.1)	1.55	0.38-6.40
	0401	0 (0.0)	3 (1.2)	NC	NC
	0501	4 (12.1)	24 (9.2)	1.42	0.40-5.03
DQB1202:	0501	11 (33.3)	79 (30.3)	1.00(Ref)	
	0502	4 (12.1)	65 (24.9)	0.43	0.13-1.41
	0503	4 (12.1)	30 (11.5)	0.98	0.29-3.34
	0504	2 (6.1)	18 (6.9)	0.77	0.15-3.82
	0601	8 (24.3)	47 (18.0)	1.17	0.44-3.15
	0602[b]	3 (9.1)	14 (5.4)	1.42	0.34-5.88
	0604[c]	1 (3.0)	81 (3.1)	0.88	0.10-7.83
DQB1204:	0301	16 (48.5)	109 (41.8)	1.00(Ref)	
	0201	2 (6.1)	32 (12.3)	0.40	0.09-1.87
	0302	10 (30.3)	99 (37.9)	0.66	0.28-1.55
	0303	1 (3.0)	9 (3.5)	0.62	0.07-5.47
	0304	0 (0.0)	4 (1.5)	NC	NC
	0401	4 (12.1)	5 (1.9)	5.24	1.25-21.91
	0402	0 (0.0)	3 (1.2)	NC	NC

[a]DQA1*0101 and *0102 had the same restriction patterns, [b]DQB1*0602 and *0603 had the same restriction patterns, [c]DQB1*0604, *0605-6 and *0609 had the same restriction patterns, *Adjusted for age and sex, by logistic regression model, NC: Not calculated.

Table 3. Association between *H. pylori* infection and HLA-DQA1-DQB1 Linked Gene Haplotype in Mataram, Lombok island, Indonesia.

Haplotype	*H. pylori* (+)	*H. pylori* (-)	OR*	95% CI*
DQA1*0601-DQB1*0501			1.00(Ref)	
DQA1*0501-DQB1*0501	9(27.3)	69(26.4)	0.89	0.27-2.91
DQA1*0501-DQB1*0502	4(12.1)	58(22.2)	0.44	0.11-1.78
DQA1*0501-DQB1*0503	4(12.1)	29(11.1)	0.94	0.23-3.92
DQA1*0501-DQB1*0504	2(6.1)	18(6.9)	0.71	0.12-4.10
DQA1*0501-DQB1*0601	6(18.2)	44(16.9)	0.85	0.24-3.08
DQA1*0501-DQB1*0602	3(9.1)	12(4.6)	1.59	0.32-7.78
DQA1*0501-DQB1*0301	14(42.4)	99(38.0)	0.98	0.29-3.34
DQA1*0501-DQB1*0201	2(6.1)	27(10.3)	0.49	0.08-2.96
DQA1*0501-DQB1*0302	10(30.3)	94(36.0)	0.71	0.20-2.48
DQA1*0501-DQB1*0303	1(3.0)	7(2.7)	0.81	0.07-8.75
DQA1*0501-DQB1*0401	2(6.1)	5(1.9)	2.50	0.3-17.86

Discussion

We investigated associations between host HLA-DQ variation and *H. pylori* prevalence in an Indonesian population with an H. pylori infection rate of 11.2% in people residing in Mataram, Lombok Island. Individuals carrying DQB1*0401 genotypes were noted to be at a significantly greater risk for developing *H. pylori* infection, compared to those with DQB1*0301 genotypes. Haplotypes of DQA1 or DQB1 were not related to *H. pylori* infection.

Human major histocompatibility complex (MHC) class II molecules, such as HLA-DP, HLA-DQ, and HLA-DR play a key role in immune reactions to pathogens, including bacteria and toxins (Liewelyn et al., 2004). The HLA-D region accounts for over 50% of the heritability in hosts (Azuma et al., 1995) and appears responsible for variation in the immune response of different individuals to various exogenous antigens, suggesting that there are varieties in the host's response to the same organism, and individuals with various HLA types differ in their immune response. Allele-specific antigenic peptides to T-cells may contribute to the differences between HLA-DQ genotypes and susceptibility or resistance to *H. pylori* infection (Herrera-Goepfere et al., 2006). Possible associations between HLA-DQ genotypes and *H. pylori* infection have been reported in China (Wang et al., 2004; Huang et al., 2005). Distributions of HLA-DQA1 and DQB1 genotypes detected in the Indonesian people in the present study may, in part, explain the low prevalence of *H. pylori* infection there.

In addition to HLA-DQ genotypes, other host factors, not only oncogenes or suppressor genes (Yasui et al., 2006) but also genetic polymorphisms, associated with bacterial infection and inflammatory cytokines, seem of interest because they are known to be related to *H. pylori* infection and *H. pylori*-associated lesions/diseases, including gastritis, gastric/duodenal ulcer and gastric cancer (Veldhuyzen et al., 1994). We are now analyzing genetic polymorphisms, including CD14, IL1-beta, IL4, IL8, TNF-alpha, and PTPN11 (Hamajima et al., 2006), and comparing the prevalence of alleles of the genetic polymorphisms between *H. pylori* infected vs. non-infected subjects in the people of Mataram, Lombok island, Indonesia.

Because bacterial infection is established via interactions among host factors, bacterial factors and environmental/vehicle factors, *H. pylori* bacterium genotypes and strains are important. There are genotypes, including cytotoxin-associated genes A (cagA) and vacuolating cytotoxin A (vacA) genotypes in respective *H. pylori* strains, including East-Asian type, South/Central Asian type, African type and European type (Yamaoka et al., 2002). There are various genotypes in different *H. pylori* strains in diverse ethnic groups, including South-east Asian countries. We also detected East-Asian type in *H. pylori* bacteria isolates from patients with gastric ulcer in Mataram, Lombok island (unpublished). Thus, associations between *H. pylori* bacterium genotypes and strains vs. *H. pylori* prevalence in the Indonesian people should be further studied.

H. pylori may be transmitted via the fecal-oral or oral-oral infection route in early childhood (Klein et al. ,1991; Kusters et al., 2006), environmental/lifestyle factors, including sanitary conditions, water sources, living conditions, family size, and socioeconomic status, appeared critical. It seemed that sanitary/environmental conditions remain basic in Mataram, Lombok island, Indonesia. Some people still use the fingers when eating (Cairncross et al., 1997), consume well, pond or river water (Cairncross et al., 1997; Mckeown et al., 1999) and use privy/latrine type toilet (Feachem et al., 1983). Prevalence of hepatitis A, for instance, a typical water-borne infectious disease, is very high at no less than 90%,

and the infection rates did not differ between the two areas (Brown et al., 1985; Hoang et al., 2008) Effects of pre- or co-infection of other organisms, including dengue, should be taken into account because the altered immune system may modify sensitivity or resistance to infection by *H. pylori* (Nurgalieva et al., 2005). Dietary factors cannot be overlooked. Investigations on consumption of fresh fruit and vegetables, isoflavone-rich soybean products (Ko et al., 2010), such as tempe (fermented soybean curd) and vegetable oils, in particular, are now in progress.

The present approaches are ecological studies using international groups/areas as units. Naturally, the level of evidence is low (Da Cunha et al., 2007). There may exist ecological fallacies when drawing individual-based inferences on the basis of group-level data. The subjects studied may not represent the Indonesian people as a whole because the subjects were not, strictly speaking, randomly sampled from the general population of Mataram, Lombok island, Indonesia. In addition, the number of study subjects did not seem to be sufficient when genomic alleles are rare, in particular, or the statistical power may not be sufficient to detect the supposed differences.

In conclusion, HLA-DQ genotypes may play an important role in *H. pylori* infection, and the low *H. pylori* infection rates in Indonesian people may be, in part, explained by the diversities in the distribution of HLA-DQ genotypes along with the differences in bacterial genotypes and strains, sanitary or environmental conditions and dietary factors. Further studies are warranted to confirm the present observations.

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