

Gene polymorphisms of pathogenic *Helicobacter pylori* in patients with different types of gastrointestinal diseases

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Abstract

Helicobacter pylori (*H. pylori*) is a kind of chronic infectious pathogen which can cause chronic gastritis, peptic ulcer, gastric cancer and other diseases. The genetic structure of the pathogenic genes of *H. pylori* varies largely, which contributes to the differences in virulence among various strains, and in clinical symptoms. Virulence genes of *H. pylori* can be categorized into three main classes: those related to adhesion and colonization, those related to gastric mucosal injury, and others. This review focuses on the relationship between genetic polymorphisms of the three classes of virulence genes of *H. pylori* and diseases. Most of the genetic polymorphisms of the main virulence factors of *H. pylori* are summarized in this paper.

Key words: *Helicobacter pylori*; Pathogenic gene; Polymorphism; Gastrointestinal disease

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Core tip: *Helicobacter pylori* (*H. pylori*) is the causative agent of gastrointestinal diseases such as atrophic gastritis and peptic ulcers. Manifestations associated with chronic *H. pylori* infection vary considerably among distinct geographic regions and these differences have been attributed at least in part to polymorphisms of *H. pylori* genes, particularly those encoding virulence factors. There are several reviews for polymorphisms

of *H. pylori* genes. However, this is the first review to report the relationship between genetic polymorphisms and diseases. Virulence genes of *H. pylori* can be categorized into three main classes. This helps to understand the gene polymorphisms of pathogenic *H. pylori* in patients with different types of gastrointestinal diseases.

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INTRODUCTION

As one of the most common pathogens, *Helicobacter pylori* (*H. pylori*) is a Gram negative microaerophilic bacterium which is closely related to chronic gastritis, peptic ulcer disease, gastric cancer and mucosa associated lymphoid tissue lymphoma^[1]. Even to the cases of non-gastrointestinal diseases, such as chronic cardiovascular disease, liver and biliary tract diseases and colorectal cancer, *H. pylori* also has a synergistic contribution^[2]. In 1994 *H. pylori* was labeled as one of the first class cancer causing factors by the International Institute for Cancer Research^[3]. Over half of the world's population are infected with *H. pylori* during their lifetime. With a small part of infected patients developing digestive diseases, gastric cancer, liver cancer and other tumors in severe cases, most of them have no dominant symptoms of infection^[4,5]. The reason for high rate of *H. pylori* infection but low incidence or different severity of the disease happening is due to the genetic polymorphisms of *H. pylori*. The polymorphisms make the differences in virulence and pathogenicity of *H. pylori*, which lead to different clinical manifestations after *H. pylori* infection. The attention paid to the research about gene polymorphisms and pathogenicity of *H. pylori* is getting high. Pathogenicity of *H. pylori* related genes including vacuolating cytotoxin (*vacA*) and cytotoxin associated protein (*CagA*) has been well studied. Meanwhile some new pathogenic genes like *homA* and *homB* have also been identified. In this paper the study of gene polymorphisms of pathogenic *H. pylori* is summarized, aiming to provide suggestions for the research on the genetic polymorphisms of *H. pylori* in the future.

GENETIC POLYMORPHISMS OF *H. PYLORI*

The whole genome of *H. pylori* 26695 strain was sequenced in the early 1997. It was showed that there exist 1590 encoding sequences in the strain,

representing 91% of chromosome DNA; in the non-coding region, gene internal sequences, non-coding repeats and stable RNA are included, which account for 6%, 2.3% and 0.7%, respectively. Of note, there are 499 unique nucleotides with high specificity in coding sequence^[6]. In 2000 chip technology was used to detect 1643 genes of all the 15 strains of *H. pylori* in Stanford University for the first time, and it was found that conservative 1281 genes constitute the core part of the functional sequences, meaning that 12%-18% of genes are unique. *H. pylori* has been confirmed to be highly variable, which is one of its most important characteristics. High frequency mutations exist in nucleotide repeat sequences contained in multiple genes of the *H. pylori* genome. Nucleotide slippage of DNA template during replication promoted by *H. pylori* leads to open reading frame shift. By doing this genes can be switched between the modes of on and off easily.

H. pylori genome owns four unique characteristics in its spatial structure^[7]. The first one is that about 1% of the genome encode a family consisting of 32 outer membrane proteins. Some members of this family, labeled as cell outer membrane pore proteins, probably are related to antibiotic sensitivity, which can result in multiple drug resistance of *H. pylori*, and development of chronic atrophic gastritis and other gastrointestinal diseases hard to cure. The second one is that more than 20 homologues contained in *H. pylori* genome are associated with DNA restriction and modification including type I, type II, type III systems which are different among various species. That homologues may be involved in intra or extracellular DNA degradation, or in DNA recombination activation. The third one is that 46%-48% of specific *H. pylori* sequences were identified to be plastic. Many of the known plastic genes are not related to pathogenicity, but rather homologous with the restriction modified enzyme. The final one is that *H. pylori* gene production is associated with the biosynthesis of lipopolysaccharide and the system of DNA restriction modification. Meanwhile high frequency of homologous gene multimers and dinucleotide repeats can be found in cell surface associated proteins and enzymes.

In addition, *H. pylori* also shows polymorphisms during the genetic evolution. *H. pylori* genome adjusted itself to adapt to the environment under generation. Representing the adaptation to the host, polymorphisms of *H. pylori* were generated *via* a variety of common mechanisms, the most prominent of which is mutation and recombination. Besides, individuals from different subsets can also be storage hosts for each other, exchanging genes that are missing.

In summary, spatio-temporal distribution of *H. pylori* polymorphisms varies significantly. The variability not only lies in different strains but also can be detected in the same infected individual. Although high polymorphisms of *H. pylori* have been confirmed, the mechanism for high rate of *H. pylori* infection but low

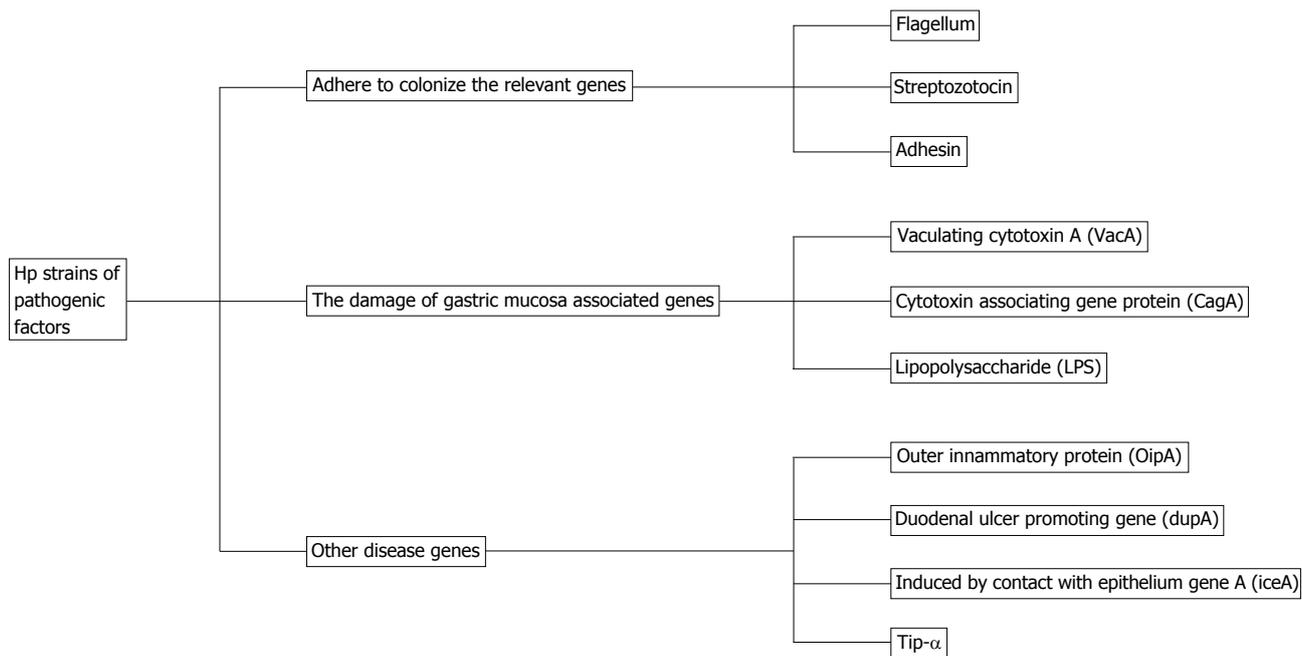


Figure 1 Pathogenic factors of *Helicobacter pylori* strains.

incidence of disease is still not well understood.

POLYMORPHISMS OF *H. PYLORI* VIRULENCE GENES

Pathogenic factors of *H. pylori* strains are categorized into three main classes: those related to adhesion and colonization, those related to gastric mucosal injury, and others. Specific pathogenic factors in the three classes are charted (Figure 1).

Genes related to *H. pylori* colonization

As a dynamic organ the flagellum is one of the most important virulence factors for colonization and pathogenicity of *H. pylori*. According to the report about the complete gene sequence of *H. pylori* 26695, more than 50 genes have been shown to play an important role in the biosynthesis, regulation and assembly of *H. pylori* flagella. Genes encoding *H. pylori* flagella mainly consist of *flaA*, *flaB*, *flgE*, *fliD*, *flhA*, *FliA*, and *flgK*^[8]. Flagellar filament of *H. pylori* is composed of multimeric flagellar structural proteins encoded by *flaA* and *flaB*. With 1533 gene sequences, *flaA* is transcriptionally regulated by the σ_{28} promoter^[9]. The protein product of *flaA* contains 510 amino acids. Nucleotide sequence is highly conserved in the 1545 bp of *flaB*, the gene expression of which is controlled by the σ_{54} promoter^[10]. And *flaB* encodes a peptide of 541 amino acids, 53.9ku. However, the restriction fragment length polymorphism analysis showed that a large number of gene mutations exist in *flaA* or *flaB* (Figure 2)^[11]. The diversity of *flaA* or *flaB* leads to the reevaluation on the sequence polymorphisms of *H. pylori* strains.

Blood-group antigen binding adhesion (BabA), encoded by *BabA*, can bind to fucosylated blood group antigen of Lewis B (Leb) or ABO (Figure 3)^[12]. Inflammatory response caused by BabA positive *H. pylori* strains is severe. However, Leb is not expressed in all of human gastric mucosal cells. In case of Leb deficiency, the interaction between BabA and Leb does not account for the adhesion of *H. pylori*. *BabA* has three genotypes: *babA1*, *babA2* and *babB*. The former two are highly homologous. Compared to *babA1*, an additional 10 bp sequence is inserted into the signal peptide of *BabA2*, forming the transcription initiation codon. Only the genotype of *babA2* has function. On the contrary, *babA1* loses function due to the incomplete signal peptide. *babA1* deficiency has no effect on the binding between *H. pylori* and Leb. Thus it is the active BabA encoded by *babA2* that strengthens inflammation response of the stomach, and induces duodenal ulcer or gastric cancer.

H. pylori outer membrane protein AlpB, is involved in *H. pylori* adhesion, especially in the first step for *H. pylori* colonization. In the stomach, *H. pylori* adhere to host cells, inducing cytokines to cause mucosal injury. Polymorphisms of *AlpB* exist not only in the adaptive strains, but also in the strains colonizing in the human body. Presumably, *AlpB* varied to adapt to specific microenvironment of the stomach, which makes the polymorphisms of this domain.

Encoded by *sabA*, sialic acid binding adhesin A (SabA) is very important in the outer membrane protein family of *H. pylori*. *SabA* can recognize X Lewis (LeX), an antigen of the human gastric epithelial cell surface. *SabA* does not correlate with anti-LeX antibodies in human^[13]. With polymorphisms, *SabA* is expressed selectively during *H. pylori* replication to

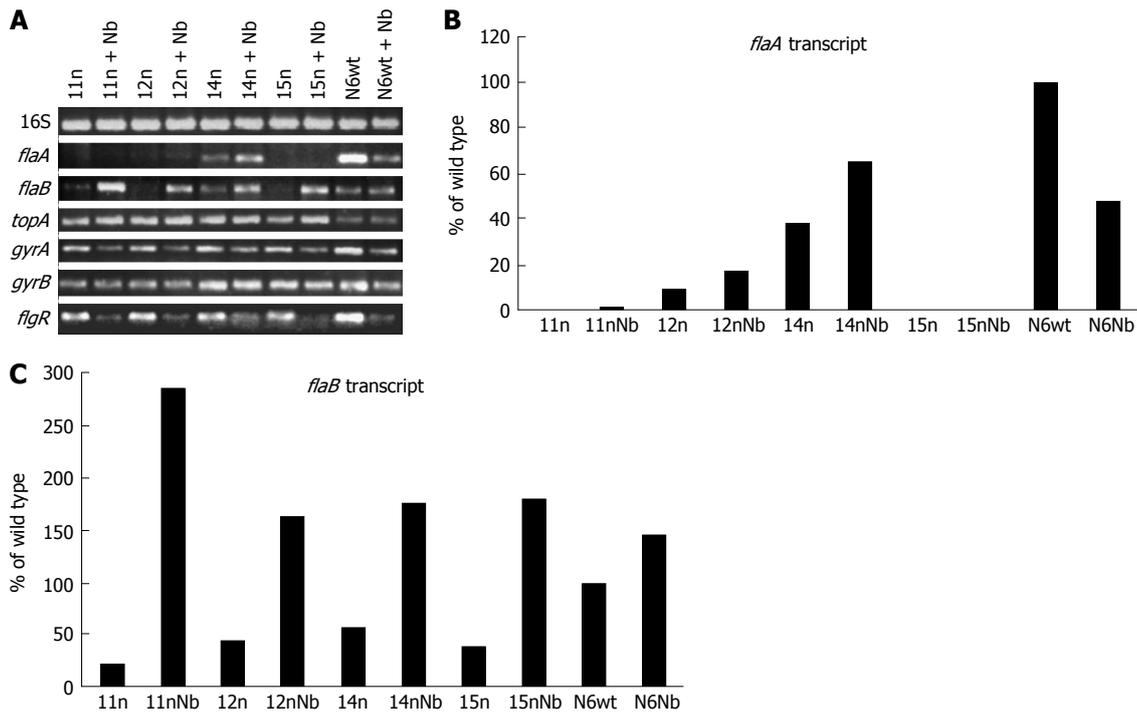


Figure 2 Analysis of *flaA* promoter spacer mutants reveals dependency of promoter activity on spacer length and supercoiling. A: Detection of *flaA*, *flaB*, *topA*, *gyrA*, *gyrB*, and *flgR* transcript abundance by RT-PCR for wild-type *flaA* promoter (13n), 11n 12n, 14n, and 15n spacer mutants, grown with and without novobiocin. Result of RT-PCR of 16S rRNA is shown to permit comparisons of mRNA quantity. Quantitation of *flaA* and *flaB* transcript levels (AnalySIS software, Soft Imaging Systems) is shown in (B) and (C).

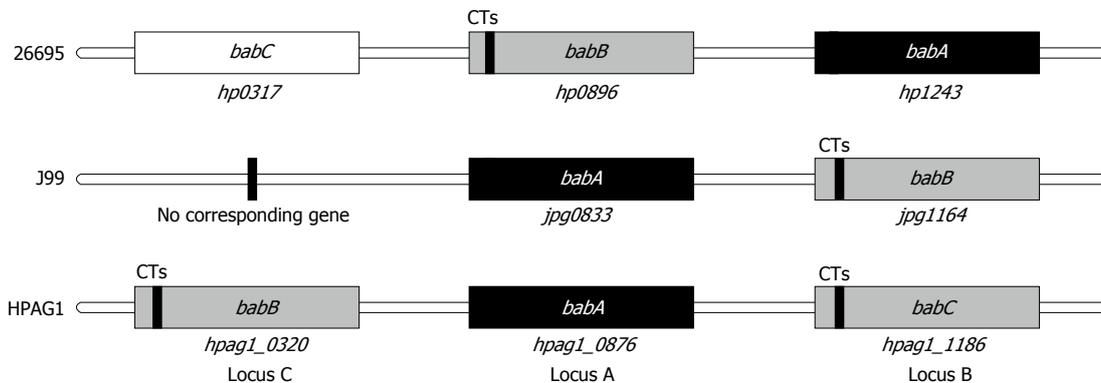


Figure 3 Genomic locations of the *babA*, *babB*, and *babC* genes in strains J99, 26695, and HPAG1. CT: CT dinucleotide repeats.

adapt to the host and avoid immune attack^[14]. When its level is high, saliva LeX correlates with *H. pylori* colonization in the stomach^[15]. The frame shift of the CT repeat in the 5' upstream region makes phase mutation of *SabA* (variation phase) to regulate its expression.

β 3N-acetylglucosamine T5 (β 3GnT5), a kind of the transferase of N-acetylglucosamine (GlcNAc), is the key for the Lewis antigen synthesis. Synergy between β 3GnT5 and *cagPAI* leads to an elevation of the adhesion ability of *H. pylori*. *CagA* and *CagE* in both β 3GnT5 and *cagPAI* positive *H. pylori* strains stimulate β 3GnT5 and Lewis antigen and result in strong colonization of *SabA* in epithelial cells^[16].

Genes related to gastric mucosal injury

VacA is one of the most important virulence factors in the pathogenesis of *H. pylori*. *VacA* exists in all of the *H. pylori*, but its virulence region is not expressed in all individuals. Western blot analysis with *VacA* antibody showed that virulence of *VacA* depends on the middle region (M) and signal area (S) of its structure. *VacA* with virulence mainly interferes phenotype and structure of epithelial cells, inducing cellular barrier dysfunction, inflammation changes, and vacuolization^[17,18]. Binding to cell surface specific receptors, *VacA* enters cells by endocytosis, then affects cellular membrane transport, results in swelling, vacuolization, and apoptosis in the end^[19]. In 2007, the

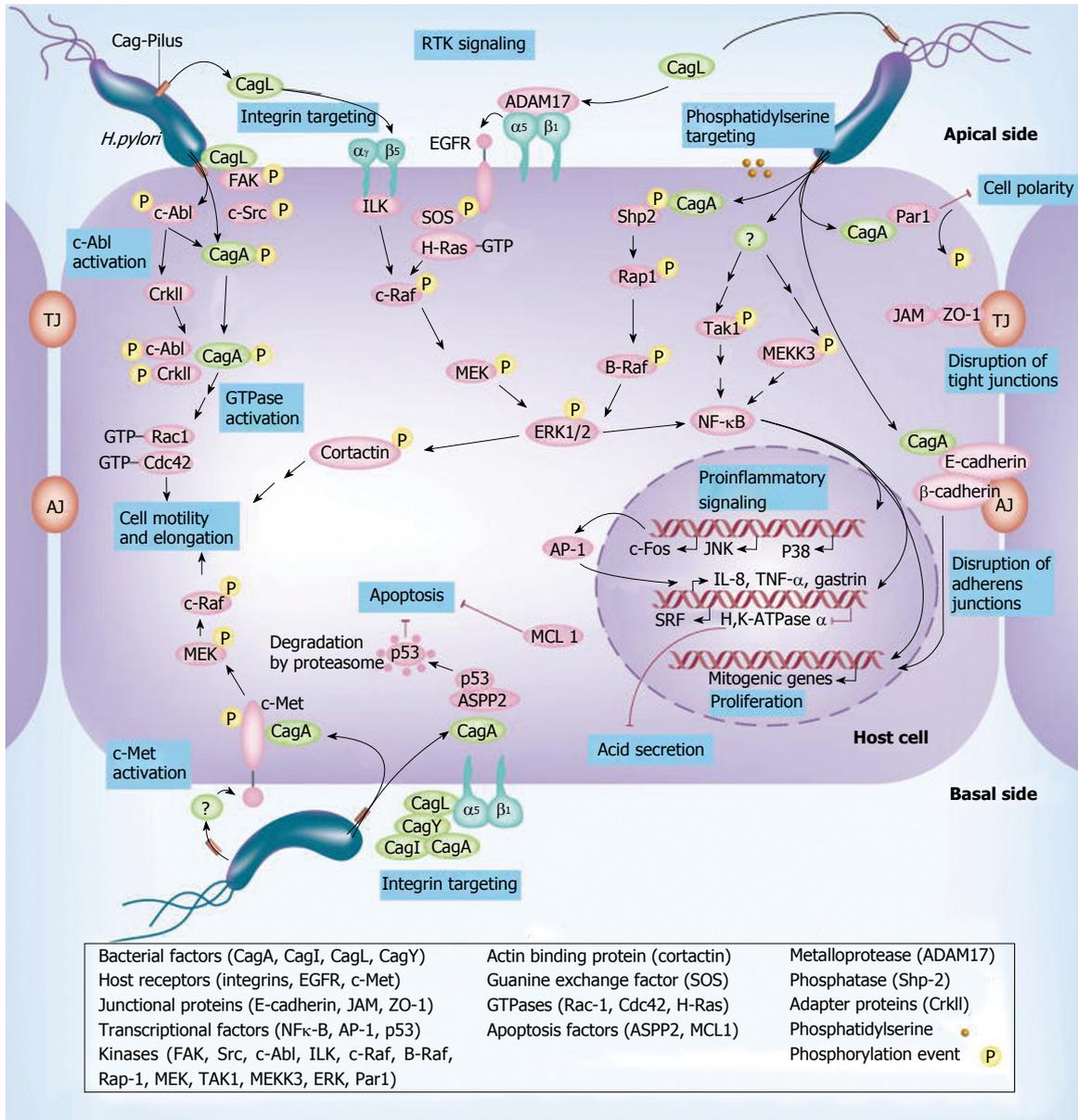


Figure 4 Model for the role of *Helicobacter pylori* T4SS effector proteins in host cell interaction and disease-associated signal transduction.

third region with polymorphism was found in *vacA*^[20], named intermediate region (i), which is between the area of S and M. *vacA* is divided into two subtypes of i1 and i2 by the difference of I region (Figure 2). Genetic linkage exists between i region and s or m area. The s1/m1 or s2/m2 displays the genotype of i1 and i2, respectively, while the s1/m2 displays genotype of i1 or i2. The relationship between i genotype and disease is region dependent^[21,22]. Both the S1 and S2 are not pathogenic. Virulence of the M1 is stronger than that of the M2 under the same condition. The i1 has virulence, but the i2 is of weak virulence or avirulence.

Another virulent factor of *H. pylori* is *cagA*. When *cagA* is transported into the epithelial cells of host gastric mucosa by type IV secretion system encoded by CagPAI, a tyrosine residue on it becomes phosphorylated. Interacting with a variety of proteins of

the host cells, CagA amplifies, causing a change in the morphology of gastric epithelial cells (Figure 4)^[23,24]. In recent years, polymorphisms of *cagA* was revealed to encode four proteins like A, B, C, and D, which play a key role in cytoskeletal rearrangement, infiltration and cell proliferation.

Gene cluster of cytotoxin associated gene pathogenicity island (*cagPAI*), is a kind of typical structure in the bacterial chromosome mainly encoding bacterial virulence related structure proteins and metabolic products. With a length of 37 kb, *cagPAI* consists of about 30 genes, and is one of the main hypervariable regions of the genome (Figure 5)^[25].

cagPAI encodes type IV secretion system (TFSS) of *H. pylori*. With a piliform appearance, TFSS is a macromolecule across both inner and outer membranes of *H. pylori*, forming a transmembrane channel.

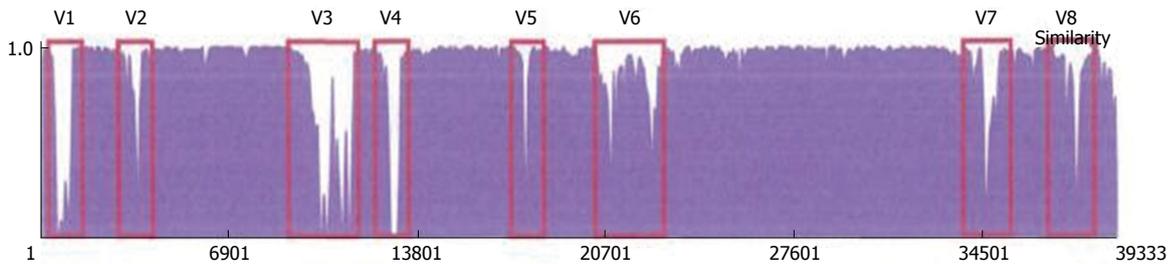


Figure 5 Eight variable regions in *cagPAI* sequences of Chinese *Helicobacter pylori* strains.

Pathogenic *H. pylori* can be transported into host cells through the channel, causing cellular lesions, inducing cytokines such as interleukin 8 (IL-8), and promoting inflammation^[26]. In the West *cagpaI* and *cagA* are used to evaluate the virulence of *H. pylori*. But in Southeast Asia 90% of the people are both *cagpaI* and *CagA* positive with different clinical symptoms. The relationship between *cagpaI* high variability and disease was studied (Figure 5). The result showed that most of *cagpaI* sequences in *H. pylori* strains worldwide are conservative. With few large fragment deletions, only a few genes of *cagPAI* are diverse, and even variations are meaningless to its virulence^[27].

Hom A and *Hom B* are newly discovered to be closely associated with gastric cancer development. Like genes encoding the outer membrane proteins of *H. pylori*, both *Hom A* and *Hom B* are present with allelic variations, but they are different in the very important intermediate region of 300 bp. The highly polymorphic region of *HomB* is located from 750 bp to 1050 bp, while in *homA* it is in the area from 720 bp to 980 bp^[27]. In addition, variability of *HomB* allele is higher than that of *HomA*. The sequence analysis of the nucleotides and amino acids showed copy number and site polymorphisms in *Hom A* and *Hom B*, which affected their function. Besides, recombination in *Hom A* and *Hom B* regulated DNA replication or *HomA/HomB* conversion^[28-30]. *Hom A* and *Hom B* consist of six allelic variants from AI to AVI. Among them, AI and AII are the main^[27]. As new virulence factors of *H. pylori*, *HomB* can be used to distinguish strains from duodenal ulcer and gastric cancer^[31,32]. *HomB* is closely related to the severity of inflammation or atrophy of the gastric mucosa^[32,33]. Analysis^[34] of 289 strains of *H. pylori* from the United States and Columbia showed that 71.9% of the strains in gastric cancer was *HomB* positive, which was significantly higher than that in strains from duodenal ulcer (52.1%). The expression of *cagA*, *HomA* and *HomB* in 138 strains of *H. pylori* from Iran was studied^[35]. It was found that 78% of the strains in gastric cancer were *HomB* positive, which was significantly higher than that in peptic ulcer (20%) or gastritis (43%). The positive rates of *cagA* in strains in gastric cancer, peptic ulcer or gastritis were 68.3% 54.8%, and 51.4%, respectively, without a significant difference. The above results suggested that compared to *cagA*, *HomB* is more likely to be a marker

for distinguishing gastric cancer and duodenal ulcer. However, it is controversial^[36,37].

Other pathogenic genes

As one of the 32 outer membrane proteins, pro-inflammatory outer membrane protein A (*OipA*) is closely related to the clinical symptoms of *H. pylori* infection, bacterial colonization density, and severe neutrophil infiltration development. *OipA* can induce the activation of adhesion kinase center and promote cytoskeletal rearrangement^[38]. The expression of *OipA* is regulated by the "slip chain mismatch" mode which involves frame shift of "CT" repeat in the signal region of *OipA*. *OipA* overexpression in *cagPAI* deleted strains induced IL-8 in gastric mucosal epithelial cells three times higher than that in strains deficient of both. Expression of *OipA* makes it functional and is related to the clinical symptoms and the severity of the disease.

Duodenal ulcer promoting gene (*dupA*) is a kind of factor encoding type IV secretion system, and it is located in the plastic zone of *H. pylori* gene. Homogenous to *virB4*, *dupA* owns two open reading frames of *jHp918* and *jHp917*^[39]. *dupA* in *H. pylori* exposes the infected patients especially from East Asia to duodenal ulcer with a high rate, but to atrophic gastritis and gastric cancer with a low rate. It was showed that related to IL-8 up-regulation in the gastric mucosa, *dupA* can promote duodenal bulb ulcer in *H. pylori* infected patients, and suppress atrophic gastritis and gastric cancer, which is obvious in strains from both Asian and Western populations.

After *CagA* and *VagA*, mucosal contact inducible factor (*iceA*) was revealed as a new pathogenic factor in recent years. Located in the region between the conserved *cysE* and *HpyIM* of *H. pylori*, *iceA1* was found to consist of two subtypes of *iceA1* and *iceA2* by multi strain sequence analysis. The correlation between *iceA* gene and gastric mucosal lesions has been studied^[40-44]. By meta-analysis and statistical analysis, *iceA1* gene was found to mainly exist in duodenal ulcer patients. There is no significant correlation between the distribution of *iceA2* and peptic ulcer disease. It appears that two subtypes of *iceA* correlated differently with peptic ulcer disease^[45]. It was recently found that the ratios of the *iceA* subtypes in disease are not the same in different countries or regions. Successful overexpression of the two indicated that positivity for

Table 1 The relationship between gastrointestinal diseases and *Helicobacter pylori* virulence factors

	HomA	HomB	DuPA	VacA						IceA		OiPA	
				VacAS2	VacAS1	VacM2	VacM1	Vaci2	Vaci1	CagA	IceA1		IceA2
Chronic gastritis	+	++++	++	+	++++	+++	++	+	++++	+++	++	+	-
Duodenal ulcer	+	++++	++	-	++	++	+	+	++	++	+	+	++
Gastric ulcer	+	++++	+	+	+	+	+	-	-	+	+	+	++
Gastric cancer	+	++++	++	-	+	+	++	+	+++	++	+	+	++++

+: Incidence of disease, 0-20%; ++, 20%-40%; +++, 40%-60%; +++++, 60%-80%; ++++++, 80%-100%.

both genotypes of *iceA1* and *iceA2* may be a marker of *H. pylori* induced acute inflammatory response in the gastric mucosa^[46-48]. The purified protein can also be used for the auxiliary diagnosis of related clinical diseases.

Tumor necrosis factor α induced protein (Tip- α) is a newly found soluble toxin, encoded by the open reading frame of 0596 gene in *H. pylori*. With a length of 519 bp, Tip- α encodes a peptide of 173 amino acids^[49]. Dimer through a pair of disulfide bonds (Cys25-Cys25 and Cys27-Cys27) in the N terminus is the active form of Tip- α which can greatly induce IL-1b, IL-8, and TNF- α , mediated by NF- κ B, to promote the inflammatory response of the host and the occurrence and development of the tumor together with a series of gastrointestinal diseases^[50].

RELATIONSHIP BETWEEN *H. PYLORI* PATHOGENIC GENES AND GASTROINTESTINAL DISEASES

The polymorphisms of virulence genes of *H. pylori* are closely related to the clinical outcome of infection, especially in cases of positivity for *VacA*, *cagA*, *SabA* or *iceA*, different genotypes of which result in different types of gastrointestinal diseases (Table 1). It was showed that 80%-100% of *HomeB* positive ones suffered from various gastrointestinal diseases, which indicated that *HomeB* can be treated as one of the main newly found virulence genes; belonging to the high virulence genes, *CagA*, *VacA* and *DupA* mainly cause gastritis disease, duodenal ulcer and gastric cancer, while *OiPA* mainly causes gastric and duodenal ulcers and gastric cancer. In addition, the research found that^[51] the progression from atrophy gastritis to cancer is regulated by *H. pylori* in the host through changing dominant microflora and thus regulating gastric epithelial cell related signal transduction, metabolism and cancer development related tumor suppressors^[52]. At the same time, the micro-evolution is very common in China, leading to changes of gastric flora. Strains of *H. pylori* with more than two kinds of genotypes exist in 99% of the hosts, resulting in repeated drug resistance and recurrence (Table 1)^[53].

CONCLUSION

The development of *H. pylori* associated diseases is

related to the virulence, the amount of pathogenic bacteria, and the immunity of oneself. The polymorphisms of pathogenic genes make the differences in the virulence of various strains, which closely correlates with the outcome of clinical infection with no clinical symptoms, ulcers, inflammation and even tumors following, and non-gastrointestinal system disease as the result. With the development of molecular biology and proteomic technology, some new pathogenic factors of *H. pylori* have been found, resulting in the amplified mechanism underlying the pathogenesis. However, pathogenic analysis of *H. pylori* is very difficult due to the presence of unknown pathogenic genes, involvement of multiple factors in diseases induced by *H. pylori* infection, and the combination of many types of strains in the same patient. Thus further study on the relationship between genetic polymorphisms of *H. pylori* and its associated clinical diseases should be conducted to fully illustrate the pathogenicity of *H. pylori*.

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