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Association of *Helicobacter pylori dupA* with the failure of primary eradication

Seiji Shiota, MD, PhD[1),2)], **Lam Tung Nguyen, MD, PhD**[2)], **Kazunari Murakami, MD, PhD**[2)], **Akiko Kuroda, MD**[1)], **Kazuhiro Mizukami, MD**[2)], **Tadayoshi Okimoto, MD, PhD**[2)], **Masaaki Kodama, MD, PhD**[2)], **Toshio Fujioka, MD, PhD**[2)], and **Yoshio Yamaoka, MD, PhD**[1),3)]

[1)]Department of Environmental and Preventive Medicine, Oita University Faculty of Medicine, 1-1 Idaigaoka, Hasama-machi, Yufu-City, Oita 879-5593, Japan

[2)]Department of General Medicine, Oita University Faculty of Medicine 1-1 Idaigaoka, Hasama-machi, Yufu-City, Oita 879-5593, Japan

[3)]Department of Medicine-Gastroenterology, Baylor College of Medicine and Michael E. DeBakey Veterans Affairs Medical Center, 2002 Holcombe Blvd. Houston, Texas 77030, United States

Abstract

Goals—To determine whether the presence of *dupA Helicobacter pylori* (*H. pylori*) influences the cure rate of primary eradication therapy.

Background—Several virulence factors of *H. pylori* have been reported to affect the efficacy of the eradication rate. However, no study has investigated whether the presence of *dupA* affects eradication failure.

Study—The presence of *dupA* was evaluated in 142 *H. pylori* strains isolated from 142 patients with gastrointestinal diseases. Of these patients, 104 received primary eradication therapy for 1 week. The risk factors for eradication failure were determined using univariate and multivariate analyses.

Results—Among 142 strains, 44 (31.0%) were *dupA*-positive. There was no association between *dupA* status and gastroduodenal diseases ($P > 0.05$). The clarithromycin (CLR) resistance rate was generally lower in the *dupA*-positive than in the *dupA*-negative group (20.4 vs. 35.7%, $P = 0.06$). However, *dupA* prevalence was higher in the eradication failure group than in the success group (36.3 vs. 21.9%). Among the CLR-resistant *H. pylori* infected group, the successful eradication rate was significantly lower in patients infected with *dupA*-positive *H. pylori* than -negative *H. pylori* ($P = 0.04$). In multivariate analysis adjusted for age, gender, and type of disease, not only CLR resistance but also *dupA* presence was independent risk factors for eradication failure (adjusted odds ratio = 3.71, 95% confidence interval = 1.07–12.83).

Conclusions—Although CLR resistant was more reliable predictor, the presence of *dupA* may also be an independent risk factor for eradication failure.

Keywords

Helicobacter pylori; *dupA*; eradication rate

Corresponding author: Yoshio Yamaoka M.D., Ph.D. Department of Environmental and Preventive Medicine, Oita University Faculty of Medicine 1-1 Idaigaoka, Hasama-machi, Yufu-City, Oita 879-5593, Japan Tel: +81-97-586-5740; Fax: +81-97-586-5749 yyamaoka@oita-u.ac.jp.

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Introduction

Eradication therapy of *Helicobacter pylori* (*H. pylori*) infection is the first-line treatment for patients with gastroduodenal disorders, such as peptic ulcer diseases, gastric mucosa associated-lymphoid tissue (MALT) lymphoma, atrophic gastritis, hyperplastic polyp, and post-endoscopic resection of early gastric cancer (GC), as well as for patients with extra-gastrointestinal disorders, such as idiopathic thrombocytopenic purpura and chronic idiopathic urticaria [1]. One week eradication therapy using 3 drugs (amoxicillin [AMX], clarithromycin [CLR], and a proton pump inhibitor [PPI]) is widely practiced in Japan [1]. However, bacterial resistance to these drugs, which is common in infectious diseases, has been encountered. Particularly, a sustained increase in the CLR resistance rate is known to correlate with the increased usage in Japan [2, 3]. CLR resistance of *H. pylori* is one of the primary reasons for eradication failure.

Virulence factors of *H. pylori* (e.g., *cagA* and *vacA*) play important roles in gastric mucosal injuries, such as gastric inflammation, peptic ulcer, atrophy, intestinal metaplasia, dysplasia, and malignancy [4]. Furthermore, the importance of *H. pylori* virulence markers in the efficacy of cure rates has been reported [5–8]. Lu *et al.* [9] described a novel virulence factor, the duodenal ulcer promoting (*dupA*) gene, which encompasses both *jhp0917* and *jhp0918* and is located in the plasticity region of the *H. pylori* genome. Interestingly, *dupA* is homologous to *virB4*, a gene encoding a component protein of the type IV secretion system (TFSS) in *Agrobacterium tumefaciens*. They reported that infections with the *dupA*-positive strains increased the risk for duodenal ulcer (DU) but were protective against gastric atrophy, intestinal metaplasia, and GC in Japanese, Korean, and Columbian subjects. Notably, *dupA* was the first genetic factor of *H. pylori* to be associated with differential susceptibility to DU and GC, and thus, it could be considered as a disease-specific virulence marker. The pathogenic mechanism of *dupA* appears to involve the induction of interleukin (IL)-8 production in the antrum, leading to the development of antrum-predominant gastritis, a well-recognized characteristic of DU [9]. Recently, we conducted a meta-analysis and showed the high prevalence of *dupA*-positive *H. pylor*i in patients with DU [10]. However, no study has investigated whether the presence of *dupA* affects eradication failure.

In this study, we aimed to determine whether the presence of *dupA* influences the cure rate of primary eradication therapy.

Materials and Methods

Patients

Patients were considered to be *H. pylori*-infected when at least one of rapid urease test, culture, and microscopic examination showed positive results. Of the 244 patients included in our previous retrospective cohort study [11], 102 were excluded because they had already received eradication treatment for *H. pylori*. Therefore, 142 Japanese patients (74 males, 67 females, aged 22–91 years [mean, 58.1 years]) were recruited. Patients with drug allergies and those with serious complications, such as cardiac disease, renal disease, and hepatic disease, were excluded from the study. Four biopsy samples (2 from the antrum and 2 from the corpus) were endoscopically obtained from each patient and used for *H. pylori* culture and histopathologic examination. Gastric ulcer (GU) and DU were determined using endoscopic observation, and non-cardia GC and chronic gastritis were diagnosed histologically. Written informed consent was obtained from all participants, and the protocol was approved by the Ethics Committee of Oita University (P-07-04).

Study protocol

Of the 142 patients, 104 were treated for 1 week with primary eradication therapy (proton pump inhibitors [PPIs] +AMX 1500mg + CLR 400mg per day). One of PPIs was selected from lansoprazole (LPZ) 60mg (n = 88), omeprazole (OPZ) 40mg (n = 8), rabeprazole (RPZ) 20mg (n = 8). PPI was prohibited at least 4 weeks from completion of eradication therapy until evaluation of *H. pylori* eradication. When eradication was observed for at least 4 weeks following the 1-week treatment, it was considered to be successful if culture, microscopic examination, and urea breath tests showed negative results. Compliance was checked by the interview from doctor.

Drug sensitivity testing was conducted using an epsilometer test (E-test). A sterile swab was dipped into the bacterial suspension equivalent to a McFarland standard of 2. After swabbing the entire plate surface with inoculums, E-test strips impregnated with CLR (concentration ranging from 0.016 to 256μg/mL) were placed on the agar surface. After an incubation period of 48 to 72 h (37°C, 98 % humidity in microaerobic atmosphere), the minimum inhibitory concentrations (MICs) of CLR were determined. When the MIC of CLR was 1 μg/mL or higher, the strain was considered as resistant, in accordance with a report by the National Committee for Clinical Laboratory Standards [12].

Detection of *dupA* and serum gastrin levels

All isolates had been previously characterized with regard to *dupA* status (positive or negative) [11]. Antral biopsy specimens were obtained for the isolation of *H. pylori* using standard culture methods as described previously [13]. Chromosomal DNA was extracted from confluent plate cultures expanded from a single colony using a commercially available kit (QIAGEN, Valencia, CA). The *dupA* status was determined using polymerase chain reaction (PCR) methods as described previously [11]. Amplified fragments were detected using 1.5% agarose gel electrophoresis and an ultraviolet transilluminator. To avoid false-negative PCR results resulting from variations in primer annealing sites, a dot blot was performed in all the cases as described previously [11]. The serum gastrin level was determined under fasting conditions using a radioimmunoassay technique (Gastrin-RIA Kit II, TFB Co. Ltd., Tokyo, Japan).

Statistical Analyses

All statistical analyses were performed by SPSS version 18 (SPSS Inc., Chicago, IL, USA). The univariate association between each group was quantified using the unpaired *t*-test, Mann-Whitney *U*-test, Fisher's exact test, and chi-square test. Multiple backward stepwise logistic regression analyses were used to examine the association of eradication failure with primary predictor variables. Predictor variables included age (continuous variable), gender (dichotomous variable), CLR resistance (dichotomous variable), type of diseases (dichotomous variable), and *dupA* status (dichotomous variable). For each variable, an odds ratio (OR) and 95% Confidence Interval (CI) were calculated. A two-tailed P value of < 0.05 was considered as statistically significant.

Results

Association between *dupA* and clinical outcomes

We analyzed 142 patients divided into 4 disease groups: chronic gastritis (n = 51), GU (n = 29), DU (n = 35), and non-cardia GC (n = 27). Of these 142 patients, 44 (31.0%) were infected with *dupA*-positive strains.

The *dupA*-positive strains were distributed nearly equally among the 4 disease groups (gastritis, 29.4%; GU, 27.6%; DU, 28.6%; and GC, 40.7%), indicating that there is no

association between *dupA* status and gastroduodenal diseases (P > 0.05). This finding is in agreement with that of a previous study in Japan [11].

Characteristics of patients infected with *dupA*-positive or *dupA*-negative *H. pylori*

A comparison of characteristics of patients infected with *dupA*-positive or *dupA*-negative *H. pylori* is shown in Table 1. There was no difference in age and gender between the 2 groups. In all, the CLR resistant rate was 30.9% (44/142). The CLR resistance rate was generally lower in the *dupA*-positive than in the *dupA*-negative group (20.4% vs. 35.7%; P = 0.06). The gastrin level was evaluated in the sera of 45 of the 51 patients with gastritis (14 from the *dupA*-positive and 31 from the *dupA*-negative groups). Gastrin levels were higher in the *dupA*-positive group than in the negative group (257.2± 289.7 vs. 142.8 ± 77.9 pg/mL), although statistical significance was not obtained probably because of the wide range and the small sample size. In the gastritis group, histological scores according to Update Sydney System including neutrophil infiltration, mononuclear cell infiltration, atrophy, and intestinal metaplasia, were not significantly different between the *dupA*-positive and the *dupA*-negative group (data not shown). In addition, the rate of endoscopic atrophy did not differ between the 2 groups (data not shown).

Factors for primary eradication failure

Among 142 patients, 38 patients refused the eradication therapy. Therefore, 104 subjects (37 chronic gastritis, 24 GU, 31 DU, and 12 non-cardia GC) received primary eradication therapy. The *dupA*-positive strains were distributed nearly equally among the 4 disease groups (gastritis, 24.3%; GU, 25.0%; DU, 25.8%; and GC, 25.0%). The compliance by the interview was 100%. The bacterium was not eradicated in 22 subjects (21.1%), the eradication therapy in per protocol analysis was 78.9%. Table 2 shows the characteristic differences between the eradication success and failure groups. Average age was significantly higher in the success group than in the failure group (59.3 ± 12.7 vs. 52.4 ± 14.6 years, P = 0.03). There was no gender difference between the 2 groups. The CLR resistant rate was 34.6% (36/104). The CLR resistance rate was significantly higher in the failure group than in the success group (63.6% vs. 26.8%, P = 0.001). The successful eradication rate was significantly higher in CLR susceptible strains than resistant strains (88.2% vs.61.1%, P = 0.001). Interestingly, the prevalence of *dupA* was higher in the failure group than in the success group (36.3% vs. 21.9%), despite the high CLR resistance rate in the *dupA*-negative group. However, the difference was not statistically significant (P = 0.16). Of the 36 CLR-resistant *H. pylori* infected group, 28.6% (2/7) of *dupA*-positive patients and 69.0% (20/29) of *dupA*-negative patients showed successful eradication (P = 0.04). The successful eradication rate was 70.2% (26/37) in chronic gastritis, 87.5% (21/24) in GU, 83.8% (26/31) in DU and 75% (9/12) in GC. There were no significant differences in univariate analysis although the successful eradication rate was tended to be higher in GU than gastritis (P = 0.10). With combining GU and DU as peptic ulcer disease (PUD), the successful eradication rate was significantly higher in PUD than gastritis (85.4% vs.70.2%, P = 0.045). The prevalence of PUD was tended to be higher in the success group than the failure group although this did not reach the statistical significance (57.3% vs.36.3%, P = 0.06).

Multivariate analysis adjusted by age, gender, CLR resistance, and type of disease was performed to evaluate the influence of *dupA* on eradication failure. Due to the inverse relationship between *dupA* and CLR resistance, the presence of *dupA* was included in the final model, although the presence of *dupA* did not show a statistically significant association in the univariate analysis. Table 3 shows the association of the presence of *dupA* and clinical outcomes in logistical analysis. Not only CLR resistance but also the presence

of *dupA* was found to be an independent risk factor for eradication failure (adjusted OR = 3.71, 95% CI = 1.07–12.83).

Discussion

To our knowledge, this is the first study showing that the presence of *dupA* influences primary eradication failure. The *dupA*-positive status was an independent risk factor for eradication failure despite a lower CLR resistance rate than that of the *dupA*-negative status.

Several studies have reported a relationship between *H. pylori* antibiotic resistance patterns and virulence factor genotypes. Elviss *et al.* [14] reported that isolates susceptible to CLR are strongly associated with the *vacA* s1m2 genotype, but not with either the highest virulence *vacA* s1m1 genotype or the lowest virulence *vacA* s2 m2 genotype. A more recent report showed that CLR-resistant strains more frequently possess the *vacA* s2m2 and are more likely to be *cagA*-negative [15]. However, the prevalence of *cagA* and *vacA* alleles did not significantly differ between CLR-susceptible and CLR-resistant strains in Italy [16]. Suzuki *et al.* [7] conducted a meta-analysis and found that the risk ratio of eradication failure in patients with the *cagA*-negative strain (cure rate, 84%) relative to those with the *cagA*-positive strain (73%) was 2.0 (95% CI: 1.6–2.4, $P < 0.01$). We found that nearly all *H. pylori* strains were *cagA* positive and *vacA* s1m1, and there was no relationship between CLR-resistance and *cagA* or *vacA* status (data not shown).

The relationship of *cagA* with the success and failure of *H. pylori* eradication therapy has been explained by the enhanced gastric mucosal inflammation. A good correlation between *cagA* positivity and severe gastric inflammation has been confirmed [17, 18]. Patients with severe inflammatory cell infiltrations in the antral mucosa experience significantly higher cure rates than those with milder inflammation [8]. Since gastric inflammation increases mucosal blood blow, increased blood flow may probably facilitate the diffusion of antibiotics [19]. However, the histological scores did not differ between the *dupA*-positive and *dupA*-negative group in this study, which suggests that the mechanism of the lower eradication rate in the *dupA*-positive group was not due to the histological differences.

Insufficient gastric acid inhibition during treatment also causes eradication failure by making antibiotics, particularly CLR and AMX, more unstable and more easily degraded in the stomach, minimizing the antimicrobial effects of the antibiotics [20, 21]. Therefore, gastric acid secretion can be potently inhibited during treatment by using acid-inhibitory drugs such as PPIs[22]. Approximately 10 to 15% of patients chronically infected with *H. pylori* exhibit antral predominant inflammation. These patients, who are predisposed to DU, produce increased amounts of acid because of the elevated basal and stimulated gastrin secretion [23]. A recent study showed that the gastric acid output is significantly higher in the *dupA*-positive than in the *dupA*-negative patients [24]. In the present study, we found that serum gastrin levels were higher in the *dupA*-positive group than in the *dupA*-negative group, suggesting that gastric acid secretion might be higher in the *dupA*-positive than in the *dupA*-negative group. Lu *et al.* reported that the presence of *dupA* was associated with increased resistance to low pH *in vitro* study [9]. *dupA*-positive strains may induce the high level of gastrin, and high gastric acid secretion . High gastric acid secretion in the *dupA*-positive group might be related to the lower eradication rate. However, the prevalence of *dupA* was not difference between DU and gastritis. If *dupA* is associated with high acid output, the prevalence of *dupA* needs to be higher in DU than gastritis. Other mechanism may relate with the low eradication rate in the patients with *dupA*-positive *H. pylori*. Further study is necessary to find the mechanism of the lower eradication rate in the *dupA*-positive group.

However, our study has several limitations. First, the number of patients infected with CLR-resistant and *dupA*-positive *H. pylori* was small due to the retrospective study. Although the number of subjects was enough to conduct multivariate analysis, larger number of subjects is necessary to confirm our findings. In addition, the prospective study based on the status of *dupA* is also necessary to confirm our results. Second, the successful eradication rates of *H. pylori* can also be affected by the type of PPIs due to the CYP2C19 polymorphism [25]. RPZ does not underly this polymorphism, while the other 2 PPI's do. There was no difference of successful eradication therapy among these 3 PPIs in this study (data not shown). This is due to the low number of patients received triple therapy including RPZ. Third, other known factors of failure of eradication treatment were not enough evaluated. The compliance, type of disease, and presence of atrophy and intestinal metaplasia may affect the treatment outcome [6]. The successful eradication rate in our study was significantly higher in PUD than gastritis consistent with previous report [26], this factor was not associated with the successful eradication in multivariate analysis. The smoking habit is also important factor for the outcome of successful eradication therapy [6]. However, unfortunately, the information for the smoking was not enough in this study. The information of smoking habit is required for the further study. However, CLR resistance is the most important factor for the treatment outcome. When we include other factors, such as the presence of atrophy and intestinal metaplasia, adjusting the conditions for statistical analysis was difficult. Finally, although *dupA* was an independent risk factor for eradication failure in multivariate analysis, the predictor was weak compared with CLR resistant. Furthermore, the high CLR resistant rate (30.9%) was found in our study. This suggests that the triple therapy included CLR might not be suitable for the first line eradication regimen in our country. In addition, it is difficult to assess the *dupA* status before eradication in clinical. This means that our findings are not enough to change the clinical practice. Eradication regimen included the antibiotics other than CLR may be suitable for better eradication rate rather than the examination of the status of *dupA*.

In conclusion, we first evaluated the influence of *dupA* on primary eradication. Although CLR resistant was more reliable predictor, the presence of *dupA* may also be an independent risk factor for eradication failure. Further studies are necessary to confirm these results.

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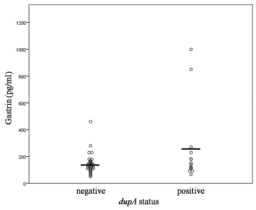

Figure 1.
The distribution of serum gastrin level between the *dupA*-positive and -negative group.

Table 1

Characteristics of the patients with *dupA*-positive or *dupA*-negative *H. pylori*

	***dupA*-positive**	***dupA*-negative**	**P value**
n	44	98	
age	58.0±15.4	58.1±13.3	0.78
male	23 (52.5%)	52 (53.0%)	0.93
CLR resistant	9 (20.4%)	35 (35.7%)	0.06

Table 2

Differences in the background of patients who experienced success or failure of eradication

	Success	Failure	P value
n	82	22	
Age	59.3±12.7	52.4±14.6	0.03
Male	48 (58.5%)	9 (40.9%)	0.14
CLR resistant	22 (26.8%)	14 (63.6%)	0.001
dupA positive	18 (21.9%)	8 (36.3%)	0.16
Peptic ulcer diseases	47 (57.3%)	8 (36.3%)	0.06

Table 3

Multivariate analyses of *H. pylori* eradication failure risk by age, gender, CLR resistant, type of disease, and *dupA* status

	Adjusted OR	95% CI	P value
Age (per one year)	0.95	0.91–0.98	0.013
Gender (male)	0.35	0.11–1.07	0.066
CLR resistant	7.96	2.45–25.8	0.001
dupA positive	3.71	1.07–12.83	0.038
Peptic ulcer diseases	0.54	0.16–1.80	0.319