Chapter 6

Helicobacter pylori Genes *jhp0940*, *jhp0945*, *jhp0947* and *jhp0949* are Associated with Gastroduodenal Disease

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Abstract

The plasticity zone (PZ) of *Helicobacter pylori* is a genomic region harbouring genes that can be exchanged between strains, contributing to the genetic diversity of this bacterium. The presence or absence of genes reflects the adaptation and coevolution of a pathogen within its host. Among the genes present in PZ, *jhp0940*, *jhp0945*, *jhp0947* and *jhp0949* have gained attention due to their association with gastroduodenal disease, and the prevalence of the latter three among *H. pylori* isolates from different geographical regions has allowed this association to be understood. With respect to *jhp0940*, also known as *ctkA* (cellular translocation kinase A), various results have been obtained regarding its prevalence. However, the presence of *jhp0940* in isolates from children seems to be higher than that in isolates from adults, and the product of this gene can induce TNF-α, IL-6 and IL-8 via translocation of NF-κB into macrophages. While little is known about the functions of *jhp0945*, *jhp0947* and *jhp0949*, their presence in *H. pylori* strains induces IL-8 and IL-12 expression at higher levels than that in strains lacking these genes. In this chapter, we aim to show a general overview of the prevalence, association with gastroduodenal disease, and currently known function of the *H. pylori* genes *jhp0940*, *jhp0945*, *jhp0947* and *jhp0949*, which are located in PZ.

Keywords: plasticity zone, gastroduodenal diseases, *jhp0940*, *jhp0945*, *jhp0947*, *jhp094*

1. Introduction

Several techniques have been used to genotype *Helicobacter pylori* strains to identify differences at the genomic level between isolates from different populations as well as between isolates from the same individual, indicating the presence of a mixed infection [1–4]. Thus,

H. pylori is considered to have a high genetic diversity due to the presence or absence of genes, which indicates the adaptation and coevolution of the pathogen within different populations worldwide [5, 6]. Recently, advances in DNA sequencing technology have enabled the comparison of hundreds of sequences from the genomes of related bacteria. These comparative genome analyses between species have led to a concept that encompasses all of the genetic content within a bacterial species. This concept is referred to as a "pan-genome", which is defined as the complete genetic repertoire of a specific species, composed of both the central genome and the accessory genome, also known as the dispensable genome [7].

Comparative genomic studies of *H. pylori* began with the sequencing of strains J99 and 26,695. The *H. pylori* genome is approximately 1.6 million base pairs (1.6 Mb) in size, containing 1500 open reading frames (ORFs) and approximately 1500 protein-coding genes, with a G + C content of approximately 39%. Sequencing of these two strains showed that approximately 6–7% of the genes present in one strain are absent in the other. These genes are referred to as strain-specific genes, almost half of which are located in hypervariable regions within the *H. pylori* genome. Such regions are called plasticity zones (PZs), based on the variability of gene content between different isolates of *H. pylori*. These regions have a lower G + C content than the rest of the genome (34–35%), which suggests horizontal transfer [8]. The *cag* pathogenicity island (PAI) is a region exhibiting this reduced G + C content [9].

Several studies have shown that *H. pylori* strains gain and lose genes during an infection, which suggests that a continuous genetic flow occurs, primarily within the PZ [4, 6, 10, 11]. The frequency of the PZ genes, notably *jhp0940*, *jhp0945*, *jhp0947* and *jhp0949*, has been studied among *H. pylori* isolates from different geographical regions, which has demonstrated that some of these genes are associated with disease. Currently, some of these PZs have roles in *H. pylori* pathogenesis and are included in one of the three categories of *H. pylori* virulence classified by Yamaoka [12].

2. Genotyping of *H. pylori* strains

After strains J99 and 26695 were sequenced, the first DNA microarray could be designed [13], allowing the first genotyping studies of diverse strains of *H. pylori* to be conducted. The first study compared 15 *H. pylori* isolates and observed that 362 genes (22%) were variable among the strains, which were called strain-specific genes. Subsequently, another study explored the genomic diversity of *H. pylori* isolates from children and adults who presented a single or a mixed infection (the presence of more than one strain). The number of variable genes in individuals with a mixed infection was found to be higher than that in individuals infected with a single strain. No difference was observed in the number of strain-specific genes between strains from children and adults [14]. However, a study of 56 strains from different geographical regions observed that 25% of the genomic content between these strains corresponded to strain-specific genes [6]. The genetic content of the strains has also been correlated with their pathogenesis in an animal model [4, 15]. Moreover, Romo-González et al. [16] identified and compared the differences in the genetic content of strains isolated from Mexican patients with non-atrophic gastritis, duodenal ulcers and gastric cancer. The authors observed that the core genome shared by these

isolates was composed of 1319 genes, while 341 genes (20.5%) were strain-specific among the assayed isolates, 37% of which were distributed within the PZs. The genotyping analysis provided an understanding of which genes are present and absent in the isolates associated with each disease, making it possible to associate some of these genes with specific diseases.

3. Structure of the *H. pylori* PZ

The PZ of strain J99 is the most studied and best characterised hypervariable region within the *H. pylori* genome. In the J99 *H. pylori* strain, the PZ is a continuous region from *jhp0916* to *jhp0961* [8]. Of the 48 ORFs that compose the PZ in strain J99, only six are present in strain 26695, and 10 are present in strain HPAG1. The PZs in strains J99 and 26695 are 45 and 68 kb in length, respectively. The PZ contains genes of unknown function as well as those encoding restriction-modification systems, topoisomerases, integrons, secretion systems, outer membrane proteins and transposons, the latter of which can be inserted into a genome without recombination. This insertion facilitates the propagation of transposons among bacterial species. These transposons are important because they can generate genomic deletions and rearrangements and even alter the expression of genes contiguous to their insertion site [17–19].

Kersulyte et al. [20] studied the nature of the PZ in the *H. pylori* genome by sequencing this locus in other strains and locating this area in strains that had been recently deposited in GenBank. The authors observed that the PZ is composed of inserted transposable elements

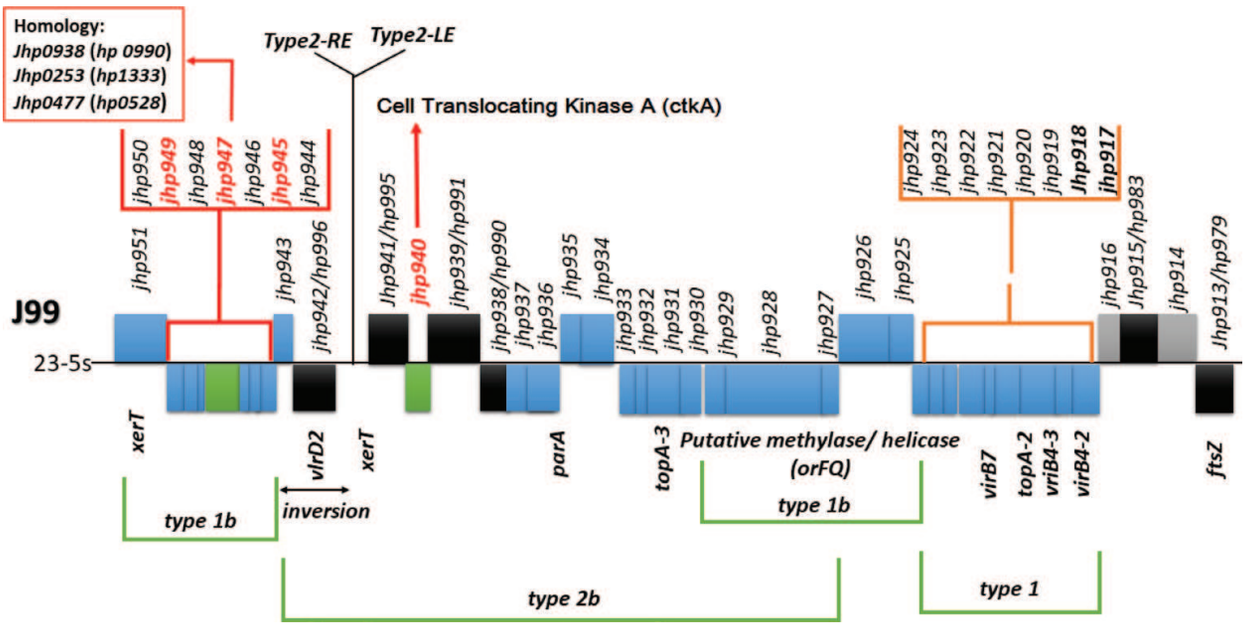

Figure 1. Plasticity zone of reference strain *Helicobacter pylori* J99 (*jhp0917-jhp0951*), figure adapted from [20]. This PZ is located between the *ftsZ* (*jhp0913*) gene and the 5S, 23S rRNA gene pair and is composed of TnPZ fragments: type 1 (*jhp0917-jhp0924*), type 1b (*jhp0944-jhp0951*; *jhp0925*, *jhp0926*, potentially part of *jhp0927-jhp0929* (*orfQ*) as well), and type 2 (*jhp0943-jhp0930*, potentially part of *orfQ* as well). Blue and green boxes indicate ORFs exclusive to J99 but not 26695 (another reference strain); black boxes indicate ORFs found in both strains; grey boxes indicate ORFs located between the *ftsZ* gene and the 5S, 23S rRNA gene pair that do not belong to the TnPZ.

that are flanked by discrete sequences of 5′AAGAATG and are each referred to as a TnPZ or "transposon, plasticity zone". Each TnPZ generally contains genes encoding type IV secretion proteins (tfs3), *xerT*, an ORF coding for a protein with helicase and DNA methylase domains and additional ORFs. Among the studied strains, several types of TnPZs with different gene arrangements or DNA sequence variations were observed and classified as type 1, type 1b and type 2 TnPZs. The genes *jhp0945*, *jhp0947* and *jhp0949* are located on a type 1b TnPZ, and *jhp0940* is located on a type 2 TnPZ in strain J99 (see **Figure 1**).

4. The PZ-associated gene *jhp0940* and its relationship with gastroduodenal disease

The prevalence of the *jhp0940* gene in various *H. pylori* isolates from different geographical regions has been explored (**Figure 2**). Studies have reported varying results regarding its prevalence and association with disease, and the presence of this gene has even been suggested to be related to a lower risk of peptic ulcers or gastric cancer [21, 22]. In a genotyping study of *H. pylori* isolates from Mexican individuals with gastroduodenal diseases, *jhp0940* was absent in all gastric cancer isolates [16]. In Brazil, in patients with duodenal ulcers or gastric cancer, the presence of *jhp0940* in *H. pylori* isolates exhibited no association with disease, as only 3 of 200 isolates had

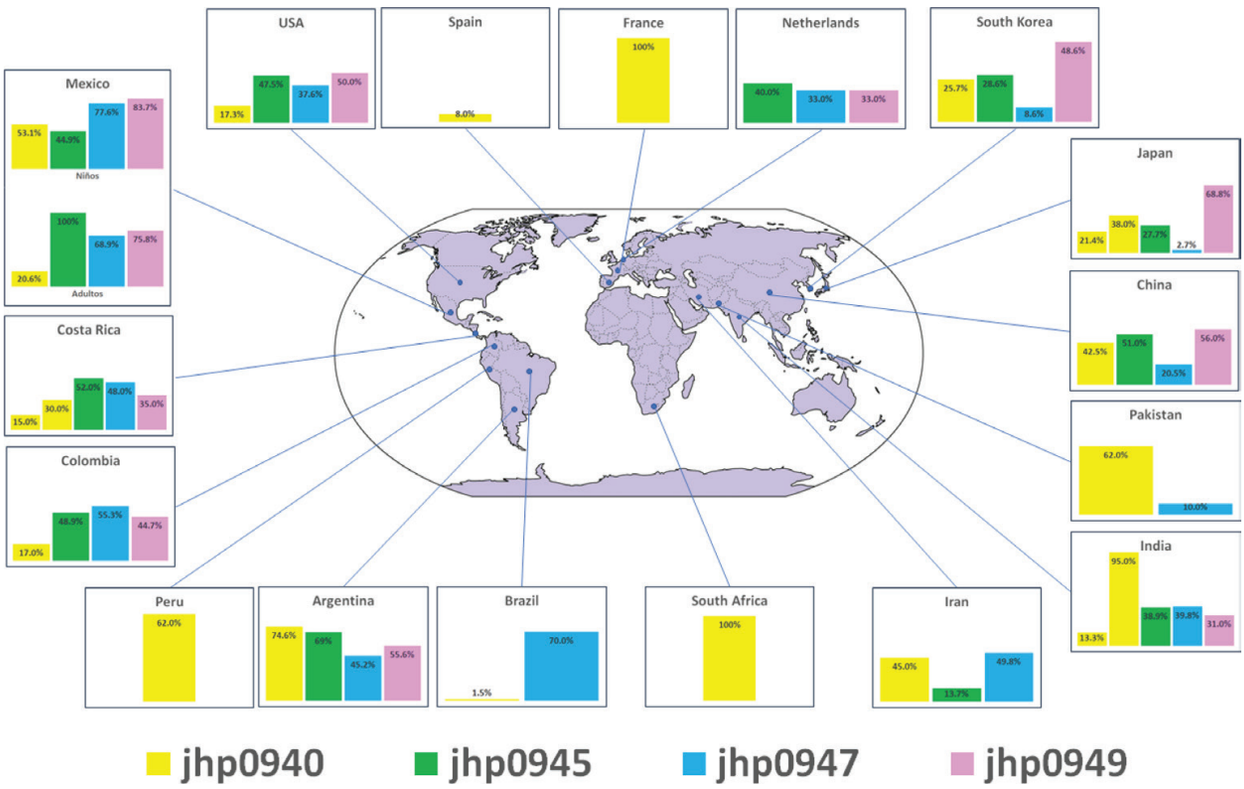

Figure 2. Frequency of the presence of the *jhp0940*, *jhp0945*, *jhp0947* and *jhp0949* genes among *H. pylori* isolates from different geographical regions. Frequencies are based on the following reports: USA, Colombia, South Korea [21]; Japan [21, 25]; Netherlands [32]; Iran [28]; India [22, 25]; Pakistan [27]; China [24]; Costa Rica [30, 25]; Brazil [23]; Argentina [26]; Peru [25]; South Africa [25]; France [25]; Spain [25]; and Mexico [16, 29].

the gene [23]. In addition, no association was found between this gene and disease in isolates from Chinese patients with chronic active gastritis, duodenal ulcers or gastric cancer [24].

A study in India observed less than a 20% prevalence of the *jhp0940* gene among *H. pylori* isolates [22]. However, in other isolates from India, the reported *jhp0940* prevalence was higher than 80% [25]. In Argentina, the frequency of the *jhp0940* gene was reported as 74.6%, and the frequency in isolates from individuals with chronic gastritis and peptic ulcer disease was similar, indicating no association with a specific disease [26]. However, Rizwan et al. [25] found no relationship between clinical results and the prevalence of *jhp0940* or the cag PAI in isolates from seven countries (India, South Africa, Japan, Costa Rica, Peru, France and Spain). The highest prevalence of this gene was observed in isolates from India, South Africa and France, in contrast to isolates from Spain, where less than 10% contained this gene.

However, Yakoob et al. [27] and Gholizade Tobnagh et al. [28] reported an association between *jhp0940* and gastric ulcers and gastric cancer, respectively. In general, the prevalence of this gene is lower than that of *jhp0945*, *jhp0947* and *jhp0949* in isolates from the different geographical regions that have been studied. There appears to be a difference between the presence of PZ genes between isolates from children and adults. Romo-González et al. [29] observed that the prevalence of *jhp0940* in *H. pylori* isolates from children is higher than that in adults and that the presence of the specific gene patterns (including *jhp0940-jhp0945-jhp0947-jhp0949* and *jhp0940-jhp0947-jhp0949*) is more common in isolates from children than in adults. Therefore, these authors suggest that this locus is more integrated in the early stages of infection, which could contribute to the bacterial virulence and evolution of the infection. These authors found no association between the presence of these four PZ-associated genes and the presence of *cagA*, cag PAI or *dupA*.

Romo-González et al. evaluated the *in vitro* expression of four PZ-associated genes in isolates from children and adults and observed the expression of only *jhp0945*, *jhp0947* and *jhp0949*, without significant differences among the expression of these three genes between the isolates obtained from children and adults. However, a correlation was observed among the expression of these three genes (unpublished data).

A possible explanation for the discordant results regarding the prevalence of *jhp0940* in different geographical regions is that geographical diversity exists in the sequence of this gene that does not allow for its identification with a single pair of primers. Another potential reason is that the absence of this gene in adult isolates is due to the loss of this gene during infection.

5. The PZ-associated genes *jhp0945*, *jhp0947* and *jhp0949* and their relationship with gastroduodenal disease

Studies on the prevalence of *jhp0945*, *jhp0947* and *jhp0949* among *H. pylori* isolates of different geographical origins have proposed that these genes are disease markers, suggesting that they could play a role in the pathogenesis of *H. pylori* [12]. This relationship was discovered in Costa Rica, where the prevalence of 21 ORFs present in the PZ of the J99 strain (*jhp0914-jhp0961*)

was assessed in 17 strains from patients with gastric cancer and 26 strains from patients with gastritis. The results showed a high prevalence of *jhp0940* and *jhp0947* in patients with gastric cancer [30]. Later, in a study conducted in Brazil that included 200 *H. pylori* isolates from patients with duodenal ulcers, gastric cancer or gastritis, only *jhp0947* continued to show an association with gastric cancer and duodenal ulcers [23]. However, in another study of strains from Brazil, an association between *jhp0947* and peptic ulcers was not observed [31]. A different study assessed the prevalence of the *jhp0945-jhp947-jhp0949* locus in a Dutch population with gastritis and duodenal ulcers. In addition to *jhp0947*, the presence of *jhp0949* was associated with duodenal ulcers, whereas *jhp0945* was not associated with this disease [32]. Another cluster of genes for which the prevalence was examined consisted of *jhp0926*, *jhp0931*, *jhp0933*, *jhp0944* and *jhp0945* in isolates from Turkish patients with gastritis and peptic ulcers. Among these genes, *jhp0931* was the most prevalent in patients with peptic ulcers [33].

Yakoob et al. [27] observed that the *jhp0947* gene is more frequently present than *jhp0940* in strains associated with duodenal ulcers and gastric cancer. This association was determined to be independent of the presence of the virulence factor *cagA* in *H. pylori* strains. A study that included 296 Western isolates (from the United States and Colombia) and 217 East Asian isolates (from Korea and Japan) reported that the prevalence of *jhp0945*, *jhp0947* and *jhp0949* differs significantly between the two geographical regions. In the Western isolates, the presence of *jhp0945* was higher in isolates obtained from individuals with gastric ulcers, duodenal ulcers or gastric cancer than in those obtained from individuals with gastritis [21].

In *H. pylori* isolates of Chinese origin, the prevalence of *jhp0945*, *jhp0947* and *jhp0949* was significantly higher in individuals with duodenal ulcers and gastric cancer than in individuals with chronic gastritis [24]. Similarly, in isolates from India, the presence of *jhp0945*, *jhp0947* and *jhp0949* in *H. pylori* isolates was associated with disease [22]. The prevalence of *jhp0945*, *jhp0947* and *jhp0949* is associated with a greater risk of serious diseases in India [28]. PZ-associated genes (outside of locus *jhp0945-jhp0947-jhp0949*) that also have exhibited an association with disease include *jhp0950* and *jhp0917-jhp0918*. The *jhp0950* gene was associated with marginal zone B cell lymphomas (MZBL) and mucosa-associated lymphoid tissue (MALT) when its prevalence was examined in patients with gastritis, duodenal ulcers and gastric cancer [34]. Another gene considered a risk factor for the development of duodenal ulcers is the *dupA* gene (duodenal ulcer-promoting gene, *jhp0917-jhp0918*); its presence in strains from patients with this gastroduodenal pathology resulted in its association with this condition.

Predominant inflammation in the antrum region of the stomach as well as the infiltration of polymorphonuclear leukocytes can lead to the appearance of a duodenal ulcer [35]. The prevalence of the *dupA* gene among *H. pylori* strains varies according to the geographic region and duodenal pathology. The *dupA* gene is present in approximately 31% of strains in Asian countries and 64% of strains in Western countries [36–40].

However, two genotypes were observed for this gene, including strains with and without an extra 600 bp in the gene sequence [41]; another important characteristic is that it has high homology with VirB4, a component of the type IV secretion system (T4SS) of *H. pylori*, and recent studies suggest that *dupA* and the six homologues of adjacent vir genes (virB8-virB11, virD4 and virD2) in the PZ could form the third T4SS [42]. Many unanswered questions still

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exist regarding this gene and its role in *H. pylori* strains. To date, *jhp0947* is considered the best disease marker of the locus *jhp0945-jhp0947-jhp0949* because it seems to meet two of the conditions that Yamaoka et al. [12] suggest for an *H. pylori* virulence factor: (1) it has a disease or other *in vivo* correlation and (2) it is epidemiologically consistent across populations and regions.

6. Functional characteristics of the *jhp0940*, *jhp0945*, *jhp0947* and *jhp0949* genes

Among the *jhp0940*, *jhp0945*, *jhp0947* and jhp0949 genes, *jhp0940* is the best characterised. Rizwan et al. [25] purified recombinant JHP0940 protein, which, when incubated with macrophage cells (TPH-1), was able to induce the synthesis of TNF-α, IL-6 and IL-8 via translocation of NF-κB. This gene is currently known as *ctkA* (cell translocation kinase A), and the encoded protein has autophosphorylation activity [43]. In addition to being a serine/threonine kinase, CtkA can increase the phosphorylation of NF-κB by inducing TNF-α in a dose-dependent manner in HeLa cells [40]. However, Tenguria et al. [44] observed that *H. pylori* can secrete the CtkA and induce the expression of caspase-1 in macrophages (RAW264.7), generating an increase in the transcription of IL-1β and promoting the recruitment of infiltrated immune cells in the gastric mucosa. In addition, CtkA may be able to decrease cell viability through the Fas receptor. Recently, a study showed that CtkA is expressed from its native host and can induce stimulation of a pro-inflammatory response from gastric epithelial cells. This interaction is dependent upon a complement of the tfs3 T4SS genes but independent of the T4SS proteins encoded by either tfs4 or the *cag* PAI [45].

The function of the genes *jhp0945-jhp0947-jhp0949* is not yet well understood. However, it has been proposed that since they are consecutive genes and are oriented in the same direction, it is possible that they are expressed as an operon [30]. A study of the Dutch population revealed that the presence of these three genes in *H. pylori* strains induced higher amounts of IL-12 than in strain 26695, which does not possess these genes. However, the disruption of this locus reduces the production of IL-12 in THP-1 monocytic cells [32]. The presence of these three genes in strains from India induces a greater amount of IL-8 and induction of cell death by apoptosis (caspase-3 activity) in AGS cells than in strains that lack these genes [22]. *jhp0947* shows homology with *jhp0938* (*hp0990*) and *jhp0253* (*hp1333*), but their functions are still unknown. This gene also shows homology in the 5′ region with *jhp0477* (*hp0528*), which encodes a *virB9* homologue, an important component of the T4SS encoded by the *cag* PAI [46].

7. Conclusion

The PZ of the *H. pylori* genome contains several genes that have not been fully explored but could be important for understanding the pathogenesis of *H. pylori* due to their location in an area of the genome associated with genetic exchange. Among the most studied genes are *jhp0945*, *jhp0947* and *jhp0949*, which have been found to be associated with gastroduodenal disease, although their mechanism is still not clearly defined. However, the prevalence and association of *jhp0940* with ulcer or gastric cancer is still not entirely clear, although progress has been made in the

characterisation of the function of this gene. It is important to continue exploring the presence and *in vivo* expression of these genes in strains isolated from children and adults from different geographical regions to elucidate their potential role in the pathogenesis of *H. pylori* infection.

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