A Systematic Review of Genetic Coevolution of *Homo Sapiens* and *Helicobacter Pylori*: Implications for Development of Gastric Cancer

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Abstract

Helicobacter pylori (H. pylori) is classified as carcinogen type I for gastric cancer (GC). Although it has accompanied man for at least 116,000 years, knowledge of the evolutionary forces that modulate the role of this bacterium within the development of the spectrum of gastric diseases is still scarce. This systematic review compiles articles that report a process of coevolution process, relate host-host ancestral components, and describe *H. pylori's* mechanisms of adaptation to the human gastric environment in order to understand if coevolution has modulated the pathogenicity of these bacteria and the development of gastric diseases. A systematic search was carried out in MEDLINE (OvidSP), Scopus (ScienceDirect), Scielo and Tree of Science (ToS). The following search terms were used: "Stomach", "Cancer", "Neoplasms", "Ethinicity", "Evolution", "Genetics", "Ancestry" and "*Helicobacter pylori*", and searches were conducted in both English and Spanish. The data were filtered by one reviewer using a standard extraction form and then reviewed by another. The risk of bias and the methodological quality of the studies were evaluated using the Critical Appraisal Skills Program (CASP). Thirty-six of the total 1,584 studies found met the inclusion criteria. The most relevant factors in the development of the spectrum of diseases associated with *H. pylori* infection are amino acid substitutions, binding and positive selection mainly in the hypervariable regions, and disruption of the coevolution process between the bacteria and their human hosts as the result of horizontal transfer of gene segments that did not evolve with their host.

Keywords (DeCs)

Helicobacter pylori, evolution, gastric neoplasms, genetic flow.

INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer in the world after lung, breast, colorectal and prostate cancer. The incidence rate among men is double that among women. In 2012, 952,000 new GC cases (6.8%) were estimated. Of this number, 70% come from developing countries, predominantly China (40%) GLOBOCAN (2012; http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx). In Latin America, incidence and mortality rates vary geographically and ethnically. The highest rates are found in the mountainous areas of the Pacific Coast, including Chile, Ecuador, Peru, Costa Rica and Colombia. (1, 2) Inter-population and ethnic variations in disease progression can be attributed to environmental and genetic risk factors (of either somatic or germinal origin). (3, 4)

The Helicobacter pylori bacterium coevolved with man from its origin and is very common in the intestinal microbiome. It affects more than 50% of the world's population and accounts for approximately 20% of all gastric diseases and GC. (4, 7, 12 -14) Since 1994, the International Agency for Research on Cancer (IARC) has considered it to be a

Type I carcinogen and the main infectious cause of cancer in men and the second in women (after cervical cancer). (1, 8) Bacterial virulence genes (cagA, vacA and oipA) activate inflammatory pathways and produce reactive oxygen species and nitrous compounds that affect DNA stability. (8, 15, 16) For 2008, HP was responsible for approximately 89% (~ 780,000 cases) of new GC cases outside of the gastric cardia which is equivalent to 39% of the two million cases of cancer attributable to infectious agents and to 6.2% of the 12.7 million new cases reported. (10)

Since the ethnic-geographic phylogeny of this pathogen is defined with specific strains for large continental areas and geographic patterns of genetic diversity which parallel those of human diversity, (1, 3-12) some studies suggest that host-pathogen genome interactions, disruption in the coevolution process by infection with strains of ancestral origin different from the host, horizontal transfer of gene segments that have not co-evolved with hosts, and positive selection of introduced strains could generate alterations in selection for virulence and disruption of the coevolution process. This could explain the high incidence rates of GC in human populations with high genetic diversity such as Colombia which has a complex genetic mix of American, European and African origins in different proportions due to a recent process of intercontinental mixing. (17)

This systematic review aims to contribute to knowledge of the interrelationships and evolutionary forces that modulate the role of the bacterium in the development of the spectrum of gastric diseases and etiology of GC through analysis of study results describing the adaptive mechanisms of H. pylori to the human gastric environment, report host-pathogen coevolutionary processes and relate ancestral and pathogenic components of the bacterium as determinants in the development of GC.

MATERIALS AND METHODS

Search Strategies

The PRISMA statement (http://www.prisma-statement.org/), MEDLINE databases (OvidSP), Scopus (ScienceDirect), Scielo and the Tree of Science - ToS (www.mytreeofscience.com) were searched using the search terms "stomach", "cancer", "neoplasms", "ethnicity", "evolution", "genetics", "ancestry" and "Helicobacter pylori" (table 1). The DOI of the articles was verified at http://www.doi.org/.

Inclusion and exclusion criteria

- Inclusion: studies of human populations, in English and Spanish, controlled trials, randomized trials, and reviews of: (I) genetic ancestry and diversity of H. pylori; (II) coevolution of H. pylori-Homo sapiens; (III) genetic mechanisms of adaptation of H. pylori to host as determinants in the development of GC.
- Exclusion: (I) clinical trials of drugs and vaccines; (II) comparison of treatments or diets in patients; (III) case reports; (IV) syndromes; (V) comments and editorials. Design data and study results were extracted according to the PICO acronym (Table 2).

Table 1. Combinations of search terms employed

Base de datos	MeSh	Number of articles*
MEDLINE (via OvidSP)	Stomach AND Neoplasms AND Genetics AND *Helicobacter Pylori*	1058
	Phylogeography AND Gastric Cancer AND *Helicobacter Pylori*	3
	Ethnicity AND Gastric Cancer AND *Helicobacter Pylori*	128
	Ancestry AND Gastric Cancer AND *Helicobacter Pylori*	159
	Evolution AND Gastric Cancer AND *Helicobacter Pylori*	64
	Evolution AND Gastric Cancer AND *Helicobacter Pylori* AND Geography	4
	Evolution AND Gastric Cancer AND *Helicobacter Pylori* AND Strains	31
Scopus (ScienceDirect)	Stomach AND Neoplasms AND Genetics AND *Helicobacter Pylori*	23+
Scielo	Stomach AND Cancer AND Genetics AND *Helicobacter Pylori*	34
Tree of Science - ToS	Stomach AND Neoplasms AND Genetics AND *Helicobacter Pylori*	80
Total articles number		1584

* Results were obtained by applying the exclusion criteria: years, species and Languages.
+ The search was limited to areas: Biochemistry, Genetics and Molecular biology.

Table 2. Inclusion criteria according to PICO *

PICO Indicators	PICO Results
Design	Controlled trials, randomized trials and reviews
Population	Patients with GC, Controls and H. pylori
Intervention	None in patients
Comparison	Studies and reviews were classified and compared
Results	Ancestry and genetic diversity of H. pylori
	Coevolution of H. pylori and Homo sapiens and relation to development of GC
	Genetic mechanisms of H. pylori's adaptation to human hosts

GC: gastric cancer.
* PICO is an acronym for patient or population (P), intervention (I), comparison (C) and outcome(s) (O).

Full-text documents were independently assessed by two reviewers. Disagreements were resolved by consensus, with the participation of a third author when necessary (Figure 1).

Ancestry Distribution Map

The sequences (MLST) of 7 constitutive genes (atpA, efp, mutY, PPA, trpC, ureI and yphC) of 325 isolates of H. pylori (Annex 1) that have been reported in the PubMLST database (http://pubmlst.org/) were used to map the distribution of H. pylori strains in INKSCAPE (https://inkscape.org/en/). The isolates were selected in such a way as to include all seven continents.

Quality Assessment

Quality of diagnostic studies, randomized controlled trials and reviews was assessed with the Critical Appraisal Skills

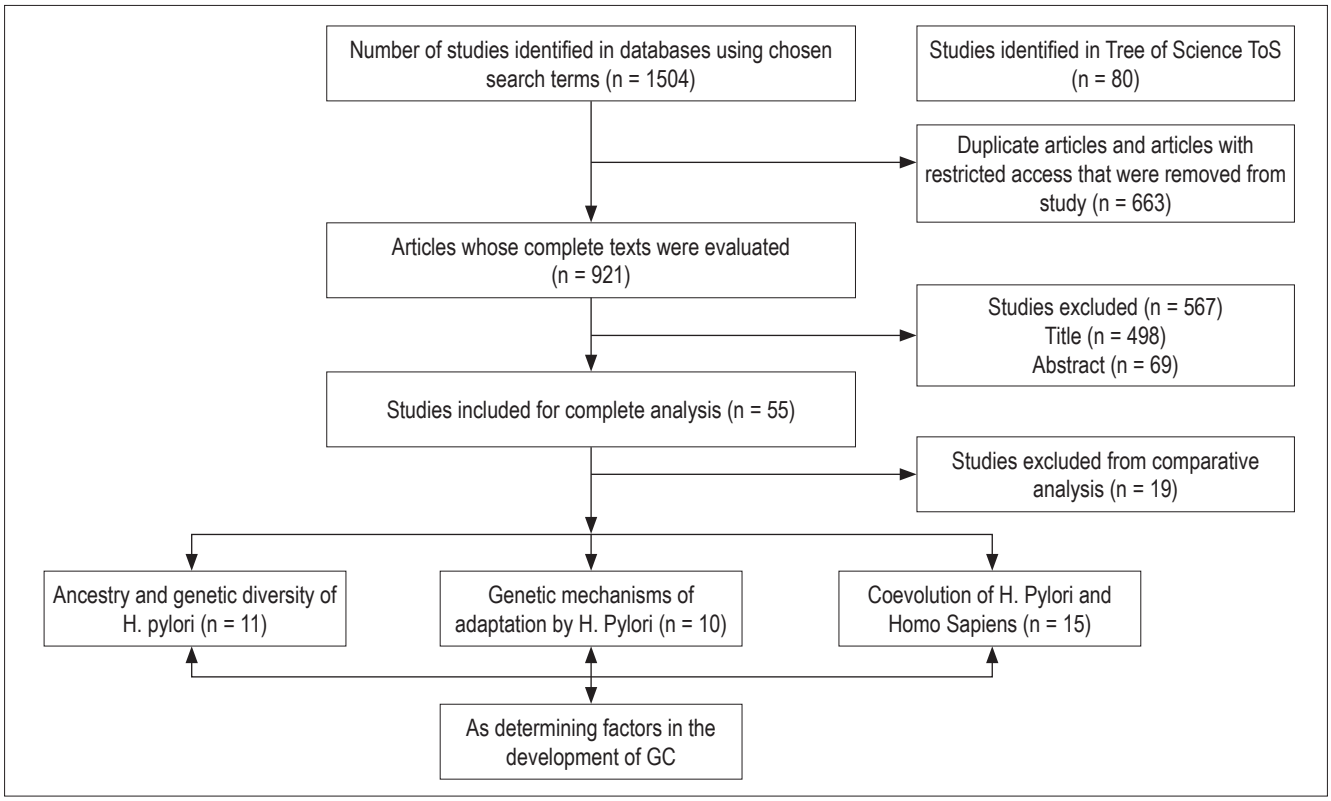

Figure 1. Flowchart of studies included in the systematic review. GC: gastric cancer.

Program (CASP) (http://www.casp-uk.net/casp-tools-checklists). A minimum inclusion score of 6/10 was established and then determined by two authors based on analysis of the published version.

The study was supported by publications of high methodological quality (88.9%, between 8 and 10 points), and the mean score was 8.33. No publication scored lower than 7.5.

RESULTS

Thirty-six studies were selected for comparative analysis. Of these, 11 (30.55%) related aspects of ancestry and host-pathogen genetic diversity related to the development of gastric lesions (9, 16, 18-25) (Table 3). Ten (27.77%) reported bacterial adaptation mechanisms (5, 11, 14, 26-33) (Table 4). Finally, 15 (41.66%) related H. pylori-Homo sapiens coevolution issues as determinants in the development of GC (1-4, 6-8, 12, 13, 15, 34-38) (Table 5). Seventy-eight percent of the studies were published in journals from the USA and UK and 69.44% were published between 2010 and 2015. Diagnostic studies accounted for 69.44% and reviews accounted for 30.56%.

H. pylori infections are usually acquired orally or through fecal-oral transmission through water, food and feces during infancy. In families, transmission requires intimate contact. The presence of H. pylori varies significantly between regions. In developing countries, there are reports of higher incidence rates due to poor hygiene and water quality, contaminated food and promiscuity. (4, 6, 9, 16, 18, 39)

Epidemiological studies agree that H. pylori is a type I carcinogen and is the most important etiological agent associated with gastritis. H. pylori induces an inflammatory response which generates pre-neoplastic sequential lesions in the gastric mucosa which are associated with the development of gastroduodenal ulcers, atrophic gastritis, dysplasia, GC and MALT lymphoma. (7, 11, 12, 14, 37) H. pylori colonization may confer protection against tuberculosis through the induction of interferon antagonistic to the causative agent, mycobacterium tuberculosis. (39)

Differences among prevalences of infections and GC incidences in Africa, Malaysia, India, China, Colombia and Costa Rica could be explained by the interaction of environmental factors with host-pathogen genetic factors. In the host, these include cytokine secretion (IL-1 And IL-8) and induction of proinflammatory signals by expression of toxins, especially cagA, vacA. In the bacterium, phylogeographic origin may be important. (2, 8, 22, 36)

Table 3. Summary of studies reporting ancestry, host-pathogen genetic diversity and their relationship to GC development

Authors, year	Design	Results
de Sablet et al., 2011 (18)	Diagnosis	HpEurope is highly predictive of increases of premalignant histological lesions and damage to epithelial DNA, while HpAfrica is associated with reduced severity of these parameters in Colombian populations.
Devi et al., 2006 (19)	Diagnosis	HpEurope predominates in the native strains of Peru. The cagPAI island, present in hpEurope, was transferred to the hspAmerindia strains during decades of colonization.
Devi et al., 2007 (25)	Diagnosis	H. pylori strains in India share ancestral origins with their European counterparts. The non-existence of other subpopulations, such as HpAfrica and hpEastAsia, in the study population suggests that HpEurope has an adaptive advantage in colonization of the gastric niche which leaves other strains out of competition.
Domínguez-Bello et al., 2008 (20)	Diagnosis	Bacterial genetic diversity is linked to success in colonization of hosts. HspAmerindia has less genetic diversity than does HpEurope. It is possible that hspAmerindia tends to disappear, since they lack the diversity necessary to survive and compete with the most diverse strains brought by non-Amerindian hosts.
Kersulyte et al., 2010 (21)	Diagnosis	hspAmerindia, present in the inhabitants of the Shimaa village, descends from Asians who arrived in America about 15 000 years ago and has been substantially displaced by HpEurope in the less isolated communities of Peru.
Latifi-Navid et al., 2010 (16)	Diagnosis	The biogeographical relationships of H. pylori are probably the result of intrafamily transmission combined with recycling within local communities. Several virulence factors of H. pylori, including cagA and vacA, vary according to ethnic group.
Martínez et al., 2013 (22)	Diagnosis	The cagA + and vacA s1/m1 strains generate significantly more severe gastric lesions in areas at high risk of GC than in areas of low risk in Colombia.
Miftahussurur et al., 2015 (23)	Diagnosis	HpEurope generates greater gastric inflammation in the population of Nepal than hpAsia2. The difference in infections between countries is not sufficient to explain the global differences in the incidence of GC.
Shiota et al., 2014 (9)	Diagnosis	HpEurope is significantly associated with severity of gastric lesions, but it is insufficient to distinguish between the risk of GC and duodenal ulcer in the Andean region of Colombia. The HpEurope strains in the Colombian population of study present a phylogenetic connection with Spanish strains.
Yamaoka et al., 2002 (24)	Diagnosis	H. pylori was present in the New World before the arrival of Columbus. H. pylori crossed the Bering Strait from Asia to the New World at different times.

Table 4. Summary of studies reporting host-pathogen genetic coevolution mechanisms

Authors, year	Design	Results
Atherton and Blaser, 2009 (5)	Review	H. pylori has adapted to humans. Genes and virulence factors have evolved rapidly through mutation and recombination which has changed the bacterium-host interaction.
Carrol et al., 2004 (14)	Review	Free recombination between populations of this bacterium, rearrangements within a strain, and horizontal transference of foreign genetic sequences.
Covacci et al., 1998 (26)	Review	Continuous selection, transduction, transformation, conjugation and horizontal gene transfer generate disruption in the clonal structure and closely related but different groups that behave as quasi-species.
Delgado-Rosado et al., 2011 (27)	Diagnosis	Positive selection of virulence genes such as EPIYA domains that modulate carcinogenicity of the cagA gene
Duncan et al., 2013 (28)	Diagnosis	Divergence, diversification by selection and positive selection of cell envelope proteins, proteins involved in DNA metabolism, and virulence factors that generate an advantage for colonization of gastric epithelium
Kawai, 2011 (29)	Diagnosis	Adaptive evolution by proteome diversification and selection through modulation of translation fidelity of proteins involved in processes of colonizing the gastric niche
Lara-Ramírez, 2011 (30)	Diagnosis	Inversion and duplication of inverted fragments contributed to the creation of new genes and gene families. The high rate of homopolynucleotide mutations, which are reversible, generate pseudogenes that can be transferred horizontally between strains
Maldonado et al., 2011 (31)	Diagnosis	DNA recombination and strain efficiency are modulated by restriction-modifying systems in which differences in cognate and active methylase recognition sites determine direction and frequency of gene flow.
Sheh et al., 2013 (32)	Diagnosis	Differential expression of genes such as virulence factors cagA, vacA and baba which are associated with an increase in inflammation, cell apoptosis and gastric lesions is associated with motility, pathogenicity and adaptation to the host environment.
Torres-Morquencho, 2010 (11)	Diagnosis	Recombination events, high mutation rates and ability to integrate unusually small pieces of exogenous DNA into its chromosomeare driven by random drift or by selective forces and favored by geographic separation of human populations. There has been strong and significant positive selection in the variable regions of cagA, baba and oipA.
Linz et al., 2013 (33)	Diagnosis	H. pylori is one of the most diverse bacterial species with a remarkably high mutation rate attributable in part to the lack of several mutation repair genes. The high rate of recombination and the ability to form aberrant genomic rearrangements and to incorporate non-homologous DNA results in remarkable bacterial diversity even within a single host.

In Colombia, patients in the high-risk area of Nariño department who are infected with H. pylori bacteria, and who are positive for cagA and vacA s1/m1, have more severe histopathological alterations than do patients in the low risk areas on the Colombian Pacific Coast. This is due to increases in the expression of the cagA protein, increases in the expression of the enzyme spermine oxidase (SMOX), and lower rates of apoptosis in strains of European phylogeographic origin than in strains of African origin. (22, 36, 40)

Origin and age of association

According to 46.1% of the studies, H. pylori is one of the oldest bacteria in the intestinal microbiome. It has co-evolved with Homo sapiens from its origin and during migrations out of Africa and thus presents a geographically and ethnically defined organism with specific strains for large continental areas and geographical patterns of genetic diversity parallel to human diversity. (3, 4, 8, 12, 13, 15, 16, 35, 39) Genetic variations in H. pylori have more discriminatory power in the determination of ancient migrations in the Ladakh region of northern India and in the Pacific (Austronesian expansion) than traditional human genetic markers such as the hypervariable region (HSV1) Of mitochondrial DNA. (6) The time of association between H. pylori and its human host reported in coevolution studies ranges from approximately 60,000 years ago to approximately 116,000 years ago. (3, 4, 6-9, 13, 15, 29, 39) The oldest date for this association is 116,000 years ago. (15)

Genetic Diversity, Geographic Phylogeny and Host Adaptation Mechanisms

Eight of the studies (30.7%) agree that the diversity of the bacterium tends to decrease with increasing distance from Africa which is in line with what is observed in human populations. They also concur that the unusual intra-population genetic flexibility is due to recombination events, a high rate of mutation and the insertion of exogenous DNA fragments into the bacterial chromosome. Together they

Table 5. Summary of studies that report on the host-pathogen genetic coevolution processes and their role in the development of GC

Authors, year	Design	Results
Akhter et al., 2007 (34)	Review	The low incidence of GC in populations with high prevalences of H. pylori suggests a possible coevolution of this pathogen with its human host.
Breurec et al., 2011 (6)	Diagnosis	Distribution of bacterial populations seems to strongly influence the incidence of GC.
Camorlinga-Ponce et al., 2011 (7)	Diagnosis	H. pylori strains of Mexican natives show a mixture of components of Asian, European and African ancestry in genes that interact with the gastric mucosa. A new Amerindian cagA group was formed by isolations originating from Mexican, Colombian, Peruvian and Venezuelan natives. Similarly, a new type of Amerindian vacA has been reported in isolates from Alaska, Mexico and Colombia.
Correa and Piazuelo, 2012 (8)	Review	The genome of the bacterium has evolved together with its human host for approximately 60,000 years. The evolutionary dynamics have been determined by local differences in host physiology, resistance and bacterial specificity that vary geographically.
Ghoshal et al., 2010 (2)	Review	There are inconsistencies between the prevalence of infection and the incidence of GC. The lesion caused by this infectious agent can be modulated by interactions with host and environmental factors.
Kodaman et al., 2014 (13)	Diagnosis	H. pylori strains of African descent are relatively benign in humans of African descent, but harmful in individuals of Amerindian descent. The coevolution process modulates the risk of disease and disruption of this process could explain the development of gastric diseases.
Kodaman et al., 2014 (35)	Review	Interruption of coevolution between the pathogen and its human host may explain variation in disease outcomes. Genome-to-genome interactions should be incorporated into genetic models of diseases caused by infectious agents.
Linz, 2007 (3)	Diagnosis	Genetic diversity in humans and H. pylori decreases with geographical distance from East Africa. H. pylori appears to have spread from eastern Africa about 58,000 years ago. Modern humans were already infected with H. pylori when they migrated from Africa. H. pylori has been closely associated with human populations since then.
Loh et al., 2011 (36)	Diagnosis	hpEurope expresses higher levels of cagA and is associated with more advanced precancerous lesions than are African-origin strains in Colombian populations.
Mane et al., 2010 (37)	Diagnosis	H. pylori has migrated and diverged with human populations. HspAmerindia is a sister group that is particularly close to H. pylori in East Asia. It shows substantial divergence of the vacA and cagA genes from old world forms indicating novel genotypes (vacA m3).
Montano et al., 2015 (4)	Diagnosis	The human-H Pylori association is at least 100,000 years old. The long and intimate association of H. pylori with humans suggests a history of adaptation of the bacteria to specific genes involved in the modulation of host adaptive immunity and of genomic changes that have occurred during acute and chronic infection and during transmission of H. pylori among human hosts.
Moodley et al., 2012 (15)	Diagnosis	H. pylori is approximately as old as anatomically modern humans (116,000 years) and has diversified in parallel with its hosts. H. pylori may have been acquired through a host leap from an unknown, non-human host.
Torres et al., 2013 (1)	Review	In the Americas, the bulk of GC mortality is concentrated in mountainous areas along the Pacific basin following the geography of the Andes from Venezuela to Chile and of the Central American range from Southern Mexico to Costa Rica. Altitude is probably a key factor in the clustering of host genetic, bacterial, dietary and environmental in mountainous regions.
Yamaoka et al., 2008 (38)	Review	Humans probably acquired H. pylori long before their migration out of Africa. Various GC rates associated with different geographic areas can be explained, at least in part, by differences in genotypes of H. pylori cagA and vacA.
Haley et al., 2015 (12)	Review	The relationship between H. pylori and its human host is complex and dynamic evidencing human host-H. pylori coevolution. Perturbation of coevolution generates deregulation of the host-pathogen interaction, leading to oncogenic effects.

generate genomic changes that allow the evolution of areas of plasticity and regulatory mechanisms that modulate gene expression. (4, 6, 7, 11, 16, 33)

Selective pressures from the host immune response during acute and chronic infection and during the transmission of the pathogen between and among human hosts combined with polymorphisms within H. pylori strains have generated evolutionary changes in bacterial phylogeny. These occur primarily in genes involved in electron transfer, redox metabolism and DNA repair. These include the nusA transcription elongation factor; HU binding proteins which protect DNA integrity; proteins activated proteins during starvation which are necessary for survival during acid stress; genes involved in methylation patterns, an epigenetic mechanism that regulates gene expression and phenotypic plasticity; genes involved in the flagellar

cascade which allow cellular motility and cell adhesion to the mucosa of the stomach which is a key factor for successful colonization of the human stomach; genes involved in metabolism of copper, cadmium, zinc, cobalt and nickel; and those involved in virulence such as cagA, vacA and oipA which can be positively selected within populations of H. pylori from different geographical origins. (2,4,6,7,11,23,29,33)

Ethnographic Evolution and Microevolution

Amino acid substitutions, binding and selective pressures primarily in the cagA, Baba, hspA, and oipA regions vary among populations of H. pylori from different geographical origins and show ethnic associations. For example, the vacA s1c region is associated with strains from East Asia whereas vacA s1b is found in strains from Spain, Portugal and Latin America. The highly polymorphic 3 'cagA region translates into different patterns of the terminal region of the protein that are differentially distributed geographically. ABD amino acid sequences flanking EPIYA (tyrosine phosphorylation) are associated with East Asian strains while the "ABC" pattern is typical of H. pylori strains in the west. (7, 11)

Positive selection of these genomic regions and the rate of recombination among strains should have allowed evolution of new lineages such as that of Southeast Asia (hspEAsia), consisting of Japanese and Korean genomes, and which is distinct from Amerindian, African and European lineages. (29) The vacA m3 locus, present in Amerindian populations, diverges from Old World forms which indicates that it is a recent genotype. (21, 37)

Ancestral Gene Populations

Multilocus sequence typing (MLST) was used by 61.5% of the studies to analyze genetic diversity in the sequences of 7 conserved genes (atpA, efp, mutY, ppa, trpC, ureI, and yphC) and genes associated with virulence (vacA, cagA, hspA and oipA) in different ethnic groups. Analysis by MLST in programs such as STRUCTURE subdivided H. pylori into 7 specific populations for large geographic areas: hpEurope, hpNEAfrica, hpAfrica1, hpAfrica2, hpAsia2, hpSahul and hpEastAsia with the hspAsia, hspMaori and HspAmerindia. (3, 4, 6-9, 11-13, 16, 18, 33, 35, 37) These are derived from 6 ancestral populations: Ancestral Europe1 (AE1), Ancestral Europe2 (AE2), Ancestral East Asia, Ancestral Africa1, Ancestral Africa2 and Ancestral Sahul. (6)

According to the analyses of 325 isolates reported in the PubMLST database, there is an expansion of hpEurope strains into North Africa, Asia and the Americas and strains of hpEurope are more prevalent than are strains from other geographical origins (Figure 2). This could be

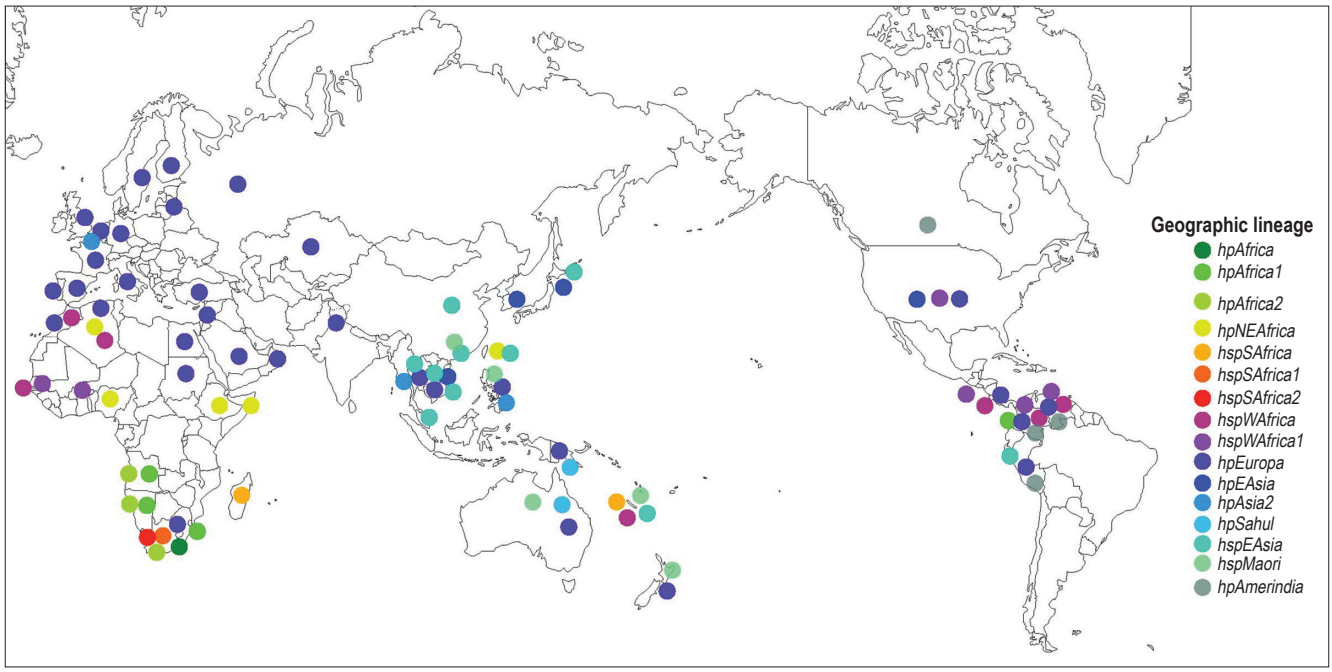

Figure 2. Geographic distribution of H. pylori lineages. We included 325 isolates from hpAfrica1, hpAfrica2, hpNEAfrica, hpEurope, hpAsia2, hpEastAsia (with subpopulations hspAsia, hspMaori and hspAmerindia) and hpSahul. Strains of African origin that did not correspond to the hpAfrica1, hpAfrica2 and hpNEAfrica lineages were categorized into hpAfrica (with the subpopulations hspWAfrica, hspWAfrica1, hspSAfrica1, hspSAfrica1 and hspSAfrica2).

the result of recent processes of human migration. In the Indian population, hpEurope hs an adaptive advantage in the colonization of the gastric niche and displaces strains such as hpAfrica and hpEastAsia. (25) Strains of several geographical origins (hpEurope, hspAmerindia, hpAfrica1, hspWAfrica) were reported in the departments of Bogotá and Nariño in Colombia. This is probably due to horizontal gene transfer and infection with strains from geographical origins other than those of the from native populations that were introduced by slaves and colonizers during colonization processes (Figure 2). (9, 13, 17, 18, 36)

Coevolution and GC

According to 46.1% of the articles, during acute and chronic host infection there have been adaptive events in bacterial-specific genes involved in the modulation of host adaptive immunity, reduction in the number of open reading frames, and reduction in the size of the bacterial genome. This is supported by findings from regions of Africa, Malaysia, India and Colombia where the prevalence of H. pylori infection is almost 100%, although GC incidence rates are low. (2, 4, 8, 11-13, 18, 23, 27, 29, 33)

Interactions between the host-pathogen genome and disruption in the coevolution process by infection with strains of ancestral origin other than that of the host are important in the development of GC. (8, 35). For example, in Colombia, the incidence of GC on the Pacific Coast is 6 cases/100,000 inhabitants/year while in Nariño it is 150 cases/100,000 inhabitants/year. However, the prevalence of H. pylori in these regions is similar (90%). It is interesting to note that on the Pacific Coast, the ancestry of human populations is mainly African (58%), while in Nariño it is Amerindian (67%). (13) This coincides with the fact that African strains have been shown to be benign in humans of African ancestry but harmful in individuals of Amerindian descent and indicates that coevolutionary relationships are determinant for the risk of developing GC and that colonization continues to influence the health of modern American populations.

DISCUSSION

Humans have coevolved with the viruses and bacteria of their microbiome including human papillomavirus (HPV), hepatitis G virus, retrovirus HTLV-1 RNA and H. pylori bacteria (12, 13, 20, 26, 35). H. pylori is one of the best examples because of its adaptation to the gastric environment through modification of genes involved in the modulation of host adaptive immunity and through the evolution of host adaptation mechanisms in various human ethnic groups. (35) This has allowed for the development of a largely innocuous and potentially symbiotic infection. (4, 6, 8, 11-13, 27-29, 32, 33, 36, 37, 39)

The genetic diversity of H. pylori tends to decrease a distance from Africa increases. This is congruent with the tendency observed for genetic diversity in human populations. (3, 4, 8, 12, 13, 15, 16, 35, 39) There are approximately 1,560 genes in the constitutive genome of the bacterium while approximately 400 to 500 are specific and vary in each strain. High rates of mutation, transduction, transformation and conjugation, horizontal gene transfer in recombination events, genomic rearrangements, insertion of non-homologous DNA fragments, loss of genes during infection with multiple strains, positive selection of cell envelope proteins involved in DNA metabolism and virulence factors explain genetic diversity in the bacterial genome. Diversity can exist within the same host where the bacteria are capable of adapting to a specific gastric niche. (4, 6, 7, 11 , 12, 16, 21, 33)

Despite high variability, H. pylori shows structured ethnic and phylogeographic patterns that correlate with those of its human hosts and which result from intrafamily transmission of infections, local dispersion of single nucleotide polymorphisms due to homologous recombination and isolation resulting from distance between human populations which promotes divergence due to genetic drift and adaptation to local conditions. (4, 6, 15, 16, 21)

Coevolution of H. Pylori, Homo Sapiens and GC

Although 80% of infected individuals are asymptomatic, H. pylori is the most important etiological agent associated with gastritis and induces an active chronic inflammatory response that can affect the entire gastric mucosa. The outcome of infection is determined by the interaction of pathogen characteristics in combination with host genetic factors and environmental factors. (12, 18)

For 2008, approximately 780,000 GC cases were caused by H. pylori infection (6.2% of the 12.7 million new cases reported that year). This confirms that H. pylori is a type I carcinogen. (10)

Estudios recientes demuestran que el proceso de coevolución de *H. pylori-Homo sapiens* es un factor determinante que modula el desarrollo de las lesiones gástricas (3, 6, 8, 13, 15, 35, 37). La disrupción del proceso de coevolución, por la transferencia horizontal de cepas y genes que no han coevolucionado con su huésped, podría explicar en parte las tasa de incidencia de GC en poblaciones con una genética compleja, como la colombiana, que ha experimentado un proceso reciente de mezcla intercontinental entre amerindios, europeos y africanos en diferentes proporciones (13,

17). Por ende, los estudios evolutivos en esta bacteria son importantes para comprender la dinámica huésped-patógeno e identificar los procesos adaptativos y coevolutivos y las interacciones que promueven el desarrollo del espectro de enfermedades asociadas con la infección (7, 8, 13, 17, 35).

Recent studies demonstrate that the H. pylori-Homo sapiens coevolution process is a determining factor that modulates development of gastric lesions. (3, 6, 8, 13, 15, 35, 37). Disruption of the coevolution process by horizontal transfer of strains and genes that have not coevolved with their host could partly explain incidence rates of GC in populations with complex genetics. One such case is the population of Colombia which has undergone a recent process of intercontinental mixture among Amerindians, Europeans and Africans in varying. (13, 17) Evolutionary studies of this bacterium are important for understanding host-pathogen dynamics and for identifying adaptive and coevolutionary processes and interactions that promote the development of the spectrum of diseases associated with infection. (7, 8, 13, 17, 35)

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Authors' contributions

Alix Andrea Guevara Tique and Mabel Elena Bohórquez L. carried out the search for studies. Alix Andrea Guevara Tique was responsible for the first draft manuscript. Ángel Criollo R., John Jairo Suarez O., Mabel Elena Bohórquez L. and María Magdalena Echeverry de Polanco contributed significantly to the final version of the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

APPENDIX 1

Information on the 325 isolates included on the distribution map

N.°	Isolate Information			H. pylori lineage	N.°	Isolate Information			H. pylori lineage	N.°	Isolate Information			H. pylori lineage
	ID	Isolated	Place			ID	Isolated	Place			ID	Isolated	Place	
1	1432	B11	Africa	*hspWAfrica*	109	732	ETH10	Ethiopia	*hpNEAfrica*	217	2022	Pt-B51-U	Portugal	*hpEurope*
2	114	bo210	Germany	*hpEurope*	110	869	ETH46	Ethiopia	*hpNEAfrica*	218	2032	Pt-4472-G	Portugal	*hpEurope*
3	118	bo279	Germany	*hpEurope*	111	597	re06060	Philippines	*hpEurope*	219	163	001uk	United Kingdom	*hpEurope*
4	123	bo414	Germany	*hpEurope*	112	642	re06006	Philippines	*hpAsia2*	220	172	097UK	United Kingdom	*hpEurope*
5	583	ku319	Germany	*hpEurope*	113	654	re13001	Philippines	*hpAsia2*	221	184	H1412	United Kingdom	*hpEurope*
6	1472	K01A2	Angola	*hpAfrica1*	114	849	re04001	Philippines	*hspMaori*	222	427	H3014	United Kingdom	*hpEurope*
7	1476	K25A1	Angola	*hpAfrica1*	115	903	fin9625	Finland	*hpEurope*	223	429	H3017	United Kingdom	*hpEurope*
8	1482	Khoisan25A	Angola	*hpAfrica1*	116	92	fi106	Finland	*hpEurope*	224	430	H3018	United Kingdom	*hpEurope*
9	1485	K03A	Angola	*hpAfrica2*	117	96	fi165	Finland	*hpEurope*	225	431	H3022	United Kingdom	*hpEurope*
10	1488	Khoisan26A	Angola	*hpAfrica2*	118	100	fi88	Finland	*hpEurope*	226	432	H3023	United Kingdom	*hpEurope*
11	658	sara3502	Saudi Arabia	*hpEurope*	119	726	B225	France	*hpEurope*	227	572	k1b	Russia	*hpEurope*
12	684	arab1921	Saudi Arabia	*hpEurope*	120	1404	ND	France	*hpEurope*	228	723	31	Russia	*hpEurope*
13	585	alg830	Argelia	*hpEurope*	121	1431	Aslimi	France	*hpEurope*	229	827	92	Russia	*hpEurope*
14	689	alg873	Argelia	*hpNEAfrica*	122	1837	GAM42	Gambia	*hspWAfrica*	230	367	D4a	Senegal	*hspWAfrica1*
15	690	alg877	Argelia	*hpEurope*	123	1838	GAM112	Gambia	*hspWAfrica*	231	1577	dak101	Senegal	*hspWAfrica*

Information on the 325 isolates included on the distribution map (*Continued*)

N.º	Isolate Information			H. pylori lineage	N.º	Isolate Information			H. pylori lineage	N.º	Isolate Information			H. pylori lineage
	ID	Isolated	Place			ID	Isolated	Place			ID	Isolated	Place	
16	1654	ALG2	Argelia	*hspWAfrica*	124	1840	GAM71A	Gambia	*hspWAfrica*	232	1578	dak106	Senegal	*hspWAfrica*
17	1436	OX34	Asia	*hspEAsia*	125	1841	GAM80A	Gambia	*hspWAfrica*	233	1580	dak109	Senegal	*hspWAfrica*
18	30	nctc11638	Australia	*hpEurope*	126	1843	GAM96A	Gambia	*hspWAfrica*	234	1581	dak110	Senegal	*hspWAfrica*
19	941	ausabrJ05	Australia	*hpSahul*	127	1844	GAM100A	Gambia	*hspWAfrica*	235	1589	dak13	Senegal	*hspWAfrica*
20	944	ausabrp98	Australia	*hpEurope*	128	1847	GAM101	Gambia	*hspWAfrica*	236	1594	dak138	Senegal	*hspWAfrica*
21	960	TS1a	Australia	*hspMaori*	129	1848	GAM103	Gambia	*hspWAfrica*	237	1596	dak14	Senegal	*hspWAfrica*
22	1035	ausabras47a	Australia	*hpSahul*	130	1849	GAM105	Gambia	*hspWAfrica*	238	1598	dak141	Senegal	*hspWAfrica*
23	1098	auseurB121	Australia	*hpEurope*	131	1850	GAM254	Gambia	*hspWAfrica*	239	1611	dak3	Senegal	*hspWAfrica*
24	599	bel7452	Belgium	*hpEurope*	132	1851	GAM114	Gambia	*hspWAfrica*	240	1614	dak33	Senegal	*hspWAfrica*
25	353	BF11a	Burkina Faso	*hspWAfrica1*	133	1852	GAM115	Gambia	*hspWAfrica*	241	1618	dak38	Senegal	*hspWAfrica*
26	359	BF3a	Burkina Faso	*hspWAfrica1*	134	1859	GAM201	Gambia	*hspWAfrica*	242	1619	dak39	Senegal	*hspWAfrica*
27	363	BF8a	Burkina Faso	*hspWAfrica1*	135	1862	GAM239	Gambia	*hspWAfrica*	243	1629	dak48	Senegal	*hspWAfrica*
28	1396	CAM1	Cambodia	*hpEurope*	136	1868	GAM250	Gambia	*hspWAfrica*	244	1635	dak58	Senegal	*hspWAfrica*
29	1398	CAM2	Cambodia	*hspEAsia*	137	1869	GAM252	Gambia	*hspWAfrica*	245	33	re7006	Singapore	*hpEurope*
30	1400	CAM4	Cambodia	*hspEAsia*	138	1874	GAM83	Gambia	*hspWAfrica*	246	35	re12001	Singapore	*hspEAsia*
31	231	inma10	Canada	*hspAmerindia*	139	1875	GAM117	Gambia	*hspWAfrica*	247	38	re12004	Singapore	*hspEAsia*
32	604	hk2559	China	*hspEAsia*	140	1878	GAMch114	Gambia	*hspWAfrica*	248	43	re8038	Singapore	*hspEAsia*
33	247	HUI1685	Colombia	*hpEurope*	141	1879	GAMch117	Gambia	*hspWAfrica*	249	372	re8030	Singapore	*hspEAsia*
34	248	HUI1688	Colombia	*hpEurope*	142	1880	GAMch124	Gambia	*hspWAfrica*	250	611	som3506	Somalia	*hpNEAfrica*
35	249	HUI1693	Colombia	*hpEurope*	143	1882	GAM97B	Gambia	*hspWAfrica*	251	1504	Khoisan04A	South Africa	*hpAfrica1*
36	250	HUI1770	Colombia	*hpEurope*	144	229	12	Guatemala	*hspWAfrica1*	252	1505	Khoisan06A	South Africa	*hpAfrica1*
37	251	HUI1986	Colombia	*hpEurope*	145	124	25	Holland	*hpEurope*	253	1506	K15C	South Africa	*hpAfrica1*
38	252	HUI1987	Colombia	*hpEurope*	146	1410	HK182	Hong Kong	*hspEAsia*	254	1507	Khoisan15A	South Africa	*hpAfrica1*
39	253	HUI1990	Colombia	*hpEurope*	147	57	L113	India	*hpEurope*	255	1508	Khoisan15C	South Africa	*hpAfrica1*
40	254	HUI1992	Colombia	*hpEurope*	148	60	L144	India	*hpEurope*	256	1513	K10A	South Africa	*hpAfrica2*
41	255	HUI1994	Colombia	*hpEurope*	149	68	L45	India	*hpEurope*	257	1514	K10C	South Africa	*hpAfrica2*
42	256	HUI1995	Colombia	*hpEurope*	150	76	J318	Israel	*hpEurope*	258	1515	K13C	South Africa	*hpAfrica2*
43	257	HUI2010	Colombia	*hpEurope*	151	77	J320	Israel	*hpEurope*	259	1518	Khoisan10A	South Africa	*hpAfrica2*
44	258	HUI2012	Colombia	*hpEurope*	152	78	J328	Israel	*hpEurope*	260	1522	Khoisan13C	South Africa	*hpAfrica2*
45	259	HUI1681	Colombia	*hspAmerindia*	153	79	J347	Israel	*hpEurope*	261	1526	Khoisan14A	South Africa	*hpEurope*
46	260	HUI1692	Colombia	*hspAmerindia*	154	80	J348	Israel	*hpEurope*	262	1527	Khoisan14C	South Africa	*hpEurope*
47	261	HUI1764	Colombia	*hspAmerindia*	155	2033	Is-3180-G	Israel	*hpEurope*	263	267	104	South Africa	*hpEurope*
48	262	HUI1769	Colombia	*hspAmerindia*	156	792	it168	Italy	*hpEurope*	264	271	170.9	South Africa	*hpEurope*
49	436	C5	Colombia	*hpEurope*	157	577	jpo145	Japan	*hspEAsia*	265	279	192.9	South Africa	*hspSAfrica1*

Information on the 325 isolates included on the distribution map (*Continued*)

N.°	Isolate Information			H. pylori lineage	N.°	Isolate Information			H. pylori lineage	N.°	Isolate Information			H. pylori lineage
	ID	Isolated	Place			ID	Isolated	Place			ID	Isolated	Place	
50	437	C5-1	Colombia	*hpAfrica1*	158	645	jpti42	Japan	*hspEAsia*	266	285	C108	South Africa	*hspSAfrica1*
51	438	C5-2	Colombia	*hpEurope*	159	2035	Jp-206B-U	Japan	*hpEAsia*	267	286	135	South Africa	*hpAfrica2*
52	439	C5-3	Colombia	*hpEurope*	160	2036	Jp-G09-260-G	Japan	*hpEAsia*	268	287	164	South Africa	*hpAfrica2*
53	440	C5-4	Colombia	*hpEurope*	161	660	jor3466	Jordan	*hpEurope*	269	289	244	South Africa	*hpEurope*
54	447	C6	Colombia	*hpEurope*	162	676	kaz3172	Kazakhstan	*hpEurope*	270	290	189.9	South Africa	*hpEurope*
55	448	C6-1	Colombia	*hpEurope*	163	842	kaz3193	Kazakhstan	*hpEurope*	271	293	14.9	South Africa	*hspSAfrica1*
56	449	C6-2	Colombia	*hpEurope*	164	816	leb3349	Lebanon	*hpEurope*	272	294	147	South Africa	*hspSAfrica1*
57	466	C7-1	Colombia	*hpEurope*	165	897	leb3438	Lebanon	*hpEurope*	273	310	162	South Africa	*hspSAfrica2*
58	467	C7-3	Colombia	*hpEurope*	166	125	5_1	Lithuania	*hpEurope*	274	314	191.9	South Africa	*hspSAfrica2*
59	468	C7	Colombia	*hpEurope*	167	1552	mada204a	Madagascar	*hspSAfrica*	275	316	167	South Africa	*hpEurope*
60	469	C7-2	Colombia	*hpEurope*	168	1553	mada209a	Madagascar	*hspSAfrica*	276	470	SA34A	South Africa	*hpAfrica2*
61	598	col360	Colombia	*hpEurope*	169	1558	mada227a	Madagascar	*hspSAfrica*	277	474	SA40A	South Africa	*hpAfrica2*
62	617	col354	Colombia	*hspWAfrica*	170	1575	mada290a	Madagascar	*hspSAfrica*	278	482	SA169A	South Africa	*hpAfrica2*
63	675	col398	Colombia	*hpEurope*	171	603	re03028	Malaysia	*hspEAsia*	279	490	SA302C	South Africa	*hpEurope*
64	830	col391	Colombia	*hpEurope*	172	615	re02007	Malaysia	*hspEAsia*	280	492	SA300C	South Africa	*hpAfrica*
65	839	col335	Colombia	*hpEurope*	173	640	re01006	Malasia	*hspEAsia*	281	500	SA174C	South Africa	*hpEurope*
66	217	nq1677	Columbia	*hpEurope*	174	780	re01003	Malasia	*hpAsia2*	282	504	SA175C	South Africa	*hpAfrica2*
67	218	nq1725	Columbia	*hpEurope*	175	672	mor3545	Morocco	*hpEurope*	283	507	SA166A	South Africa	*hpAfrica2*
68	219	nq267	Columbia	*hpEurope*	176	770	mor3621	Morocco	*hspWAfrica*	284	514	SA171A1	South Africa	*hpEurope*
69	220	nq299	Columbia	*hpEurope*	177	785	mor3055	Morocco	*hspWAfrica*	285	527	SA156A1	South Africa	*hpAfrica*
70	221	nq315	Columbia	*hpEurope*	178	1490	K02C	Namibia	*hpAfrica1*	286	531	SA47A1	South Africa	*hpAfrica2*
71	222	nq331	Columbia	*hpEurope*	179	1492	Khoisan23A	Namibia	*hpAfrica1*	287	553	SA47C1	South Africa	*hpAfrica2*
72	223	nq351	Columbia	*hpEurope*	180	1497	K28A	Namibia	*hpAfrica2*	288	568	SA157A1	South Africa	*hpAfrica*
73	224	nq352	Columbia	*hpEurope*	181	1502	Khoisan29C	Namibia	*hpAfrica2*	289	369	su1	Sudan	*hpEurope*
74	225	nq367	Columbia	*hpEurope*	182	638	nigh1448	Nigeria	*hpNEAfrica*	290	370	su2	Sudan	*hpEurope*
75	226	nq372	Columbia	*hpEurope*	183	857	nigh2491	Nigeria	*hpNEAfrica*	291	2002	Sw-C577-G	Sweden	*hpEurope*
76	227	nq392	Columbia	*hpEurope*	184	860	nigh2494	Nigeria	*hpNEAfrica*	292	2005	Sw-C166-G	Sweden	*hpEurope*
77	228	nq366	Columbia	*hspWAfrica1*	185	990	NCMel38	New Caledonia	*hspMaori*	293	2007	Sw-569-U	Sweden	*hpEurope*

Information on the 325 isolates included on the distribution map (*Continued*)

N.°	Isolate Information			H. pylori lineage	N.°	Isolate Information			H. pylori lineage	N.°	Isolate Information			H. pylori lineage
	ID	Isolated	Place			ID	Isolated	Place			ID	Isolated	Place	
78	452	K3-2	Korea	*hpEAsia*	186	992	NCPol34	New Caledonia	*hspMaori*	294	584	TH03	Thailand	*hpEurope*
79	460	K5	Korea	*hpEAsia*	187	1155	NCMel53	New Caledonia	*hspEAsia*	295	620	Thai8	Thailand	*hpEurope*
80	1528	CRPCG006	Costa Rica	*hpEurope*	188	1168	NCMel45	New Caledonia	*hspMaori*	296	621	Thai7	Thailand	*hpAsia2*
81	1529	CRPCG012	Costa Rica	*hpEurope*	189	1205	NCPol52	New Caledonia	*hspMaori*	297	623	Thai4	Thailand	*hpAsia2*
82	1530	CRPCG014	Costa Rica	*hpEurope*	190	1418	NCEur03	New Caledonia	*hspWAfrica*	298	624	Thai3	Thailand	*hspEAsia*
83	1531	CRPCG017	Costa Rica	*hpEurope*	191	1427	NCMel16	New Caledonia	*hspMaori*	299	673	th8842	Thailand	*hspEAsia*
84	1532	CRPCG051	Costa Rica	*hpEurope*	192	1430	NCPol20	New Caledonia	*hspSAfrica*	300	707	TH08	Thailand	*hpAsia2*
85	1534	CRPCG123	Costa Rica	*hspWAfrica*	193	1	ne605	New Zealand	*hpEurope*	301	710	TH11001	Thailand	*hpAsia2*
86	1535	CRPCG149	Costa Rica	*hpEurope*	194	2	ne614	New Zealand	*hpEurope*	302	744	TH11012	Thailand	*hspEAsia*
87	1536	CRPCG157	Costa Rica	*hspWAfrica*	195	7	inma53	New Zealand	*hspMaori*	303	910	Thai5	Thailand	*hpAsia2*
88	1540	CRPCG182	Costa Rica	*hpEurope*	196	8	inma54	New Zealand	*hspMaori*	304	759	tai190	Taiwan	*hspEAsia*
89	576	egy2199	Egypt	*hpEurope*	197	9	M49	New Zealand	*hspMaori*	305	938	Tw3392	Taiwan	*hspMaori*
90	133	17ch	Spain	*hpEurope*	198	10	ne600	New Zealand	*hspMaori*	306	977	Tw2958	Taiwan	*hspMaori*
91	144	28ad	Spain	*hpEurope*	199	16	ne610	New Zealand	*hspMaori*	307	1041	TwT4	Taiwan	*hspMaori*
92	151	34s	Spain	*hpEurope*	200	18	ne612	New Zealand	*hspMaori*	308	1160	Tw7c	Taiwan	*hspMaori*
93	154	37s	Spain	*hpEurope*	201	24	ne620	New Zealand	*hspMaori*	309	1194	Tw101Pa	Taiwan	*hspMaori*
94	199	j99	USA	*hspWAfrica1*	202	26	ne622	New Zealand	*hspMaori*	310	1228	Tw49Ya	Taiwan	*hspEAsia*
95	201	lsu1040-1	USA	*hpEurope*	203	607	oman3383	Oman	*hpEurope*	311	2034	Tw-254-U	Taiwan	*hpNEAfrica*
96	202	lsu1013-2	USA	*hspWAfrica1*	204	612	nl600	Netherlands	*hpEurope*	312	773	tur3155	Turkey	*hpEurope*
97	203	lsu1014-1	USA	*hspWAfrica1*	205	644	nl585	Netherlands	*hpAsia2*	313	875	tur3069	Turkey	*hpEurope*
98	204	j166	USA	*hpEurope*	206	570	pal3399	Palestine	*hpEurope*	314	569	tur673	Turkey	*hpEurope*
99	235	96-228	USA	*hpEurope*	207	591	pal3412	Palestine	*hpEurope*	315	263	V189	Venezuela	*hpEurope*
100	443	H3	USA	*hpEurope*	208	896	pal3358	Palestine	*hpEurope*	316	265	V225	Venezuela	*hspAmerindia*
101	445	H2-3	USA	*hpEAsia*	209	940	PNGhigh62A	Papua New Guinea	*hpEurope*	317	266	V185	Venezuela	*hspWAfrica1*
102	85	E115	Estonia	*hpEurope*	210	1147	PNGhigh12A	Papua New Guinea	*hpSahul*	318	595	vz17	Venezuela	*hpEurope*
103	89	E152	Estonia	hpEurope	211	1170	PNGhigh102A	Papua New Guinea	hpSahul	319	738	vz2	Venezuela	hpEurope
104	91	E64	Estonia	*hpEurope*	212	646	pe9041	Peru	*hpEurope*	320	811	vz503	Venezuela	*hpEurope*
105	663	ETH39	Ethiopia	*hpNEAfrica*	213	717	pe9040	Peru	*hspAmerindia*	321	829	vz435	Venezuela	*hspWAfrica*
106	665	ETH35	Ethiopia	*hpNEAfrica*	214	778	pe9023	Peru	*hpEurope*	322	587	VIE2870	Vietnam	*hspEAsia*
107	669	ETH31	Ethiopia	*hpNEAfrica*	215	230	hp1	Peru	*hspEAsia*	323	784	VIE2771	Vietnam	*hspEAsia*
108	695	ETH24	Ethiopia	*hpNEAfrica*	216	2017	Pt-B104-U	Portugal	*hpEurope*	324	879	VIE2692	Vietnam	*hspEAsia*
										325	2037	Vn-HN75-G	Vietnam	*hpEAsia*

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