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

da Costa DM *et al*. What exists beyond *cag*A and *vac*A?

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**Abstract**

The *Helicobacter pylori* (*H. pylori*) infection is present in more than half the world’s population and it has been associated with several gastric disorders, as gastritis, peptic ulceration and gastric adenocarcinoma. The clinical outcome of this infection depends on host and bacterium factors where *H. pylori* virulence genes seem to play a relevant role. Until now, *cag*A and *vac*A genes were studied and established in the literature as determining factors in gastric pathogenesis. However, there are percentages of gastric cancer cases that are *cag*A-negative. Several othervirulence genes have been searched but these genes still remain in the shadow of *cag*A and *vac*A. Thus, this review aimed to bring up 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 its relevance shown in several studies in the literature.

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

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**Core tip:** The *Helicobacter pylori* (*H. pylori*) infection is present in more than half the world’s population and it has been associated with several gastric disorders. The clinical outcome of this infection depends on host and bacterium factors. Until now, *cag*A and *vac*A *H. pylori* genes were established in the literature as determining factors in gastric pathogenesis. Thus, this review aimed to bring up which genes have been suggested as potentially relevant virulence factors for *H. pylori* focused on the *cag*-pathogenicity island, adherence and motility genes and *ice*A based on its 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 used for motility and several virulence factors which vary with the strains[1,2]. *H. pylori* was isolated by 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 supports that the relationship between *H. pylori* and its human host exists for at least 60000 years. One piece of evidence is the fact that the genetic diversity of bacteria evolved in parallel to the human species, showing that both have been evolving intimately ever since. Furthermore, the genetic diversity distribution of *H. pylori* is in consonance 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]. The infection by *H. pylori* is present in more than half the world’s population. However, not all infected people exhibit diseases associated to 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 bacterium virulence factors and on factors related to the host. Several virulence genes are well studied and established in the literature as determining factors in gastric pathogens such as *cag*A and *vac*A genes. Several other genes, although previously studied, still remain in the shadow of *cag*A and *vac*A. Thus, the objective of this review is to discuss about current knowledge of *H. pylori* virulence factors that bring out other genes of *cag* Pathogenicity Island – *cag*-PAI, genes that codify outer membrane proteins (*bab*A, *oip*A*, sab*A*, hop*Q), motility genes (*fla*A and *fla*B) and *ice*A, which are pointed out in the literature as potentially relevant for the development of more severe lesions.

**Well-Established Virulence Factors**

The *cag*A (cytotoxin-associated gene A) and *vac*A (vacuolating cytotoxin 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 once injected into the gastric epithelial cell cytoplasm interacts with host cell proteins, inducing cell morphological changes (hummingbird phenotype), pro-inflammatory and mitogenic responses. Several studies in cell culture and animal models indicate the importance of the *cag*A gene involvement in human gastric cancer, one of them showing that its deletion prevents the development of the disease in 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 e D). EPIYA-A and -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 IL-8 release from gastric epithelial cells when compared to strains containing the A-B-C-type of CagA[13,14].

The *vac*A gene is not part of the *cag*-PAI gene. 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 receptors membrane, followed by a pro-inflammatory response[15,16].Nonetheless, considerable differences in vacuolating activities are observed between strains according to variations in *vac*A gene structures within the signal (s), the 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 do s1/m2 strains, and there is typically no vacuolating activity in s2/m2 strains[17].

In agreement with in vitro data, studies in Middle East, Africa and Western countries showed 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]. On its turn, the “m” region in East Asia shows variations suggesting that it may play a role in the 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 north region[20,21]. A Brazilian study indicated that in the absence of *cag*A, there was a relevance *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 with 40 kilobase which contains 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 isolation by distance that has shaped this bacterial species since modern humans migrated out of Africa. Carriage of *cag*-PAI varies from almost universal presence in the strains hpEastAsia and hpAfrica1, through intermediate presence (hpEurope) to complete absence (hpAfrica2). When compared to other bacteria of the same genus, the absence of *cag*-PAI seems to be an ancestral state. 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 to 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 with important roles in the translocation of CagA[32].These include CagE, VirB11, CagT, CagM and CagG, whose importance will be described below (Figure 1).

***cag*E and *vir*B11**

*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 six monomeric units. These genes codify 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, few studies have described an association with gastric cancer[36-38].Two of these studies show the presence of such genes in early tumor stages strains and its association with other virulence genes, showing that there is a participation of *cag*E and *vir*B11 with gastric carcinogenesis[34,39].

***cag*T**

The *cag*T gene is a homologue of *A*. *tumefaciens* vir B7 and it 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 play important roles in the induction of the proinflammatory cytokine IL-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.

***cag*M**

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 form a surface structure which acts as the NF-kB-inducing agent, mediating IL-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 is associated with the development of gastritis, peptic ulcers and gastric cancer[45,49,56,57].Thus, CagT 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.

***cag*G**

*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 IL-8[41,52].

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

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

**Genes that Codify Outer Membrane Proteins**

Approximately 4% of the *H. pylori* genome encodes a diverse repertoire of Outer Membrane Proteins (OMPs) that have been grouped into five 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 Lewisb antigen (Leb) 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 the BabAadhesin 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 *cag*A and *vac*A s1 alleles, it leads to an even greater risk of developing more severe diseases[68,69]. BabA binding to Leb 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 (~70 KDa) is the second best characterized adhesin of *H. pylori,* which 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-Lex, 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 expression *sab*A gene is regulated at transcriptional level by some mechanisms. Indeed, the dinucleotide CT repeats present in the 5' coding region of *sab*A to regulate 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 was 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 was associated with the development of intestinal metaplasia, gastric atrophy and gastric cancer[65,68]. After *H. pylori* induced gastritis, neutrophils and monocytes infiltrated 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 outer membrane proteins. It functions in adhesion and it 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*Afunctional status “on” has been associated with other virulence factors, 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, and severe neutrophil infiltration and high mucosal IL-8 levels[83]. Researchers have demonstrated that OipA can induce inflammation and 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 the *H. pylori* virulence[10].

***hop*Q**

The *hop*Q gene encodes HopQ, an outer membrane protein 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 two forms: types I and II. Some studies have reported an association between the presence of type I *hop*Qalleles and other *H. pylori* virulence markers, including type s1 *vac*Aalleles[89-92]. In Western patients, the inflammatory cell infiltration and atrophy scores were significantly higher in patients with *hop*Qtype 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].

A 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*Qreduced T4SS-dependent activation of NF-κB, induction of MAPK signaling and secretion of interleukin 8 (IL-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 to conferring contacts of *H. pylori*’s T4SS to 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 conferred the motility of *H. pylori* that possesses a unipolar bundle of 3 to 5 flagella, which are composed of three 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 made of two flagellins: the major, FlaA, and the minor, FlaB[97]. Mutation of *fla*Aresults 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 nine-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 seven *O*-linked pseudaminic acid (Pse5Ac7Ac) residues, while FlaB is modified with ten *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 clear yet[105,106].*ice*A1demonstrated 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 (IL)-8 expression and acute antral inflammation[61].

Some reports have associated the relationship between the *ice*Aallelic types and clinical outcomes[108]. The *ice*A1variant was associated with peptic ulcer disease, while *ice*A2variants with gastritis[109,110].However, this association varies among populations. In Brazil, for instance, *ice*A1allele is associated with gastritis[111]. Additionally, it was described in Cuba, Europe, Saudi Arabia, and Turkey that the *ice*A2allele is associated with non-peptic ulcer dyspepsia (NUD) as well as strains with more virulent types[109,112].Thus, the *ice*Agene may be considered a useful marker in patients with gastroduodenal diseases.

**Conclusion**

The relationship between *H. pylori* and humans date back to 50000 years ago and during this time these two species have co-evolved. During this evolution, there was a major change in the genome of this bacterium with the horizontal acquisition of the *cag* pathogenicity island, which seems to have been important in the colonization, although it was responsible for the development of gastric diseases. In spite of the fact that 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 strain with an incomplete pathogenicity island in a more severe gastric lesion was observed, suggesting that there must be genes with overlapping function ensuring the functioning of the secretory apparatus. Besides, 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 the adhesion of the bacteria, the *bab*A gene stands for a successful colonization.

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**Figure 1 Schematic representation of the *cag*-PAI 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.