



Expression Assessment of the *Helicobacter pylori* *babA* and *sabA* Genes in Patients with Peptic Ulcer, Duodenal Ulcer and Gastric Cancer

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Original Article

Helicobacter pylori as a common gastrointestinal (GI) pathogen must possess certain virulence characteristics to colonize the stomach, evade host immune responses, and subsequently induce GI diseases. This research aimed to investigate the expression level of two important genes, the sialic acid-binding adherence (*SabA*) and the blood group antigen-binding adhesion (*BabA*) in *H. pylori* strains isolated from adult patients living in the northern part of Iran, and their association with peptic ulcer disease (PUD) and gastric cancer (GC). This cross-sectional study was carried out on adult patients referring to the GI clinic of the hospitals affiliated to Babol University of Medical Sciences, Iran. New cases diagnosed with gastritis, peptic ulcer or gastric cancer were included. Endoscopic-guided gastric biopsies were examined and *H. pylori* positive colonies were analyzed to determine the expression of *babA* and *sabA* genes, utilizing specific primers and the SYBR Green dye. Among 175 patients with mean age of 51.6±15.6 years, 101 (57.7%) of the individuals tested positive for *H. pylori* infection. Statistical analysis revealed a significant correlation between *sabA* (P=0.003) and *babA* (P=0.002) gene expression and development of PUD and GC. Smoking (P=0.052), gender (P=0.004) and positive *babA* gene expression (P=0.009) had the greatest association with occurrence of PUD or GC in *H. pylori* positive patients. In summary, the presence of the *sabA* gene in people infected with *H. pylori* increased the risk of GC compared to gastritis, while, the presence of the *babA* gene was significantly increased in gastric ulcer patients. Considering the diversity of *H. pylori* isolates and the varying results observed in different geographical regions, further comprehensive studies are required to evaluate the function of these genes in *H. pylori* pathogenesis and their relationship with clinical outcomes.

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Introduction

Helicobacter pylori (*H. pylori*) infection has been represented as an important cause of gastrointestinal disorders such as gastritis, peptic ulcer disease (PUD) and gastric cancer (GC) (1). In 1994, it was identified as a carcinogen factor, and now this pathogen is the most frequent cause of infection-related malignancies in different regions (2).

The worldwide occurrence of *H. pylori* infection in females and males was reported to be 42.7% and 46.3%, respectively. The prevalence in adults aged 18 years and over is significantly higher than in children (3). The different prevalence rates of this infection in various countries are attributed to economic factors, the coverage of screening programs and social conditions (4).

Most of the infected patients might be asymptomatic, or only have mild gastritis which can be investigated through endoscopic examination; while 15% of individuals can develop to have PUD, and less than 1% may develop to GC. The wide range of clinical features of *H. pylori* infection is a result of interaction between genetic characteristics of the host (such as interleukin(s) or tumor necrotizing factors), bacterial virulence characteristics, and environmental factors (e.g. dietary pattern, smoking, alcohol or substance use) (5).

H. pylori virulence factors have been shown to be involved in three primary processes of pathogenesis, namely colonization, immune evasion, and the progression of disease. The process of adherence is regarded as a crucial mechanism for the successful establishment of *H. pylori* colonization within the stomach. A review of the literature has highlighted the significance of outer membrane proteins (OMPs) in the adhesion of this pathogen to gastric epithelial cells. Numerous genes encoding OMPs belonging to different gene families have been discovered. Notably, the outer membrane protein (Hop) group, the blood group antigen-binding adhesion (*BabA*), and the sialic acid-binding adhesion (*SabA*) are among the most extensively investigated OMPs in *H. pylori* (5). *BabA* and *SabA* share a high degree of similarity; however, *SabA* does not possess the four-strand antiparallel sheet crown which is essential for *BabA* to bind to its receptor Leb on gastric epithelial cells (6). The *SabA* protein was described as a “club shaped” molecule which impacts on the interaction of *H. pylori* with host-cell glycoproteins. It has been suggested that *SabA* may not only interact with sialyl-Lewis receptors, but also with non-sialylated antigens (5).

Different studies examined the association of various *H. pylori* virulence factors with development of serious gastrointestinal disorders (7, 8). However, research into potential virulence factors is critical in order to provide useful clinical data. Because there is no information available about *babA* and *sabA* gene expression in *H. pylori* strains within our specific region in Iran, this study aimed to investigate the association of *babA* and *sabA* gene expression with PUD and GC.

Materials and methods

Study design and Patients

This cross-sectional was carried out on adult patients aged 18 years and over referring to the gastroenterology (GI) clinic at teaching hospital affiliated to Babol University of Medical Sciences, north of Iran.

A total of 175 participants with gastrointestinal disorders, including gastritis, PUD or GC who were diagnosed by the research gastroenterologist were included. Individuals who had a history of taking antibiotics, antacids or proton pump inhibitors for 14 days before initiation of the research, and people who underwent chemotherapy were excluded (9).

All participants signed written informed consent before enrolment. This study was approved by the Ethics Committee of the Babol University of Medical Sciences (approval no. MuBabol.REC.1394171).

Gastric biopsy and transferring the samples to the microbiology laboratory. All the participants underwent upper endoscopy by the research gastroenterologist, a faculty member; and a biopsy specimen from the antrum of patients were taken. The biopsy specimen was transported using microtubes containing Brucella broth (Himedia, India) to the microbiology laboratory within 3-5 h. Microbial culture and detection of *H. pylori* colonies

The antral gastric biopsies were immediately dissected and inoculated onto Brucella agar (Himedia, India) enriched with 7% sheep blood and specific antibiotics (amphotericin B 2.5 mg, trimethoprim 5 mg vancomycin 10 mg and polymyxin B 2500 IU). Then, media were incubated at 37 °C under microaerobic conditions for 5-10 days. Identification was based on the Gram staining results, as well as positive catalase, oxidase, and urease tests. The pure cultures were then stored at -70 °C in a mixture of Brucella broth, glycerol. Molecular detection and expression of *babA* and *sabA* genes

RNA was extracted from exponential phase *H. pylori* cultures with a commercial RNA extraction kit according to the manufacturer's instructions (Roche, high pure RNA isolation kit, Roche Company, Germany). Moreover, cDNA was synthesized with a commercial cDNA synthesized kit according to the manufacturer's instructions (Thermo Scientific™ Fermentas, Company, UK).

Then, the expression of *babA*, and *sabA* genes, and 16S ribosomal RNA (as the control gene) was investigated using the specific primers (Table 1) and the use of SYBR Green dye (SYBR Green qPCR master mix, Yekta Tajhiz Azma Company, Iran) in the ABI 7300 real time PCR machine (USA). Statistical Analytical analyses were conducted using SPSS version 22 (IBM Corporation, Armonk, NY, USA). The normalized average expression of the target genes compared to the housekeeping gene was calculated with QGene software. Also, quantitative data such as the normalized average of the gene expression were measured by the Wilcoxon Test and Kruskal Wallis Test. Moreover, the ORs and their corresponding 95% CIs were used to assess qualitative data. A p-value of less than 0.05 was considered statistically significant.

Table 1. Characteristics of the primers used for assessment of *babA*, and *sabA* gene expression, and 16S ribosomal RNA.

Primer name	Primer sequences	Amplicon size
<i>babA</i>	F*: GCACCCTAAACACCCTTATCAAA R **: ATACCCTGGCTCGTTGTTGAA	254 (bp)
<i>sabA</i>	F: AGCATTCAAAACGCCAACA R: AAAAACCCAATACCGAAGTGATAA	145 (bp)
16S ribosomal RNA	F: GGAGTACGGTCGCAAGATTTAA R: CTAGCGGATTCTCTCAATGTCAA	127 (bp)

*F=Forward primer; **R=Reverse primer

Results

In total, 175 patients with mean age of 51.6±15.6 years including 92 (52.6%) men and 83 (47.4%) women were recruited. Among them, 62 (35.4%) had gastritis, 70 (40%) had PU and 43 (24.6%) had GC. The mean age among the persons diagnosed with gastritis was 45.4±13.1 years; in patients with peptic ulcer: 48.7±13.3 and in persons with gastric cancer were 65.1±14.6 years, respectively. Out of all collected samples, 101 (57.7%) of the patients had *H. pylori* infection based on culture as previously described (9).

Gene expression by Real-time qRT-PCR

Among the 101 patients with positive *H. pylori* infection, expression of *babA* and *sabA* genes in three defined disease groups showed that in the group with gastritis, 25 patients (83.3%) had *sabA*, and 9 (30.0%) had *babA* gene expression.

In patients with PU, 35 (87.5%) were *sabA* positive, and 20 (50.0%) were *babA* positive, in patients with GC, 13 (41.9%) had *sabA* and 4 (12.9%) had *babA* gene expression. Furthermore, in the gastric group, 25 (83.3%) had *sabA* gene expression and 9 (30%) had *babA* gene expression. A Comparison of *sabA* and *babA* gene expression in these three disease groups is presented in Table 2. Accordingly, there are significant associations between expression of *sabA* and *babA* and Gastric cancer ($p < 0.001$ and $p = 0.004$), respectively.

Table 2. Investigating the qualitative expression of genes related to pathogenesis in *H. pylori* by disease groups.

Genes	Disease groups			Total (%)	P- value	
	Gastric	Gastric ulcer	Gastric cancer			
	No (%)	No (%)	No (%)			
Qualitative gene expression <i>sabA</i>	Positive	25 (83.3)	35 (87.5)	13 (42)	73 (72.3)	<0.001
	Negative	5 (16.7)	5 (12.5)	18 (58)		
Qualitative gene expression <i>babA</i>	Positive	9 (30)	20 (50)	4 (12.9)	33 (32.7)	0.004
	Negative	21 (70)	20 (50)	27 (87.1)		

The numbers in the table are reported as numbers (percentages) and $P < 0.05$ is considered significant.

According to Table 3, the chance of developing GC was higher in *H. pylori* infected individuals with the presence of the *sabA* gene compared to those without the gene ($p = 0.010$), suggesting that the *sabA* gene may be an important factor in the development of GC. Table 3. Comparison of *sabA* and *babA* gene expression in gastric ulcer and gastric cancer.

Table 3. Comparison of *sabA* and *babA* gene expression in gastric ulcer and gastric cancer.

Characteristics	PU		GC	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Positive <i>sabA</i> gene expression	1.051	0.952	0.069	0.010
Positive <i>babA</i> gene expression	4.046	0.032	1.02	0.98

* Likelihood ratio test; GC: Gastric cancer, PU

Characteristics PU GC

Additionally, the presence of the *babA* gene in *H. pylori* infected individuals was associated with a 4.04-fold increase in the risk of developing PU compared to gastritis, indicating that the *babA* gene may be an important risk factor for PU ($p = 0.032$).

The mean, standard error of the mean, and median of the normalized values of the two genes, *sabA* and *babA*, in different disease groups were examined using the Kruskal-Wallis test in Table 4. Based on the results, no correlation was observed between the normalized values of the two genes and gastrointestinal diseases. However, based on the median, it was indicated that *sabA* was expressed more than *babA*. Furthermore, based on the type of disease, it was indicated that *sabA* was expressed more in the GC samples than in the PU samples. On the other hand, *babA* was expressed more in the PU samples than in the GC samples. Table 4: The mean, standard error of the mean, and median of the normalized expression values of *sabA* and *babA* genes in different disease groups.

Table 4. The mean, standard deviation, and median of the normalized expression values of *sabA* and *babA* genes in different disease groups.

Genes	Type of disease	<i>sabA</i>	<i>babA</i>
		Mean \pm SD** (Median)	Mean \pm SD (Median)
Gastric		2.71 \pm -1.89 (-1.60)	3.26 \pm 3.68- (-3.26)
Gastric ulcer		2.12 \pm 1.69- (1.35)	2.12 \pm 2.45- (1.99)
Gastric cancer		3.54 \pm 2.73- (0.83)	5.1 \pm 5.19) 3.38)
P- value*		0.898	0.372

* Kruskal Wallis Test

** SD: standard deviation \pm mean

Discussion

In earlier investigations, it has been demonstrated that individuals with *H. pylori* infection and gastric ulcers face a higher risk of developing GC, whereas only a small number of DU cases progress to GC.

According to our findings, of the 175 patients studied, 40%, 35%, and 25% had PU, gastritis, and GC, respectively, with 57.7% of them having *H. pylori* infection. Additionally, the mean age of the referring patients was 65.1 years, and among those with *H. pylori* infection, the average age was 64 years, which is considered a probable risk factor for cancer.

It is interesting to note that there was a significant relationship between gender and gastrointestinal diseases. Among the referring patients, men were more often than women suffering from PU and GC. This result was contrary to gastric inflammation, as women had more cases of gastritis than men. Moreover, the prevalence of *H. pylori* depends on geographic regions, age, social and economic status, occupation, and living environment (10, 11).

The virulence factors expressed by *H. pylori* can serve as a predictive indicator for the development of diverse gastroduodenal diseases. Studies have shown that the expression of the *babA* and *sabA* genes, adhesins found in *H. pylori*, is significantly higher in patients with PU and GC compared to healthy individuals (12, 13). This implies that *babA* and *sabA* are the main adhesin genes of *H. pylori*, facilitating both colonization and motility processes.

Accordingly, another important finding of ours was that 72.3% and 32.7% of isolates had expression of the *sabA* and *babA* genes, respectively. PU and GC samples had the highest and lowest expression of the *sabA* gene, respectively. Recent studies have demonstrated that the *sabA* gene is the primary factor in the

initial colonization of *H. pylori* and is more active during chronic inflammation, which is in agreement with the findings(14).

The expression of the *sabA* gene in *H. pylori* varies depending on the geographic region (15). In some regions, such as Europe, the *sabA* gene is found in up to 90% of *H. pylori* strains, whereas in other regions, such as Africa, the frequency is much lower, ranging from 0-20%.

In the current study, the presence of the *sabA* gene in people infected with *H. pylori* increased the risk of GC compared to gastritis, and was an important factor in supporting GC. However, it was not significant in relation to PU. These results are consistent with those of other studies conducted in Iran (83.6-100%)(16-18), Taiwan (80%) (19), France (86%) (20), and the Netherlands (93%) (21), while our findings do not support the previous research in Iran (28.7%) (22) and Turkey (7.3%) (13). This result revealed that *sabA* genetically varies among different strains and geographic areas (23), and may not be present in all *H. pylori* isolates.

Numerous epidemiological studies have examined the significance of *SabA* in the progression of gastroduodenal diseases. *SabA* has been linked to conditions such as atrophic gastritis, intestinal metaplasia, and gastric cancer (24). Nevertheless, the relationship between *SabA* and diseases within the gastroduodenal tract remains a subject of controversy (25).

Moreover, the *babA* gene was detected among 50% of peptic ulcer patients. This finding of the current study is consistent with those of other studies that found 40.6% of *H. pylori* isolates had the *babA* gene. However, Talebi *et al* demonstrated that the presence of the *babA* gene is associated with gastric cancer(25).

Furthermore, Kpoghomou *et al.* have proposed that the presence of *H. pylori* carrying the positive *babA2* gene may potentially elevate the risk of gastric cancer, particularly within the Asian population (26). In the present study, the presence of the *babA* gene was significantly increased in gastric ulcer patients. Additionally, the results of our study showed that the *babA* gene can be a risk factor for PU, such that the presence of the *babA* gene in people infected with *H. pylori* compared to the absence of *babA* in infected people increases the risk of developing gastric ulcers (OR = 4.04). This inconsistency may be due to the expression of different virulence factors, host genetics, and environmental factors (27).

The results of this study did not show any significant expression of the *sabA* and *babA* genes and gastrointestinal diseases. However, the results showed that the expression of *sabA* was higher than *babA* regardless of the type of gastrointestinal infection. Doohan *et al.* demonstrated that the absence of *babA* expression can lead to a decrease in the capacity of *H. pylori* to adhere to the Lewis antigen on the surface of gastric epithelial cells (12).

Numerous investigations have proposed a connection between *babA2* and heightened inflammation of the gastric mucosa, along with an increased risk of developing clinical outcomes (12). In a study conducted by Fujimoto *et al.*, it was observed that strains with low *BabA* production exhibited more extensive mucosal damage and were linked to gastritis (28). Ansari *et al.* concluded that while high-level *BabA* expression is correlated with severe clinical outcomes, several reports have also indicated that low-level expression can lead to severe outcomes, although the underlying mechanism remains unclear (6).

Previous research has indicated that the *sabA* gene's "on/off" switch allows for a swift response to changing conditions in the gastric, which may help prevent the host's immune system from reacting (12). It

is also possible that the expression of the *sabA* gene is regulated by the secretion of gastric acid. Various animal models have shown that the expression of functional *BabA* is lost during the infection phase, which suggests that the adhesion function of *BabA* is highly dynamic and similar to that seen in human infections (29, 30). This may be related to *H. pylori*'s ability to avoid unfavorable colonization environments and evade the host's immune response (12). Limited studies have focused on research outcome variables similar to our research, and this makes it difficult to compare our findings with similar or opposite studies. We did not examine the participants' blood group, dietary pattern, or comorbid disorders such as diabetes mellitus or immunosuppressive disorders, which can alter the patient's biologic profile. These points can be presented as the limitations of this research. Multi-center studies and recruitment of patients with different genetic characteristics are recommended for further research.

The current study found that, similar to most other studies, the expression of *sabA* was greater than that of *babA*. However, the expression of *sabA* was notably lower compared to other findings reported in the literature. Considering the diversity of *H. pylori* isolates and the varying results observed in different geographical regions, further comprehensive studies are required to evaluate the function of these genes in *H. pylori* pathogenesis and their relationship with clinical outcomes in Iran. It is imperative to conduct studies with a substantial sample size to gain deeper insights into the interplay between environmental factors, bacterial genotype, and host factors concerning the risk of GC.

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