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TOPIC HIGHLIGHT

2015 Advances in *Helicobacter pylori*

What exists beyond *cag*A and *vac*A? *Helicobacter pylori* genes in gastric diseases

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Abstract

Helicobacter pylori (*H. pylori*) infection is present in more than half the world's population and has been associated with several gastric disorders, such as gastritis, peptic ulceration, and gastric adenocarcinoma. The clinical outcome of this infection depends on host and bacterial factors where *H. pylori* virulence genes seem to play a relevant role. Studies of *cag*A and *vac*A genes established that they were determining factors in gastric pathogenesis. However, there are gastric cancer cases that are *cag*A-negative. Several other virulence genes have been searched for, but these genes remain less well known that *cag*A and *vac*A. Thus, this review aimed to establish which genes have been suggested as potentially relevant virulence factors for *H. pylori*-associated gastrointestinal diseases. We focused on the *cag*-pathogenicity island, genes with adherence and motility functions, and *ice*A based on the relevance shown in several studies in the literature.

Key words: *Helicobacter pylori*; Virulence genes; Cag-pathogenicity island; Motility genes; Adhesion genes

Core tip: *Helicobacter pylori* (*H. pylori*) infection is present in more than half the world's population and has been associated with several gastric disorders. The clinical outcome of this infection depends on host and bacterial factors. Studies have established that *cag*A and *vac*A *H. pylori* genes are determining factors in gastric pathogenesis. This review aimed to examine which genes have been suggested as potentially relevant virulence factors for *H. pylori*, focusing on the *cag*-pathogenicity island, adherence and motility genes, and *ice*A based on the relevance shown in several studies.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a spiral shaped Gram-negative bacterium that selectively colonizes the gastric mucous layer by adhering to the epithelial lining of the stomach. It is a urease-, catalase-, and oxidase-positive bacterium that possesses 4 to 6 polar flagella for motility, and several virulence factors which vary with the strain[1,2]. *H. pylori* was isolated for the first time in 1983 by Warren and Marshall from gastric biopsy samples of patients with chronic gastritis and peptic ulcer. However, the finding of spiral bacteria in the stomach of animals dates back to 1906[3,4].

Evidence suggests that the relationship between *H. pylori* and its human host has existed for at least 60000 years. One piece of evidence is that the genetic diversity of bacteria evolved in parallel with the human species, showing that both have been evolving intimately ever since. Furthermore, the genetic diversity distribution of *H. pylori* is consistent with the colonization of the earliest humans and with co-migration out of East Africa[5]. In 1994, the World Health Organization recognized this bacteria as a type Ⅰ (definite) carcinogen in humans, based on evidence that *H. pylori* is involved in the development of gastric adenocarcinoma[6]. *H. pylori* infection is present in more than half the world's population. However, not all infected people exhibit diseases associated with this bacterium. It is the main cause of gastric disorders, such as gastritis in about 20%, peptic ulceration in 10%, gastric adenocarcinoma in 1%-2%, and gastric MALT lymphoma in less than 0.1% of the people infected[7,8].

The clinical outcome of infection by *H. pylori* depends on the presence of bacterial virulence factors and on factors related to the host. Several virulence genes have been well studied and established in the literature as determining factors in gastric pathogenesis, such as *cag*A (cytotoxin-associated gene A) and *vac*A (vacuolating cytotoxin A) genes. Several other genes, although previously studied, remain less well recognized than *cag*A and *vac*A. Thus, the objective of this review is to discuss current knowledge of *H. pylori* virulence factors that highlight other genes in the *cag*-pathogenicity island (*cag*-PAI), genes that code outer membrane proteins (*bab*A, *oip*A, *sab*A, *hop*Q), motility genes (*fla*A and *fla*B), and *ice*A, which have been identified in the literature as potentially relevant in the development of more severe lesions.

WELL-ESTABLISHED VIRULENCE FACTORS

The *cag*A and *vac*A genes are both well established and extensively studied as *H. pylori* virulence factors. Whereas not all *H. pylori* strains possess the *cag*A gene, essentially, all strains possess the *vac*A gene. However, not all secrete a VacA product, which depends on the gene structure.

The *cag*A gene is a recognized marker for the presence of *cag*-PAI. This gene encodes a 121-145 kDa immuno-dominant protein (CagA) that, when injected into the gastric epithelial cell cytoplasm, interacts with host cell proteins, inducing cell morphological changes (hummingbird phenotype), and pro-inflammatory and mitogenic responses. Several studies in cell culture and animal models indicate the importance of *cag*A gene involvement in human gastric cancer, and that its deletion prevents the development of the disease in a gerbil model[9-11]. Most of the *H. pylori* strains in East Asia have the *cag*A gene, regardless of the disease. Thus, the pathogenic difference in this region is difficult to explain in terms of the presence or absence of the *cag*A gene alone[12].

The CagA protein contains tyrosine phosphorylation motifs (glutamate-proline-isoleucinetyrosine-alanine, EPIYA) within the carboxyl-terminal variable region of the protein. Studies show the existence of four EPIYA motifs (A, B, C, D). EPIYA-A and EPIYA-B are present throughout the world, EPIYA-C is predominantly found in strains from Western countries, and EPIYA-D is found almost exclusively in East-Asian strains (Japan, South Korea, and China). *H. pylori* strains containing EPIYA-D motifs induce significantly higher levels of interleukin-8 release from gastric epithelial cells compared with strains containing the A-B-C-type of CagA[13,14].

The *vac*A gene is not part of the *cag*-PAI. It induces vacuolization and various cellular activities such as the formation of membrane channels, the release of cytochrome *c* from mitochondria leading to apoptosis, and binding to cell membrane receptors, followed by a pro-inflammatory response[15,16]. However, considerable differences in vacuolating activities are observed between strains according to variations in the *vac*A gene structure within the signal (s), middle (m), and intermediate (i) regions[17]. The "s" and "m" regions are stratified into s1 or s2, and m1 or m2 subtypes, and the possible combinations generate proteins with different cytotoxicity. *In vitro* experiments showed that *vac*A s1/m1 strains induce greater vacuolation than s1/m2 strains, and there is typically no vacuolating activity in s2/m2 strains[17].

In agreement with *in vitro* data, studies in the Middle East, Africa, and Western countries have shown that individuals infected with *vac*A s1 or m1 *H. pylori* strains have an increased risk of peptic ulcer or gastric cancer compared with individuals infected with s2 or m2 strains[18,19]. On the other hand, in East Asia, as most strains are *vac*A s1, the differences in pathogenesis cannot be explained by the type of "s" region[20]. In turn, the "m" region in East Asia shows variations suggesting that it may play a role in the

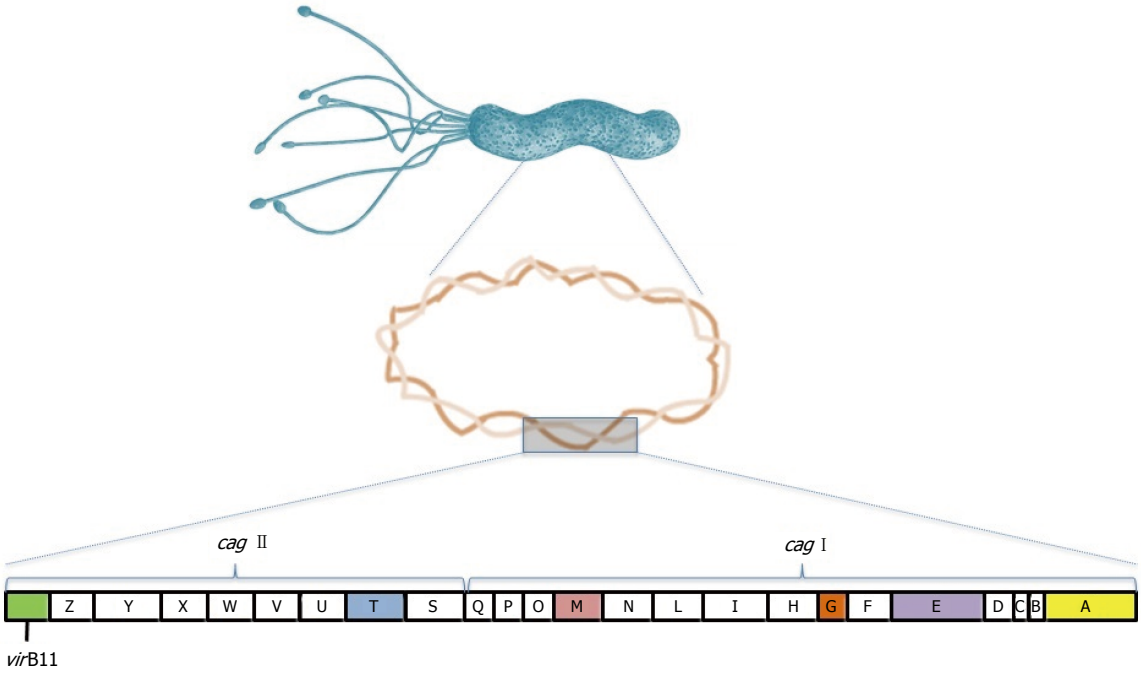

Figure 1 Schematic representation of the *cag*-pathogenicity island of *Helicobacter pylori* deduced from strain 26695. The localizations of *cag* Ⅰ and *cag* Ⅱ are shown. Highlighted squares represent genes cited in this review.

regional difference. In northern East Asia, there is a higher prevalence of strains *vac*A m1 and incidence of gastric cancer, whereas in the south of East Asia, where the strains *vac*A m2 are prevalent, the incidence of cancer is lower than in the northern region[20,21]. A Brazilian study indicated that in the absence of *cag*A, there was a role for *vac*A s1 in the development of gastric cancer, since most of the negative strains had the *vac*A s1 gene[22].

VARIABILITY AND INTEGRITY OF *CAG* PATHOGENICITY ISLAND

cag-PAI is a segment of *H. pylori* DNA of 40 kb containing 31 genes[23]. Most of these genes encode functional components of a type 4 bacterial secretion system (T4SS) used for the translocation of bacterial products directly into the host cell cytoplasm, including the *cag*A gene product[24]. *cag*-PAI is found in about 60% of Western strains, whereas almost all of the East Asian strains isolated are *cag*-PAI positive[25]. The positive *cag*-PAI strains are more related to peptic ulcer and gastric cancer than the negative strains, showing that *cag*-PAI plays an important role in *H. pylori* pathogenesis[26,27].

A phylogeny study showed by sequencing that most *cag*-PAI genes were similar to those of housekeeping genes, indicating that *cag*-PAI was probably acquired only once by *H. pylori.* Thus, *H. pylori* genetic diversity seems to reflect the geographic isolation that has shaped this bacterial species since modern humans migrated out of Africa. Carriage of *cag*-PAI varies from an almost universal presence in the strains hpEastAsia and hpAfrica1, through an intermediate presence (hpEurope) to complete absence (hpAfrica2). When compared with other bacteria of the same genus, the absence of *cag*-PAI seems to be an ancestral trait. Thus, the pathogenicity island would have been acquired by horizontal gene transfer from an unknown source after *H. pylori* had established itself in humans[11].

Initial studies on the integrity of *cag*-PAI analyzed sequences of *cag* Ⅰ and *cag* Ⅱ regions and genes present in these regions separately[28,29]. A study that analyzed *cag*-PAI integrity showed that rearrangement in this island is a prevalent phenomenon, with less rearrangement in the *cag*E and *cag*T genes than in the *cag*A gene. *cag*-PAI was disrupted in the majority of isolated strains throughout the world. Conservation of *cag*-PAI was highest in Japanese isolates and minimal in European and African strains[30]. Infection with a strain containing a complete set of *cag*-PAI genes was associated with the development of ulcer disease, showing the importance of these genes to gastric diseases outcomes[31].

OTHER GENES LOCATED IN *CAG*-PAI

Several Cag proteins have been detected as constituents of *H. pylori cag* T4SS apparatus and have important roles in the translocation of CagA[32]. These include CagE, VirB11, CagT, CagM and CagG, whose importance will be described below (Figure 1).

cagE and virB11

*cag*E is located in the right half of *cag*-PAI, and studies

have suggested that this gene is a more accurate marker of an intact pathogenicity island and can be used as a *cag*-PAI marker with *cag*A[33,34]. *vir*B11 codifies a protein that has a ring-shaped structure composed of 6 monomeric units. These genes code transmembrane proteins with ATPase activity that provides the energy for apparatus assembly and/or substrate transport[24,35].

Although there is a well-established relationship between *cag*E and *vir*B11 genes with gastritis, peptic ulcer, and duodenal ulcer, only a few studies have described an association with gastric cancer[36-38]. Two of these studies showed the presence of such genes in early tumor stages and an association with other virulence genes, indicating that there is a role for *cag*E and *vir*B11 in gastric carcinogenesis[34,39].

cagT

The *cag*T gene is a homologue of *A. tumefaciens* vir B7 and has been reported to be a marker of the *cag* Ⅱ region[40]. Some studies revealed that CagT localized in both inner and outer membranes plays an important role in the induction of the proinflammatory cytokine interleukin-8 when localized in the outer membrane[41-43]. It may also interact with CagA and facilitate its translocation into host cells, acting as a chaperone-like protein localized in the inner membrane[44].

The expression of CagT in *H. pylori* is also closely associated with severe gastric disease[45]. Deletion frequencies of *cag*T genes were higher in benign cases compared with isolates from severe ulcers and gastric cancers[46,47]. Studies reported an association of the *cag*T gene with the development of peptic ulcer disease, suggesting a high virulence gene in *H. pylori*[40,48,49]. The *cag*T gene, as well as the *cag*A gene, have been associated with other virulence factors, such as *vac*A s1, *vac*A m1, and the genotype *vac*A s1m1, occurring in smaller percentages concomitantly with *vac*A s2 strains, *vac*A m2, and *vac*A s2m2[49,50]. Therefore, CagT seems to be a very important protein in *H. pylori*, not only for the integrity of the *cag*-PAI apparatus, but also for determining disease severity.

cagM

The *cag*M gene has been reported to be a marker of the *cag* Ⅰ region[51]. Some studies revealed that the protein encoded by this gene forms a surface structure which acts as a nuclear factor (NF)-κB-inducing agent, mediating interleukin-8 secretion[41,52,53]. It is also involved in the repression of H/K-ATPase transcription, which causes the downregulation of human gastric H/K-ATPase expression, significantly inhibiting acid secretion by gastric cells[54,55]. CagM expression may represent a first line of *H. pylori* defense against gastric acid, which may otherwise be upregulated by the presence of CagM-deficient Gram-negative bacteria.

Expression of CagM in *H. pylori* is also associated with severe gastric disease. Some studies revealed that the *cag*M gene was associated with the development of gastritis, peptic ulcers, and gastric cancer[45,49,56,57]. Thus, CagM is a very important protein, not only for the integrity of the *cag*-PAI apparatus, but also for determining disease severity, and a line of *H. pylori* defense against gastric acid.

cagG

*cag*G is located in the right side of *cag*-PAI, and it has been reported to be a marker of the *cag* Ⅰ region. This gene is not a *vir* homologue, but it has weak homology with the flagellar motor switch protein gene or toxin co-regulated pilus biosynthesis protein gene[23,51,58]. It may also play an important role in the induction of the proinflammatory cytokine interleukin-8[41,52].

Some studies suggest that *cag*G may have a function related to adhesion to gastric epithelial cells. *cagG*-deleted strains adhere less to gastric epithelial cells, and these strains cause a reduction in the amount of interleukin-8 secreted from the cells[59,60]. The frequency of the *cag*G gene has been high in several gastrointestinal diseases, but a specific disease related to it has not been established[51,61].

Given the above, we suggest that the integrity of *cag*-PAI seems to be more relevant than the presence of the gene alone. It is believed that the presence of *cag*A alone is not sufficient for bacterial pathogenicity, but the set of genes which form an efficient T4SS confers pathogenicity.

GENES THAT CODE OUTER MEMBRANE PROTEINS

Approximately 4% of the *H. pylori* genome encodes a diverse repertoire of Outer membrane proteins (OMPs) that have been grouped into 5 major families[62]. The *Helicobacter* outer membrane protein (Hop) family is the largest and includes adhesins such as BabA (HopS), SabA (HopP), OipA (HopH) and HopQ. Adherence of *H. pylori* to the gastric mucosa plays important roles in the initial colonization and long-term persistence on the gastric mucosa, as well as in the intensity of the resulting inflammatory response[63].

babA

Blood group antigen-binding adhesin (*bab*A) is a 78-kDa outer membrane protein encoded by the *babA2* gene, which binds the fucosylated Lewis^b antigen (Le^b) on the surfaces of gastric epithelial cells and is the best described *H. pylori* OMP[64,65]. Although three *bab* alleles have been identified (*bab*A1, *bab*A2, and *bab*B), only the *bab*A2 gene product is functionally active[66]. Analyses of binding characteristics of *H. pylori* strains worldwide suggest that BabA has evolved in response to host mucosal glycosylation patterns to permit *H. pylori* to adapt to its host and to maintain persistent colonization[67].

Some researchers have demonstrated that *bab*A2 is associated with increased risk of duodenal ulcer disease and adenocarcinoma, and when found in conjunction with the *cag*A and *vac*A s1 alleles, leads to an even greater risk of developing more severe diseases[68,69]. BabA binding to Le^b is also important for the induction of DNA double-strand breaks in host cell lines, and may promote cancer-associated gene mutations[70]. Adherence *via* BabA also enhances the ability of the type Ⅳ secretion apparatus to contact host cells, leading to a stronger inflammatory response[71]. Therefore, BabA is important not only for *H. pylori* to adhere to the stomach surface but also to anchor the bacterial secretion system to the host cell surface so that bacterial factors can be effectively injected into the host cell cytosol.

sabA

The sialic acid-binding adhesin, SabA or HopP or OMP17 (about 70 KDa) is the second best characterized adhesin of *H. pylori,* and binds sialyl-Lewis antigens that are expressed on inflamed gastric tissue[64,72]. *H. pylori* modulates the expression of the SabA ligand, the sialyl-dimeric-Le^x, in human gastric cell lines *via* the induction of a specific glycosyltransferase, β3 GlcNAc T5 (β3GnT5), involved in the biosynthesis of Lewis antigens, thereby strengthening the epithelial attachment necessary to achieve successful colonization[73].

The *sab*A gene expression is regulated at transcriptional level by some mechanisms. Indeed, the dinucleotide CT repeats present in the 5′ coding region of *sab*A regulates their expression by phase variation through a slipped strand repair mechanism (SSM)[74,75], and the *sab*A promoter region modulates its transcriptional activity through a variable homopolymeric thymidine tract[76]. The frequent "on/off" switch of SabA expression suggests that SabA expression can rapidly respond to changes exerted by the gastric niche. SabA-positive status is inversely related to the ability of the stomach to secrete acid, suggesting that its expression may be regulated by changes in acid secretion and/or in antigens expressed by the atrophic mucosa[67,75].

SabA-positive status is associated with the development of intestinal metaplasia, gastric atrophy and gastric cancer[65,68]. After *H. pylori* induces gastritis, neutrophils and monocytes infiltrate into the gastric mucosa. SabA of non-opsonized *H. pylori* strains specifically binds to neutrophils through sialylated carbohydrates. Consequently, the stimulated neutrophils produce reactive oxygen species causing oxidative damage of the gastric epithelium, showing that SabA is a virulence factor[72,77].

oipA

OipA (about 34 kDa) was identified in 2000. It is one of the OMPs. It functions in adhesion and is located approximately 100 kbp from the *cag*-PAI on the *H. pylori* chromosome[58,78,79]. The functional status of OipA is regulated by slipped strand mispairing that is determined by the number of CT dinucleotide repeated in the 5′ region of the gene (switch "on" and OipA is functional; switch "off" and OipA is nonfunctional)[80].

H. pylori with the *Oip*A functional status "on" has been associated with other virulence factors, such as *cag* PAI, *vac*A, *ice*A and *bab*A[65,68,81,82]. OipA "on" status is significantly associated with more severe gastric diseases (duodenal ulcer and gastric cancer), high *H. pylori* density, severe neutrophil infiltration, and high mucosal interleukin-8 levels[83]. Researchers have demonstrated that OipA can induce inflammation and affect actin dynamics through the phosphorylation of multiple signaling pathways that usually interact with *cag*-PAI (CagA)-related pathways[84,85]. *H. pylori*-related inflammatory signaling related to gastric carcinogenesis is regulated by the activation of the phosphoinositide-3 kinase (PI3K)/Akt signaling pathway[86]. OipA regulates IL-8 secretion through PI3K/Akt and this regulation is dependent on forkhead transcription factors of class O (FoxO) 1/3a inactivation[87]. Inactivation of *oip*A also results in a decreased level of nuclear β-catenin *in vitro* and a reduced incidence of cancer in gerbils, indicative of this OMP's importance in *H. pylori* virulence[10].

hopQ

The *hop*Q gene encodes HopQ, an OMP that attenuates the adherence of *H. pylori* strains to gastric epithelial cells and thus may play an important role in the initial colonization and long-term persistence of the bacterium in the stomach[88]. The *hop*Q gene is present in 2 forms: types Ⅰ and Ⅱ. Some studies have reported an association between the presence of type Ⅰ *hop*Q alleles and other *H. pylori* virulence markers, including type s1 *vac*A alleles[89-92]. In Western patients, the inflammatory cell infiltration and atrophy scores were significantly higher in patients with *hop*Q type Ⅰ strains than those with type Ⅱ[63]. Only one study so far showed that the *hop*QⅡ genotype is frequently present in *H. pylori* strains isolated from gastric cancer patients[93].

Another study conducted an analysis of 3000 *H. pylori* mutants and revealed that the *hop*Q gene affected NF-κB nuclear translocation. HopQ was essential for CagA translocation and for CagA-mediated host cell responses such as formation of the hummingbird phenotype and cell scattering. It also showed that the deletion of *hop*Q reduced T4SS-dependent activation of NF-κB, induction of MAPK signaling and secretion of interleukin-8 in the host cells, but it did not affect motility or the quantity of bacteria attached to host cells. Therefore, HopQ exhibits adhesive properties and could be useful in facilitating contact of *H. pylori*'s T4SS with the host cell surface[94].

Although BabA and SabA are the most prominent

adhesins described so far, it seems probable that additional adhesins described in this review are involved in the colonization process. The adhesins are important not only for *H. pylori* to adhere to the stomach surface but also to anchor the bacterial secretion system and consequently the delivery of virulence factors to host epithelial cells.

MOTILITY GENES

Flagella provide the motility of *H. pylori* which possess a unipolar bundle of 3 to 5 flagella, composed of 3 structural elements: the basal body, the hook, and the filament[67,95,96]. The filament acts as a propeller when rotated at its base and it is composed of 2 flagellins: the major, FlaA, and the minor, FlaB[97]. Mutation of *fla*A results in flagellar truncation and decreased motility *in vitro*[98]. *In vivo*, FlaA and other proteins necessary for flagellar assembly are essential for persistent infection in rodent and gnotobiotic piglet models[99-101].

H. pylori flagellin filaments are post-translationally modified by glycosylation with a 9-carbon pseudaminic acid (Pse) sugar derivative that resembles sialic acid, which is typically found on mammalian cell surfaces[102]. The FlaA protein is modified with a total of 7 *O*-linked pseudaminic acid (Pse5Ac7Ac) residues, while FlaB is modified with 10 *O*-linked Pse5Ac7Ac residues. Deletion of genes responsible for the glycosylation process leads to loss of late flagellar structures (hook and filaments) and loss of motility[103,104]. Motility is essential for successful gastric colonization and may contribute to pathogenesis.

iceA

Another virulence gene designated *ice*A (induced by contact with epithelium) has been recently described. Some studies showed that *ice*A has two main allelic variants, *ice*A1 and *ice*A2, but the function of these variants is not yet clear[105,106]. *ice*A1 demonstrated sequence homology with a gene from *Neisseria lactamica*, *nla*IIIR, which encodes a CTAG-specific restriction endonuclease[107]. On the other hand, *ice*A2 has no homology to known genes and the function of the *ice*A2 product remains unclear. The expression of *ice*A1 is upregulated on contact between *H. pylori* and human epithelial cells, and the *ice*A1 genotype was linked with enhanced mucosal interleukin-8 expression and acute antral inflammation[61].

Some reports have reported an association between *ice*A allelic types and clinical outcomes[108]. The *ice*A1 variant was associated with peptic ulcer disease, and *ice*A2 variants with gastritis[109,110]. However, these associations vary among populations. In Brazil, for instance, the *ice*A1 allele is associated with gastritis[111]. Additionally, in Cuba, Europe, Saudi Arabia, and Turkey the *ice*A2 allele is associated with non-peptic ulcer dyspepsia as well as strains with more virulent types[109,112]. Thus, the *ice*A gene may be considered a useful marker in patients with gastroduodenal diseases.

CONCLUSION

The relationship between *H. pylori* and humans dates back 50000 years and during this time these 2 species have co-evolved. During this evolution, there has been a major change in the genome of the bacterium with horizontal acquisition of the *cag* pathogenicity island, which seems to be important in colonization, and responsible for the development of gastric diseases. Although only the *cag*A gene is well defined as an *H. pylori* pathogenicity marker, over the course of our review it was observed that other genes are also essential components for a functional *cag* T4SS. Furthermore, the fact that some strains with an incomplete pathogenicity island in more severe gastric lesions were observed, suggests that there must be genes with overlapping roles to ensure the functioning of the secretory apparatus. In addition, the product of some of these genes could be capable of stimulating an exacerbated inflammatory response which is characteristic of gastric lesions. Although there are several genes associated with adhesion of the bacteria, the *bab*A gene is associated with successful colonization.

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