

World Journal of *Gastroenterology*

World J Gastroenterol 2020 August 28; 26(32): 4729-4888



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ABOUT COVER

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The *WJG* is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2020 edition of Journal Citation Report® cites the 2019 impact factor (IF) for *WJG* as 3.665; IF without journal self cites: 3.534; 5-year IF: 4.048; Ranking: 35 among 88 journals in gastroenterology and hepatology; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yan-Liang Zhang; Production Department Director: Yun-Xiaojian Wu; Editorial Office Director: Ze-Mao Gong.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

August 28, 2020

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INSTRUCTIONS TO AUTHORS

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PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Novel virulence factor *dupA* of *Helicobacter pylori* as an important risk determinant for disease manifestation: An overview

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Supported by Council of Scientific and Industrial Research, Government of India, No. 12458; Department of Science and Technology, India, No. IF140909; and the Council of Scientific and Industrial Research, India, No. 09/482(0065)/2017-EMR-1.

Conflict-of-interest statement: All authors declare no conflicts of interest.

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Abstract

Helicobacter pylori (*H. pylori*) is a microaerophilic, Gram-negative, human gastric pathogen found usually in the mucous lining of stomach. It infects more than 50% of the world's population and leads to gastroduodenal diseases. The outcome of disease depends on mainly three factors: Host genetics, environment and bacterial factors. Among these, bacterial virulence factors such as *cagA*, *vacA* are well known for their role in disease outcomes. However, based on the global epidemiological results, none of the bacterial virulence (gene) factors was found to be associated with particular diseases like duodenal ulcer (DU) in all populations. Hence, substantial importance has been provided for research in strain-specific genes outside the *cag* pathogenicity island, especially genes located within the plasticity regions. *dupA* found within the plasticity regions was first demonstrated in 2005 and was proposed for duodenal ulcer development and reduced risk of gastric cancer in certain geographical regions. Due to the discrepancies in report from different parts of the world in DU development related to *H. pylori* virulence factor, *dupA* became an interesting area of research in elucidating the role of this gene in the disease progression. In this review, we shed light on the detailed information available on the polymorphisms in *dupA* and their clinical relevance. We have critically appraised several pertinent studies on *dupA* and discussed their merits and shortcomings. This review also highlights *dupA* gene as an important biomarker for DU in certain populations.

Key words: *Helicobacter pylori*; Plasticity region; Duodenal ulcer; Gastric cancer; *dupA* gene

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Manuscript source: Invited manuscript

Received: February 20, 2020

Peer-review started: February 20, 2020

First decision: February 29, 2020

Revised: June 23, 2020

Accepted: August 3, 2020

Article in press: August 3, 2020

Published online: August 28, 2020

P-Reviewer: Fagoonee S, Huang YQ, Ulaşoğlu C

S-Editor: Yan JP

L-Editor: Filipodia

P-Editor: Zhang YL



Core tip: A novel virulence factor *dupA* located in the plasticity region of *Helicobacter pylori* genome was found to be associated with duodenal ulcer development in certain geographical regions. Well-known bacterial virulence factors in this pathogen like *cagA*, *vacA* are not found to be associated with duodenal ulcer in Asia. Studies focused on the epidemiology and clinical relevance of *dupA* around the world exhibit significant variations. Hence, we focused on the variations in *dupA* and the plausible role of such variation in disease etiology with the goal of bringing attention to this topic to the scientific community and eventually opening up avenues for further research.

Citation: Alam J, Sarkar A, Karmakar BC, Ganguly M, Paul S, Mukhopadhyay AK. Novel virulence factor *dupA* of *Helicobacter pylori* as an important risk determinant for disease manifestation: An overview. *World J Gastroenterol* 2020; 26(32): 4739-4752

URL: <https://www.wjgnet.com/1007-9327/full/v26/i32/4739.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v26.i32.4739>

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a curved rod-shaped, Gram-negative, microaerophilic bacterium found usually in the mucous lining of the stomach. *H. pylori* infects more than 50% of the world's population and 70%-80% of the Indian population^[1,2]. *H. pylori* is acquired during childhood and remains in the stomach throughout the life if not treated effectively^[3]. Infection with *H. pylori* causes duodenal ulcer (DU), gastric ulcer (GU), gastric cancer (GC) and gastric mucosa-associated lymphoid tissue lymphoma^[4-7]. Considering its clinical importance, the World Health Organization has declared *H. pylori* as a class I carcinogen and enlisted GC as the fifth most common cancer and the third most common cause of cancer-related death^[8,9]. Infection of *H. pylori* is comparatively more prevalent in developing countries than Western countries due to socioeconomic and sanitary conditions^[10]. The mode of transmission of *H. pylori* is not clearly understood. However, most of the studies suggest that *H. pylori* is transmitted from person to person *via* oral-oral and fecal-oral route and also through contaminated food and water^[11-14].

The enigma of *H. pylori* research is that the majority of infected patients remain asymptomatic, whereas around 15%-20% of infected individuals develop symptoms of peptic ulcer (duodenal or gastric) as a long-term consequence of infection. It is not clear what governs the manifestation of *H. pylori* infection in some people. This apparent puzzle prompted the proposal that the sheer presence of *H. pylori* in the stomach is inadequate to develop acute gastric disease and that other conditions are required. However, it is assumed that the responsible factors in *H. pylori*-associated diseases are due to its virulence factors, host genetics, immunity and environmental influences. Host factors like polymorphism in the genes (pro-inflammatory cytokine genes) increase the risk of the specific clinical outcome^[15]. None of the *H. pylori* virulence factors such as *cagA*, *vacA*, the blood group antigen *babA* and *oipA* have been linked with specific diseases like DU or GC uniformly in all populations^[16-20].

Analysis of the full genome sequences of different *H. pylori* strains reported specific genetic locus whose G+C content was lower than that of the rest of the *H. pylori* genome. This indicates the possibility of horizontal deoxyribonucleic acid (DNA) transfer from other species. *H. pylori* carry an open pan-genome, which maintain a discrete group of strain-specific genes. These strain-specific genes mostly reside in genomic regions that had earlier been coined as plasticity zones. This term was previously used to describe a specific genetic segment with high variation between the *H. pylori* genome sequences^[21,22]. The complete genome sequence of *H. pylori* reveals that part of the plasticity zone is normally arranged as genomic islands that may be integrated in the genetic loci. About 50% of the strain-specific genes of *H. pylori* are located in the plasticity region. Here, our focus is on the gene *dupA*, which is located within the plasticity region. This gene was first reported in 2005 as an important biomarker for DU^[23]. During subsequent years, several investigations were carried out on *dupA*, and this has become an interesting area of research, as shown in [Table 1](#).

Table 1 Important finding on *dupA* of *Helicobacter pylori* in chronological order

Year	Observation and conclusion	Sample location	Sample size	Techniques used in the study	Proposed name	Ref.
2005	<i>dupA</i> was novel marker associated with increased risk for DU and reduced risk for gastric cancer in East Asia and South America	Japan, Korea, Colombia	500	PCR, southern blot	<i>dupA</i>	Lu <i>et al</i> ^[23]
2007	Significant association of <i>dupA</i> gene with DU	North India	166	PCR, Dot-blot hybridization, partial sequencing	<i>dupA</i>	Arachchi <i>et al</i> ^[24]
2007	Presence of <i>dupA</i> significantly associated with GC than DU	Belgium, South Africa, china, North America	258	PCR	<i>dupA</i>	Argent <i>et al</i> ^[25]
2008	<i>dupA</i> gene was not associated with any diseases outcome	Iran	157	PCR, partial sequencing	<i>dupA</i>	Douraghi <i>et al</i> ^[30]
2008	<i>dupA</i> was not associated with <i>H. pylori</i> associated diseases in children and adults	Brazil	482	PCR, partial sequencing	<i>dupA</i>	Gomes <i>et al</i> ^[26]
2008	<i>dupA</i> was associated with peptic ulcer in Iraqi population but not with Iranian population	Iraq and Iran	108	PCR	<i>dupA</i>	Hussein <i>et al</i> ^[29]
2008	There was no association between the occurrence of <i>dupA</i> and DU	Brazil (Sao Paulo)	79	PCR	<i>dupA</i>	Pacheco <i>et al</i> ^[27]
2008	The prevalence of <i>dupA</i> was significantly higher in DU patients than in gastric cancer	china	360	PCR	<i>dupA</i>	Zhang <i>et al</i> ^[38]
2009	There was no consistent association between <i>dupA</i> and DU or GC development	Sweden, Australia, Malaysia (ethnic groups Indian, Malaya)	243	PCR, partial sequencing	<i>dupA</i>	Schmidt <i>et al</i> ^[41]
2010	<i>dupA</i> was not associated with gastroduodenal diseases or IL-8 production	Japan	244	PCR, partial sequencing RT-PCR, IL-8 assay	<i>dupA</i>	Nguyen <i>et al</i> ^[45]
2010	<i>dupA</i> is not association with DU in patients from Turkey	Turkey	91	PCR	<i>dupA</i>	Tuncel <i>et al</i> ^[37]
2010	Meta-analysis of case control studies confirmed the presence of <i>dupA</i> gene for DU	Asian and western countries	2466	-	<i>dupA</i>	Shiota <i>et al</i> ^[44]
2010	Meta-analysis of previous report showed <i>dupA</i> gene promotes DU formation some population and GU and GC in others	Around the world	2358		<i>dupA</i>	Hussein <i>et al</i> ^[43]
2010	In Taiwanese female population, MMP-3 promoter polymorphism is correlated with DU rather than <i>dupA</i> gene	Taiwan female	181	PCR	<i>dupA</i>	Yeh <i>et al</i> ^[40]
2010	<i>dupA</i> and gastric cancer is negatively associated with GC in Japanese population	Japan	136	PCR	<i>dupA</i>	Imagawa <i>et al</i> ^[46]
2010	Proposed two alleles of <i>dupA</i> [<i>dupA1</i> (intact), <i>dupA2</i> (truncated)]. <i>dupA1</i> (not <i>dupA2</i>) increased IL-12p40 and IL-12p70 production from CD14 ⁺ mononuclear cell	United Kingdom, United States, Belgium, South Africa, China	34	PCR, full Sequencing, Cytokine ELISA, real time PCR, flow cytometry	<i>dupA1</i>	Hussein <i>et al</i> ^[52]
2011	Presence of mutation on <i>dupA</i> at 1311 and 1426 leads to stop codon called truncated <i>dupA</i>	Brazil	252	PCR, full sequencing	<i>dupA</i>	Queiroz <i>et al</i> ^[50]
2011	Intact <i>dupA</i> (<i>dupA1</i>) without stop codon was associated with decreases rate of gastric carcinoma in Brazilian population	Brazil	6	Full sequencing	<i>dupA1</i>	Queiroz <i>et al</i> ^[57]
2012	Found a positive association between presence of <i>dupA</i> and DU [OR 24.2; 95%CI: 10.6-54.8] and inverse association	Iran	216	PCR	<i>dupA</i>	Abadi <i>et al</i> ^[31]

	between presence of <i>dupA</i> and GU [OR 0.34; 95%CI: 0.16-0.68] and GC [OR 0.16; 95%CI: 0.05-0.47]					
2012	Prevalence of <i>dupA</i> was higher in the eradication failure group than in the success group (36.3% vs 21.9%)	Japan	142	PCR, Drug sensitivity test	<i>dupA</i>	Shiota <i>et al</i> ^[60]
2012	The logistic analysis report in Brazilian population showed the presence of intact <i>dupA</i> independently associated with duodenal ulcer (OR = 5.06; 95%CI: 1.22-20.96, <i>P</i> = 0.02)	Brazil	75	Sequencing	Intact <i>dupA</i>	Moura <i>et al</i> ^[51]
2012	<i>dupA</i> gene was found to be significantly associated with DU than in NUD in south east Indian population	India	140	PCR, partial sequencing, real time PCR,	<i>dupA</i>	Alam <i>et al</i> ^[47]
2012	Found a significant association between <i>dupA1</i> and DU (<i>P</i> < 0.01) along with a significant higher level of gastric mucosa IL-8 in <i>dupA1</i> than in <i>dupA2</i> or <i>dupA</i> negative Iraqi strain	Iran	68	PCR, full sequencing, IL-8 ELISA	<i>dupA1</i>	Hussein <i>et al</i> ^[54]
2012	classified <i>dupA</i> into two types (long types and short types) depend on the presence of 615 bp at the N-terminal of <i>dupA</i> . Found high prevalence of intact long type <i>dupA</i> (24.5%) than short type <i>dupA</i> (6.6%) and significantly associated with GU and GC than gastritis (<i>P</i> = 0.001 and <i>P</i> = 0.019) in Japanese population	Japan	319	PCR, full sequencing	Long type and short type	Takahashi <i>et al</i> ^[53]
2012	Complete <i>dupA</i> cluster (<i>dupA</i> with six <i>virB</i> homologues) was associated with DU rather than <i>dupA</i> gene only in United States population	United States	245	PCR and cytokine ELISA	<i>dupA</i> cluster	Jung <i>et al</i> ^[75]
2013	Prevalence of long type <i>dupA</i> (2499 bp) was significantly higher in GU, GC and DU (40.3%) than from gastritis (20.4%) (<i>P</i> = 0.02) in China	China	116	PCR, Full sequencing	<i>dupA</i> cluster	Wang <i>et al</i> ^[59]
2013	PUD was significantly associated with <i>cagA</i> (<i>P</i> ≤ 0.017; OR 0.4; 95%CI: 0.18-0.85) rather than <i>dupA</i>	Iraq	154	PCR	<i>dupA</i>	Salih <i>et al</i> ^[34]
2014	<i>dupA</i> was found to play an important role in the development of DU, BGU and dysplasia in South Korean population	South Korea	401	PCR	<i>dupA</i>	Kim <i>et al</i> ^[59]
2014	<i>dupA</i> was associated with <i>cagA</i> and <i>vacAs1m1</i> genotypes	Brazil	205	PCR	<i>dupA</i>	Pereira <i>et al</i> ^[28]
2014	The prevalence of <i>dupA</i> and <i>cagA</i> were more in MTZ, CLR and AML resistance strain as compared to other virulence factor in Pakistan	Pakistan	46	PCR	<i>dupA</i>	Rasheed <i>et al</i> ^[61]
2015	<i>cagA</i> , complete <i>dupA</i> cluster and smoking were significantly associated with increased level of IL-8 production from gastric mucosa of Iraqi population	Iraq	81	PCR, IL-8 ELISA	<i>dupA</i>	Hussein <i>et al</i> ^[55]
2015	Prevalence of <i>dupA1</i> was significantly higher in DU than NUD (<i>P</i> = 0.02) in Indian strains and <i>dupA1</i> positive strains were similar to East Asian strains and distinct from western strains.	India	170	PCR, sequencing, IL-8 ELISA	<i>dupA1</i>	Alam <i>et al</i> ^[58]
2015	Significant association of complete <i>dupA</i> cluster with IL-8 production (<i>P</i> < 0.01) in north East of China	China	262	PCR, western blotting, IL-8 ELISA	<i>dupA</i> cluster	Wang <i>et al</i> ^[76]
2015	DupA protein have ATPase activity and play a role in apoptosis of gastric cancerous cells through mitochondrial pathway but neither adhere nor translocate to host cell	China	1 (WH21)	PCR, western blotting, ATPase, Adhesion, translocation and cytotoxic assay	Long type <i>dupA</i>	Wang <i>et al</i> ^[79]
2015	<i>dupA1</i> have a significant association with A2147G clarithromycin resistance strain but not with IL-8 production from gastric mucosa	Iraq	74	PCR, IL-8 ELISA, antibiotic susceptibility test	<i>dupA1</i>	Hussein <i>et al</i> ^[56]
2015	Significant association between the presence of <i>dupA</i> and DU diseases (<i>P</i> = 0.03 OR 3.14, 95%CI: 1.47-7.8).	Iran	128	PCR	<i>dupA</i>	Haddadi <i>et al</i> ^[35]
2015	There was no significant relationship between <i>dupA</i> status and duodenal ulcer disease (<i>P</i> = 0.25) but, there was a converse relationship between <i>dupA</i> negative strains and gastric cancer disease (<i>P</i> = 0.02)	Iran	123	PCR	<i>dupA</i>	Souod <i>et al</i> ^[36]
2015	There was no association of <i>dupA</i> gene with the ethnic group (Indian, Chinese, Malaya) of Malaysia	Malaysia	105	PCR	<i>dupA</i>	Osman <i>et al</i> ^[42]

2017	Significant association of <i>dupA</i> gene with non-severe clinical outcome ($P = 0.0032$, OR 0.25, 95%CI: 0.09-0.65) and play a role in protecting against gastric cancer in Chile	Chile	132	PCR	<i>dupA</i>	Paredes et al ^[48]
2017	A complete <i>tfs</i> plasticity zone cluster including <i>dupA</i> is a virulence factor that may be important for the colonization of <i>H. pylori</i> and to the development of severe outcomes of the infection with <i>cagA</i> -positive strains	Portugal	18	PCR, whole genome sequencing, cytokine assay	<i>dupA</i>	Silva et al ^[78]
2019	<i>dupA</i> was significantly associated with decreased risk of duodenal ulcer ($P = 0.024$)	Costa Rica	151	PCR	<i>dupA</i>	Molina Castro et al ^[49]
2019	Significant relationship was observed between the occurrence of DU and the presence of the 112 bp segment ($P = 0.002$; OR 6.98; 95%CI: 1.94-25.00)	Iran	143	PCR	<i>dupA</i>	Fatahi et al ^[32]
2019	The prevalence of <i>dupA</i> was 53.4% in South African population, but it was not associated with duodenal ulcer	South Africa	234	PCR	<i>dupA</i>	Idowu et al ^[64]
2019	The prevalence of <i>dupA</i> was higher (30.4%) in peptic ulcer (mild diseases) than gastric cancer (severe diseases) 18.2%	Northern Spain	102	PCR	<i>dupA</i>	Fernandez-Reyes et al ^[72]
2019	<i>dupA</i> was present in 10/41 (24.4%) of population, and it was not associated with severe gastritis	Switzerland	41	Whole genome sequence	<i>dupA</i>	Imkamp et al ^[63]
2019	Significant association was found between metronidazole resistance and <i>dupA</i> genotypes ($P = 0.0001$)	Iran	68	PCR	<i>dupA</i>	Farzi et al ^[33]

CI: Confidence interval; DU: Duodenal ulcer; GC: Gastric cancer; GU: Gastric ulcer; IL-8: Interleukin-8; MMP-3: Matrix metalloproteinase -3; NUD: Non-ulcer dyspepsia; OR: Odds ratio; PCR: Polymerase chain reaction.

METHODOLOGY

To review the importance of *dupA*, we have searched the “NCBI-PubMed” using the keywords: “*dupA*”, “*H. pylori*” and a total of 80 articles were found, of which 76 were published in English till January 2020. Out of 76, 13 are published as review articles and two as meta-analysis of previous data. The remaining 61 documented as research articles. The research on *dupA* has spanned 15 years with contradictory findings. In this review, we summarize the result of relevant studies and discuss the pathogenesis of *dupA* since its early stage to recent advancements. Finally, this review highlights the significance of *dupA* gene of *H. pylori* as a virulence factor (virulence marker) and its role in pathogenesis including the progression of DU.

DISCREPANCIES OF *DUPA* WITH CLINICAL OUTCOMES

Studies conducted with *H. pylori* strains from East Asia and South America identified a novel *H. pylori* virulence factor encoded in the *dupA* that was associated with increased risk of DU and decreased risk of GC. However, this perception seems to be region specific. This *dupA* was homologous to *virB4* gene, located in the plasticity zone of *H. pylori*. *dupA* contained two open reading frames (ORFs), *jhp0917* and *jhp0918*, with an overlap of twelve bases and an insertion of either base thymine (T) or cytosine (C) after the position 1385 of the *jhp0917* that leads to continuous gene of 1839 bp. Since 2005, several studies have been conducted from different geographical areas to check the

association of *dupA* with disease outcome considering the *dupA* has two ORFs (*jhp0917/jhp0918*) with the insertion of one base (T/C) at position 1385 of *jhp0917*. Studies performed in North India during 2007 support the finding of Lu et al^[24]. However, studies conducted in different countries (Belgium, South Africa, China, North America and Brazil) found that *dupA* is not associated with DU in the respective population^[25-27].

Investigations made in Sao Paulo, Brazil showed that *dupA* was detected in *H. pylori* strains of 41.5% patients, which was less from a previous study made by Gomes et al^[26] (2008), in which *dupA* was present in 89.5% patients^[28]. This study showed an association of *dupA* with *cagA* and *vacA s1m1* genotypes but without any link to disease outcome. The difference in the results of these two studies from Brazil could be explained by variation in geographic regions, a re-arrangement in the plasticity zone distribution in *H. pylori* and various methods used for the analysis.

The distribution of *dupA* in *H. pylori* was similar in Iraqi and Iranian population, but there was an association between peptic ulcer and *dupA* only in the Iraqi population^[29]. An independent study by Douraghi et al^[30] (2008) reported a non-significant higher distribution of *dupA* in DU than non-cardia GC patients in the Iranian population^[30]. Another study by Talebi Bezmin Abadi et al^[31] (2012) found a positive association between the presence of *dupA* and DU along with an inverse association between *dupA* and GU in Iranian population^[31]. The discrepancy in the finding of Douraghi et al^[30] (2008) and Talebi Bezmin Abadi et al^[31] (2012) may be due to differences in the study populations. Douraghi et al^[30] (2008) focused mainly in Tehran (the densely populated capital of Iran), whereas Talebi Bezmin Abadi et al^[31] (2012) collected samples from the extremely rural northern areas of Iran. Recently, Fatahi et al^[32] (2019) tested a highly conserved region of *dupA* and showed a significant relationship between the occurrence of DU and the presence of an 112 bp segment of *dupA* in the Iranian population^[32]. Another group from Iran studied the relationship between antibiotic resistance pattern and virulence genotype among 68 *H. pylori* strains and found that metronidazole resistance was significantly associated with the strains harboring *cagA*, *sabA* and *dupA*^[33]. One study from Kurdistan region of Northern Iraq reported that *cagA* gene was significantly associated with peptic ulcer disease rather than *dupA*, which contradicts the result of Hussein et al^[29] (2008). This might be due to the differences in sample size and also in the geographical location of Iraq^[34]. In the Shiraz area of Iran, a significant relationship was found between strains with *dupA*, CagA motif (ABC types) and DU disease, which supports the previous finding in this region^[35]. Another study from Western Iran indicated that presence of *dupA* gene could be considered as a marker for the onset of severe gastroduodenal diseases^[36]. However, there was no association of *dupA* with DU in the results obtained from the Turkish population^[37].

In China and South Korea, presence of *dupA* in clinical *H. pylori* isolates is significantly associated with DU and peptic ulcer (DU, benign GU, dysplasia), respectively^[38,39]. In the Taiwanese female population, the host factor matrix metalloproteinase-3/tissue inhibitor matrix metalloproteinase-1 genotypes rather than *dupA* was found to increase the risk of DU in *H. pylori* infected cases^[40]. A case control study conducted in Sweden, Australia, Malaysia and Singapore showed that there was significant variation in the prevalence of *dupA* in different locations and among different ethnic groups (Chinese, Indian and Malaya) within a country^[41]. Another study in ethnic groups (Indian, Chinese and Malaya) of Malaysia reported that the prevalence of *dupA* was 22.9% in patients, which was in line with previous data (21.3%) conducted in Malaysia by Schmidt et al^[41] (2009). In the later study, there was no association between *dupA* and clinical outcome^[42].

Two independent systematic review and meta-analyses showed that *dupA* is more associated with DU in some Asian populations than in Western populations^[43,44]. Between 2005 and 2009, almost all the studies used polymerase chain reaction (PCR) of two ORFs *jhp0917*, *jhp0918* and sequencing to identify the *dupA*. Functional analysis of *dupA* in the Japanese population showed no association with DU but another study from different parts of Japan showed that *dupA* is inversely related to GC^[45,46].

Results from a study using different molecular methods [PCR, dot-blot hybridization, sequencing and reverse transcription PCR (RT-PCR)] indicated that *dupA* gene was prevalent more than six times in DU than in non-ulcer dyspepsia patients, indicating its significant association in India^[47]. This result also corroborated the finding of Arachchi et al^[24] (2007) from North India. The RT-PCR analysis of South and East Indian population revealed that all PCR positive strains were not able to produce *dupA* transcripts, which was inconsistent with the finding of Nguyen et al^[45] (2009) where all the *dupA* positive strains showed the expression of the gene^[47]. Further, the real-time PCR analysis revealed that the expression level of the *dupA*

transcripts varied from strain to strain in this study.

Studies conducted in Chile supported a significant association of *dupA* gene with non-severe clinical outcome like DU and also played a role in protecting severe diseases like GC^[48]. The Costa Rica study with 151 dyspeptic patients showed that presence of *dupA* was significantly associated with decreased risk of DU^[49].

Some of the above-mentioned studies verified the finding of Lu *et al*^[23] (2005), but others could not find an association between *dupA* and disease outcome in their study populations. The differences in the results could be explained due to variation in the distribution of plasticity region genes and differences in the study population and techniques chosen for detection of *dupA* gene. Several studies on *dupA* were restricted to PCR of *jhp0917* and *jhp0918* along with sequencing of only the 3' region of *jhp0917* to find the insertion of T/C at 1385 position of *jhp0917*. Numerous studies have shown the presence of frame shift mutation within *dupA* gene leading to the formation of truncated non-functional DupA. These findings provide evidence that only PCR based analysis of *dupA* may yield erroneous interpretation. Studies conducted by Queiroz *et al*^[50] (2011) and Moura *et al*^[51] (2012) from Brazil showed the presence of a mutation in *dupA* that results in a stop codon, making the gene truncated or non-functional. In addition, these studies revealed the importance of sequence analysis of *dupA* amplicons^[50,51]. Truncated *dupA* might not be involved in the pathogenesis of *H. pylori*.

Hussein *et al*^[52] (2010) coined the term “*dupA1*”. The *dupA* positive *H. pylori* strains were categorized into two alleles based on the sequence; *dupA1* (intact 1884 bp) and *dupA2* (truncated). It was shown that the intact *dupA1* positive strains induced the production of interleukin (IL)-12 subunit p40 (IL-12p40) and IL-12p70 from CD14 (+) mononuclear cells and IL-8 expression in the human stomach, respectively^[52]. Takahashi *et al*^[53] (2012) first reported the presence of an additional 615 bp in the 5' region of ORF *jhp0917* (absent in strain J99) and 45 bp in the 3' of *jhp0918* (consist of 37 bp of intergenic region of *jhp0918-jhp0919* and 8 bp of 5' region of *jhp0919* in J99) to make 2499 bp of *dupA* in the Japanese population (Figure 1). This variation formed the basis for classification of *dupA* into two types; “long and short types”. The long type of intact 2499 bp (with an additional 615 bp at 5' region of *jhp0917*) has been considered as an actual virulence factor, and the absence of the additional segment should be interpreted with caution^[53].

None of the *H. pylori* strains from Iraq carried the complete *dupA* cluster containing *virB8*, *virB9*, *virB10*, *virB11*, *virD4* and *virD2*, but there was a significant association between *dupA1* and DU. Moreover, higher levels of gastric mucosa IL-8 production were documented in *dupA1* than in *dupA2* or *dupA* negative strains^[54]. Further studies with *H. pylori* infected patients showed that *cagA*, complete *dupA* cluster and smoking habit were associated with increased levels of IL-8 production from gastric mucosa^[55]. It was also shown in another study that the high IL-8 level in gastric mucosa was neither significantly associated with *dupA1* positive strains nor with *dupA* negative strains^[56]. A significant association has also been found between *dupA1* and A2147G clarithromycin resistance mutation. However, the result of *dupA1* and IL-8 association in the Iraqi population was not well elucidated. In Brazilian *H. pylori* strains, it was found that *H. pylori* strains had the 45 base at the 3' end of *dupA*, similar to that of *dupA1*^[57].

dupA gene of Indian *H. pylori* strains has been classified into two forms based on the presence of additional 615 bp at the 5' region of *dupA* followed by a stop codon. This includes *dupA1* without any frameshift mutation (either long type or short type) and *dupA2* with the truncated version having frameshift mutation^[58]. Among these, *dupA1* (intact *dupA*) was significantly associated with DU. Phylogenetic analysis of complete *dupA* gene sequencing revealed that Indian *H. pylori* strains intermingled with the East Asian strains, but differed from European strains^[58]. *dupA* is the first known genetic element of Indian *H. pylori* strains, which phylogenetically formed the same cluster with the East Asian strains. *In vitro* study showed that IL-8 production was significantly associated with DU in intact *dupA1* rather than truncated *dupA2* or *dupA* negative strains^[58]. In Chinese strains, the prevalence of long type *dupA* (2499 bp) was significantly higher in patients with GU, GC and DU than in those with gastritis^[59].

In the Japanese population, prevalence of *dupA* was higher in the group where *H. pylori* cannot be eradicated, indicating that *dupA* may be an associated risk factor in the eradication failure^[60]. A study from Pakistan on the influence of *dupA* in the eradication failure showed that *H. pylori* strains harboring *dupA* and *cagA* were multidrug (metronidazole, clarithromycin and amoxicillin) resistant as compared to strains having other virulence factors. This finding was similar to the observation made in the Japanese population^[61]. In the northern part of Spain, *dupA* was more prevalent in mild diseases (peptic ulcer) than severe diseases (GC)^[62]. In Switzerland and South Africa, *dupA* of *H. pylori* was not associated with severe gastritis or DU^[63,64].

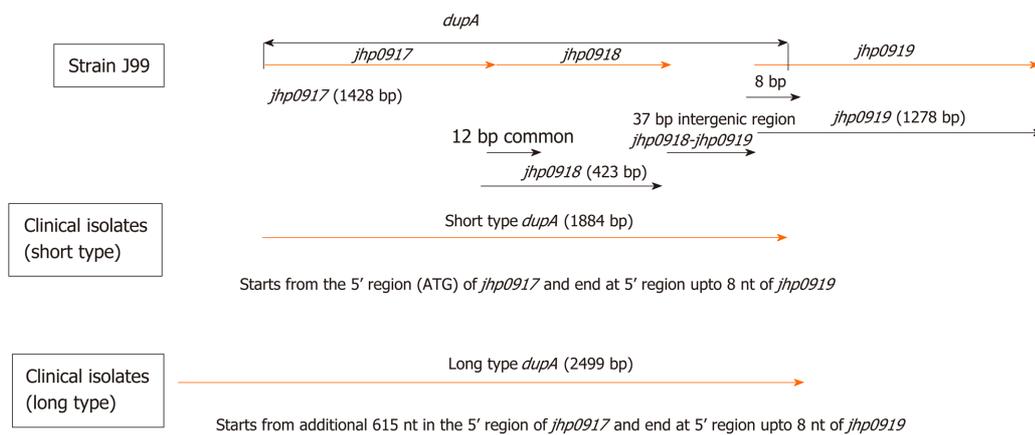


Figure 1 Schematic representation of the *jhp0917*, *jhp0918* and *jhp0919* gene in strain J99 and that of the *dupA* alleles in the clinical isolates. The long type *dupA* (2499 nt) in some clinical isolates contained an additional 615 nt in 5' region before *jhp0917* gene and ended 5 bp after the start codon of *jhp0919* gene. The short type *dupA* (1884 nt) in some clinical isolates starts from the 5' region of *jhp0917* gene and ended 5 bp after the start codon of *jhp0919* gene.

DUPA CLUSTER: THIRD TYPE IV SECRETION SYSTEM (T4SS) OF *H. PYLORI*

The T4SS is an important bacterial transport system, and it is involved in the transport of large molecules (e.g., DNA, protein, etc.) across the bacterial cell envelope^[65,66]. Till now, three types of T4SS have been identified in *H. pylori*, of which much work has been done for the first two categories (*cagPAI* and *ComB*) and little is known about the third T4SS termed *dupA* cluster or *tfs3* (Figure 2)^[67,68]. The third putative type IV secretion system (*tfs3*) is a 16 kb gene fragment present in the plasticity zone of *H. pylori*, whose seven ORFs (*virB4*, *virB8*, *virB9*, *virB10*, *virB11*, *virD4* and *virD2*) were homologous to *virB4/D* of *Agrobacterium tumefaciens* (*A. tumefaciens*). The function of the *tfs3* elements is not yet clear as there is no direct evidence to show its role in transformation, conjugation or mouse colonization^[69,70]. Some researchers divided the *tfs3* into *tfs3a* (all six *virB* homologues with *dupA*) and *tfs3b* (all six *virB* homologues with *virB4*), whereas others named all six *virB* homologues with *virB4* as *tfs3* and all six *virB* homologues with *dupA* as *tfs4*^[71-73]. In order to avoid confusion, we will use the term *tfs3a* or *dupA* cluster (all six *virB* homologues with *dupA*). *VirB8*, *VirB9* and *VirB10* are expected to form the core complex that bridges cytoplasm and the outer membrane. The *VirB4*, *VirB11*, *VirD4* may be localized to the inner bacterial membrane and recognize the substrate and energize translocation and assembly of T4SS^[74]. Further, the novel putative T4SS (*tfs3a*) or *dupA* cluster has been divided into three groups: Viz, a complete *dupA* cluster (*dupA*-positive and all six *virB* genes-positive), an incomplete *dupA* cluster (*dupA*-positive but one/more than one *virB* genes negative) and *dupA*-negative group (*dupA* negative and *virB* gene positive/negative).

The study of *dupA* cluster from the United States population showed that the complete *dupA* cluster (*dupA* with six *virB* homologues) was associated with DU rather than *dupA* gene only^[75]. Another report from the northeast part of China showed a significant association of complete *dupA* cluster with IL-8 production ($P < 0.01$), but it did not show any correlation between *dupA* cluster and disease outcome^[76]. The studies from United States and China were conducted to check the prevalence of *tfs3a* or *dupA* cluster in their population by PCR only. However, the mere presence of the gene does not express functional protein and there is no direct evidence that shows *tfs3a* or *dupA* cluster forming a functional T4SS. The earlier studies on *tfs3a* did not find a direct pathogenic role of *tfs3a* in *H. pylori*, but found increased colonization fitness and up-regulation of pro-inflammatory signaling from cultured cells. A novel pathogenicity island (PAI) called *tfs3-PAI* was identified in China that had 17 ORFs, of which six are functionally homologues of T4SS and coordinate with the well-studied *cag-PAI*^[77]. The complete *tfs3* plasticity cluster was associated with IL-8 induction. The expression of some of the genes of *tfs3a/tfs4* (*virB2*, *virB4*, *virB6*, *virB8*, *virB10*) in *H. pylori* is up-regulated in low pH and enhances bacterial adhesion that support the role of *tfs3a/tfs4* in the colonization and virulence^[78]. It is not known whether the *virB* genes of *dupA* cluster work independently or in a coordinated manner by interacting among themselves or complementing each other's function. We checked the interaction of

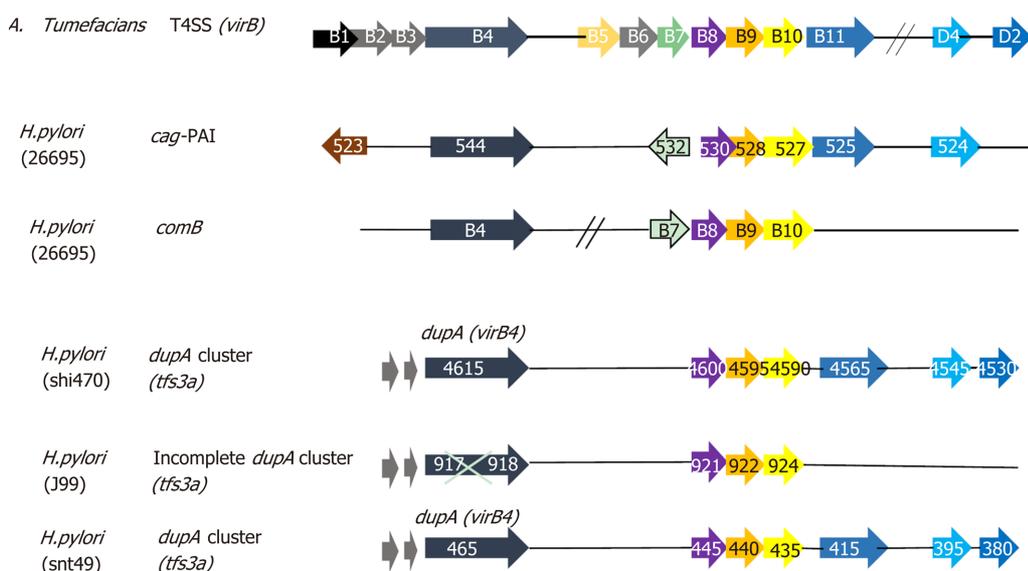


Figure 2 Organization of three types of type IV secretion system in the *Helicobacter pylori* compared to *Agrobacterium tumefaciens* prototype type IV secretion system. Genes are not drawn to scale. *H. pylori*: *Helicobacter pylori*; *A. tumefaciens*: *Agrobacterium tumefaciens*; T4SS: Type IV secretion system.

dupA with six *virB* genes of *tfs3a* to identify the assembly and function of complete *tfs3* using *in vivo* studies (yeast two-hybrid system) and found that *dupA* gene did not interact directly with any *virB* gene. It seems that *dupA* may interact with some intermediates or work independently (unpublished data). This interpretation supports our earlier finding that *tfs3* is not significantly associated with DU in Indian population. More studies are required to know the structure, assembly and functions of the VirB proteins in *H. pylori*.

THE PROSPECTIVE FUNCTIONS OF DUPA

The bioinformatics analysis (PDB search tool, UniProt database) showed that the *dupA* gene is homologous to VirB4 adenosine triphosphate (ATP)ase of *virB/virD* of *A. tumefaciens* and is predicted to be involved in DNA/protein transfer. The N-terminal of long type DupA has no homologous motif. Only the middle portion (*jhp0917*) and C-terminal (part of *jhp0918*) showed homologous motifs suggesting that the N-terminal region might act as signal sequence. The amino acid sequence (210-406 AA) of *jhp0917* gene protein was homologous to CagE_TrbE_VirB family, a component of type IV transporter secretion system. The first middle region of the DupA protein (430-500 AA) is homologous to FtsK/SpoIIIE family, which contains ATP binding P-loop motif. This was found in the Ftsk protein of *Escherichia coli* involved in peptidoglycan synthesis and spoIIIE of *Bacillus subtilis*, facilitating in the intercellular chromosomal DNA transfer.

The second middle region (464-503aa) is homologous to TrwB, which has an ATP binding domain, and a part of T4SS may be responsible for the DNA binding and horizontal DNA transfer. The C-terminal region (668-738aa) is homologous to TraG_C_D, which is involved in the interaction of DNA-processing (Dtr) and mating pair formation (Mpf) system, leading to DNA transfer in bacterial conjugation. Many reports have shown that the growth rate of *dupA* positive strains is higher in low pH as compared to *dupA* deleted/negative strains. This phenomenon indicates that DupA protein acts as an interactive protein and hence regulates urease secretion in *H. pylori* [79].

The *in vitro* and *in vivo* studies showed the role of *dupA* gene in the activation of transcription factors nuclear factor kappa light chain enhancer of activated B cells and activator protein-1, which leads to IL-8 production. DupA protein act as an ATPase associated efflux pump, which probably confers its virulence. Evidence suggests that DupA is involved in the pathogenesis of *H. pylori* by activating the mitochondria dependent apoptotic pathway of the host's cell, which ultimately inhibits gastric cell growth.

Studies to understand the apoptotic effect of *dupA* on human gastric adenocarcinoma epithelial cell line (commonly known as AGS) by propidium iodide staining and fragmentation assay determined that *dupA* gene can induce apoptosis in AGS cells during an early stage of infection (unpublished data). This finding supports the results of Wang *et al*^[79] (2015) and finds that *dupA* may act as a pathogenic factor of *H. pylori* to cause gastroduodenal diseases. Further studies are required to confirm the pathogenic effect of *dupA* in an *in vivo* model.

The growth kinetics between wild type *dupA* positive strains and its isogenic mutant strain showed that exponential phase was retarded in *dupA* mutant cells as compared to the wild type strain. Our growth curve results, supported by the microarray data, showed that cell division gene in the mutant *H. pylori* was downregulated (unpublished data). It has also been suggested that motility is an essential feature in the colonization and therefore the pathogenicity of *H. pylori*. The decrease in motility in *dupA* mutant strain as compared to wild type inferred the role of *dupA* gene in the motility. This motility result was further confirmed by the gene expression profile of *dupA* mutant strain whose flagella proteins (FlgE, FlhD and FlhG) were found to be down-regulated (unpublished data). It might be possible that *dupA* gene is directly or indirectly involved in negatively affecting the expression of cell division and flagellar genes of *H. pylori*.

As predicted from the bioinformatics analysis, our experimental data (unpublished data) have shown that natural transformation ability in *dupA* mutant strains has been totally inhibited in comparison to their wild type counterparts. There is a need for more studies on the heat-shock transformation efficiency, which will confirm the natural transformation assay, if any. Resistance to antimicrobials is of serious concern in *H. pylori* infection, as this may be the basis for eradication failure. It is important to use therapeutic regimens based on the results of antibiotic susceptibility testing. Metronidazole is considered a key drug in several therapies against *H. pylori* infection. The results of the metronidazole susceptibility test showed that inactivation of *dupA* gene transforms the *H. pylori* strains to resistance phenotype. This phenomenon has not been explained very well. It is possible that the *dupA* gene might help in the DNA/protein/drug import (unpublished data).

The *dupA* or *dupA* cluster may have an intermediate function to link *cagPAI* and *comB* system, as *dupA* gene shows homology with *cagE* of *cagPAI* and *comB4* of *comB* system. So, there is a need of an *in vivo* study to establish the precise function of *dupA*. It is assumed that the *dupA* in combination with other six *vir* genes form a novel third T4SS called *tfs3a* or *dupA* cluster that might play a pathogenic role in gastroduodenal diseases.

CONCLUSION

H. pylori is one of the most diverse bacterial species. *H. pylori* demonstrate panmictic population structure. DNA-fingerprint of two strains isolated from two different persons generally displays a non-identical pattern, which suggests genetic exchange along with co-evolution of this gastric pathogen with its host. One study from the Indian population demonstrated that all the tested patients carried multiple *H. pylori* strains in their gastric mucosa^[80]. Analyses of certain genetic loci showed the micro diversity among the colonies from a single patient, which may be due to the recombination events during long-term carriage of the pathogen. From the results of this study, researchers predicted that many patients from the developing world acquired infections of *H. pylori* due to repeated exposure to this pathogen with different genetic make-up^[80]. This may enhance the probability of super infections, which favor genetic exchanges among these unrelated *H. pylori* strains. As a result, this led to the genesis of certain *H. pylori* variants with different genetic makeup than the parental strain, which in turn increases the chance of the severe infection. Therefore, the exploration of appropriate biomarker(s) that envisage the clinical condition in *H. pylori*-infected patient is a challenging area of research.

There is a lack of relevant biomarker(s) capable of predicting important digestive diseases in clinical settings. Even though there is ample information regarding the *dupA* of *H. pylori*, many unanswered questions still exist, especially regarding the specificity of the *dupA* proposed for clinical manifestation. *dupA* was categorized as long and short types in one study, but in another study, this gene was typed as *dupA1* (intact *dupA1* may be long type or short type) and *dupA2* (truncated version). This gene classification should be resolved for international use to avoid any misperception. We propose the long *dupA* as *dupA1* and short type *dupA* as *dupA2*, and the truncated

version of *dupA* has to be disregarded, as it has no role in pathogenesis. *dupA* should be screened by PCR, sequencing of the full-length gene (1884 and 2499 nt) and western blotting. Nevertheless, the discrepancy prevails between the association of *dupA* (short type or long type) or *dupA* cluster and the disease outcome. Currently, the prevalence of intact *dupA* in East Asian countries is lower than Western countries. DupA with another six Vir proteins (VirB8, VirB9, VirB10, VirB11, VirD4 and VirD2) predicted to form novel third type-IV secretion system (*tfs3a*), which may be involved in transformation/conjugation or injection of DNA/new effector molecules in gastric epithelial cells. However, the function of specific Vir protein of complete *dupA* cluster (*tfs3a*) is not well characterized. Recent reports and other unpublished data showed that DupA has multifunctional biological activities, and it can be considered as an important biomarker for DU. It is also not clear whether the DupA works alone or in combination with other VirB proteins. There is an urgent need for reliable *in vitro* and animal models from diverse geographical areas of the world to elucidate further the pathogenic role of *dupA* and *dupA* cluster in gastroduodenal diseases, particularly the DU and GC.

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