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Helicobacter pylori homB, but Not *cagA*, Is Associated with Gastric Cancer in Iran[▽]†

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While several distinct virulence factors of *Helicobacter pylori* have been shown to be associated with different clinical outcomes, there is still much to learn about the role of different bacterial factors in gastric carcinogenesis. This study looked at the distribution of the *cagA*, *homA*, and *homB* genes in strains isolated from patients suffering from gastroduodenal diseases in Iran and assessed if there was any association between disease state and the presence of the aforementioned virulence factors. Genomic DNA from 138 *H. pylori* strains was isolated and genotyped via PCR. Strains were obtained from dyspeptic patients (35 from gastritis patients, 62 from peptic ulcer patients, and 41 from gastric cancer patients) at the Teaching Touba Clinic and Imam Hospital of the Mazandaran University of Medical Sciences in Sari, Iran. The overall prevalence rates of *cagA*, *homA*, and *homB* were 58%, 54%, and 43%, respectively. Stratification of patients showed a significant difference in the prevalence of *H. pylori* virulence genes across the disease states. The frequency of *homB* was statistically significantly higher in gastric cancer patients (78%) than in patients suffering from peptic ulcers (20%) or gastritis (43%) ($P < 0.0001$). The presence of *homB* was also associated with the presence of *cagA* ($r = 0.243$). These data suggest that in this population the presence of *homB* may be a predictor of more virulent strains of *H. pylori* and influence the severity of disease manifestation.

Helicobacter pylori is a Gram-negative, spiral-shaped, microaerophilic bacterium that infects more than 50% of the world's population (2, 30, 31). Colonization and long-term persistence of *H. pylori* can induce a complex immune response that can potentiate severe mucosal damage, including atrophy, intestinal metaplasia, and dysplasia, thereby making *H. pylori* the etiologic agent of acute and chronic gastritis, peptic ulcer disease (75% of gastric ulcers and 90% of duodenal ulcers), and two forms of gastric cancer (mucosa-associated lymphoid tissue lymphoma and gastric adenocarcinoma) (8, 15, 41, 42, 51). The association with the development of two forms of cancer led to the classification of *H. pylori* by the World Health Organization as the only bacterial class I carcinogen (24).

H. pylori's association with cancer, combined with the fact that gastric cancer is the second most common cause of cancer-associated death (33), has led to numerous studies designed to elucidate the bacterial factors responsible for progression to this disease. However, understanding why some individuals develop severe disease and others develop only mild disease has not been a straightforward task. This is due to the complex nature of interactions between the bacterium and the host. Important variables include variation in genetic content across bacterial strains and the role of host factors, such as host genetics, dietary intake, and other environmental factors in the disease process. Among the bacterial factors that have been implicated to impact disease development are a number of virulence factors that show heterogeneity across strains. Included among these are the toxins CagA and VacA, the IceA (for induced by contact with epithelium) protein, the proinflammatory outer membrane protein OipA, and the *Helicobacter* outer membrane proteins HomA and HomB (4, 11, 21, 37, 38, 43, 46, 53). The virulence factor that has emerged to be one of the major determinants of severe disease manifestations is *cagA*, and carriage of the gene is associated with peptic ulcers, atrophic gastritis, and adenocarcinoma (9, 17). In fact, *H. pylori*-infected gastric cancer patients are at least twice as likely to be infected with *cagA*-positive strains (9, 18). *cagA* is the last gene on the *cag* pathogenicity island (PAI), the majority of which encodes a type IV secretion apparatus that is used to directly inject CagA into host cells (10). Once injected, CagA is phosphorylated and forms a complex with SHP-2 (Src homology region 2-containing phosphatase 2 [22]), thereby altering multiple host signaling pathways (20–22, 32, 47, 52).

The *Helicobacter* outer membrane (Hom) adhesion molecules constitute a small paralogous family of proteins that contain alternating hydrophobic motifs and signal sequences in the C terminus, which are typical of other outer membrane proteins (1). *homA* and *homB* are the best-studied members of the Hom family, and *H. pylori* contains two possible genomic locations that can carry these two adhesion molecules (38).

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TABLE 1. Primer sequences

Primer name	Sequence	Gene(s) amplified	Amplicon size (bp)	Reference
glmM forward	5′-AAGCTTTTAGGGGTGTTAGGGGTTT-3′	*glmM*	294	28
glmM reverse	5′-AAGCTTACTTTCTAACACTAACGC-3′			
F1-jph0870/jhp0649	5′-AGAGGGTFTTTFAAACGCTCAATA-3′	*homA*	128	38
R1-jhp0870/jhp0649	5′-GGTGAATTCTTCTGCGGTTTG-3′	*homB*	161	
D008	5′-ATAATCGTAAATTAGACAACTTGAGCGA-3′	*cagA*	298	19
R008	5′-TTAGAATAATCAACAAACATCACGCCAT-3′			

The *homA* and *homB* genes are 90% identical, and the variability between these genes is contained in the central domain (1). Adding to the complexity, six distinct different allelic variants within a 300-bp region within this central domain have been identified. Three of these variants are exclusively found in *homB*-positive strains, while only one of these variants is found exclusively in *homA*-positive strains (35, 36). There are also geographic differences in the sequences at both the 5′ and 3′ ends of the *homB* gene, and these differences can be divided among East Asian and Western strains (35). Strains can have a single *homA* or *homB* gene, in which the other locus remains empty; two copies of *homA* (*homA* and *homA*) or *homB* (*homB* and *homB*); a single copy of each gene (*homA* and *homB*); or neither of these genes (34). Studies have suggested that the number of *homB* genes affects the number of bacteria adhering to host cells and that the presence of *homB* is associated with secretion of the proinflammatory cytokine interleukin-8 (IL-8) (34). Studies to address whether the presence of *homB* is associated with increased disease severity have shown that the presence of *homB* is associated with peptic ulcer disease but not gastritis (34). More recently, the presence of *homB* has been suggested to be a discriminative factor between development of gastric cancer and duodenal ulcer (25).

Residents in the northern regions of Iran are at high risk for development of gastric cancer. Specifically, gastric cancer clusters exist within the Mazandaran region (29). Given the complexity of *H. pylori* virulence factors, the rather poorly understood distribution of these factors in Iran, and the high incidence of gastric cancer in this region, the prevalence of the virulence genes *cagA*, *homA*, and *homB* in patients with gastroduodenal disorders within a population at risk for gastric cancer from the northern section of Iran was assessed (29). In this population, we found that while *cagA* presence had no significant effect on disease type, there was a strong association between the presence of *homB* and the progression to gastric cancer. Additionally, there was an association between the presence of the *homB* and *cagA* genes. These data suggest that within this population, *homB* may serve as a better predictor of severe disease development than *cagA*.

MATERIALS AND METHODS

Study participants. Biopsy samples were obtained from patients undergoing endoscopic procedures for dyspepsia at the Teaching Touba Clinic and Imam Hospital of Mazandaran University of Medical Sciences, Sari, Iran. Exclusion criteria for the study included previous gastric surgery; *H. pylori* eradication treatment; and previous use of antibiotics, nonsteroid anti-inflammatory drugs, proton pump inhibitors, or H2-receptor blockers in the previous 30 days. Additionally, patients who had received antisecretory drugs, bismuth salts, or sucralfate within the 2 weeks prior to the endoscopy procedure were excluded. Three biopsy specimens were obtained from the gastric antrum of each patient and were used for pathological examination, urease test (*H. pylori* Quick Test; Biohit Diagnostics Helsinki, Finland), and microbial culture, respectively. Patients were included in the study upon a positive urease test, and written informed consent was obtained from all participants. The study protocol was approved by the Medical Research Ethics Committee of Mazandaran University of Medical Sciences. Diagnosis of gastric disorders was based on clinical presentation, endoscopic findings, and histopathologic confirmation (14, 26). A total of 138 *H. pylori*-positive patients were enrolled in the study.

Isolation of *H. pylori* isolates. Biopsy specimens were placed in sterile thioglycolate broth (Merck, Germany) and transferred to the microbiology laboratory for further processing. The specimens were dissected and then plated on Columbia agar (Mast, United Kingdom) plates containing 7% fetal calf serum (Gibco), 10% defibrinated sheep blood (Jihad Daneshgahi, Iran), and *H. pylori*-selective antibiotic tablets (Mast, United Kingdom). These plates were incubated under microaerobic conditions at 37°C for a maximum of 7 days. *H. pylori* colonies were confirmed via morphology, Gram stain, and positive oxidase, catalase, and urease activity tests, as well as by successful amplification of the housekeeping gene *glmM* (13). PCR amplification of the *glmM* gene for the detection of *H. pylori* isolates was performed with the *glmM* forward and reverse primers described by Lu et al. (28).

***homA*, *homB*, and *cagA* genotyping.** Genomic DNA was extracted from a single colony per patient using an AccuPrep genomic DNA extraction kit (Bioneer, South Korea) according to the manufacturer's directions. All primers used in this study are listed in Table 1. The presence of *cagA* was indicated by a 298-bp amplicon when the gene was amplified with primers D008 and R008 using the conditions described previously (19) (Fig. 1). Identification of the presence of the *homA* and/or *homB* gene was accomplished through a single PCR using the F1-jhp0870/jhp0649 and R1-jhp0870/jhp0649 primers, which yielded a 128-bp product denoting the presence of the *homA* gene and a 161-bp product denoting the presence of the *homB* gene using conditions described previously (38) (Fig. 1). These primers amplify an internal region of both genes that lies approximately 505 to 530 bp from the start of the genes. This region contains variations between the *homA* gene and the *homB* gene, but the conserved nature of the primers allows amplification of all *homA* and *homB* variants currently identified. Reference strain 26695 was used as a positive control for *homA*, and strain J99 was used as positive control for *homA* and *homB* (38).

Data analysis. Isolates were assessed for the presence of the *cagA*, *homA*, and *homB* genes, according to disease state, age, and gender. Comparisons of continuous and discontinuous variables were performed with the Student *t* test, analysis of variance, the Fisher exact test, or the chi-square test. Logistic regression analysis was used for multivariate analysis, and log linear modeling was used to assess any higher-order associations, fitting a saturated model using categorical variables representing *cagA*, *homA*, *homB*, disease state, gender, and age. Higher-order associations were identified using a backward-selection algorithm with statistical significance assessed at the 5% level. Data were analyzed using SPSS (version 16) software (SPSS Inc., Chicago, IL).

RESULTS

Sample acquisition and virulence gene genotyping. A complete list of isolates and epidemiological data (age and gender), disease state, and virulence factor status is available in Table S1 in the supplemental material. *H. pylori* was successfully cultured from 138 patients suffering from gastroduodenal disorders from northern Iran. The presence of *H. pylori* was ver-

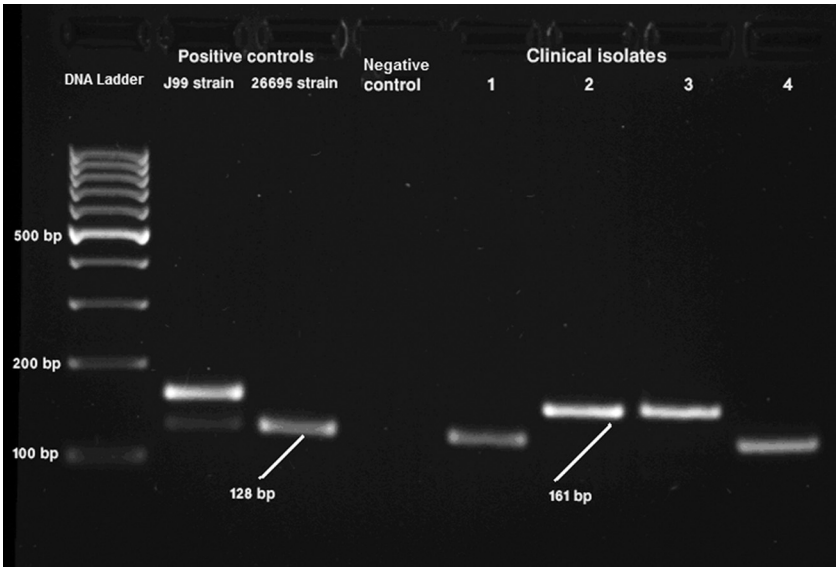

FIG. 1. Genotyping of *homA* and *homB* in *H. pylori* isolates. The image is from a representative gel electrophoresis of PCR amplification products of *homA* (128 bp) and *homB* (161 bp) genes from clinical isolates and J99 and 26695 as positive-control strains for both *homA* and *homB* and only *homA*, respectively. The negative-control lane represents a PCR performed with no template DNA.

ified via morphology, Gram stain, and positive oxidase, catalase, and urease activity tests and further confirmed by successful amplification of the housekeeping gene *glmM*. The mean age of the overall population was 42.9 ± 13.5 years. The population was fairly evenly distributed across gender, with 63 (45.7%) being female and 75 (54.3%) being male. Moreover, the *H. pylori*-positive samples were distributed across the different disease states: 35 (25.4%) from gastritis patients, 62 (44.9%) from peptic ulcer disease patients, and 41 (29.7%) from gastric cancer patients. The complete breakdown of the virulence gene status and epidemiological factors across the different disease states is shown in Table 2. There were no significant differences in mean age ($P = 0.151$) or gender ($P = 0.500$) across the disease spectrum.

Virulence factors. (i) Cytotoxin-associated gene A, *cagA*. The presence of *cagA* has been linked to the development of more severe disease states (9, 27, 40) and therefore is an important virulence factor to assess within this population. A majority of the strains (80 [58%]) were found to be *cagA* positive, while 58 (42%) were *cagA* negative. Of the 80 *cagA*-positive strains, 39 (48.75%) were from female patients and 41 (51.25%) were from male patients. Eighteen isolates were from gastritis patients, 34 were from peptic ulcer disease patients, and 28 were from patients presenting with gastric cancer. Of the 58 *cagA*-negative strains, 24 (41.4%) were from female patients and 34 (58.6%) were from male patients. Seventeen of these isolates were from gastritis patients, 28 isolates were from peptic ulcer disease patients, and 13 isolates were from gastric cancer patients (Table 2).

The presence or absence of the *cagA* gene was not statistically significantly linked to gender ($P = 0.4888$). Even though the *cagA*-positive strains were more prevalent in patients suffering from gastric cancer (68.3%; Table 2 and Fig. 2A), *cagA* status did not have a statistically significant effect on disease state in this population ($P = 0.2654$). In fact, *cagA* status did not statistically impact any breakdown of disease states: cancer versus gastritis and peptic ulcer disease ($P = 0.3291$), cancer versus peptic ulcer disease ($P = 0.2185$), cancer versus gastritis ($P = 0.1618$), peptic ulcer disease versus gastritis and gastric cancer ($P = 0.6033$), peptic ulcer disease versus gastritis ($P =$

TABLE 2. Breakdown of epidemiological and virulence factors of a north Iranian population

Characteristic	No. of patients with the following disease state[a]:			
	Total	Gastritis	Peptic ulcers	Gastric cancer
Overall population				
Total	138	35	62	41
Female	63	15	26	22
Male	75	20	36	19
cagA status				
Positive	80	18	34	28
Female	39	7	16	16
Male	41	11	18	12
Negative	58	17	28	13
Female	24	8	10	6
Male	34	9	18	9
homA status				
Positive	75	20	49	6
Female	35	8	22	5
Male	40	12	27	1
Negative	63	15	13	35
Female	28	7	4	17
Male	35	8	9	18
homB status				
Positive	60	15	13	32
Female	26	7	4	15
Male	34	8	9	17
Negative	78	20	49	9
Female	37	8	22	7
Male	41	12	27	2

[a] The mean ages ± 1 standard deviation are 42.9 ± 13.5, 43.6 ± 14.7, 44.7 ± 12.9, and 39.5 ± 13.2 years for all patients and patients with gastritis, peptic ulcers, and gastric cancer, respectively.

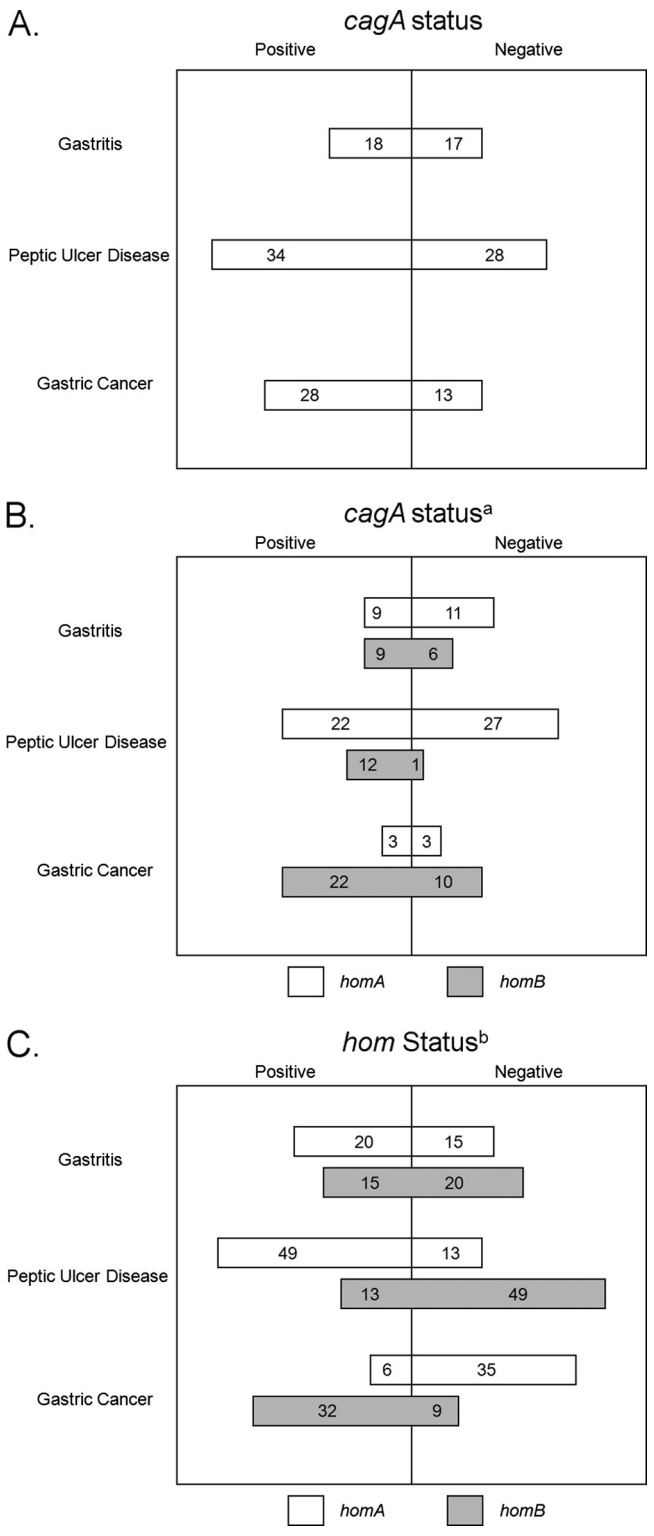

FIG. 2. Schematic depiction of the distribution of the different virulence factors stratified by disease state within the Iranian population of this study. (A) The distribution of the *cagA* gene stratified by disease state is depicted. (B) The distribution of *cagA*, *homA*, and *homB* stratified by disease state is depicted. Only *homA*- or *homB*-positive strains are depicted among the *cagA*-positive or -negative isolates. [a], positive correlation between the presence of the *cagA* gene and the *homB* gene ($r = 0.243$) and an inverse correlation between the presence of the *cagA* gene and the *homA* gene ($r = -0.279$). (C) The distribution of the different *hom* genes stratified by disease state is depicted. [b], a significant association exists between the distribution of the *homA* gene and disease state ($P < 0.0001$) and the distribution of the *homB* gene and disease state ($P < 0.0001$), and the progression to gastric cancer is influenced by the presence of the *homB* gene.

TABLE 3. Distribution of virulence factors across the different disease states

Gene and groups compared	*P* value[a]
Distribution of *cagA*	
Gastric cancer vs peptic ulcer disease and gastritis	0.3291
Gastric cancer vs peptic ulcer disease	0.2185
Gastric cancer vs gastritis	0.1618
Peptic ulcer disease vs gastric cancer and gastritis	0.6033
Peptic ulcer disease vs gastritis	0.8331
Gastritis vs gastric cancer and peptic ulcer disease	0.4293
Distribution of *homA*	
Gastric cancer vs peptic ulcer disease and gastritis	<0.0001
Gastric cancer vs peptic ulcer disease	<0.0001
Gastric cancer vs gastritis	0.0001
Peptic ulcer disease vs gastric cancer and gastritis	<0.0001
Peptic ulcer disease vs gastritis	0.0348
Gastritis vs gastric cancer and peptic ulcer disease	0.8445
Distribution of *homB*	
Gastric cancer vs peptic ulcer disease and gastritis	<0.0001
Gastric cancer vs peptic ulcer disease	<0.0001
Gastric cancer vs gastritis	0.0022
Peptic ulcer disease vs gastric cancer and gastritis	<0.0001
Peptic ulcer disease vs gastritis	0.0348
Gastritis vs gastric cancer and peptic ulcer disease	1

[a] Shading indicates *P* values that are statistically significant, as defined in the Materials and Methods.

0.8331), or gastritis versus gastric cancer and peptic ulcer disease ($P = 0.4293$) (Table 3). However, the presence of the *cagA* gene was significantly linked to the distribution of both *homA* ($P = 0.0017$) and *homB* ($P = 0.0054$) (Fig. 2B).

(ii) *Helicobacter* outer membrane family members *homA* and *homB*. In a population where the presence of *cagA* is not a good indicator of progression to more severe disease manifestations, other bacterial factors must play a more important role in disease progression. Recently, the presence of different outer membrane proteins has been linked to more severe disease manifestations (25, 34, 38). In fact, the presence of the *Helicobacter* outer membrane protein B (*homB*) has been linked to progression to gastric cancer (25). In order to assess if this correlation existed within this population, the presence of either *homA* or *homB* was assessed. The presence of *homA* was identified by the presence of a 128-bp amplicon, whereas the presence of *homB* was indicated by the presence of a 161-bp amplicon, as previously described (38) (Fig. 1). Either *homA* or *homB* was present in 135 (97.8%) of all strains; 3 gastric cancer strains were negative for both the *homA* and *homB* genes. However, all three *homA*- and *homB*-negative strains carried *cagA*. Seventy five isolates (54.3%) were *homA* positive and 60 isolates (43.5%) were positive for *homB*. Of note, with the exception of the three *homA*- and *homB*-negative strains, strains carried just one or the other *hom* gene, and no strains carried both *homA* and *homB*.

(a) homA status. Of the 75 *homA*-positive strains, 35 (46.7%) were from female patients and 40 (53.3%) were from male patients. Twenty isolates were from gastritis patients, 49 isolates were from peptic ulcer disease patients, and 6 were from patients diagnosed with gastric cancer. Of the 63 *homA*-negative strains, 28 (44.4%) were isolated from females and 35 (55.6%) were isolated from males. Fifteen isolates were from gastritis patients, 13 isolates were from peptic ulcer disease patients, and 35 were from gastric cancer patients (Table 2 and Fig. 2C).

The presence or absence of the *homA* gene was not statistically significantly linked to gender ($P = 0.8643$). However, the distribution of *homA* had a statistically significant effect on disease state ($P < 0.0001$; Fig. 2): cancer versus gastritis and peptic ulcer disease ($P < 0.0001$), cancer versus peptic ulcer disease ($P < 0.0001$), cancer versus gastritis ($P = 0.0001$), peptic ulcer disease versus gastritis and gastric cancer ($P < 0.0001$), and peptic ulcer disease versus gastritis ($P = 0.0348$). However, the presence of *homA* did not statistically significantly impact gastritis versus peptic ulcer disease and gastric cancer ($P = 0.8445$). The presence of the *homA* gene was significantly linked to the distribution of both *cagA* ($P = 0.0017$) and *homB* ($P < 0.0001$). The association with *homB* is due to the fact that, with the exception of the three *homA*-negative and *homB*-negative strains, strains that carry *homA* do not carry *homB* and vice versa.

(b) homB status. Of the 60 *homB*-positive strains, 26 (43.3%) were from female patients and 34 (56.7%) were from male patients. Fifteen isolates were from gastritis patients, 13 isolates were from peptic ulcer disease patients, and 32 were from gastric cancer patients. Of the 78 *homB*-negative strains, 37 (47.4%) were from female patients and 41 (52.6%) were from male patients. Twenty isolates were from gastritis patients, 49 isolates were from peptic ulcer disease patients, and 9 were from patients diagnosed with gastric cancer (Table 2).

The presence or absence of the *homB* gene was not statistically significantly linked to gender ($P = 0.7306$). However, the status of *homB* had a statistically significant effect on disease state ($P < 0.0001$). In fact the presence or absence of *homB* status statistically significantly impacted most of the disease states (Fig. 2C and Table 3): cancer versus gastritis and peptic ulcer disease ($P < 0.0001$), cancer versus peptic ulcer disease ($P < 0.0001$), cancer versus gastritis ($P = 0.0022$), peptic ulcer disease versus gastritis and gastric cancer ($P < 0.0001$), and peptic ulcer disease versus gastritis ($P = 0.0348$). However, the presence of *homB* did not statistically significantly impact gastritis versus peptic ulcer disease and gastric cancer ($P = 1.0000$). Indeed, the majority of isolates from gastric cancer patients (78%) carried *homB.* The presence of the *homB* gene was significantly linked to the distribution of both *cagA* ($P = 0.0054$) and *homA* ($P < 0.0001$). Again, the association with *homA* is due to the fact that, with the exception of the three *homA*- and *homB*-negative strains, strains that carry *homA* do not carry *homB* and vice versa.

***cagA*, *homA*, and *homB* genotypes.** Next, we wanted to examine the association between *cagA* and either of the *hom* genes. Through statistical analysis, a significant inverse correlation between the presence of the *cagA* and *homA* genes was identified ($r = -0.279$, $P = 0.001$). This means that *homA* positivity was more frequently found in strains lacking the *cagA* gene (Table 3). Moreover, a statistically significant positive correlation was observed between *cagA* positivity and *homB* status ($r = 0.243$, $P = 0.004$). This positive correlation indicates that there is an association between being positive for *homB* and being positive for *cagA*. Indeed, the majority of *homB*-positive strains were *cagA* positive (71.7%), whereas among *homB*-negative strains, the *cagA* status was evenly distributed: 47.4% were *cagA* positive, and 52.6% were *cagA* negative.

Since both the *homA* and *homB* genes showed a direct association with disease and *cagA*, we wanted to know if there was any association between *homA*, *cagA*, and disease state or *homB*, *cagA*, and disease state. However, neither of these associations reached statistical significance ($P = 0.178$ and $P = 0.073$, respectively). Next we wanted to know if either *homA* or *homB* was a predictor of gastric cancer independent of *cagA*. Logistic regression analysis revealed that the *homB*-positive genotype was a predictor of gastric cancer independent of *cagA* (odds ratio = 8.453, $P < 0.001$). Unfortunately, due to the almost inverse relationship of *homA* and *homB* status, we were unable to assess the association between these two genes.

DISCUSSION

Gastric cancer is the fourth most common malignancy and is responsible for over 700,000 deaths per year (16), and infection with *H. pylori* has been attributed to over 63% of all cases of gastric cancer worldwide (39). Additionally, *H. pylori* is responsible for 75% of all gastric ulcers and 90% of all duodenal ulcers (8), making *H. pylori* a medically important bacterium. Given only this evidence, eradication of this gastric intruder seems to be the most logical course of action. However, recent epidemiological studies have identified protective correlates between *H. pylori* colonization and different diseases, specifically, active tuberculosis, which is a worldwide health concern (44); asthma (45), which is on the rise in developed countries; and esophageal cancer, which is also on the rise (7). Thus, scientists are attempting to determine what makes some strains more virulent than other strains. If bacterial factors that are responsible for increased virulence are identified, then perhaps highly virulent strains can be eradicated without losing the protective effects generated through colonization with less virulent strains.

The bacterial factor that has emerged to be the major bacterial determinant for progression to more severe disease is *cagA* (9, 27, 40). In fact, *cagA*-positive *H. pylori* strains have been associated with the severe mucosal inflammation that underlies peptic ulcer, atrophic gastritis, and gastric carcinoma (9, 27). Even though the rate of gastric cancer is high in Iran, the prevalence of infection with *cagA*-positive *H. pylori* strains varies from 68% (48) to 76% (23). In our study, only 58% of isolates were *cagA* positive, and the distribution of the *cagA* gene was not statistically significantly linked to disease. While they are surprising, our results are congruent with those of another study that showed that *cagA* presence was not significantly associated with peptic ulcer disease in Iran (23). Indeed, Iran seems to represent a gastric cancer enigma in terms of *H. pylori* virulence factors; several studies have shown that the presence of *cagA* does not influence progression to peptic ulcers or gastric cancer (6, 12, 23, 29, 49, 50). However, we do note that though not significant in our population, the majority

(68.3%) of isolates from gastric cancer patients did carry the *cagA* gene and the three gastric cancer isolates that were *homA* and *homB* negative also carried the *cagA* gene. These findings suggest that in this population, *cagA* alone is not an adequate predictor of disease and suggest that other virulence genes are important. Indeed, this finding presents the opportunity to assess the impact of other virulence factors on severe disease progression.

Outer membrane proteins are very important during infection and can influence the levels of bacterial colonization. Additionally, an increased number of *H. pylori* cells adherent to the gastric epithelium could induce greater changes in host cell signaling pathways. *H. pylori* carries two paralogous outer membrane proteins, HomA and HomB, which have recently been suggested to be important determinants of disease severity (25). While the *homA* and *homB* genes are 90% identical (1), the differences between *homA* and *homB* translate to different impacts on disease manifestations; *homB* presence is associated with gastric cancer (25).

In this population, the presence of *homB* was associated with progression to gastric cancer; *homB* was present in 78% of all isolates from gastric cancer patients (Table 2). In fact, logistic regression revealed that *homB* was a predictor of gastric cancer independent of *cagA*. However, we did note a positive correlation between the presence of *cagA* and *homB* (Table 2). This suggests that *cagA* and *homB* may interact in some fashion. Of note, *homB* has been shown to be prevalent in the majority of East Asian strains, while the presence of *homA* within these strains is rare (37): East Asian strains typically carry the most virulent form of CagA (5, 21). Despite these correlations, a three-way association between *homB*, *cagA*, and disease state was not identified within this population. If *homB* was influencing only adherence of the bacteria to the gastric epithelium, we would expect that gastric cancer development would still be linked to *cagA*, that there would be a three-way interaction, or that *homB* is not an independent contributor to the progression to gastric cancer. However, data from this population suggest that the presence of *homB* does more than just influence bacterial adherence. Interestingly, it has been demonstrated that the presence of *homB* increases secretion of the proinflammatory cytokine IL-8 (34), and increased inflammation is indicative of more severe disease presentations, such as gastric ulcers and gastric cancer (3). Thus, perhaps HomB promotes more severe inflammation, which in turn affects gastric cancer progression. Since the identification of allelic variants within the central domain of *homB* is recent (35), the impact of these alleles within both Western and East Asian populations still needs to be elucidated. For instance, it would be interesting to determine if different *homB* variants/mutants with point mutations are more prevalent among gastric cancer strains than noncancer strains. If this was the case, then isogenic strains that vary only in the *homB* variant carried could be created and then progression to gastric cancer could be monitored in an animal model. Clearly, the exact mechanistic role of the *homB* gene product in gastric pathology, particularly corpus inflammation, mucosal atrophy, and metaplasia, still needs to be defined.

While it is clear that *H. pylori*-induced disease pathology is influenced by multiple host, dietary, environmental, and bacterial factors, it is clear from this study that the presence of *homB* correlates with severe disease progression. We have shown that there is a statistically significant association between development of gastric cancer and the presence of *homB*. Currently, the reason for this correlation is unclear, and further studies are required to elucidate the molecular role that *homB* plays in cancer development. This study also demonstrates the importance of *H. pylori* virulence factor polymorphism in disease progression, since there is a functional discrepancy between two highly similar genes.

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