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Prevalence of two homologous genes encoding glycosyltransferases of *Helicobacter pylori* in the United States and Japan

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Abstract

Background and aims—*jhp0562* and β -(1,3)*galT* (*jhp0563*) of *Helicobacter pylori* have been suggested as novel virulent factors; however the clinical associations and functions of these genes remain unclear. We examined the prevalence of *jhp0562*, β -(1,3)*galT*, and *cagA* in the United States (U.S.) and Japanese populations.

Methods—A total of 308 strains (171 from the U.S. and 137 from Japan) were examined for the status of *jhp0562*, β -(1,3)*galT*, and *cagA* by polymerase chain reaction.

Results—There were significant differences in the status of *jhp0562*, β -(1,3)*galT* and *cagA* between the U.S. and Japanese populations ($P < 0.001$). In the U.S., the prevalence of β -(1,3)*galT* was significantly lower in strains isolated from patients with duodenal ulcer (DU) or gastric ulcer (GU) than those with gastritis (47.8% and 32.1% vs. 72.0%, $P < 0.01$), and the absence of β -(1,3)*galT* was an independent factor discriminating DU and GU from gastritis (adjusted odds ratios, 4.21 and 8.52; 95% confidence intervals, 1.75 to 10.12 and 2.76 to 26.33, respectively). In the U.S., the prevalence of the *jhp0562*-positive/ β -(1,3)*galT*-negative genotype was significantly higher in strains from DU and GU patients than in those from gastritis patients (50.0%, 67.9%, and 24.4%, $P < 0.01$) and the *cagA* status was significantly correlated with that of *jhp0562* and inversely correlated with that of β -(1,3)*galT*. In contrast, the prevalence of these three genes was not significantly different in Japan.

Conclusions—*jhp0562* or β -(1,3)*galT* can be used to discriminate peptic ulcers from gastritis in the U.S., but not in Japan.

Keywords

Helicobacter pylori; *jhp0562*; β -(1,3)*galT*; glycosyltransferase

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Potential competing interests: None

Introduction

Helicobacter pylori (*H. pylori*) infection is etiologically associated with gastritis, peptic ulcer diseases, gastric atrophy, and gastric cancer (GC)¹, although most infected people remain asymptomatic. Factors thought to be associated with clinical gastroduodenal diseases include *H. pylori* virulence, host genetics, and environmental factors such as diet². There has been considerable interest in the molecular epidemiology of *H. pylori* putative virulence factors, especially CagA, VacA, and OipA^{3,4}. However, no such factors have been exclusively linked to a specific *H. pylori*-related disease (e.g., GC).

jhp0562, which encodes a glycosyltransferase involved in the synthesis of lipopolysaccharide (LPS), was reported to be associated with peptic ulcer diseases in children, but not in adults, in the Portuguese population⁵. The sequence of β -(1,3)*galT* (*jhp0563*), which is involved in the Lewis (Le) antigen expression of LPS, is highly similar to that of *jhp0562*^{6,7}. In a subsequent study by the same group in the Portuguese population, the presence of *jhp0562* alone (*jhp0562*-positive/ β -(1,3)*galT*-negative) was associated with peptic ulcers rather than with gastritis, and the presence of β -(1,3)*galT* alone (*jhp0562*-negative/ β -(1,3)*galT*-positive) was associated with gastritis rather than with peptic ulcers⁸.

However, no previous study investigated the association between these two genes and *H. pylori*-related diseases in other countries. This study investigated whether there was also an association between these genes and clinical outcomes in populations from another Western country (the United States [U.S.]) where there is a low prevalence of *H. pylori* (e.g., 10–15 % at the aged > 50 years)⁹ and an Asian country (Japan) where there is a high prevalence of *H. pylori* (e.g., over 60 % at the aged > 50 years)¹⁰.

Methods

Patients and *H. pylori*

H. pylori strains were obtained from the gastric mucosa of *H. pylori*-infected patients who underwent endoscopy at Oita University Faculty of Medicine (Oita, Japan) and Michael E. DeBakey Veterans Affairs Medical Center (Houston, TX). Presentations included gastritis, duodenal ulcer (DU), gastric ulcer (GU), and GC. DU, GU, and GC were identified by endoscopy, and GC was further confirmed by histopathology. Gastritis was defined as *H. pylori* gastritis in the absence of peptic ulcers or gastric malignancy. Patients with a history of partial gastric resection were excluded. Patients who received *H. pylori* eradication therapy or treatment with antibiotics, bismuth-containing compounds, H₂-receptor blockers, or proton pump inhibitors within 4 weeks prior to the study were also excluded. Informed consent was obtained from all participants, and the protocol was approved by local hospital ethics committees.

H. pylori genotyping

Antral biopsy specimens were obtained for the isolation of *H. pylori* using standard culture methods as previous described¹¹. Chromosomal DNA was extracted from confluent plate cultures expanded from a single colony using a commercially available kit (QIAGEN, Valencia, CA). Two *H. pylori* strains with fully sequenced genomes deposited in GenBank, strain 26695 (ATCC 700392), which is negative for *jhp0562* and positive for β -(1,3)*galT*, and strain J99 (ATCC 700824), which is positive for both genes, were used as control strains. Polymerase chain reaction (PCR) amplification for *jhp0562* and β -(1,3)*galT* was performed using one primer pair, 5'-TGA AAA GCC CTT TTG ATT TTG-3' and 5'-GCT GTA GTG GCC ACA TAC ACG-3', as described by Oleastro *et al.*, who originally reported the importance of the genes⁵. The PCR conditions were initial denaturation for 5 min at 95°C, 35 amplification steps (95°C for 30 s, 56°C for 30 s, and 72°C for 30 s), and a final

extension cycle of 7 min at 72°C, as described by Oleastro *et al*⁵. These primers generated two PCR products with 301 and 602 bp in the strain J99, corresponding to *jhp0562* and β -(1,3)*galT* (*jhp0563*), respectively, and only one PCR product with 558 bp in the strain 26695, corresponding to β -(1,3)*galT* (HP0619). Two copies of β -(1,3)*galT* gene fragments of different lengths were found in several cases. For this study, we constructed a new primer pair, 5'-ATG CAA GCC TTA GAA GAT TG-3' and 5'-ATA TCC ACC GGC TCT ATG AT-3'. These primers generated two PCR products with 404 and 704 bp in the strain J99, corresponding to *jhp0562* and β -(1,3)*galT*, respectively, and only one PCR product with 661 bp in the strain 26695, corresponding to β -(1,3)*galT*. The PCR products obtained using primers for *jhp0562* had the same lengths (301 bp for the first primer and 404 bp for the second primer) in all experiments, but the PCR products obtained using primers for β -(1,3)*galT* had several lengths (approximately 550–600 bp for the first primer and 660–700 bp for the second primer) with 21 nt-tandem repeat sequences, consistent with a previous finding⁸. The status of *cagA* was determined by PCR using primer pair 5'-ACC CTA GTC GGT AAT GGG-3' and 5'-GCT TTA GCT TCT GAY ACY GC-3' (Y = C + T) as described previously¹². The amplified fragment was detected by a 1.5% agarose gel electrophoresis using an ultraviolet transilluminator.

Statistical analysis

Variables such as gender, mean age, and the status of *jhp0562*, β -(1,3)*galT*, and *cagA* (negative or positive for the three genes) were evaluated. The univariate association between each genotype and the clinical outcomes were quantified by the chi-square test. A multivariate logistic regression model was used to calculate the odds ratios (OR) of the clinical outcomes by including age, sex, and the *H. pylori* genotypes. All determinants with P values of < 0.10 were entered together in the full model of logistic regression, and the model was reduced by excluding variables with P values of > 0.10. OR and 95% confidence intervals (CIs) were used to estimate the risk. Spearman rank coefficients (*r*) were also determined to evaluate the association between the different genotypes of the strains. A P value of less than 0.05 was accepted as statistically significant. The SPSS statistical software package version 18.0 (SPSS, Inc., Chicago, IL) was used for all statistical analyses.

Results

Prevalence of candidate genes in the U.S. and Japan

A total of 308 patients were included in this study: 171 from the U.S. (82 with gastritis, 46 with DU, 28 with GU, and 15 with GC) and 137 from Japan (37 with gastritis, 45 with DU, 39 with GU, and 16 with GC). The distribution of the status of *cagA*, *jhp0562*, and β -(1,3)*galT* in the two countries are shown in Table 1. There were significant differences in the *cagA*, *jhp0562*, and β -(1,3)*galT* status between strains isolated from the U.S. and Japanese populations ($P < 0.001$, 0.001 , and 0.001 , respectively). Regarding *jhp0562* and β -(1,3)*galT*, four different combinations of the two genes were observed (Figure 1): single fragment of *jhp0562* (*jhp0562*-positive/ β -(1,3)*galT*-negative) (profile 1), single fragment of β -(1,3)*galT* (*jhp0562*-negative/ β -(1,3)*galT*-positive) (profile 2), double positive for *jhp0562* and β -(1,3)*galT* (profile 3), and two β -(1,3)*galT* fragments with different lengths (profile 4). The prevalence of the *jhp0562*-positive/ β -(1,3)*galT*-negative genotype was significantly higher in strains from Japan than in strains from the U.S. (81.0% vs. 39.3%, $P < 0.001$). The *jhp0562*-negative/ β -(1,3)*galT*-positive genotype, and two fragments of β -(1,3)*galT* were found only in strains isolated from the U.S. The prevalence of double positive genotype was significantly higher in strains from the U.S. than in strains from Japan (19.0% vs. 41.0%, $P = 0.006$).

The association between candidate genes and clinical outcomes

The prevalence of *cagA* was significantly higher in strains from the U.S. patients with DU, GU, and GC than in those with gastritis (89.1%, 92.9%, and 100% vs. 75.6%, $P < 0.05$) (Table 2). In contrast, that of β -(1,3)*galT* was significantly lower in strains from the U.S. patients with DU and GU than in those with gastritis (47.8% and 32.1% vs. 72.0%, $P < 0.01$). The prevalence of *jhp0562* or β -(1,3)*galT* were not different between gastritis and GC. Considering the ethnicity in U.S., the same tendency was observed although the differences were not statistically significant probably due to the lack of ethnic data from approximately 30% of the U.S. patients (data not shown). Table 3 shows the association between clinical outcomes and the presence of *cagA*, *jhp0562*, and β -(1,3)*galT* in multivariate analysis in the U.S. population. Interestingly, both age and the absence of β -(1,3)*galT* were independent factors for discriminating DU from gastritis (adjusted OR = 4.21; 95% CI = 1.75–10.12). Likewise, the absence of β -(1,3)*galT* was an independent factor discriminating GU from gastritis (adjusted OR = 8.52; 95% CI = 2.76–26.33). On the other hand, the prevalence of *cagA*, *jhp0562*, and β -(1,3)*galT* was not significantly different between patients with these two diseases in Japan.

The association between the combination of the two genes and clinical outcomes in the U.S.

Considering the four different combinations of the two genes, the prevalence of the *jhp0562*-positive/ β -(1,3)*galT*-negative genotype was significantly higher in strains isolated from the U.S. patients with DU and GU than those with gastritis (50.0% and 67.9% vs. 24.4%, $P < 0.01$). Even in the case of three combination of *cagA*, *jhp0562* and β -(1,3)*galT*, the tendency was not changed because all of *jhp0562*-positive strains possess *cagA*. Double positivity for *jhp0562* and β -(1,3)*galT* was significantly less frequent in strains from GU patients than in those from gastritis patients (10.7% vs. 53.7%, $P < 0.001$). Although statistical significance was not observed, double positivity for *jhp0562* and β -(1,3)*galT* tended to be less prevalent in strains from DU patients than in those from gastritis patients (37.0% vs. 53.7%, $P = 0.05$). The prevalence of the *jhp0562*-negative/ β -(1,3)*galT*-positive genotype was neither related with DU nor GU. These combinations of the two genes did not associate with GC compared with gastritis.

Correlations between *cagA* and *jhp0562* or β -(1,3)*galT*

In the U.S., there was a significant positive correlation between the presence of *cagA* and *jhp0562* ($r = 0.58$, $P < 0.001$). In contrast, there was a negative correlation between the presence of *cagA* and β -(1,3)*galT* ($r = -0.25$, $P < 0.001$), and the prevalence of *jhp0562* was inversely correlated with that of β -(1,3)*galT* ($r = -0.23$; $P = 0.001$) in the U.S. In Japan, the prevalence of *jhp0562* and β -(1,3)*galT* in the *cagA*-positive strains was 100% and 19.6%, respectively.

Discussion

Our study revealed that the absence of β -(1,3)*galT* might be an independent discriminating factor for distinguishing DU and GU from gastritis in the U.S. population. Interestingly, multivariate analysis showed that the absence of β -(1,3)*galT*, but not the presence of *cagA*, was an independent factor discriminating DU and GU from gastritis. Regarding the expression patterns of these two genes, the *jhp0562*-positive/ β -(1,3)*galT*-negative genotype was significantly associated with peptic ulcer, consistent with previous findings⁸. In addition, we found that the prevalence of double positivity for *jhp0562* and β -(1,3)*galT* was lower in strains from patients with peptic ulcer in the U.S., although the previous report in Portugal did not elucidate a difference between gastritis and peptic ulcer. The prevalence of

the *jhp0562*-positive/ β -(1,3)*galT*-negative genotype was higher in strains from patients peptic ulcer in the U.S. than that reported previously (56.7% vs. 33.3%)⁸.

Oleastro *et al.* originally reported that *jhp0562* was significantly more prevalent in peptic ulcer than in gastritis in children but not adults⁵. They did not examine the prevalence of β -(1,3)*galT* in adults⁸. We revealed *jhp0562* and β -(1,3)*galT* as candidate markers for peptic ulcers, even in adults in the U.S. Although the presence of β -(1,3)*galT* alone (*jhp0562*-negative/ β -(1,3)*galT*-positive) was associated with gastritis in their report, we did not find any association between the *jhp0562*-negative/ β -(1,3)*galT*-positive genotype and clinical outcomes. The prevalence of the *jhp0562*-negative/ β -(1,3)*galT*-positive genotype in the U.S. in our study was lower than that in their report (16.2 vs. 37.6%). The difference in subjects (children or adults) between that report and our study may have contributed to this discrepancy. Oleastro *et al.* reported that the prevalence of *jhp0562* was 48.8% (22/45) in children and 66.6% (60/90) in adults. There are several reports indicating that the prevalence of strains harboring more virulent genotypes such as *cagA* and *vacA* s1 alleles was higher in older patients than in younger patients^{13, 14}. Oleastro *et al.* gave the following hypothesis: after infection in childhood, a specific strain will undergo changes during the course of infection in response to (i) changes occurring in the gastric mucosa and (ii) the evolution of the associated pathology¹⁴. On the other hand, the most common *H. pylori* genotypic pattern among children was similar to the pattern in adults in the U.S.¹⁵. These differences may once more reflect geographical variations in the strain reservoirs and host immune response. It is necessary to examine the prevalence of *jhp0562* and β -(1,3)*galT* in children in the U.S.

There were significant differences in the *jhp0562* and β -(1,3)*galT* status between strains isolated from the U.S. and Japanese populations. These findings were consistent with other virulent factors such as *cagA* and *vacA*; the prevalence of the virulent genotypes (i.e., East Asian type *cagA* and *vacA* s1 type) were extremely high in Japan regardless of clinical outcomes¹⁶. High prevalence of *jhp0562* and low prevalence of β -(1,3)*galT* also supports that most *H. pylori* strains in Japan show high virulence compared with these in the U.S. In this study, the prevalence of *jhp0562* was strongly associated with that of *cagA* in the U.S. population. Consistent with our result, Oleastro *et al.* reported a positive association of *jhp0562* with the *cag* pathogenicity island (PAI)⁸. Although the correlation could not be calculated because of the high prevalence of *cagA* in Japan, all *cagA*-positive strains were also positive for *jhp0562*. These patterns were consistent with the relationship between *cagA* and other virulent factors in Japan. The *cagA* status is also linked to the *vacA* s region type, and it is further closely linked to the presence of *babA* and *oipA* “on” status, which are other virulence factors coding outer membrane proteins^{4, 17, 18}. As a result, almost all *H. pylori* strains circulating in Japan are extremely virulent, harboring *cagA*, *vacA* s1 genotype, *oipA* “on” status, and *babA* irrespective of the clinical outcomes^{4, 19, 20}. Thus, it is likely that the phenotype resulting from the expression of *cagA*, *vacA* s1, and *jhp0562* confers a biological advantage to the strain, with the cumulative action of each factor contributing simultaneously to the fitness of the strains in vivo and a more pronounced pro-inflammatory response. It might be better to hypothesize that these factors interact synergistically with each other and induce serious diseases than to discuss which of these factors is the most virulent. In addition, we found that the prevalence of β -(1,3)*galT* was inversely associated with that of *cagA*, although the inverse correlation was not strong. Multivariate analysis showed that the absence of β -(1,3)*galT* but not the presence of *cagA* was an independent factor for discriminating DU and GU from gastritis in the U.S. This means that the absence of β -(1,3)*galT* may be the true candidate marker for peptic ulcer in the U.S. When we compared the sequence of *jhp0562* and β -(1,3)*galT* by using Asian strains (full-sequenced strains 51 and 52) and Western strains deposited by Oleastro in Genbank, we could not find the genetic polymorphism among these two area (data not shown). This suggests that the prevalence of these genes but not polymorphism associated with the clinical outcomes.

jhp0562 encodes a glycosyltransferase involved in the synthesis of the chemical structure of LPS and is located immediately upstream of β -(1,3)*galT*, which in turn encodes a β -(1,3) galactosyltransferase involved in type I Le antigen synthesis (Le^a and Le^b synthesis of the LPS)^{21, 22}. Although these Le antigenic structures were reported to be important for bacterial colonization, adhesion, and evasion of host immune response^{23–25}, the role of these in *H. pylori* infection has not been elucidated. Therefore, additional in vitro and in vivo studies are necessary to elucidate the causal relationship between *jhp0562* and β -(1,3)*galT* and to investigate the mechanisms by which these gene products correlate with clinical outcomes. Because these two genes were inversely correlated, the products of the two genes may have the same cell function, thus producing functional redundancy.

In conclusion, the absence of β -(1,3)*galT* was independent factor discriminating DU and GU from gastritis in the U.S., but not in Japan. The *jhp0562*-positive/ β -(1,3)*galT*-negative genotype was significantly associated with the presence of peptic ulcer in the U.S. *jhp0562* and β -(1,3)*galT* were correlated with *cagA* similarly as other virulence factors, and there was a difference in the presence of *jhp0562* or β -(1,3)*galT* among strains isolated from the U.S and Japan. In the U.S., the status of *jhp0562* or β -(1,3)*galT* can predict the future development of peptic ulcer for the patients with gastritis. Prospective study is necessary to elucidate it. Moreover, the study of the distribution of these genes in other populations would also be interesting to further elucidate the associations found in the present study and the possible virulent role of these factors in *H. pylori* infection.

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Figure 1.

jhp0562 and β -(1,3)*galT* profiles observed in *Helicobacter pylori* strains. Four different combinations of the two genes were observed: single fragment of *jhp0562* (*jhp0562*-positive/ β -(1,3)*galT*-negative) (profile 1), single fragment of β -(1,3)*galT* (*jhp0562*-negative/ β -(1,3)*galT*-positive) (profile 2), double positive for *jhp0562* and β -(1,3)*galT* (profile 3), and two β -(1,3)*galT* fragments of different lengths (profile 4). MW, molecular weight marker

Table 1

Prevalence of *jhp0562* and β -(1,3)*galT*

n	Japan		U.S.		P value
	137	171	137	171	
mean age	60.1 $\pm$ 12.3	50.8 $\pm$ 14.5			
male	76	137	79.2%		
<i>cagA</i> positive	132	144	83.2%		<0.001
<i>jhp0562</i> positive	137	140	80.9%		<0.0001
β -(1,3) <i>galT</i> positive	26	99	57.2%		<0.0001
<i>jhp0562</i> -positive/ β -(1,3) <i>galT</i> -negative	111	68	39.3%		<0.0001
<i>jhp0562</i> -negative/ β -(1,3) <i>galT</i> -positive	0	28	16.2%		<0.0001
double positive	26	71	41.0%		0.006
Two β -(1,3) <i>galT</i> with different lengths	0	4	2.3%		0.07

Table 2

Relationship between *cagA*, *jhp0562*, and β -(1,3)*galT* and clinical outcomes in the U.S. (a) and Japan (b)

(a) US					
	n	gastritis	DU	GU	GC
		82	46	28	15
mean age		43.8 ± 13.0	54.5 ± 12.6	56.1 ± 12.3	68.4 ± 6.9
male		60	39	27	12
		73.2%	84.8%	96.4%	80.0%
<i>cagA</i> positive		62	41	26	15
		75.6%	89.1%*	92.9%*	100.0%*
<i>jhp0562</i> positive		65	40	22	13
		79.3%	87.0%	78.6%	86.7%
β -(1,3) <i>galT</i> positive		59	22	9	9
		72.0%	47.8%*	32.1%*	60.0%
<i>jhp0562</i> -positive/ β -(1,3) <i>galT</i> -negative		20	23	19	6
		24.4%	50.0%*	67.9%*	40.0%
<i>jhp0562</i> -negative/ β -(1,3) <i>galT</i> -positive		15	5	6	2
		18.3%	10.9%	21.4%	13.3%
double positive		44	17	3	7
		53.7%	37.0%	10.7%*	46.7%
Two β -(1,3) <i>galT</i> with different lengths		3	1	0	0
		3.7%	2.2%	0.0%	0.0%
(b) Japan					
	n	gastritis	DU	GU	GC
		37	45	39	16
mean age		60.4 ± 12.6	50.3 ± 13.0	62.5 ± 11.5	64.7 ± 9.3
male		22	25	20	9
		59.5%	55.6%	51.3%	56.3%
<i>cagA</i> positive		34	45	37	16
		91.9%	100.0%	94.9%	100.0%
<i>jhp0562</i> positive		37	45	39	16
		100.0%	100.0%	100.0%	100.0%
β -(1,3) <i>galT</i> positive		5	11	7	3
		13.5%	24.4%	17.9%	18.8%
<i>jhp0562</i> -positive/ β -(1,3) <i>galT</i> -negative		32	34	32	13
		86.5%	75.6%	82.1%	81.3%
<i>jhp0562</i> -negative/ β -(1,3) <i>galT</i> -positive		0	0	0	0
		0.0%	0.0%	0.0%	0.0%
double positive		5	11	7	3
		13.5%	24.4%	17.9%	18.8%
Two β -(1,3) <i>galT</i> with different lengths		0	0	0	0
		0.0%	0.0%	0.0%	0.0%
DU; duodenal ulcer, GU; gastric ulcer, GC; gastric cancer					

DU; duodenal ulcer, GU; gastric ulcer, GC; gastric cancer
* P < 0.05 compared with gastritis

Table 3

Multivariate analyses of the risk for DU (a) and GU (b) by age, gender, *cagA* status, and β -(1,3)*galT* status in the U.S. population

(a) DU			
	Adjusted OR	95% CI	P value
Age (per 1 year)	1.07	1.03–1.10	<0.001
Gender (female)	0.54	0.18–1.57	0.26
<i>cagA</i> positive	1.83	0.51–6.54	0.35
β -(1,3) <i>galT</i> negative	4.21	1.75–10.12	0.001

(b) GU			
	Adjusted OR	95% CI	P value
Age (per 1 year)	1.08	1.03–1.12	<0.001
Gender (female)	0.10	0.01–1.01	0.05
<i>cagA</i> positive	1.54	0.26–9.06	0.63
β -(1,3) <i>galT</i> negative	8.52	2.76–26.33	<0.001