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The association of *dupA* and *Helicobacter pylori*-related gastroduodenal diseases

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Abstract *Helicobacter pylori* is associated with the development of ulceration and gastric cancer. Recently, a novel virulence factor, duodenal ulcer promoting gene A (*dupA*), has been identified and found to associate with disease in some populations but not others. We investigated the relationship of *dupA* genotypes and *H. pylori*-related clinical outcomes by meta-analysis using previous reports of 2,358 patients from around the world. *dupA*-positive genotypes was found in 48% and was associated with duodenal ulcer ($p=0.001$, odds ratio [OR]=1.4, confidence interval [CI]=1.1–1.7). The prevalence of *dupA*-positivity and its association with disease differed among the various regions around the world. In South America, the highest prevalence was recorded (Colombia and Brazil) and a significant relationship was found between *dupA*-negative strains and both gastric ulcer (GU) and gastric cancer (GC) (for GU, $p=0.001$, OR=0.2, CI=0.1–0.4 and for GC, $p=0.001$, OR=0.3, CI=0.2–0.6). In China, a significant correlation between *dupA*-positive strains and GU ($p=0.001$, OR=5.5, CI=2.4–12.4) and GC ($p=0.009$, OR=2, CI=1.1–3.1) was found. To conclude, *dupA* promotes duodenal ulceration in some populations and GU and GC in others. This is typical of other virulence factors, such as *cagA*. Hence, it was concluded that the *H. pylori* virulence factor, *dupA*, is a true virulence factor.

Introduction

Helicobacter pylori infects approximately half of the world's population and is the major cause of gastric ulcer (GU), duodenal ulcer (DU) and gastric cancer (GC). *H. pylori* has a wide genetic diversity amongst isolates from different subjects. Among infected persons, who develops disease depends on the bacterial strain's virulence, the host's genetic susceptibility and environmental factors. *H. pylori* virulence factors associated with the development of ulceration and GC include VacA, CagA, BabA and OipA (see review by Atherton 2006 [1]).

More recently, a novel virulence factor, *dupA*, has been identified that may also play a role in IL-8 secretion [2]. The duodenal ulcer promoting gene A (*dupA*) gene has homology to *virB4* and comprises two overlapping genes (*jhp0917* and *jhp0918*) in genome sequence strain J99, but Lu et al. showed that *dupA* formed a single open reading frame (ORF) in *H. pylori* strain C142 and 23 other strains, due to a single nucleotide insertion (at position 1386). They showed that the presence of *dupA* was significantly associated with duodenal ulceration, but negatively associated with gastric cancer, in populations from South Korea, Japan and Colombia [2].

Although it has been 5 years after the first *dupA* publication, it is still unclear whether the *dupA* gene is associated with an increased risk for gastrointestinal disease or not because of the small sample size used in some reports. Therefore, this study was designed to elucidate the relationship between the *dupA* gene and GC and peptic ulcer susceptibility in *H. pylori*-infected patients using systematic analyses that avoids type 2 error.

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Table 1 The dupA status studies used in the meta-analysis

Disease	No. of cases	Positive %	Disease	No. of cases	Positive %	Disease	No. of cases	Positive %	Disease	No. of cases	Positive %	Positive %
Japan [2]												
G	50	7	14.0	G	68	34	50.0	G	15	11	73.3	15
DU	30	11	36.7	DU	30	15	50.0	DU	13	12	92.3	16
GU	50	13	26.0	GU	23	9	39.1	GU	0	0	GU	0
GC	30	3	10.0	GC	36	20	55.6	GC	18	16	88.9	22
Total	160	34	21.3	Total	157	78	49.7	Total	46	39	84.8	Total
Korea [2]												
G	30	2	6.7	G	70	16	22.9	G	76	29	38.2	G
DU	65	24	36.9	DU	96	36	37.5	DU	40	20	50.0	DU
GU	30	5	16.7	GU	0	0	GU	0	0	GU	0	0
GC	50	3	6.0	GC	0	0	GC	19	10	52.6	GC	21
Total	175	34	19.4	Total	166	52	31.3	Total	135	59	43.7	Total
Colombia [2]												
G	40	16	40.0	G	133	80	60.2	G	12	3	25.0	G
DU	45	25	55.6	DU	101	59	58.4	DU	11	2	18.2	DU
GU	30	12	40.0	GU	47	42	89.4	GU	5	2	40.0	GU
GC	50	6	12.0	GC	79	54	68.4	GC	1	1	100.0	GC
Total	165	59	35.8	Total	360	235	65.3	Total	29	8	27.6	Total
Iraq [4]												
G	29	5	17.2	G	78	23	29.5	G	42	3	7.1	G
DU	15	9	60.0	DU	62	17	27.4	DU	0	0	DU	0
GU	5	2	40.0	GU	59	17	28.8	GU	0	0	GU	0
GC	0	0	0	GC	34	10	29.4	GC	0	0	GC	0
Total	49	16	32.7	Total	233	67	28.8	Total	42	3	7.1	Total
Brazil [8]												
G	144	133	92.4	G	20	9	45.0	Brazil [9]	18	11	61.11	
DU	126	110	87.3	DU	21	9	42.9	DU	13	8	61.54	
GU	0	0	0	GU	3	2	66.7	GU	14	8	57.14	
GC	81	71	87.7	GC	0	0	GC	0	0	0		
Total	351	314	89.5	Total	44	20	45.5	Total	45	27	60	

Materials and methods

Previous publications studying the *dupA* gene in *H. pylori* strains and its association with clinical outcomes were enrolled in this study. All eligible studies were identified by searching the PubMed database for manuscripts written in English and published up to January 2010 using the following search criterion: “*dupA H. pylori*”. A meta-analysis was conducted to determine the association of *dupA* with the risk of developing gastrointestinal diseases.

Data analysis

Statistical differences in the frequencies of *dupA* among the individual countries were determined by one-way analysis of variance (ANOVA) or the Chi-square test using Minitab

15 software. The effects of *dupA* on the risk of gastric cancer and peptic ulcer development were expressed as odds ratios (ORs) with 95% confidence intervals (CIs) with reference to non-ulcer dyspepsia (NUD) subjects with *H. pylori* infection using Excel 2007. NUD was regarded as the control group in this study. All *p*-values were two-tailed and *p*-values less than 0.05 were considered to be statistically significant.

Results and discussion

Ten studies investigating the *dupA* gene and its relationship with clinical outcomes in different populations were found. Reports from Lu et al., Argent et al., Hussein et al. and Schmidt et al. included more than one population in their studies [2–5]. Of ten studies, six did not demonstrate the

Table 2 Summary of *dupA* status in different regions around the world. The * indicates significant correlations

Diseases	No. of samples	No. of <i>dupA</i> -positive samples	%	<i>p</i> -value (G versus other clinical outcomes)
Worldwide				
G	938	421	44.88	
DU	682	366	53.67	0.001*
GU	252	104	41.27	0.097
GC	441	219	49.66	0.305
	2,313	1,110	47.99	
East Asia (Japan, China and Korea)				
G	355	130	36.62	
DU	285	123	43.16	0.093
GU	191	79	41.36	0.277
GC	216	83	38.43	0.665
	1,047	415	39.64	
South America (Colombia and Brazil)				
G	202	160	79.21	
DU	184	143	77.72	0.7
GU	44	20	45.45	0.001*
GC	131	77	58.78	0.001*
	561	400	71.30	
Middle East (Iraq and Iran)				
G	97	39	40.21	
DU	45	24	53.33	0.143
GU	28	11	39.29	0.9
GC	36	20	55.56	0.113
	206	94	45.63	
Europe (Sweden and Belgium)				
G	96	42	43.75	
DU	51	27	52.94	0.288
GU	0	0		
GC	40	23	57.50	0.144
	187	92	49.20	

association between gastroduodenal diseases and *dupA*. Studies from Iraq, China, India, Colombia, Korea and Japan showed a significant relationship between *dupA* and DU [2, 4, 6, 7]. Argent et al. studied samples from Belgium, South Africa, USA and China [3]. There was no significant association between the presence of *dupA* and clinical outcomes in any individual population. However, when they combined the Belgian and South African populations, a higher proportion of *dupA*-positive genotypes was found in gastric cancer patients than that which was found among patients with gastritis alone [3] (Table 1).

In this study, it was found that, worldwide, *dupA*-positive genotypes were found in 48% (1,137/2,358) of the samples and significantly increased the risk of DU ($p=0.001$, OR=1.4, CI=1.1–1.7) (Table 2). The prevalence of *dupA*-positivity differed significantly among the various regions around the world, with highest prevalence found in South Africa (84%) and Brazil (89%) ($p<0.001$ when the South African and Brazilian populations were compared with other populations) (Table 1). In South Africa, no significant correlation between *dupA* and disease could be found. Probably, the *dupA* gene's ubiquity makes it not a good disease indicator. Two reports studied samples from Brazil, but neither of them showed any significant relationship with clinical outcome [8, 9]. When we combined samples from both studies, *dupA*-positivity in NUD patients was much higher than that of GU, which reflects protectivity from GU ($p=0.001$, OR=0.16, CI=0.05–0.5). The sample size, probably, may have been too small to reveal a true effect in the individual studies. In South America (Colombia and Brazil), a significant relationship was found between *dupA*-negative strains and both GU and GC (for GU, $p=0.001$, OR=0.2, CI=0.1–0.4 and for GC, $p=0.001$, OR 0.3, CI=0.2–0.6) (Table 2).

The *dupA*-positivity rate in South Africa and South America was significantly higher than that of East Asia (40%, $p=0.0001$), such as Japan, China and Korea, where the cancer rate is high. Three reports studied samples from China [3, 5, 7] and two from Japan [2, 10]. When we combined the Chinese samples, we found a significant correlation between *dupA*-positive strains and GU ($p=0.001$, OR=5.5, CI=2.4–12.4) and GC ($p=0.009$, OR=2, CI=1.1–3.1). In Japan, no significant relationship was found between *dupA* and clinical outcomes, even after the combination of both studies. This may be partly attributable to the overall lower prevalence of *dupA*-positive strains (25%) in this population. The prevalence of *dupA*-positivity in the Middle East and India was 45 and 31%, respectively, and was significantly lower than that of South America and South Africa ($p=0.001$). Among the USA and European samples, 45 and 49% of samples, respectively, carried *dupA*-positive strains, and signifi-

cantly less than South Africa and South America ($p=0.001$). In Europe, the USA and the Middle East, the positivity rate of *dupA* was almost similar. This is in agreement with other studies that showed a similarity in *H. pylori* virulence factor between Western countries and the Middle East. No significant relationships between *dupA* and disease were found in these populations. There is a general trend of low *dupA*-positive rates in countries where the gastric cancer rate is high.

Although five reports studied the association of *dupA* with other virulence factors, there were no detailed data of each patient [2, 4, 6–8]. In Brazil, the presence of *dupA* was associated with *cagA* status in the group of adults with DU [8]. In China and Iraq, the presence of *dupA* was not associated with the other *H. pylori* virulence factors [4, 7]. In Iran, it was found that 86% of strains with more than three phosphorylation motifs were *dupA*-positive, which is significantly more than the 36% of strains with only three phosphorylation motifs [4].

Conclusion

As summarised in Table 1, the sample number of some studies was small and insufficient to clarify the significance of the correlation between the duodenal ulcer promoting gene A (*dupA*) of *Helicobacter pylori* and gastroduodenal diseases. Therefore, by meta-analysis using many patients, the association between *dupA* and disease risk worldwide needed to be clarified. The prevalence of *dupA*-positivity differed significantly among the various regions around the world. We speculated that differences in *dupA* prevalence between populations could be associated with the selected nature of the dyspeptic populations studied or there may be genetic differences between versions of the *dupA* gene in different strains, similar to the difference found in *vacA* alleles and *cagA* phosphorylation motifs. To conclude, *dupA* promotes duodenal ulceration in some populations and gastric cancer in others. This is typical of other virulence factors, such as the *cagA* gene, which, like *dupA*, is thought to induce disease largely through inducing gastric inflammation.

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