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Helicobacter pylori virulence factors in relation to gastrointestinal diseases in Iran

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ABSTRACT

Purposes: *Helicobacter pylori* as an important pathogenic bacterium that colonizes in gastric mucosa, is one of the causative agents in development of some types of gastric diseases, such as chronic active gastritis, peptic ulcer disease (PUD) and gastric cancer (GC). In this review, the aim is studying different genotypes of *H. pylori*, and the extent of their participation in the pathogenesis of this bacterium which creates gastroduodenal disorders.
Results: Some genotypes of *H. pylori* have a major role in creation of gastroduodenal diseases, whereas some other genotypes of the bacterium do not cause gastric diseases in Iran. It was also reported that some genotypes of this bacterium in different conditions and among different ethnic groups demonstrate different effectiveness.
Conclusion: Role of genotypes of *H. pylori* in creation of gastroduodenal diseases is different among various regions and ethnic groups of Iran.

Contents

1. Introduction 211
1.1. Bacterial virulence factors 212
1.1.1. Correlation of the genes of *cag* PAI region with gastroduodenal diseases 212
1.1.2. The relationship between *vacA* alleles and gastric diseases 212
1.1.3. The relationship between the *iceA1* and *iceA2* genotypes and gastroduodenal diseases 214
1.1.4. *dupA*$^{+}$ strains of *H. pylori* and gastric diseases 215
1.1.5. *babA* genotype 215
1.1.6. *homB* gene 216
1.1.7. *tnpA* and *tnpB* 216
1.1.8. *oipA* gene 216
1.1.9. Other factors 216
2. General considerations 216
3. Conclusion 216
References 216

1. Introduction

Gastric cancer is the second leading cause of death from cancer and the fourth type of cancer in terms of frequency worldwide [1]. A comparison among the continents has shown that about two-

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thirds of people with gastric cancer (GC) are from Asia [1–3]. Iran ranks fourth in Asia in terms of the prevalence of GC after three countries of China, Japan and Korea [1,2,4]. *H. pylori* is the major human pathogen that proliferates and colonizes in human gastric epithelial cells. There is the most virulence and the highest prevalence of this pathogen in the developing countries rather than developed countries [5,6].

About 90% of Iranians are infected with *H. pylori* bacterium [6,7]. Clinical manifestations of gastric disorders are caused by *H. pylori* including gastroduodenal diseases such as chronic atrophic gastritis, peptic ulcer diseases (PUD), gastric adenocarcinoma (GC), duodenal ulcer (DU), dysplasia, intestinal metaplasia, and mucosa associated lymphoid tissue (MALT) [1,6–11]. Bacterial infection in combination along with other factors including host genetic factors, environmental factors and types of bacterial genotypes cause various manifestations of gastrointestinal disorders [12–14].

There is a high frequency of *H. pylori* infection in Iran (69%) [8,15]. The highest frequency is observed in Ardabil, northwestern province of Iran (89%), after that other cities in north of Iran such as Guilan, Mazandaran, Golestan and East Azerbaijan are the other high risk regions [8]. In moving from the north to the southern parts of Iran, the frequency reduction of gastrointestinal diseases is considerable [5,8,16–18].

The characteristics of the bacterium are as follows: gram-negative bacterium, microaerophilic and spiral-shaped [5,19–21]. All the types of *H. pylori* genetically are located in two major groups, including *cagA*$^+$ (cytotoxin-associated gene A) and *cagA*$^-$, such that CagA is the main virulence factor of this bacterium and after that second intensive virulence factor of the bacterium is the vacuolating cytotoxin A, VacA [6,22].

In the present study, the effects of *cagA* and *vacA* and other genotypes of *H. pylori* such as *iceA, oipA, babA, dupA,* etc. in correlation with gastrointestinal diseases in Iranian patients are reviewed.

1.1. Bacterial virulence factors

1.1.1. Correlation of the genes of cag PAI region with gastroduodenal diseases

The *cag* PAI (*cag* Pathogenicity Island) region divides into two areas including *cag*I and *cag*II. Pathogenesis of combined genes in *cag* PAI is much higher than that of a single gene. On the other hand, genes in either of the *cag*I and *cag*II regions are not effective in creation of gastric diseases alone [9]. The *cag* PAI consists of some pathogenic factors, including CagE, -G, -H, -I, -L, -M, -T and -Y. CagE, -G, -H, -I, -L and -M are promoting factors for producing of NFKβ that causes apoptosis in gastric epithelial cells. CagT and CagY create needle-shaped structures that allow penetration of CagA toxin into the gastric epithelial cells [5,23,24]. In some studies no association was seen between the genes of *cag* PAI region, for example *cagA, -E* and *-T*, and gastric diseases [7,9].

1.1.1.1. cagA. The *cagA* gene is present downstream of 40 kb cluster of *cag* PAI [9,25]. *H. pylori*, using a type IV secretion system can inject CagA into gastric epithelial cells [23,24,26]. The *cagA* genotype is not conserved among strains of *H. pylori* [26]. The *cagA* genotype has the most frequency among Iranian *H. pylori* strains [7,27]. In a study conducted in Tehran_ capital of Iran a significant correlation was found between only the *cagA* genotype and severe active chronic gastritis ($P = 0.011$) [14]. In another research, researchers did not observe any correlation between *cagA* status and ulcer in selected children group, whereas the correlation of *cagA* with more severe gastric inflammation was seen ($P < 0.05$) [27].

In general, there have been some inconsistent reports about the *cagA* positivity and the risk of GC in Iran. In some studies, it was shown that the *cagA* genotype is not associated with gastric diseases ($P > 0.05$) [9,26,28–33], whereas in a study, researchers have found a significant relationship between the *cagA* genotype and gastric diseases such as DU and GC (Relative risk was 1.30; 95% CI 1.01–1.69, 1.81; 95% CI 1.44–2.29, respectively) [5] (Table 1).

For instance, in a study from Tehran it was noticed that there is not any correlation between *cagA* genotype and GC or PUD. On the other hand, the frequency of this genotype is almost equal among three groups of patients with GC, PUD and non–ulcer dyspepsia (NUD). Also in the mentioned study, no significant discrimination was found between the three Iranian ethnic groups including Fars (65%), Turks (73%) and other ethnic groups (71%) in terms of *cagA*$^+$ status [7]. However, in other study from the same region, it was reported that *cagA* status is in correlation with the risk of gastric diseases ($P = 0.011$) [14]. A study, which was performed on a larger number of strains from different ethnic and geographic origins in Iran, showed a significant correlation between the presence of *cagA* and GC, the odds ratio (OR) (95% confidence interval, CI) was 2.59 (1.09–6.12) [34]. Moreover, recently, Shakeri et al. conducted a case (n = 272)-control (n = 524) study to examine the association between different multiplex serology antigens and the risk of gastric cardia adenocarcinoma (GCA) and gastric non-cardia adenocarcinoma (GNCA) in northeastern Iran. They found that *cagA* and *vacA* significantly increased the risk of all the gastric adenocarcinoma and GNCA. Interestingly, only the CagA was significantly associated with an increased risk of GCA [35]. These the last two important studies however revealed the significance of CagA in the development of GC in Iran.

In patients with DU disease who are infected by the *cagA*$^+$ genotype of *H. pylori*, the amount of IL12 —an inflammatory cytokine — is higher than normal individuals ($P = 0.0001$). The amount of IL13 secretion is not affected by *cagA* strains of *H. pylori* ($P > 0.05$) [6]. In response to the CagA toxin, IL8 is produced by gastric epithelial cells ($\chi^2 = 10.47$; $P = 0.005$) [26,36,37].

1.1.1.2. cagE. The *cagE* gene is located in *cag*I from *cag* PAI whose product is the inducer for producing IL8 [9,25,38]. It also helps the penetration of CagA toxin into the gastric epithelial cells. In a unique study of Tehran population concerning gastric disorders about *cagE* status, which in this study, the investigated ethnic groups consist of Persians, Turks and other ethnic groups including Kurds, Lurs, Afghanis and Arabs, the most prevalence of this gene was seen among ethnic groups (77%) except the Turks (30%) and Persians (47%) ($P = 0.008$), but no remarkable association was noticed between *cagE* status and gastrointestinal disorders ($P = 0.23$) [7].

1.1.1.3. cagT. The *cagT* gene is located in *cag*II region of *cag* PAI. In an investigation conducted in Tehran, it was seen that *cagT* status is not associated with various gastric diseases ($P = 0.344, 0.791$) [9].

1.1.2. The relationship between vacA alleles and gastric diseases

One of the loci that involves in the pathogenesis of this bacterium is the *vacA* locus which produces the VacA toxin. This gene is conserved, and has some polymorphism regions including s (signal), m (middle), i (intermediate) and finally d (deletion) that is located between i and m regions. Each area has two alleles such as s1/s2 [8,39,40]. The s region is the creator of both peptide signal and the N terminus of VacA toxin [26,41]. The s1 region is divided into three subtypes including s1a, s1b and s1c.

It has been reported that the correlation of the *vacA* s1a allele with ulcer diseases is higher than that of *vacA* s1b and s2 alleles. The m1 region is divided into three subtypes including m1a, m1b and m1c. The m1 allele has high correlation with ulcer diseases rather than m2 allele [7]. The m (mid region) also creates the