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BRIEF ARTICLE

Association between *TNF-α* and *IL-1β* genotypes *vs* *Helicobacter pylori* infection in Indonesia

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Abstract

AIM: To investigate the correlation between the *Helicobacter pylori* (*H. pylori*) infection and host genetic background of healthy populations in Indonesia.

METHODS: In March 2007, epidemiological studies were undertaken on the general population of a city in Indonesia (Mataram, Lombok). The participants included 107 men and 187 women, whose ages ranged from 6 to 74 years old, with an average age of 34.0 (± 14.4) (± SD). The *H. pylori* of subject by UBT method determination, and through the polymerase chain reaction with confronting two-pair primers (PCR-CTPP) method parsing the single nucleotide polymorphism of interleukin (IL)-8, IL-4, IL-1β, CD14, tumor necrosis factor (TNF-α) and tyrosine-protein phosphates non-receptor type 11 (PTPN11) genotypes. The experimental data were analyzed by the statistical software SAS.

RESULTS: The *H. pylori* infection rates in the healthy Indonesian population studied were 8.4% for men and 12.8% for women; no obvious differences were noted for *H. pylori* infection rates by sex or age. TC genotypes of IL-4, TC and CC genotypes of TNF-α, and GA genotypes of PTPN11, were higher in frequency. Both CC and TC genotype of TNF-α T-1031C loci featured higher expressions in the healthy Indonesian population Indonesia studied of (OR = 1.99; 95%CI: 0.67-5.89) and (OR = 1.66; 95%CI: 0.73-3.76), respectively. C allele of IL-1β T-31C gene locus was at a higher risk (OR = 1.11; 95%CI: 0.70-1.73) of *H. pylori* infection, but no statistical significance was found in our study.

CONCLUSION: We reveal that the association between the TNF-α and IL-1β genotypes may be the susceptibility of *H. pylori* in the studied population.

Key words: *Helicobacter pylori*; Tumor necrosis factor; Interleukin-1β; Infection; Allele

Core tip: We found single nucleotide polymorphism of tumor necrosis factor-α and allele of interleukin-1β having high frequency in the healthy Indonesian population, which may be associated with potential contact with *Helicobacter pylori* (*H. pylori*) infection. Throughout, *H. pylori* studies were conducted in patients, and treatment was based on quadruple antibiotics to eradicate *H. pylori* infection in clinical trials. However, the implications of the individual differences in recurrent infections and drug resistance of *H. pylori* and other issues must be addressed. Therefore, vaccine development for prevention of *H. pylori* will be a topical issue in the coming years.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a microaerophilic (G-) bacteria that colonizes the area of stomach and duodenum, causing chronic inflammation of the gastric mucosa, the development of the stomach ulcers and even gastric cancer[1]. *H. pylori* is a class I carcinogen, and has been identified by the WHO as a cancer-causing prokaryotes[2]. More than 50% of the world's population infected with *H. pylori*, but 80% of people infected with *H. pylori* show no symptoms[3]. The *H. pylori* infection occurs mainly in economically underdeveloped regions, and the *H. pylori* infection rates of China, Japan and Korea were higher than developed countries[4-6], while the infection rates of Thailand and Vietnam were higher than Indonesia in Southeast Asia[7]. Regarding the ethnic groups of Singapore, *H. pylori* infection and the incidence of digestive diseases was higher in the Indian and Chinese than the Malay population[8]. The above studies have shown that *H. pylori* infection and geographical, ethnic and host genetic background is relational, and that the bacteria play a key role in the development of gastric cancer.

Single nucleotide polymorphism (SNP) is caused by a single nucleotide mutation in the genomic level DNA sequence polymorphisms. It is the most common type of genetic variation in humans. Accounting for more than 90% of all known polymorphisms, SNP is widespread in the human genome and there is a close relationship between the incidences of the disease[9]. Interleukin-8 (IL-8) is an important regulatory factor in the development of gastritis for *H. pylori* associated infection[10]. The interleukin-4 (IL-4) promotes HLA class Ⅱ antigen expression in B-cells[11], and IL-1β protein is an important inflammatory mediator, involved in infected *H. pylori* of the stomach inflammation reaction[12,13]. Have a study reported that the cluster of differentiation 14 (CD14) is an important receptor in the submission of *H. pylori* lipopolysaccharide (LPS). The relationship is between CD14 with the weakening of the immune response in the body to LPS of *H. pylori* and to reduce the proinflammatory cytokine secretion levels[14]. Tumor necrosis factor-α (TNF-α) is involved in inflammation, immune regulation and tissue repair, and the TNF-α is an important factor in the development of digestive diseases[15]. The tyrosine-protein phosphates non-receptor type 11 (PTPN11) gene is located in chromosome 12, and it has been found that the expression product of SHP-2 to participate in the cytotoxin-associated protein A (cagA) deformation caused by gastric epithelial cells eventually causes gastric cancer[16].

The purpose of this study was to investigate the correlation of *H. pylori* infection in a healthy Indonesian population and host genetic background, and to reveal susceptibility genes of *H. pylori*, as well as new strategies for the prevention and treatment of gastric cancer.

MATERIALS AND METHODS

Study population

In recent years, we have conducted long-term international cooperation in research, exploring the impact of environmental factors on the risk factors of gastric cancer in Southeast Asia, including the countries of Thailand, Vietnam and Indonesia, as well as Gansu Province in China. In March 2007, epidemiological studies were undertaken on the general population of a city in Indonesia (Mataram, Lombok). The participants included 107 men and 187 women, whose ages ranged from 6 to 74 years old, with an average age of 34.0 (± 14.4) (± SD). We detected and analyzed the *H. pylori* of the observation target as well as the genetic background of the host, namely the *IL-8*, *IL-4*, *IL-1β*, *CD14*, *TNF-α* and *PTPN11* genotypes. All the subjects' informed consent was approved by the Nagoya City University Graduate School of Medical Ethics Committee.

Urea breath test

H. pylori infection was determined by UBT, UBiT-IR300 kits (Otsuka Pharmaceutical Co., Tokyo, Japan) with ⩾ 2.5‰ considered as positive. All subjects were classified as *H. pylori* -positive (+) or -negative (-) in this study[7,8].

Genotyping of DQA1 and DQB1

A template of genomic DNA was isolated from 100 μl of peripheral blood leukocytes by the Nucleic Acid Purification System (MagExtractor MFX-6000 TOYOBO, Japan). We carried out a single nucleotide polymorphism (SNP) analysis of the *IL-8*, *IL-4*, *IL-1β*, *CD14*, *TNF-α* and *PTPN11* genotypes by two pairs of polymerase chain reaction (PCR-CTPP)[17-21].

Table 1 *Helicobacter pylori* infection by sex and age in Indonesian people *n* (%)

Indonesia	*H. pylori* (+) *n* = 33	*H. pylori* (-) *n* = 261
Sex		
Male	9 (8.4)	98 (91.6)
Female	24 (12.8)	163 (87.2)
Age, yr		
⩽ 30	12 (9.6)	113 (90.4)
31-40	9 (11.5)	69 (88.5)
41-50	7 (14.6)	41 (85.4)
51-60	3 (9.4)	29 (90.6)
⩾ 60	2 (18.2)	9 (81.8)
Mean age, yr	36.3 ± 14.6 (SD)	33.7 ± 14.4 (SD)

H. pylori: *Helicobacter pylori*.

Statistical analysis

Differences in distribution by age according to prevalence of *H. pylori* infection were examined by *t*-test, while differences in distribution by sex and genotype were assessed with a Chi-square test. Hardy-Weinberg equilibrium was examined for *IL-8*, *IL-4*, *IL-1β*, *CD14*, *TNF-α* and *PTPN11* gene polymorphisms. Multi-comparisons for *IL-8*, *IL-4*, *IL-1β*, *CD14*, *TNF-α* and *PTPN11* genotypes were made according to the Bonferroni method. Associations of the *IL-8*, *IL-4*, *IL-1β*, *CD14*, *TNF-α* and *PTPN11* genotypes and SNP with *H. pylori* infection were examined by OR and 95%CI using unconditional logistic regression analysis. Statistical significance was determined as $P < 0.05$. All the statistical analyses were performed using the 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. TC genotypes of IL-4, TC and CC genotypes of TNF-α, and GA genotypes of PTPN11 were frequent. Individuals carrying TC and CC allele of TNF-α was noted to be at higher risk of *H. pylori* infection, compared with those carrying TT allele of TNF-α (OR = 1.66, 95%CI: 0.73-3.76) and (OR = 1.99, 95%CI: 0.67-5.85), We also found TT and CT genotypes of CD14 C-159T (OR = 1.09, 95%CI: 0.37-3.20) and (OR = 1.26, 95%CI: 0.50-3.19), but no statistical significance was found in our study (Table 2). We found C allele had a higher frequency than T allele of IL-1β genotype in the studied population (OR = 1.11, 95%CI: 0.70-1.73), but again no statistical significance was found (Table 3).

DISCUSSION

In 50% of the world's population was infected *H. pylori* infection rates in developing countries were higher than in developed countries, and it has been reported that hosts at an early age have been infected[22]. Indonesia, located in Southeast Asia, is a developing country, but

Table 2 Association between *Helicobacter pylori* infection and interleukin 1β, interleukin 4, interleukin 8, CD14, tumor necrosis factor-α, tyrosine-protein phosphates non-receptor type 11 single nucleotide polymorphism in Indonesian people *n* (%)

Polymorphism	*H. pylori* (+) *n* = 33	*H. pylori* (-) *n* = 261	OR[1]	95%CI[1]
IL-1β T-31C				
TT	8 (24.2)	59 (22.6)	ref	
CC	8 (24.2)	73 (28.0)	0.82	0.29-2.32
TC	17 (51.5)	129 (49.4)	1.05	0.42-2.59
TC/CC	25 (75.8)	202 (77.4)	0.96	0.41-2.26
IL-4 T-33C				
TT	15 (45.5)	128 (49.0)	ref	
CC	2 (6.1)	19 (7.3)	0.83	0.17-3.99
TC	16 (48.5)	114 (43.7)	1.24	0.58-2.64
CC/TC	18 (54.5)	133 (51.0)	1.18	0.56-2.45
IL-8 T-251A				
TT	14 (42.4)	98 (37.6)	ref	
AA	8 (24.2)	49 (18.8)	1.25	0.48-3.27
TA	11 (33.3)	114 (43.7)	0.74	0.32-1.72
TA/AA	19 (57.6)	163 (62.5)	0.89	0.42-1.88
CD14 C-159T				
CC	7 (21.2)	65 (24.9)	ref	
TT	8 (24.2)	65 (24.9)	1.09	0.37-3.20
CT	18 (54.6)	131 (50.2)	1.26	0.50-3.19
CT/TT	26 (78.8)	196 (75.1)	1.2	0.50-2.92
TNF-α T-1031C				
TT	11 (33.3)	120 (46.0)	ref	
CC	6 (18.2)	36 (13.8)	1.99	0.67-5.89
TC	16 (48.5)	105 (40.2)	1.66	0.73-3.76
CC/TC	22 (66.7)	141 (54.0)	1.74	0.80-3.76
PTPN11 G/A at intron 3				
GG	17 (51.5)	151 (57.9)	ref	
AA	1 (3.0)	17 (6.5)	0.6	0.07-4.86
GA	15 (45.5)	93 (35.6)	1.49	0.70-3.15
GA/AA	16 (48.5)	110 (42.2)	1.37	0.65-2.85

[1]Odds rate with CI adjusted for age and sex by logistic regression model. *H. pylori*: *Helicobacter pylori*; IL: Interleukin; PTPN11: Tyrosine-protein phosphates non-receptor type 11.

we found that the country has an *H. pylori* infection rate which was very low. We investigated associations between SNP of the host *IL-8*, *IL-4*, *IL-1β*, *CD14*, *TNF-α* and *PTPN11* gene polymorphisms and *H. pylori* prevalence in an Indonesian population with an *H. pylori* infection rate of 11.2% in people residing in Mataram, Lombok Island. Although SNP of host *IL-8*, *IL-4*, *IL-1β*, *CD14*, *TNF-α* and *PTPN11* genotype with *H. pylori* infection were not found to have statistical significance in our study, we saw that an observation target who had the CC and TC genotype of *TNF-α* gene were at a higher risk of contracting *H. pylori* infection. Perhaps, *TNF-α* gene plays a key role in the *H. pylori* infection process.

H. pylori is widely present in the environment, and it can be isolated in surface waters[23], *i.e.*, transmitted by the fecal - oral route[24]. Studies have shown that through certain digestive diseases and strains of *H. pylori*, Cytotoxin-associated protein A (cagA) is now known as the most important virulence factors of *H. pylori*[25]. CagA is an *H. pylori* cag poison island (cag-PAI) flag, and by cag-PAI coded protein is composed of a bacterial type Ⅳ secretion system into gastric epithelial cells, which ultimately

Table 3 Association between *Helicobacter pylori* infection and allele of interleukin 1β, interleukin 4, interleukin 8, CD14, tumor necrosis factor-α, tyrosine-protein phosphates non-receptor type 11 in Indonesian people *n* (%)

Allele	*H. pylori* (+) *n* = 66	*H. pylori* (-) *n* = 522	OR[1]	95%CI
IL-1β T-31C				
T	33 (50.0)	247 (47.3)	ref	
C	33 (50.0)	275 (52.7)	1.10	0.70-1.73
IL-4 T-33C				
T	46 (69.7)	370 (70.9)	ref	
C	20 (30.3)	152 (29.1)	0.95	0.58-1.56
IL-8 T-251A				
T	39 (59.1)	310 (59.4)	ref	
A	27 (40.9)	212 (40.6)	0.99	0.62-1.57
CD14 C-159T				
C	32 (48.5)	261 (50.0)	ref	
T	34 (51.5)	261 (50.0)	0.95	0.60-1.49
TNF-α T-1031C				
T	38 (57.6)	345 (66.1)	ref	
C	28 (42.4)	177 (33.9)	0.73	0.46-1.15
PTPN11 G/A at intron 3				
G	49 (74.2)	395 (75.7)	ref	
A	17 (25.8)	127 (24.3)	0.94	0.56-1.57

[1]Odds rate with CI adjusted for age and sex by logistic regression model. *H. pylori*: *Helicobacter pylori*; IL: Interleukin; PTPN11: Tyrosine-protein phosphates non-receptor type 11.

causes gastric mucosal epithelium, the morphological changes of the cells and the formation of a humming-bird-like structure[26]. Host infected cagA-positive *H. pylori* is less likely to cause digestive diseases, but may damage the gastric mucosal barrier and is cagA related. *H. pylori* infection with strains, geographical, ethnic, and environmental and host genetic background was a correlation.

The IL-8 as a neutrophil chemoattractant and activating factor, which relates to *H. pylori* infection, resulting in second messenger of the mucosal inflammatory response in the *H. pylori* pathogen city, plays an important role of intermediary. But what components of *H. pylori* surface play a major role in the induction of IL-8 expression is still one of the main points about *H. pylori* pathogenesis. Of *H. pylori* cytotoxin-associated protein (cagA) and vacuolating cytotoxin (vacA) on gastric epithelial IL-8 secretion, showing expression of cagA and vacA *H. pylori* strains (vacA+, cagA+) direct stimulation of gastric epithelial cell lines IL-8 mRNA expression and protein secretion of IL-8, suggests that expression of the gene product and cagA *H. pylori* strains induced gastric epithelial expression of IL-8 in the main factors[11]. In addition to *H. pylori* gastric epithelial cells directly stimulating the production of IL-8, the inflammation locally produced of TNF-α, transcription factor activation of the IL-1, was also an up-regulated expression of IL-8[11]. Furthermore *H. pylori*, in addition to the expression of IL-8 induced gastric epithelial cells, also stimulates gastric epithelial cells TNF-α, IL-1β expression[27,28]. In *H. pylori* infection, IL-8 chemotaxis of neutrophil infiltration and epithelial damage caused by *H. pylori* vacuoles toxins can promote mucous membrane endocytosis bacterial products and induction of mucosal phagocytic cells to secrete cytokines IL-1β, TNF-α and IL-8; neutrophils are attracted to the infected local, while neutrophils becomes the main source of iL-1, TNF-α and iL-8 induced inflammatory cytokines. Neutrophil elastase also relates to the epithelial cells induced by IL-8 gene expression, suggesting that the neutrophil enzyme release cytokines can induce a continuity of the inflammatory process itself[29], and *H. pylori*-induced IL-8, IL-1β cytokine expression throughout the entire *H. pylori* infection period[30]. Studies found that Protein-tyrosine phosphatase, non-receptor-Type11 (PTPN11) encoding Srchomology 2 domain-containing pro-Tein tyrosine phosphatase-2 (SHP-2) in CagA-induced gastric epithelial cell deformation, that eventually cause the gastric process, played a very important role, and the genetic background of the PTPN11 shows certain racial difference[31,32]. The IL-4 by CD4+ T cell subsets, B cells and mast cells secreted pleiotropic cytokines involved in inflammation, mucosal repair, cell proliferation and apoptosis and other physiological and pathological processes; changes in the expression levels may also affect pathogenesis of *H. pylori* infection, resulting in a host of different clinical results. The *H. pylori* infection caused by non-ulcerative gastritis can lead to local Th0 cells producing and secreting large amounts of cytokines IL-4; however, in patients with peptic ulcers, *H. pylori* infection can be caused by the polarization of Th1 cells[33]. Studies suggest that the CD14 gene C/T mutation may lead to the activation of the CD14 promoter enhanced transcription of the CD14 gene, while monocytes' high expression of CD14 and CD14 can regulate the secretion of LPS-induced IL-1 and TNF-α[15,34]. TNF-gene coding region mutations may affect TNF-α activity, caused by TNF-α allele or genetic type associated with *H. pylori* associated gastric duodenal disease susceptibility. In an infected *H. pylori* host of Japan, it was found that the genotype of the TNF-α-857 C/C and 1031 C/C group serological detection of *H. pylori* was the lowest positive rate, and in the TNF-α-857 T/T and TNF-B-1031 T/T genotype the serum *H. pylori* positive rate was the highest[35]. The C/C and T/C genotypes of TNF-α T-1031C locus were at the highest risk from *H. pylori* infection in our study.

The development of gastric cancer is a complex process, *H. pylori* infection is caused by one of the risk factors of gastric cancer. In addition, there are environmental factors, social factors, host genetic background and lifestyle. Directly use hand grasp to pilaf is very common, and the schistosome liver disease has also been often reported in Indonesia[36]; however, *H. pylori* infection and gastric cancer incidence rate were very low. In addition, have also been reports that complications of the esophagus caused by reflux esophagitis after sterilization of cancer have tended to increase[37]. And resistant strains of *H.pylori* by sterilization treatment have been reported[38]. Therefore, it appears that sterilization treatment is not the best means of prevention of gastric cancer. This study explored *H. pylori* infection with immune response

gene polymorphisms in a healthy Indonesian population. Although there was no statistical significance in SNP of *IL-8*, *IL-4*, *IL-1β*, *CD14*, *TNF-α* and *PTPN11* gene polymorphisms, we found SNP of TNF-αT-1031C locus was the highest risk of *H. pylori* infection. Our study provides the basis for future research data, and a new direction for the prevention of *H. pylori* infection.

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COMMENTS

Background

Helicobacter pylori (H. pylori) infection in developing countries is high in comparison with developed countries. Indonesia is a developing country located in Southeast Asia, but the prevalence of *H. pylori* in Indonesia is lower than other countries of Southeast Asia.

Innovations and breakthroughs

Throughout, *H. pylori* studies were conducted in patients, and treatment was based on quadruple antibiotics to eradicate *H. pylori* infection in clinical settings. However, the implications of the individual differences in recurrent infections and drug resistance of *H. pylori* and other issues must be addressed. The authors observed that the object was a healthy crowd, which reveals that in the host genetic background there is a certain association with *H. pylori* infection.

Applications

This study provided basic vaccine development data for the prevention of *H. pylori*, and for the prevention of gastric cancer through the advancement of new ideas.

Terminology

H. pylori is a Gram-negative, microaerophilic bacterium found in the stomach. It was identified in 1982 by the Australian scientists Barry Marshall and Robin Warren, who found that it was present in patients with chronic gastritis and gastric ulcers, conditions that were not previously believed to have a microbial cause. It is also linked to the development of duodenal ulcers and stomach cancer. However, over 80 percent of individuals infected with the bacterium are asymptomatic, and it has been postulated that it may play an important role in the natural stomach ecology.

Peer review

The manuscript is interesting, but the absence of statistical significance is an important issue.

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