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MINIREVIEWS

Role of *dupA* in virulence of *Helicobacter pylori*

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Abstract

Helicobacter pylori (*H. pylori*) is a gastric human pathogen associated with acute and chronic gastritis, 70% of all gastric ulcers, 85% of all duodenal ulcers, and both forms of stomach cancer, mucosal-associated lymphoid tissue (MALT) lymphoma and adenocarcinoma. Recently, attention has focused on possible relationship between presence of certain virulence factor and *H. pylori*-associated diseases. Some contradictory data between this bacterium and related disorders has been observed since not all the colonized individuals develop to severe disease. The reported diseases plausibility related to *H. pylori* specific virulence factors became an interesting story about this organism. Although a number of putative virulence factors have been identified including cytotoxin-associated gene a (*cagA*) and *vacA*, there are conflicting data about their actual participation as specific risk factor for *H. pylori*-related diseases. Duodenal ulcer promoting gene a (*dupA*) is a virulence factor of *H. pylori* that is highly associated with duodenal ulcer development and reduced risk of gastric cancer. The prevalence of *dupA* in *H. pylori* strains isolated from western countries is relatively higher than in *H. pylori* strains from Asian countries. Current confusing epidemiological reports will continue unless future sophisticated and molecular studies provide data on functional and complete *dupA* cluster in *H. pylori* infected individuals. This paper elucidates available knowledge concerning role of *dupA* in virulence of *H. pylori* after a decade of its discovery.

Key words: *Helicobacter pylori*; *dupA*; Bacterial virulence; Infection; Clinical outcome

Core tip: *Helicobacter pylori* (*H. pylori*) is one of the most common bacterial infections worldwide. Ten years ago, *virB4* homologue was identified as a new virulence factor, *dupA* "duodenal ulcer promoting gene A" by Lu and her colleagues. Nowadays, new genetical analysis using available sequences can help scientists to draw a better conclusion about *dupA* and its actual role in pathogenesis of *H. pylori*-related diseases. In this paper, we aim to draw a new shaped overview regarding *H. pylori* and its virulence factors with emphasis of *dupA*.

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INTRODUCTION

Due to the difficulty in diagnosis and fastidious condition of an optimal growth, *Helicobacter pylori* (*H. pylori*) was an unculturable and thus forgotten microorganism for many years[1]. Following the clinical and histological observations in gastritis and duodenal ulcer patients, Marshall and Warren were able to isolate and characterize this bacterium around thirty-three years ago[1,2]. New era had been started after this groundbreaking discovery and revealed as a publication in *Lancet* written by those Australian scientists[1]. As most of other human bacteria, *H. pylori* is mainly acquired during childhood and persists for the whole life of the colonized individual if not treated efficiently[3]. From bacteriologic point of view, *H. pylori* is a rod-shaped, microaerophilic Gram-negative organism which colonizing more than half of the world population[4]. Bacterial colonization induces acute inflammation in the gastric mucosa, a clinical manifestation which can be followed by diverse gastroduodenal disorders, but noted that only a minority of infected individuals develop severe diseases include duodenal ulcer and gastric cancer[4-8]. Many virulence-associated genes of *H. pylori*, including outer inflammatory protein a (*OipA*), vacuolating cytotoxin gene a (*vacA*), cytotoxin-associated gene a (*cagA*) and blood-group antigen-binding adhesion (*babA2*) are believed to have a critical role in determining the final clinical manifestation of the infection[9,10]. Therefore, various studies have conducted to discover better insights into the role of these proposed virulence factors in pathogenesis of digestive diseases[11-14]. None of the mentioned virulence factors have distinguished as discriminating factor in the development of peptic ulcer disease and gastric cancer. The main rationale for different diseases outcome observed among colonized individuals is still under debate, though scientists proposed different array of virulence biomarkers in this bacterium as regular answer to this question. In this paper, we aim to open a new window for defining a better description of a specific *H. pylori* virulence factor duodenal ulcer promoting gene a (*dupA*) based on current available knowledge.

VIRULENCE OF *H. PYLORI*

The definition of a virulence factor is referring to the ability of a bacterium to induce and develop a disease with a spectrum of severity[15]. Strains possessing these virulence factors are isolated more frequently from patients with the more serious clinical manifestations. It is logic to consider that for increase the chance of survival within harsh gastric condition *H. pylori* needs such smart strategies to keep the colonization. However, virulence factors can induce more cell damage with infiltrate immune cells to the location and thus inflammation will be the high priority event in epithelial cells[3]. Due to the chronic characteristic of *H. pylori* infection, scientists should expect to have particular definition of virulence factors for this bacterium. Virulence factors of *H. pylori* play an inevitable role in the development of gastroduodenal diseases through mucosal inflammation[10]. Basically, the criteria for being a virulence factor are (1) biologic rationale; (2) epidemiologic consistency; and (3) enough evidences for being linked with certain disease[15,16]. In order to define a virulence factor for each bacterium, it should pass many *in vivo* and *in vitro* experiments[17-20]. However, it is worthwhile to emphasize that only a limited number of proposed virulence factors had been successfully confirmed for *H. pylori*[17-19]. It had been well-documented that all *H. pylori* strains have several virulence factors such as flagella and urease enzyme since they have a critical role in bacterial colonization[4]. Urease enzyme (as cytoplasmic protein) is necessary to establish primary bacterial colonization in the gastric mucosa. *H. pylori* flagella provide sufficient ability to quickly penetrate the gastric mucosa layer to avoid exposure with harsh acid condition in the stomach[4]. In addition, some adhesines such as *babA2*, *iceA1* and Sialic acid-binding adhesin (*sabA*) are mostly present in *H. pylori* strains, and these factors help the bacterium to attach properly to the epithelial cells and serve as a unique virulence factor[9,21]. Clinically, gastric cancer and duodenal ulcer are standing in quite opposite sides of *H. pylori*-related disease spectrum. It brings a big query in the mind about disease plausibility which only can be explained with existence of diverse, but, specific virulence factors in this microorganism.

cagA

cagA is located at the end of the cag pathogenicity island (PAI), which is a 39-kb region transferred horizontally from an unknown bacterial source. The "pathogenicity islands" include *cagA* encode proteins contributing in signal transduction cascades that result in cytoskeletal rearrangement *via* actin polymerization and host cell protein phosphorylation[4]. Virulent strains of *H. pylori* possess the *cagPAI*. Many of *H. pylori* strains from patients with peptic ulcer or gastric cancer carry *cagA*, whereas many of those strains from asymptomatically infected persons lack this gene[4]. Currently, we identify two major types of *H. pylori* isolates: *cagA* gene-negative and *cagA* gene-positive strains. Counting a virulence factor for *cagA* needs another classification which is based on polymorphism in Glu-Pro-Ile-Tyr-Ala (EPIYA) motifs[4]. In *cagA* positive strains, there is a region contains the EPIYA motifs, which contains a tyrosine phosphorylation site[4]. Brief-

ly, two major types (Western and Eastern *cagA*) were determined according to this polymorphism. Though, we need more biologic rationale to be consistent with clinical evidences to present better information on how to interoperate this classic virulence factor in *H. pylori*.

vacA

To now, *vacA* is the second most extensively investigated virulence factor of *H. pylori*. Virtually all *H. pylori* strains have a functional *vacA* gene which codes for the secreted pore-forming protein *vacA*[22]. The main difference in bacteria carrying *vacA* is expression levels and disease severity which are associated with sequence variation in different domains of secreted protein[4]. There is a big gap on our knowledge regarding biologic function of this protein since still many contradictory findings are exist[23-26]. So we need more investigation to determine how to count on *vacA* as useful *H. pylori* virulence factor.

dupA

As first time, in 2005, it has been described that a new virulence factor which was located in the plasticity region of the *H. pylori* genome. PR or "plasticity region" where composed the dupA, has a relatively high rate of allelic diversity in *H. pylori* genomic DNA[27,28]. Whole genome analysis of J99 and 26695 revealed regions where G + C content was lower than rest of the *H. pylori* genome (34% against 40%)[29]. Later, since high variability was observed in this region, it termed as "plasticity region". Currently, we know that more than 60% of strain-specific genes of H. pylori are located in this area. In J99 and 26695 strains, two regions with lower G + C content and 45 kb and 69 kb long has been named as plasticity zones[30]. More than 50% of strain specific open reading frames (ORFs) are located in plasticity zone which are 46% and 48% unique genes from 26695 and J99, respectively. Interestingly, in comparison with 26695, the strain J99 has 33 more ORF in plasticity region (*jhp914-jhp951*)[30]. Lu *et al*[31] investigated this region and reported a continuous gene covering *jhp0917* and *jhp0918* genes for first time which is a risk factor for duodenal ulcer diseases. Accordingly, they named the *jhp0917-jhp0918* gene the dupA gene. To date, many of putative *H. pylori* genes have been suggested to be linked with increasing risk of digestive diseases, while none have been confirmed to be actually associated with unique and specific *H. pylori*-related disease such as gastric cancer or duodenal ulcer. Therefore, *dupA* can be named as first candidate to have achieved this distinction. Following the primary study by Lu *et al*[31], a large number of controversial examinations has been published[32-42]. The global prevalence of *dupA* in patients with gastritis was reported around 45% which is highly differed among subjects with various nationality (31% in Asian and 64% in Western countries)[43,44]. Therefore, among most of Asian countries, a significant association between disease development and *dupA* status can be reported[38,45-54]. In two studies, first by Imagawa *et al*[37] patients infected with *dupA*-positive strains showed higher risk to suffer from duodenal ulcer than *dupA*-negative patients. In second study, we have found that higher acid resistance of the *dupA*-positive strains can explain the adaptation of those strains to human stomach with high gastric acid output[35]. Indeed, Lu *et al*[31] described that infections with *H. pylori dupA*-negative strains can increase the risk for duodenal ulcer, but it reduce the chance of occurrence for gastric[31]. Antral induction of IL-8 production is a main character of *dupA* pathogenesis causing predominant gastritis[46]. The mentioned mucosal inflammation and polymorphonuclear leukocytes (PMN) infiltration can lead to the occurrence of duodenal ulcer[31]. In a systematic review by Shiota *et al*[55] with more than 2466 patients, they confirmed an association between certain clinical outcomes and the *dupA* status. Moreover, presence of an extra 600 bp in *dupA* ORF in *H. pylori* strains such as g27 showed that the length of the *dupA* is differ among various strain, mostly declared that *dupA* has two main genotypes accordingly, (long and short type)[35,38,55]. Unfortunately, most of studies in past did not consider this two types of *dupA* and thus the final results by them might be cautiously useful. Another interesting topics about *dupA* is existence of several mutations in gene length[38,56]. At different positions, these mutations can create a premature stop codon with considerable effects on its produced proteins function[56]. Strains isolated from patients with duodenal ulcer mostly carrying *dupA* without stop codon in comparison with other diseases types[27]. Notwithstanding, without frameshift mutation *dupA* which called intact long-type *dupA* rather short-type *dupA* is highly associated with gastric cancer[57]. It has been extensively reported that there is an association between increased expression levels of IL-8 and *dupA* in the gastric mucosa of *H. pylori*-colonized individuals. As expected, many reports are indicating on gastric mucosal inflammatory cell infiltration was significantly higher in patients with *dupA*-positive *H. pylori* than in patients with *dupA*-negative strain[56,57]. As such, current data suggesting that only intact long type *dupA* can produce DupA protein and also serve as real virulence factor for *H. pylori* strains. In brief, current knowledge about *dupA* positive strain and its subsequent diseases vulnerability insist on significant associations between the *dupA* gene and an increased risk for duodenal ulceration rather gastric cancer. As final remarks about *dupA*, we can mention to these sentences as follow: (1) Additional tests of the *dupA* DNA sequence are necessary to determine actual importance of intact *dupA*; also in level of proteins with immunoblotting techniques; (2) Similar to the *cagA*, it has been asserted that *dupA* is forming a Type 4 secretion system (T4SS) as a full gene cluster. Noted that *virB4* and *dupA* as homologous genes together

are the major constituents of T4SS where located in plasticity region[52]; (3) Jung *et al*[38] recently examined South American population from Colombia to see association between *dupA* and *virB* gene homologs and clinical outcomes. In total, we concluded that intact *dupA* without shift mutation can serve as actual virulence factor with consistent results worldwide. It is no doubt that evaluation of various genes located in plasticity region are required and new data in close future can enrich our knowledge about this mysterious region of *H. pylori* genome; and (4) Broadly defined, virulence of *H. pylori* play an essential role in the development of severe gastroduodenal diseases such as duodenal ulcer through mucosal inflammation. With this regard, *dupA* as one of important risk factor was in focus of many researches in last years. The discrepancy observed among the epidemiologic studies can be explained by using various methods to determine existence of *dupA*, variation in ORF and different population's bias. Thus, despite advances in our understanding of the development of *H. pylori*-related diseases, further work is required to clarify the roles of *H. pylori* virulence factors.

CONCLUSION

H. pylori plays a critical role in the development of severe digestive diseases; though, the main virulence determinant acting in this field are still not completely defined. Now the question is to find the determining item to represent this interesting disease pattern. For sure, we admitted that *H. pylori* is involved in pathogenesis of both gastric cancer and duodenal ulcer while they are in quite opposite side of digestive diseases, again, how we can still accept a crucial role for *H. pylori* in these gastroduodenal diseases? Many studies had been performed to elucidate actual biologic role of *dupA* in development of severe gastroduodenal diseases such as gastric cancer[46-48]. The observed discrepancy of *dupA* link with disease outcomes might be associate with the plasticity region of *H. pylori* or the limitation of PCR to detect the various forms of *dupA* gene; however, in order to draw a better conclusion further experiments are required[58,59]. Interestingly, the presence of *dupA* was significantly associated with *H. pylori* eradication failure with no biologic explanation[60-62]. In conclusion, it sounds that rather than promoting gastric cancer or duodenal ulceration in all populations, dupA is an effective factor for some of populations. Because of microarray analysis as new technology many new genes can be proposed as novel virulence biomarker for *H. pylori*.

REFERENCES

1 **Marshall BJ**, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; **1**: 1311-1315 [PMID: 6145023]

2 **Mégraud F**. A humble bacterium sweeps this year's Nobel Prize. *Cell* 2005; **123**: 975-976 [PMID: 16360024 DOI: 10.1016/j.cell.2005.11.032]

3 **Abadi AT**, Kusters JG. Management of Helicobacter pylori infections. *BMC Gastroenterol* 2016; **16**: 94 [PMID: 27520775 DOI: 10.1186/s12876-016-0496-2]

4 **Yamaoka Y**. Mechanisms of disease: Helicobacter pylori virulence factors. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 629-641 [PMID: 20938460 DOI: 10.1038/nrgastro.2010.154]

5 **Talebi Bezmin Abadi A**. Therapy of Helicobacter pylori: present medley and future prospective. *Biomed Res Int* 2014; **2014**: 124607 [PMID: 24800203 DOI: 10.1155/2014/124607]

6 **Karlsson A**, Ryberg A, Nosouhi Dehnoei M, Borch K, Monstein HJ. Variation in number of cagA EPIYA-C phosphorylation motifs between cultured Helicobacter pylori and biopsy strain DNA. *Infect Genet Evol* 2012; **12**: 175-179 [PMID: 22085823 DOI: 10.1016/j.meegid.2011.10.025]

7 **Talebi Bezmin Abadi A**. Vaccine against Helicobacter pylori: Inevitable approach. *World J Gastroenterol* 2016; **22**: 3150-3157 [PMID: 27003991 DOI: 10.3748/wjg.v22.i11.3150]

8 **Talebi Bezmin Abadi A**. Helicobacter pylori and Gastric Cancer. *Front Med* (Lausanne) 2016; **3**: 36 [PMID: 27597945 DOI: 10.3389/fmed.2016.00036]

9 **Talebi Bezmin Abadi A**, Taghvaei T, Mohabbati Mobarez A, Vaira G, Vaira D. High correlation of babA 2-positive strains of Helicobacter pylori with the presence of gastric cancer. *Intern Emerg Med* 2013; **8**: 497-501 [PMID: 21604199 DOI: 10.1007/s11739-011-0631-6]

10 **Yamaoka Y**, Kikuchi S, el-Zimaity HM, Gutierrez O, Osato MS, Graham DY. Importance of Helicobacter pylori oipA in clinical presentation, gastric inflammation, and mucosal interleukin 8 production. *Gastroenterology* 2002; **123**: 414-424 [PMID: 12145793]

11 **Abadi AT**, Lee YY. Helicobacter pylori vacA as marker for gastric cancer and gastroduodenal diseases: one but not the only factor. *J Clin Microbiol* 2014; **52**: 4451 [PMID: 25399000 DOI: 10.1128/JCM.02640-14]

12 **Kolaylı F**, Karadenizli A, Bingöl R, Schneider T, Kist M. [Differences of vacA alleles and cagA gene positivity of Helicobacter pylori strains isolated from two different countries: Turkey and Germany]. *Mikrobiyol Bul* 2012; **46**: 332-334 [PMID: 22639323]

13 **Talebi Bezmin Abadi A**, Ierardi E, Lee J. Why do we still have Helicobacter pylori in our Stomachs? *Malays J Med Sci* 2015; **22**: 70-75

14 **Abdullah SM**, Hussein NR, Salih AM, Merza MA, Goreal AA, Odeesh OY, Majed HS, Assafi MA, Hawrami K. Infection with Helicobacter pylori strains carrying babA2 and cagA is associated with an increased risk of peptic ulcer disease development in Iraq. *Arab J Gastroenterol* 2012; **13**: 166-169 [PMID: 23432983 DOI: 10.1016/j.ajg.2012.12.001]

15 **Graham DY**, Yamaoka Y. Disease-specific Helicobacter pylori virulence factors: the unfulfilled promise. *Helicobacter* 2000; **5** Suppl 1: S3-S9; discussion S27-S31 [PMID: 10828748]

16 **Graham DY**. Helicobacter pylori infection in the pathogenesis of duodenal ulcer and gastric cancer: a model. *Gastroenterology* 1997; **113**: 1983-1991 [PMID: 9394739]

17 **Yamaoka Y**. Pathogenesis of Helicobacter pylori-Related Gastroduodenal Diseases from Molecular Epidemiological Studies. *Gastroenterol Res Pract* 2012; **2012**: 371503 [PMID: 22829807 DOI: 10.1155/2012/371503]

18 **Taghvaei T**, Talebi Bezmin Abadi A, Ghasemzadeh A, Naderi BK, Mohabbati Mobarez A. Prevalence of horB gene among the Helicobacter pylori strains isolated from dyspeptic patients: first report from Iran. *Intern Emerg Med* 2012; **7**: 505-508 [PMID: 21559747 DOI: 10.1007/s11739-011-0614-7]

19 **Abadi AT**, Mobarez AM, Bonten MJ, Wagenaar JA, Kusters JG. Clinical relevance of the cagA, tnpA and tnpB genes in Helicobacter pylori. *BMC Gastroenterol* 2014; **14**: 33 [PMID: 24552154 DOI: 10.1186/1471-230X-14-33]

20 **Shafiee A**, Amini M, Emamirad H, Talebi Bezmin Abadi A. Recombination and phenotype evolution dynamic of Helicobacter pylori in colonized hosts. *Int J Syst Evol Microbiol* 2016; Epub ahead of print [PMID: 27082852 DOI: 10.1099/ijsem.0.001072]

21 **Ishijima N**, Suzuki M, Ashida H, Ichikawa Y, Kanegae Y, Saito I, Borén T, Haas R, Sasakawa C, Mimuro H. BabA-mediated adherence is a potentiator of the Helicobacter pylori type IV secretion system activity. *J Biol Chem* 2011; **286**: 25256-25264 [PMID: 21596743 DOI: 10.1074/jbc.M111.233601]

22 **Figura N**, Valassina M, Moretti E, Vindigni C, Collodel G, Iacoponi F, Giordano N, Roviello F, Marrelli D. Histological variety of gastric carcinoma and Helicobacter pylori cagA and vacA polymorphism. *Eur J Gastroenterol Hepatol* 2015; **27**: 1017-1021 [PMID: 26067222 DOI: 10.1097/MEG.0000000000000414]

23 **Yahiro K**, Hirayama T, Moss J, Noda M. Helicobacter pylori VacA toxin causes cell death by inducing accumulation of cytoplasmic connexin 43. *Cell Death Dis* 2015; **6**: e1971 [PMID: 26561781 DOI: 10.1038/cddis.2015.329]

24 **Yahiro K**, Akazawa Y, Nakano M, Suzuki H, Hisatune J, Isomoto H, Sap J, Noda M, Moss J, Hirayama T. *Helicobacter pylori* VacA induces apoptosis by accumulation of connexin 43 in autophagic vesicles via a Rac1/ERK-dependent pathway. *Cell Death Discov* 2015; **1**: 15035 [PMID: 27551466 DOI: 10.1038/cddiscovery.2015.35]

25 **Feliciano O**, Gutierrez O, Valdés L, Fragoso T, Calderin AM, Valdes AE, Llanes R. Prevalence of Helicobacter pylori vacA, cagA, and iceA Genotypes in Cuban Patients with Upper Gastrointestinal Diseases. *Biomed Res Int* 2015; **2015**: 753710 [PMID: 25945344 DOI: 10.1155/2015/753710]

26 **Abadi AT**, Mobarez AM, Teymournejad O, Karbalaei M. Concomitant Colonization of Helicobacter pylori in Dental Plaque and Gastric Biopsy. *J Pathog* 2014; **2014**: 871601 [PMID: 25120932 DOI: 10.1155/2014/871601]

27 **Talebi Bezmin Abadi A**. The Helicobacter pylori dupA: A Novel Biomarker for Digestive Diseases. *Front Med* (Lausanne) 2014; **1**: 13 [PMID: 25767798 DOI: 10.3389/fmed.2014.00013]

28 **Shiota S**, Suzuki R, Yamaoka Y. The significance of virulence factors in Helicobacter pylori. *J Dig Dis* 2013; **14**: 341-349 [PMID: 23452293 DOI: 10.1111/1751-2980.12054]

29 **Alm RA**, Ling LS, Moir DT, King BL, Brown ED, Doig PC, Smith DR, Noonan B, Guild BC, deJonge BL, Carmel G, Tummino PJ, Caruso A, Uria-Nickelsen M, Mills DM, Ives C, Gibson R, Merberg D, Mills SD, Jiang Q, Taylor DE, Vovis GF, Trust TJ. Genomic-sequence comparison of two unrelated isolates of the human gastric pathogen Helicobacter pylori. *Nature* 1999; **397**: 176-180 [PMID: 9923682 DOI: 10.1038/16495]

30 **Alm RA**, Trust TJ. Analysis of the genetic diversity of Helicobacter pylori: the tale of two genomes. *J Mol Med* (Berl) 1999; **77**: 834-846 [PMID: 10682319]

31 **Lu H**, Hsu PI, Graham DY, Yamaoka Y. Duodenal ulcer promoting gene of Helicobacter pylori. *Gastroenterology* 2005; **128**: 833-848 [PMID: 15825067]

32 **Kavermann H**, Burns BP, Angermuller K, Odenbreit S, Fischer W, Melchers K, Haas R. Identification and characterization of Helicobacter pylori genes essential for gastric colonization. *J Exp Med* 2003; **197**: 813-822 [PMID: 12668646 DOI: 10.1084/jem.20021531]

33 **Alam J**, Maiti S, Ghosh P, De R, Chowdhury A, Das S, Macaden R, Devarbhavi H, Ramamurthy T, Mukhopadhyay AK. Significant association of the dupA gene of Helicobacter pylori with duodenal ulcer development in a South-east Indian population. *J Med Microbiol* 2012; **61**: 1295-1302 [PMID: 22653921 DOI: 10.1099/jmm.0.038398-0]

34 **Gomes LI**, Rocha GA, Rocha AM, Soares TF, Oliveira CA, Bittencourt PF, Queiroz DM. Lack of association between Helicobacter pylori infection with dupA-positive strains and gastroduodenal diseases in Brazilian patients. *Int J Med Microbiol* 2008; **298**: 223-230 [PMID: 17897881 DOI: 10.1016/j.ijmm.2007.05.006]

35 **Abadi AT**, Taghvaei T, Wolfram L, Kusters JG. Infection with Helicobacter pylori strains lacking dupA is associated with an increased risk of gastric ulcer and gastric cancer development. *J Med Microbiol* 2012; **61**: 23-30 [PMID: 21903829 DOI: 10.1099/jmm.0.027052-0]

36 **Hussein NR**, Tuncel IE. Helicobacter pylori dupA and smoking are associated with increased levels of interleukin-8 in gastric mucosa in Iraq. *Hum Pathol* 2015; **46**: 929-930 [PMID: 25791584]

37 **Imagawa S**, Ito M, Yoshihara M, Eguchi H, Tanaka S, Chayama K. Helicobacter pylori dupA and gastric acid secretion are negatively associated with gastric cancer development. *J Med Microbiol* 2010; **59**: 1484-1489 [PMID: 20829397 DOI: 10.1099/jmm.0.021816-0]

38 **Jung SW**, Sugimoto M, Shiota S, Graham DY, Yamaoka Y. The intact dupA cluster is a more reliable Helicobacter pylori virulence marker than dupA alone. *Infect Immun* 2012; **80**: 381-387 [PMID: 22038914 DOI: 10.1128/IAI.05472-11]

39 **Nguyen LT**, Uchida T, Tsukamoto Y, Kuroda A, Okimoto T, Kodama M, Murakami K, Fujioka T, Moriyama M. Helicobacter pylori dupA gene is not associated with clinical outcomes in the Japanese population. *Clin Microbiol Infect* 2010; **16**: 1264-1269 [PMID: 19832706 DOI: 10.1111/j.1469-0691.2009.03081.x]

40 **Salih AM**, Goreal A, Hussein NR, Abdullah SM, Hawrami K, Assafi M. The distribution of cagA and dupA genes in Helicobacter pylori strains in Kurdistan region, northern Iraq. *Ann Saudi Med* 2013; **33**: 290-293 [PMID: 23793434 DOI: 10.5144/0256-4947.2013.290]

41 **Wang MY**, Shao C, Li J, Yang YC, Wang SB, Hao JL, Wu CM, Gao XZ, Shao SH. Helicobacter pylori with the Intact dupA Cluster is more Virulent than the Strains with the Incomplete dupA Cluster. *Curr Microbiol* 2015; **71**: 16-23 [PMID: 25847580 DOI: 10.1007/s00284-015-0812-z]

42 **Zhang Z**, Zheng Q, Chen X, Xiao S, Liu W, Lu H. The Helicobacter pylori duodenal ulcer promoting gene, dupA in China. *BMC Gastroenterol* 2008; **8**: 49 [PMID: 18950522 DOI: 10.1186/1471-230X-8-49]

43 **Hussein NR**. The association of dupA and Helicobacter pylori-related gastroduodenal diseases. *Eur J Clin Microbiol Infect Dis* 2010; **29**: 817-821 [PMID: 20419465 DOI: 10.1007/s10096-010-0933-z]

44 **Hussein NR**, Mohammadi M, Talebkhan Y, Doraghi M, Letley DP, Muhammad MK, Argent RH, Atherton JC. Differences in virulence markers between Helicobacter pylori strains from Iraq and those from Iran: potential importance of regional differences in H. pylori-associated disease. *J Clin Microbiol* 2008; **46**: 1774-1779 [PMID: 18353934 DOI: 10.1128/JCM.01737-07]

45 **Arachchi HS**, Kalra V, Lal B, Bhatia V, Baba CS, Chakravarthy S, Rohatgi S, Sarma PM, Mishra V, Das B, Ahuja V. Prevalence of duodenal ulcer-promoting gene (dupA) of Helicobacter pylori in patients with duodenal ulcer in North Indian population. *Helicobacter* 2007; **12**: 591-597 [PMID: 18001398 DOI: 10.1111/j.1523-5378.2007.00557.x]

46 **Argent RH**, Burette A, Miendje Deyi VY, Atherton JC. The presence of dupA in Helicobacter pylori is not significantly associated with duodenal ulceration in Belgium, South Africa, China, or North America. *Clin Infect Dis* 2007; **45**: 1204-1206 [PMID: 17918084 DOI: 10.1086/522177]

47 **Douraghi M**, Mohammadi M, Oghalaie A, Abdirad A, Mohagheghi MA, Hosseini ME, Zeraati H, Ghasemi A, Esmaieli M, Mohajerani N. dupA as a risk determinant in Helicobacter pylori infection. *J Med Microbiol* 2008; **57**: 554-562 [PMID: 18436587 DOI: 10.1099/jmm.0.47776-0]

48 **Haddadi MH**, Bazargani A, Khashei R, Fattahi MR, Bagheri Lankarani K, Moini M, Rokni Hosseini SM. Different distribution of Helicobacter pylori EPIYA- cagA motifs and dupA genes in the upper gastrointestinal diseases and correlation with clinical outcomes in iranian patients. *Gastroenterol Hepatol Bed Bench* 2015; **8**: S37-S46 [PMID: 26171136]

49 **Matteo MJ**, Armitano RI, Granados G, Wonaga AD, Sánches C, Olmos M, Catalano M. Helicobacter pylori oipA, vacA and dupA genetic diversity in individual hosts. *J Med Microbiol* 2010; **59**: 89-95 [PMID: 19643933 DOI: 10.1099/jmm.0.011684-0]

50 **Parzecka M**, Szaflarska-Popławska A, Gasiorowska J, Gorzkiewicz M, Grzybowski T. [The prevalence of dupA (duodenal ulcer-promoting gene) of Helicobacter pylori in children and adolescents--own observation]. *Pol Merkur Lekarski* 2013; **34**: 277-280 [PMID: 23894779]

51 **Queiroz DM**, Moura SB, Rocha AM, Costa RF, Anacleto C, Rocha GA. The genotype of the Brazilian dupA-positive Helicobacter pylori strains is dupA1. *J Infect Dis* 2011; **203**: 1033-1034 [PMID: 21402555 DOI: 10.1093/infdis/jiq147]

52 **Wang MY**, Chen C, Shao C, Wang SB, Wang AC, Yang YC, Yuan XY, Shao SH. Intact long-type DupA protein in Helicobacter pylori is an ATPase involved in multifunctional biological activities. *Microb Pathog* 2015; **81**: 53-59 [PMID: 25745877 DOI: 10.1016/j.micpath.2015.03.002]

53 **Osman HA**, Hasan H, Suppian R, Hassan S, Andee DZ, Abdul Majid N, Zilfalil BA. Prevalence of Helicobacter pylori cagA, babA2, and dupA genotypes and correlation with clinical outcome in Malaysian patients with dyspepsia. *Turk J Med Sci* 2015; **45**: 940-946 [PMID: 26422871]

54 **Miftahussurur M**, Syam AF, Makmun D, Nusi IA, Zein LH, Zulkhairi F, Uswan WB, Simanjuntak D, Uchida T, Adi P, Utari AP, Rezkitha YA, Subsomwong P, Nasronudin Y. Helicobacter pylori virulence genes in the five largest islands of Indonesia. *Gut Pathog* 2015; **7**: 26 [PMID: 26442711 DOI: 10.1186/s13099-015-0072-2]

55 **Shiota S**, Matsunari O, Watada M, Hanada K, Yamaoka Y. Systematic review and meta-analysis: the relationship between the Helicobacter pylori dupA gene and clinical outcomes. *Gut Pathog* 2010; **2**: 13 [PMID: 21040520 DOI: 10.1186/1757-4749-2-13]

56 **Queiroz DM**, Rocha GA, Rocha AM, Moura SB, Saraiva IE, Gomes LI, Soares TF, Melo FF, Cabral MM, Oliveira CA. dupA polymorphisms and risk of Helicobacter pylori-associated diseases. *Int J Med Microbiol* 2011; **301**: 225-228 [PMID: 21050811 DOI: 10.1016/j.ijmm.2010.08.019]

57 **Takahashi A**, Shiota S, Matsunari O, Watada M, Suzuki R, Nakachi S, Kinjo N, Kinjo F, Yamaoka Y. Intact long-type dupA as a marker for gastroduodenal diseases in Okinawan subpopulation, Japan. *Helicobacter* 2013; **18**: 66-72 [PMID: 23067336 DOI: 10.1111/j.1523-5378.2012.00994.x]

58 **Abadi AT**, Loffeld RJ, Constancia AC, Wagenaar JA, Kusters JG. Detection of the Helicobacter pylori dupA gene is strongly affected by the PCR design. *J Microbiol Methods* 2014; **106**: 55-56 [PMID: 25128081 DOI: 10.1016/j.mimet.2014.07.027]

59 **Alam J**, Ghosh P, Ganguly M, Sarkar A, De R, Mukhopadhyay AK. Association of Intact dupA (dupA1) rather than dupA1 cluster with duodenal ulcer in Indian population. *Gut Pathog* 2015; **7**: 9 [PMID: 25829953 DOI: 10.1186/s13099-015-0056-2]

60 **Shiota S**, Nguyen LT, Murakami K, Kuroda A, Mizukami K, Okimoto T, Kodama M, Fujioka T, Yamaoka Y. Association of helicobacter pylori dupA with the failure of primary eradication. *J Clin Gastroenterol* 2012; **46**: 297-301 [PMID: 22298090 DOI: 10.1097/MCG.0b013e318243201c]

61 **Senatore FJ**, Wilmot J, Birk JW. Helicobacter pylori treatment: Still a work in progress. *Postgrad Med* 2016; **128**: 152-157 [PMID: 26490697 DOI: 10.1080/00325481.2016.1103194]

62 **Hussein NR**, Tunjel I, Majed HS, Yousif ST, Aswad SI, Assafi MS. Duodenal ulcer promoting gene 1 (dupA1) is associated with A2147G clarithromycin-resistance mutation but not interleukin-8 secretion from gastric mucosa in Iraqi patients. *New Microbes New Infect* 2015; **6**: 5-10 [PMID: 26042186 DOI: 10.1016/j.nmni.2015.02.005]

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