



# Frequency of *Helicobacter pylori* *hopQI*, *hopQII* and *sabA* Genes Among Iranian Patients with Gastroduodenal Diseases

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## Abstract

**Background:** *Helicobacter pylori* has been recognized as the most common pathogen of human gastroduodenal tract and it has been suggested that adhesins, including HopQ and SabA, are associated with the organism's virulence.

**Objectives:** The current study aimed at determining the frequency of *hopQI*, *hopQII*, and *sabA* genes among *H. pylori* isolates from patients with gastroduodenal disorders in Shahrekord, Iran.

**Methods:** Gastric corpus samples were obtained from 150 symptomatic patients admitted to the endoscopy unit at gastroenterology clinic. After DNA extraction from all corpus samples, *H. pylori* molecular confirmation and genotyping was performed by the polymerase chain reaction (PCR), using specific primers for *glmM*, *16SrRNA* and *hopQ*, *sabA* genes, respectively.

**Results:** The *hopQI*, *hopQII*, and *sabA* genes were found in 74 (49.3%), 59 (39.3%), and 43 (28.7%) cases, respectively. The *hopQI* gene was detected in 75% of patients with gastric cancer (GC), 42.4% with chronic gastritis (CG), and 57.4% with peptic ulcer disease (PUD). The *hopQII* among patients with GC, CG, and PUD was also detected in 50%, 38.8%, and 39.3%, respectively. Moreover, *sabA* was diagnosed in 50% of patients with GC, 29.4% with CG, and 26.2% with PUD.

**Conclusions:** No significant association was observed between *hopQI*, *hopQII*, and *sabA* genes with clinical outcomes.

**Keywords:** Gastroduodenal Diseases, *Helicobacter pylori*, *hopQ*, *sabA*

## 1. Background

*Helicobacter pylori* as microaerophilic and Gram-negative spiral shaped bacteria, are strongly associated with chronic gastritis (CG), peptic ulcer disease (PUD), and gastric cancer (GC) (1). In all patients, the infection can cause gastritis, yet only 10% to 15% will develop clinical signs (1, 2). Binding of *H. pylori* to the gastric epithelia, can result in the colonization, evasion from the immune system, and transfer of virulence factors to the gastric cells.

*Helicobacter pylori* outer membrane proteins (OMPs) can play an important role in binding to the gastric epithelia (1). About 4% of the genome is responsible for encoding OMPs, including SabA, AlpA and B, BabA, OipA, and HopQ (OMP 27) (1, 3-6). HopQ is divided to two families, HopQI and HopQII, which have amino acid sequence homology between 61% and 72% (7). Although the function of this pro-

tein is unknown, it has been suggested that it is involved in organism colonization, adhesion, and progress of peptic ulceration (7-9). The distribution of *hopQI* and *hopQII* genes varies in different populations and geographic regions (10-12). The *hopQ* shows a high degree of genetic diversity and *H. pylori* *hopQI* is more common in patients with peptic ulcer. Moreover, HopQI and HopQII are mostly present in *cagA*<sup>+</sup> strains (13). On the other hand, SabA is a sialic acid-binding protein and can mediate binding of *H. pylori* to gastric mucosa cells. Sialyl-Lewis x/a (sLe<sup>x</sup> and sLe<sup>a</sup>) antigens act as adhesin receptors for the SabA protein.

Sialylated glycoconjugates are found in small amounts in the stomach of healthy individuals yet in the presence of *H. pylori* infection, the expression of these antigens, especially sLe<sup>a</sup>, are associated with gastric malignancies in both developed and developing countries. This issue represents the important role of SabA in gastric atrophy and gastric cancer. Therefore, more studies on SabA, particularly in

developing countries, is suggested (14, 15). The association of different genotypes of *H. pylori* with clinical outcomes varies in different populations. Hence, investigation of putative virulence factors is crucial to provide useful clinical data in medical practice.

## 2. Objectives

Since there have been limited published epidemiologic studies on the prevalence of *hopQ* and *sabA* in *H. pylori* strains isolated from patients with gastrointestinal disorders in Iran, the present study aimed at evaluating the frequency of these genes among *H. pylori* isolates from patients with gastroduodenal disorders in an Iranian symptomatic population.

## 3. Methods

### 3.1. Ethics Statement

This study was approved by the Ethics Committee of Shahrekord University of Medical Sciences (EC = 92-11-31).

### 3.2. Patients, Endoscopy and Biopsies

In this cross-sectional study, conducted between March 2013 and April 2015, 150 *H. pylori*-positive patients, who underwent upper gastrointestinal endoscopy for a variety of indications at the Endoscopy Services of Hajar Hospital in Shahrekord, center of Iran, were included. Based on endoscopic and histological findings, the participants were classified to chronic gastritis (CG = 85), peptic ulcer disease (PUD = 61), and gastric cancer (GC = 4) groups. Some samples were taken from previously performed studies (16, 17). Written informed consent was obtained from all patients. Patients, who had undergone anti-*H. pylori* eradication therapy within the past three months, were excluded. During gastroscopy, biopsy samples were taken from the corpus for rapid urease test (RUT) and DNA extraction.

### 3.3. Rapid Urease Test (RUT)

For each patient, corpus samples were taken and tested for the presence of urease enzyme. The campylobacter-like organism (CLO) test (Romania) was used in this study. After 10 to 15 minutes at room temperature, if *H. pylori* urease was present in the tissue sample, it changed the gel from yellow to bright magenta.

### 3.4. Genomic DNA Extraction and Polymerase Chain Reaction (PCR)

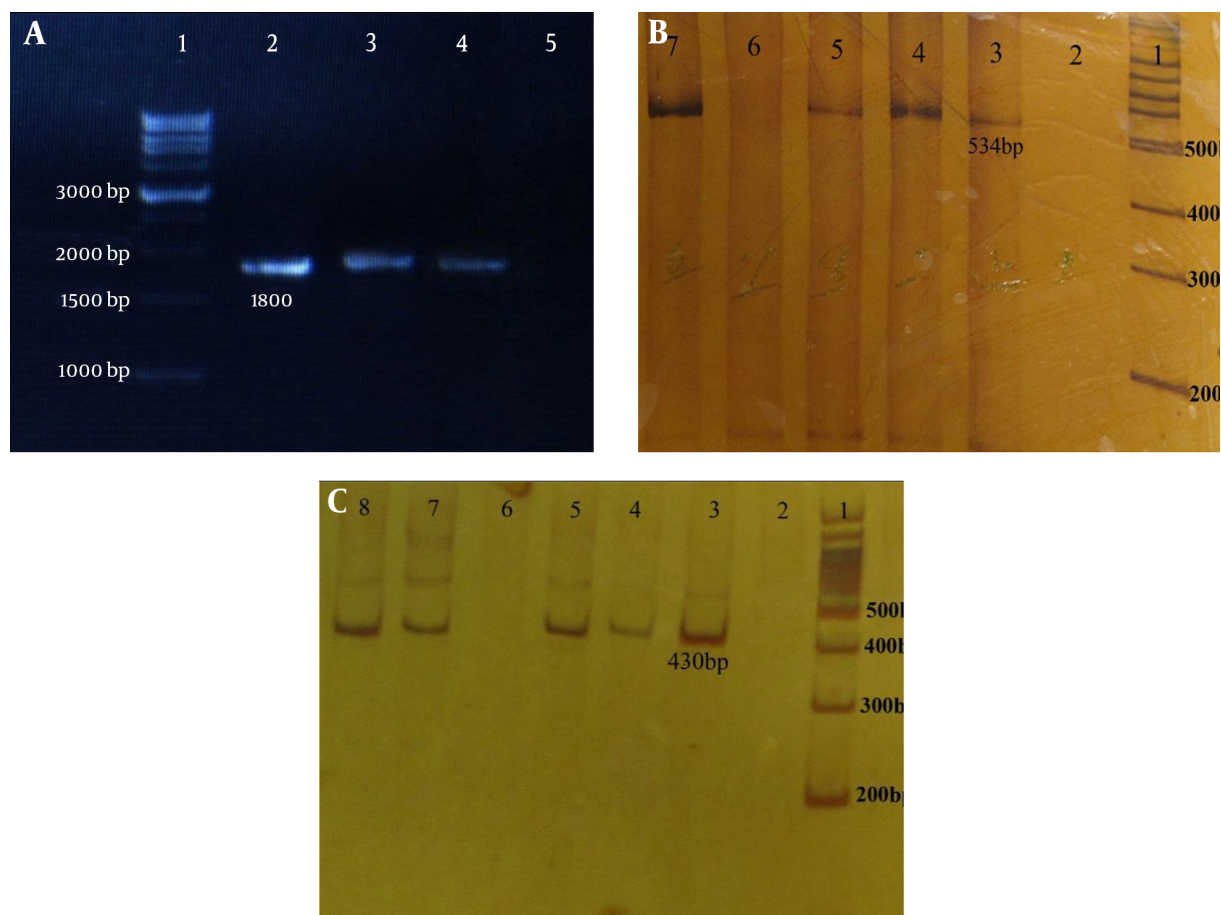
The phosphate buffer saline (pH = 7.2) microtubes containing corpus biopsies for DNA extraction were sent to the Cellular and Molecular Center, Shahrekord University of Medical Sciences. Genomic DNA was extracted using the DNA extraction kit (BioFlux Co., Japan), according to the manufacturer's instructions. For *H. pylori*, molecular diagnosis at the species level (*glmM* and 16S *rRNA*), and for the presence of *hopQI*, *hopQII* and *sabA* genes, PCR assays were performed by previously described primers (7, 18, 19). Each PCR amplification was performed in a reaction volume of 25  $\mu$ L, containing 1  $\times$  PCR buffer, 200 ng DNA, 4 mM MgCl<sub>2</sub>, 1.6 mM dNTP, 0.02 U Taq DNA polymerase and 0.16 pM primer (for *hopQI*) and 300 ng DNA, 4 mM MgCl<sub>2</sub>, 1.6 mM dNTP, 0.02 U Taq DNA polymerase, and 0.2 pM primer (for *hopQII*). To detect *sabA*, 200 ng DNA, 6 mM MgCl<sub>2</sub>, 3.2 mM dNTP, 0.02 unit Taq DNA polymerase, and 0.2 pM primer was used. The amplification of individual genes was done in a thermocycler (Corbett Research, Australia), as described previously (10, 19, 20). Amplicons were analyzed on 1% agarose gel and stained by the ethidium bromide (0.5  $\mu$ g/mL) for *sabA* and 6% polyacrylamide gel with TBE 5  $\times$  for *hopQI* and *hopQII* genes, and examined under UV illumination (Figure 1).

### 3.5. Data Analysis

The Chi-square ( $\chi^2$ ) and Fisher's exact tests were used for analysis of significant differences between the studied virulence genes with the clinical outcome results using the SPSS software (version 22.0; IBM Co., Armonk, NY, USA). The results of demographic and clinical manifestations were presented as descriptive statistics in terms of relative frequency. P values of < 0.05 were considered statistically significant.

## 4. Results

In the current study, 150 *H. pylori* strains obtained from patients (85 females and 65 males, ranging in age from 15 to 85 years with a mean age of 43 years, which were categorized to three groups, including patients < 30, between 30 and 50, and > 50 years old) with gastroduodenal disorders after confirmation by RUT and PCR (for detection of *glmM* and 16S *rRNA* genes), were evaluated for the presence of *hopQI*, *hopQII* and *sabA* genes. The *hopQI*, *hopQII*, and *sabA* genes were detected in 74 (49.3%), 59 (39.3%), and 43 (28.7%) of the isolates, respectively ( $P > 0.05$ ). The distribution of these genes in CG, PUD, and GC cases, were as follows: *hopQI* (42.4%, 57.4%, and 75%), *hopQII* (38.8%, 39.3%, and 50%) and *sabA* (29.4%, 26.2%, and 50%). No significant difference ( $P >$



**Figure 1.** Agarose gel electrophoresis of *sabA* and polyacrylamid gel of *hopQI* and *hopQII* genes in *H. pylori* isolates. A, *H. pylori sabA*: lane 1: 1kb DNA ladder marker, lanes 2 - 4 (1800 bp): *sabA* positive strains, and lane 5 is negative for *sabA*. B, *H. pylori hopQI*: lane 1: 100 bp DNA ladder marker, lanes 3 - 5 and 7 (525 bp): *hopQI* positive strains and lanes 2 and 6 are negative for *hopQI*. C, *H. pylori hopQII*: lane 1: 100 bp DNA ladder marker, lanes 3 - 5 and 7 - 8 (430 bp): *hopQII* positive strains, and lanes 2 and 6 are negative for *hopQII*.

0.05) was observed between age or gender and clinical outcome (Tables 1 and 2). The association between disease type and the presence of *hopQI*, *hopQII* and *sabA* genes was also not significant ( $P > 0.05$ ).

**Table 1.** Distribution of Different Clinical Diseases According to Patients' Gender<sup>a,b</sup>

Gender	Disease Group		Total
	Group 1	Group 2	
Female	29 (44.6)	56 (65.9)	85 (56.7)
Male	36 (55.4)	29 (34.1)	65 (43.3)
Total	65 (100)	85 (100)	150 (100)

<sup>a</sup>Values are expressed as No. (%).

<sup>b</sup>Group 1: Patients with peptic ulcer disease and gastric cancer, group 2: patients with chronic gastritis.

## 5. Discussion

The present study evaluated the frequencies of *H. pylori hopQI*, *hopQII*, and *sabA* genes among patients with gastro-duodenal diseases in Shahrekord, Iran. The *hopQI* gene

**Table 2.** Distribution of Different Clinical Diseases According to Patients' Age<sup>a,b</sup>

Age	Disease Group		Total
	Group 1	Group 2	
Group 1	17 (26.2)	18 (21.2)	35 (23.3)
Group 2	31 (47.7)	45 (52.9)	76 (50.7)
Group 3	17 (26.2)	22 (25.9)	39 (26)

<sup>a</sup>Values are expressed as No. (%).

<sup>b</sup>Age group 1: patients less than 30 years old, age group 2: patients between 30 to 50 years old, age group 3: patients more than 50 years old, disease group 1: patients with peptic ulcer disease and gastric cancer, disease group 2: patients with chronic gastritis.

was predominant (49.3%) in comparison with *hopQII* and *sabA* genes with frequencies of 39.3% and 28.7%, respectively. Host's genetics, environmental factors, such as diet, and *H. pylori* virulence determinants are associated with the severity of clinical outcomes (21, 22). Genotypic analysis of *H. pylori* is also a useful method in screening of gastric diseases (20). In the recent years, the role of *H. pylori* OMPs, such as *hopQ* and *sabA*, in developing of digestive diseases have been investigated. Therefore, the association of virulence genes with clinical outcome needs to be further investigated in clinical practice. It has shown that *hopQ* can be a candidate adhesin to gastric epithelium cells (8).

The frequencies of *hopQI* and *II* alleles vary depending on geographic regions. Previous studies in Western and Eastern countries have shown that there is a higher prevalence of *hopQI* than *hopQII*. The prevalence of *hopQI* and *hopQII* genes in the United States and East Asian countries were reported as 55.5%, 30.9% and 88.8%, 0.7%, respectively (10). Moreover, this frequency for *hopQI* among Colombian and Italian patients was reported as 72% and 29%, respectively (11, 12). The current results (49.3% for *hopQI* and 39.3% for *hopQII*) are similar with a study conducted in the United States (10). Indeed, in the study of Ohno et al. (9) among Asian and Western population, no significant association was observed between *hopQ* genotypes and clinical outcome. In the first ever study conducted in Iran, the frequency of *hopQI* (33%) was mentioned lower than *hopQII* (52%), and the *hopQII* genotype was found to be associated with gastric cancer (20). The reported results are in contrast with the current study, so that no association was found between gastrointestinal diseases and *hopQ* alleles ( $P > 0.05$ ). The current findings are consistent with the results of two other studies from Iran (23, 24).

Due to the absence of sLe<sup>x</sup> in normal gastric epithelia, the *sabA* can be related to the *H. pylori* chronic persistence and severe clinical outcomes, such as gastric cancer (14, 25). The present data (28.7%) compared to studies in Taiwan (80%), France (86%), and Netherland (93%), revealed a much lower rate (26-28). The *sabA* frequency among Japanese patients from different population and times, was also found to be 81% and 91%, respectively (29, 30). Yamaoka et al. in the United States reported that *sabA* frequency in patients with gastritis, duodenal ulcer and gastric cancer was 66%, 44%, and 70%, respectively, and a significant association was established between *sabA* and gastritis and gastric cancer (31).

In three previous studies from Iran, the frequency of *sabA* was reported as 86.6%, 83.6%, and 100%, respectively, with no association with the severity of clinical outcomes (32-34), and this was in line with the current findings and another study from Japan (29). In comparison with the above-mentioned studies from different countries, the cur-

rent results showed a considerably lower rate of *sabA*. This issue highlights that *sabA* genetically varies among different strains and geographic areas (30), and might not be present in all *H. pylori* isolates (14). On the other hand, to establish an association between *H. pylori* virulence determinants and clinical outcome, patient selection is crucial because the studied participants should be sufficiently large and heterogeneous (35).

### 5.1. Conclusions

Consistent with most other studies, the rate of *hopQI* in the current study was higher than *hopQII*; however, *sabA* frequency in contrast to other reports was considerably low. Taken together, regarding the heterogeneity of *H. pylori* isolates and diverse results from different geographic areas, further intensive studies are needed to assess the role of the above-mentioned genes in *H. pylori* pathogenesis and their association with clinical outcomes in Iran.

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### Footnotes

**Authors' Contribution:** Study concept and design, Reza Khashei; acquisition of data and sampling, Zahra Sedarat, Nader Bagheri, Marzieh Sadeghiani, and Heshmat Shahi; analysis and interpretation of data, Zahra Sedarat, Nader Bagheri, Marzieh Sadeghiani, and Heshmat Shahi; drafting of the manuscript, Zahra Sedarat and Reza Khashei; critical revision of the manuscript for important intellectual content, Reza Khashei; study supervision, Behnam Zamanzad; study advisor, Hedayatollah Shirzad.

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