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REVIEW

Comparative genomics of *Helicobacter pylori*

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Abstract

Genomic sequences have been determined for a number of strains of *Helicobacter pylori* (*H pylori*) and related bacteria. With the development of microarray analysis and the wide use of subtractive hybridization techniques, comparative studies have been carried out with respect to the interstrain differences between *H pylori* and inter-species differences in the genome of related bacteria. It was found that the core genome of *H pylori* constitutes 1111 genes that are determinants of the species properties. A great pool of auxillary genes are mainly from the categories of *cag* pathogenicity islands, outer membrane proteins, restriction-modification system and hypothetical proteins of unknown function. Persistence of *H pylori* in the human stomach leads to the diversification of the genome. Comparative genomics suggest that a host jump has occurs from humans to felines. Candidate genes specific for the development of the gastric diseases were identified. With the aid of proteomics, population genetics and other molecular methods, future comparative genomic studies would dramatically promote our understanding of the evolution, pathogenesis and microbiology of *H pylori*.

Key words: *Helicobacter pylori*; Genomics; Pathogenesis; Cancer

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INTRODUCTION

The gastric pathogen, *Helicobacter pylori* (*H pylori*), is a member of the epsilon-bacteria. This microaerophilic, Gram-negative bacterium colonizes the human stomach[1]. It is estimated that over half of the human population are infected by *H pylori*[2]. The infection causes mucosal inflammation, atrophy, ulceration and cancer[3,4]. Five strains of *H pylori* and a number of related bacteria have been sequenced. Genomics, evolutionary studies and population genetics have advanced our understanding of this bacterium.

GENOMIC FEATURES

In 1997, *H pylori* strain 26 695 was firstly sequenced[5]. It was isolated from an English patient with chronic gastritis. The chromosome of strain 26 695 is circular and composed of 1 667 867 base pairs. The average GC content is approximately 39%. In the initial annotation, it has 1590 open reading frames that are possibly protein-coding[5], in addition to the RNA coding genes (2 copies of 16S rRNA and 23S rRNA genes, 36 tRNA genes). Later analysis of the genome sequence suggested a smaller number of ORFs in strain 26 695[6]. The ongoing studies have found genes that were neglected in the initial analysis. A general secretion machinery is widely present in bacteria, which functions in secretion of outer membrane proteins from the inner membrane and delivery of proteins to extracellular environments[7]. The initial annotation revealed a partial general secretion machinery because it lacked SecE in 26 695[5]. A further analysis of the genome sequences with GeneMark, Glimmer and BlastX found a small open reading frame between nusG and rmpG (HP1203-HP1204)[8]. It has a high homology and structural similarity to the SecE protein in related bacteria. Therefore, strain 26 695 has a complete general secretion machinery, which is consistent with the fact that the bacterium is capable of protein secretion. In addition, small RNA genes are universally present in bacteria[9]. The tmRNA gene (*ssrA*) has been found in *H pylori*, which encodes a functional RNA molecule and a small peptide that is involved in

quality control of translation[10]. In addition, *H pylori* also possesses a sRNA gene encoding the RNA component of Rnase P and the 4.5S RNA gene which is involved in secretion[11,12].

In 1999, strain J99 was sequenced which was isolated from an American patient with a duodenal ulcer[6]. Compared to strain 26 695, it has a slightly smaller circular chromosome (1 643 831). The overall genomic organization, gene order and predicted proteomes of the sequenced strains are very similar. The predicted open reading frames are less in strain J99, amounting to 1495. There are 1406 genes shared by both strains, but 86 open reading frames are absent from strain 26 695. Both strains contain a complete *cag* pathogenicity island that codes for a type Ⅳ secretion system which delivers the CagA cytotoxin protein into gastric epithelial cells[13]. Comparison of the two genomes reveals the occurrence of translocation and inversion events. A 83 kb inversion contains most of the strain specific genes. This region was named a plasticity zone since it has a much lower GC content (35%) than the rest of the genome.

In 2006, a chronic atrophic gastritis *H pylori* strain, HPAG1, was sequenced[14]. It was isolated from an 80 year-old female patient who was enrolled in a Swedish case-control study of gastric cancer[15]. Similar to the sequenced strains 26 695 and J99, HPAG1 is a type 1 strain that contains *cagA* and a virulent allele of *vacA*[15]. The genome of HPAG1 (1 596 366 bp) is the smallest in the three sequenced strains. A total of 1536 open reading frames were predicted. Of these, 43 genes are only present in HPAG1. Analysis revealed that 29 genes that are found in both J99 and 26 695 were missing from HPAG1. If genes in a strain are absent from other strains, they are called strain-specific genes. The comparison of three sequenced *H pylori* strains shows that the majority of strain-specific genes are functionally unknown. Another group of strain-specific genes is composed of genes of the R-M system (restriction-modification). They encode proteins involved in DNA restriction or modification. Other strain-specific genes include those encoding outer membrane proteins and *cag* proteins.

H pylori strain G27 was sequenced recently[16]. It was originally isolated from an Italian patient[17] and has been used widely in *H pylori* research. This strain is naturally transformable[18], capable of delivering CagA into epithelial cells in culture[19,20], and capable of adapting to variable environments[21].

The G27 genome has a similar size to the other three sequenced strains. It is 1 652 983 bp long and has a GC content of 38.9%. 1515 open reading frames was predicted. In addition, G27 also contains one 10 032 bp AT rich (65.2%) plasmid resembling that found in strain HPAG1[14]. The plasmid encodes 11 genes. In agreement with the previous report[6], the *cag* pathogenicity island of G27 is disrupted by a transposon. This, however, does not seem to interfere with any of the open reading frames or to the delivery of CagA into host cells. Unlike strain 26 695, there is a single plasticity region in G27 which contains a large number of *H pylori* specific genes. It is predicted that strain G27 has 58 genes that are not found in 26 695, J99, or HPAG1.

The *H pylori Shi470* genome has also been sequenced by Washington University Medical School. It is 1.61 Million bp long and contains approximately 1609 predicted genes. The sequences are available on the university website (http://hpylori.ucsc.edu).

The finding of strain-specific genes from the comparison of the sequenced strains is in agreement with the earlier studies which demonstrated the high diversity of the *H pylori* genome[22-24]. No identical strains of *H pylori* have been found in their genetic types unless they are isolated from a family[25-27]. *H pylori* has great mutation and recombination capacities. Analysis of the genomic sequences failed to identify a complete mismatch repair system controlling the confidentiality of replication, despite the presence of a homology of MutS[28,29]. This results in a high mutation rate of *H pylori*. Examination of 29 clinical isolates revealed that approximately 1/4 of them had mutator phenotype with higher mutation frequencies than Enterobacteriaceae mismatch-repair defective mutants[30]. In another study, examination of paired strains isolated from a patient at different times suggested a mutation rate of 4.1×10^{-5}, which is comparable to that of *E. coli* mutator[31]. *H pylori* is naturally competent for transformation[32]. Nonrandomly distributed repetitive sequences are found in the genome, which leads to frequent recombination events[33]. The recombination rate (recombination events starting at any particular nucleotide) is estimated to be 6.9×10^{-5}[34,35]. High levels of recombination and mutation could explain the observed genomic diversity in *H pylori*.

DETERMINATION OF THE CORE GENOME OF *H PYLORI*

Inter-strain diversity, represented by variations in number and contents of genes, chromosomal rearrangements and allelic diversities, is not unique to *H pylori*[36]. This has been noted in a number of other bacterial species. For *H pylori*, each strain contains many strain-specific genes[7,14]. It has been proposed that a particular bacterial species contains a core set of genes and the auxiliary genes[37]. The core genome contains genes that are present in all or nearly all of the strains. It determines the properties that are characteristic of the species. The auxiliary genes are present in some of strains. They are determinants of the biological properties unique to some of the strains. Salama *et al*[38] firstly explored the core set of genes in *H pylori*. A total of 15 strains of *H pylori* mainly isolated from Western countries were examined using a microarray method[38]. It was found that 1281 genes were common to all the examined strains, therefore constituting the core genome of *H pylori*. Considering the limited number of strains examined and the fact that *H pylori* is highly prevalent in human, could these genes represent the actual core set of the *H pylori* species? Additionally, these strains were only isolated from Western individuals. In fact, molecular typing of global strains has found that the modern population of *H pylori* divides into five major

groups, hpEurope, HpAfrica1, hpafrica2, hpEastAsia and hpAsia2[39,40]. They are possibly derived from different ancestral groups. Gressmann *et al*[41] further examined 56 globally representative strains of *H pylori*. The number of the genes in the core set of *H pylori* was diminished to 1150. The author concluded through a calculation that the core genome of *H pylori* only consists of 1111 genes.

The auxiliary set of genes in *H pylori* amounts to 22%-27% of the genome[14,41]. In agreement with the findings from the whole genome sequencing of *H pylori* strains, the auxiliary genes consist of those coding for functionally unknown proteins, cag protein, outer membrane proteins and proteins of DNA metabolism[7].

Candidate genes specific for development of gastric diseases.

The long term clinical outcomes of the *H pylori* infection are diverse. The infected gastric mucosa may develop inflammation, atrophy, intestinal metaplasia, ulceration, cancer and MALT lymphoma[1,3,4]. Genes in the auxiliary set are specific only for some strains. Do they play roles in the determination of the final outcome of an infected individual? *H pylori* broth culture filtrates cause the formation of intracellular vacuoles in mammalian cells[42]. The protein which has the vacuolation activity was purified and named VacA (Vacuolating cytotoxin). Despite of the universal presence of the *vacA* gene in *H pylori*, some strains do not cause the vacuolation of epithelial cells. This is attributed to the mosaic structure of *vacA*[42]. A signal region in the N-terminal and a mid region of *vacA* are polymorphic. The signal region affects the vacuolating activity of the cytotoxin: a 12 amino acid extension on the s2 form blocks the activity, although not all s1 forms have the cytotoxic activity[43]. The mid region is a determinant of the cell specificity of VacA[44]. There are three vacA genotypes, s1/m1, s1/m2 and s2/m2 in *H pylori*. The association of s1/m1 strains with severe diseases has been observed in some studies. A recent study found an intermediate region (i-region) of *vacA* between the signal region and the mid region that also contributes to the levels of vacuolating activity[45]. The genotype i1 was more frequently found in gastric cancer associated *H pylori* than the i2[45]. Strains possessing *vacA* i1 are strongly associated with peptic ulcer[46]. Another protein has been found to be co-present in almost all of the strains possessing the vacuolating activity[47]. The protein was named as cytotoxin-associated gene A (*cagA*) protein. The gene is present in the majority of strains. Those possessing the vacuolating activity and the CagA expression are called type I strains, or virulent strains[48]. The presence of *cagA* is generally the marker for a large DNA region called *cag* pathogenicity island[49]. Proteins produced by the *cag* island make up a type Ⅳ secretion system which delivers CagA into the epithelial cells[50,51]. The type Ⅳ secretion system locates across the inner and outer membrane and forms a pilus-like structure at the surface[51,52].The CagL protein is a specialized adhesin that is targeted to the pilus surface[53]. Through an arginine-glycine-aspartate motif, it binds to and activates integrin $\alpha5\beta1$ receptor on gastric epithelial cells. This interaction triggers CagA delivery into target cells[54] and activation of Src of gastric epithelial cells[55]. Translocated CagA remains associated with the host membrane and becomes tyrosine phosphorylated on carboxyl-terminal repeat motifs (Glu-Pro-Ile-Tyr-Ala, or EPIYA motifs)[56,57] by members of the Src family of protein tyrosine kinases such as c-Src, Fyn, Lyn, and Yes[58]. Phosphorylated CagA interacts with SHP-2[59], which thereafter activates a number of phosphorylases inducing alteration of signaling pathways. This alters the spreading, migration, adhesion, polarity and cytoskeletal structures of epithelial cells[60-63] . A large European study, demonstrated that *cagA* positive strains are significantly associated with the development of gastric cancer[64]. The *cag* island is thus an important determinant of the clinical outcomes of the *H pylori* infection. Most *H pylori* strains, and almost all in certain geographical locations, however, are virulent (that is they expressing CagA and VacA). Are there any other genomic differences associated with the clinical outcomes?

Comparison of the genomic contents of different strains has found genes that are potentially disease-specific. Peptic ulcer disease frequently occurs in humans with severe, or even lethal complications. The disease may also affect children. Oleastro *et al*[65] reported the study of the genomic comparison of a *H pylori* strain isolated from a child presenting with duodenal ulcer and a strain from a sex and age matched child with gastritis. It was found that genes jhp0562 and jhp0870 are more frequently seen in children with peptic ulcer than in those with gastritis. Both genes are located in the plasticity zone. Jhp0562 encodes a putative LPS glycosyltransferase involved in LPS biosynthesis[66], whereas jhp0870 codes for an outer membrane protein. LPS and outer membrane proteins play roles in the induction of an inflammatory response from the gastric mucosa[66,67]. Whether jhp0562 and jhp0870 contribute to the development of ulceration in children deserves further study. Other genomic comparison studies have found that the *cag* island and a 670 bp-long DNA fragment that is partially homologous to the hymidylate kinase gene are potentially associated with peptic ulcer diseases[68]. Gastric mucosa infected by *H pylori* develops inflammation, and gradually become atrophic. Mucosal atrophy is an important stage in stomach carcinogenesis. A thorough examination of the genome of 6 strains from atrophic gastritis found a set of 121 "ChAG-associated" (ChAG, chronic atrophic gastritis) genes[14,69]. They are universally present in these 6 strains but absent from 56 globally derived strains of *H pylori*[69]. Their putative roles in the development of atrophy and promotion of carcinogenesis are yet to be studied. Intestinal metaplasia of gastric mucosa is a precancerous lesion. *H pylori* in the patient with intestinal metaplasia is likely associated with progression into gastric cancer. Comparison of a cancer strain and a duodenal ulcer strain of *H pylori* found a novel sequence named Clone P32 with homology to GepA in *Dichelobacter nodosus*[70]. Examination of strains from diverse gastric diseases demonstrated that Clone P32 is inversely associated with intestinal metaplasia. Gastric B cell lymphoma of mucosa associated lymphoid tissue is highly associated with the *H pylori* infection[1]. Eradication of the bacterium leads to the alleviation of the disease. Comparing

the genome of a strain from gastric B cell lymphoma with that from gastritis revealed that jhp0950 encoding a *H pylori* specific protein of unknown function was potentially associated with the development of the disease[71]. It was present in about 3 quarters of strains from gastric lymphoma, but only present in about half of strains from gastritis, duodenal ulcer or gastric adenocarcinoma. If other virulent factors were taken into account, the odds of having gastric MZBL among patients harbouring JHP950, *iceA1* (coding for a restriction enzyme), and *sabA* (coding for a major adhesin) "on" strains were 10 times higher than for the others[72]. Although these genes are specific for strains from a specified disease, it is uncertain whether they are pathogenic for a particular disease. Actually, different gastric diseases greatly differ in a variety of environmental factors that have potential impacts on the biological behaviors and genetics of the bacterium. For example, secretion of gastric acid is varied in different diseases[73]. Therefore, further studies are required to say that a gene is specific for the pathogenesis of a particular disease.

INTRA-HOST EVOLUTION OF THE *H PYLORI* GENOME

It is believed that the *H pylori* infection is usually acquired in childhood[74]. The bacterium is transmitted from parents to their children with a bias of mother to children transmission[75,76]. Once the infection is established, the bacterium persists in the host for decades unless eradicated with antibiotics. Transmission of bacteria to a new host is a major barrier for bacterial spreading. It may affect the bacterial genome contents. Four healthy adults were experimentally infected with *H pylori*. Examination of isolates form 15 d or 90 d postinfection demonstrated that their genomic contents were identical to the challenging strain[77]. A similar result was found in a study of experimental infected mice[78]. These findings suggest that for *H pylori*, transmission does not cause any alteration of the gene components of the genome, or, in the other words, the establishment of the *H pylori* infection does not require the involvement of novel genes. Further evidence supporting this conclusion comes from a study of the analysis of the strains from a mother and her three children[75]. Microarray analysis demonstrated that the genomic contents of isolates from the mother were identical to those from the children. *H pylori* persists in the human stomach for decades, probably from childhood. It may experience a variety of ecological alterations, which may in turn have large impacts on the genome of the organism. The output of gastric acid alters with aging and with infection by *H pylori*. Alterations of the constituents and the quantity of the gastric mucus underneath which the bacterium resides are observed during the course of the *H pylori* infection. The gastric epithelial cells may undergo metaplasia and changes in surface proteins, which affect adhesion and the supply of nutrients. The gastric mucosa may produce immune and inflammatory products against the bacterium. The co-infection with other microbes is also frequent seen in the stomach. These alterations may affect genomic contents of *H pylori*. Kraft *et al*[79] examined paired strains of *H pylori* with respect to their genomic contents using the microarray method. Paired strains were isolated from the same patients at an interval from 3 to 36 mo. Of 21 pairs of strains examined, 4 pairs showed differences in their genomic contents, suggesting the occurrence of evolutionary events. These included a complete deletion and a partial loss of the *cag* pathogenicity island, a replacement of an open reading frame of unknown function with the restriction-modification system HpyAIV, an acquisition of 14 genes in the plasticity zone, a duplication of the *ceuE* genes (HP1561/HP1562) and a truncation of tandem arranged *ackA* and *pta* genes resulting in the formation of pseudogenes. A study has compared 2 pairs of strains obtained from the same patients at an interval of 4 years[69]. The patients had progressed from atrophic gastritis to cancer. Six genes were absent, including 3 genes involved in DNA repair, an outer membrane protein and two hypothetical proteins. Nine genes were gained, including a ligase, a metalloprotease, a tRNA formyltransferase, a putative ribonuclease, a restriction enzyme and four hypothetical genes. The comparison suggests that with the progression of the atrophy to cancer, the bacterium may have a propensity for losing its diversifying capacity. Findings from these studies demonstrate that *H pylori* may acquire or lose genes during the intra-host colonization[80]. The genes involved fall into the same categories as the strain specific genes. This was further supported by the results from the comparison of the sequenced strain J99 with isolates obtained 6 years later[81]. These comparative studies of the *H pylori* genome draw a picture of the genomic changes during the cycle of invasion, colonization and transmission to a new host. It appears that invasion into a new host has little effect on the gene composition of the genome. This indicates that the current genome of *H pylori* has sufficient capacities for permitting bacterial invasion into a human host or even into a host of different species under experimental conditions. Once the infection is established, the bacterium has to cope with the dynamic changes of the ecology during the long-term coexistence with the host. Genomic diversifications, or gain and/or loss of genes, occur in response to these changes. The diversifications involve genes that are mainly those strain specific genes observed from comparative studies of unrelated strains of *H pylori*. Intra-host evolution of *H pylori*, thus, results in the creation of a pool of genes that are generally needed by some strains. This pool of genes can be considered as the auxiliary set of genes of *H pylori*.

COMPARATIVE STUDIES OF *H PYLORI* AND ITS RELATED BACTERIA

Since the isolation of *H pylori*, a number of closely related bacteria have been identified, constituting a

Table 1 General genomic features of *helicobacters* and *campylobacters*

Species	*Helicobacter pylori*			*H. acinonychis*	*H. hepaticus*	*W. succinogenes*	*C. jejuni*	*C. coli*	*C. lari*	*C. upsaliensis*
Strain	26695	j99	HPAG1	Sheeba	ATCC51449	DSM1740	NCTC11168	RM2228	RM2100	RM3195
Origin	Clinical	Clinical	Clinical	Felines	Rodents	Cattle	Clinical	Chicken	Clinical	Clinical
Genome size (bp)	1667867	1643831	1596366	1553928	1799146	2110355	1641481			
GC content (%)	39.0	39.0	-	38.2	35.9	48.5	30.5	31.3	29.6	34.5
Coding sequences										
Predicted number	1590	1459	1536	1611	1875	2046	1634	1764	1554	1782
Coding area (%)	91.0	90.8	-	89.7	93.0	93.0	94.3	-	-	-
Average length (bp)	945	998	-	865	1082	964	948	-	-	-
Flexible genome pool										
Plasmids	None	None	pHPAG1	pHac1	None	None	None	pCC178	pCL46	pCU3, pCu110
Insertion elements	IS605, IS606	IS606	None	ISHa1675, ISHa1942, ISHa1152	None	ISWsu1302, ISWsu1203	None	IS605	-	-
Genomic islands	cag PAI	cag PAI	cag PAI	HacGI	HHGI1	WSUGI I and II	None	-	-	-

new bacterial genus named Helicobacter genus[82,83]. Bacteria within this genus have been shown to colonise the gastrointestinal tract of mammals. Many of these Helicobacter species are involved in the pathogenesis of gastrointestinal diseases[82,83]. Phylogenetic analysis has shown that the *helicobacters* can be separated into two clusters[84]. Gastric species that colonise the stomach of mammals form a cluster. Species that inhabit the intestine and biliary tracts cluster together to form the enterohepatic cluster. In addition to *H pylori*, the genome sequences have been determined for several other *helicobacters*, including *H. mustelae* from ferret, *H. acinonychis* from large felines (cheetahs, lions and tigers)[85], *H. hepaticus* from mice which causes hepatoma[86], and Wolinella succinogenes from cattle[87].

General genomic features of these *helicobacters* are listed in Table 1, which also includes information for several species of *campylobacter*[88-91]. Of these related bacteria, the size and GC content of *H. acinonychis* are most similar to those of *H pylori*[85]. Comparison of 612 orthologues that are present in both *H. acinonychis* and *H pylori* found that they differ at only few of their amino acids. The Blast scores against *H pylori* of most coding sequences in *H. acinonychis* are very high. These findings lead to the conclusion that a host jump has occurred from human to felines[85]. This event probably occurred 100000 years ago. More studies are required to confirm this conclusion considering that universally accepted criteria to identify a host jump event are currently unavailable. The study also found a set of fragmented genes and newly acquired genes in *H. acinonychis*. These genes include a set of genes encoding outer membrane proteins and a cluster of genes encoding proteins for sialylation of bacterial surface carbohydrates. It has been suggested that these genes are probably beneficial for the bacterium to evade host immune defenses[92].

Information from comparative genomics has greatly enhanced our understanding of the microbiology, physiology, evolution and pathogenesis of *H pylori*. Candidate genes specific for the development of the gastric disease, particularly gastric cancer have been identified. Considering the striking diversities in the *H pylori* genome which are intensified by intra-host evolution, further studies exploring these genes must take account of them.

REFERENCES

1 **Blaser MJ**, Atherton JC. Helicobacter pylori persistence: biology and disease. *J Clin Invest* 2004; **113**: 321-333
2 **Lehours P**, Yilmaz O. Epidemiology of Helicobacter pylori infection. *Helicobacter* 2007; **12** Suppl 1: 1-3
3 **Blaser MJ**. Helicobacter pylori and gastric diseases. *BMJ* 1998; **316**: 1507-1510
4 **Sipponen P**, Hyvarinen H, Seppala K, Blaser MJ. Review article: Pathogenesis of the transformation from gastritis to malignancy. *Aliment Pharmacol Ther* 1998; **12** Suppl 1: 61-71
5 **Tomb JF**, White O, Kerlavage AR, Clayton RA, Sutton GG, Fleischmann RD, Ketchum KA, Klenk HP, Gill S, Dougherty BA, Nelson K, Quackenbush J, Zhou L, Kirkness EF, Peterson S, Loftus B, Richardson D, Dodson R, Khalak HG, Glodek A, McKenney K, Fitzegerald LM, Lee N, Adams MD, Hickey EK, Berg DE, Gocayne JD, Utterback TR, Peterson JD, Kelley JM, Cotton MD, Weidman JM, Fujii C, Bowman C, Watthey L, Wallin E, Hayes WS, Borodovsky M, Karp PD, Smith HO, Fraser CM, Venter JC. The complete genome sequence of the gastric pathogen Helicobacter pylori. *Nature* 1997; **388**: 539-547
6 **Alm RA**, Ling LS, Moir DT, King BL, Brown ED, Doig PC, Smith DR, Noonan B, Guild BC, deJonge BL, Carmel G, Tummino PJ, Caruso A, Uria-Nickelsen M, Mills DM, Ives C, Gibson R, Merberg D, Mills SD, Jiang Q, Taylor DE, Vovis GF, Trust TJ. Genomic-sequence comparison of two unrelated isolates of the human gastric pathogen Helicobacter pylori. *Nature* 1999; **397**: 176-180
7 **Bieker KL**, Silhavy TJ. The genetics of protein secretion in E. coli. *Trends Genet* 1990; **6**: 329-334
8 **Medigue C**, Wong BC, Lin MC, Bocs S, Danchin A. The secE gene of Helicobacter pylori. *J Bacteriol* 2002; **184**: 2837-2840
9 **Wassarman KM**, Repoila F, Rosenow C, Storz G, Gottesman S. Identification of novel small RNAs using comparative genomics and microarrays. *Genes Dev* 2001; **15**: 1637-1651
10 **Dong Q**, Zhang L, Goh KL, Forman D, O'Rourke J, Harris A, Mitchell H. Identification and characterisation of ssrA in members of the Helicobacter genus. *Antonie Van Leeuwenhoek* 2007; **92**: 301-307
11 **Kazantsev AV**, Pace NR. Bacterial RNase P: a new view of an ancient enzyme. *Nat Rev Microbiol* 2006; **4**: 729-740
12 **Vogel J**, Bartels V, Tang TH, Churakov G, Slagter-Jager JG, Huttenhofer A, Wagner EG. RNomics in Escherichia coli detects new sRNA species and indicates parallel transcriptional output in bacteria. *Nucleic Acids Res* 2003; **31**:

6435-6443
13 **Kutter S**, Buhrdorf R, Haas J, Schneider-Brachert W, Haas R, Fischer W. Protein subassemblies of the Helicobacter pylori Cag type IV secretion system revealed by localization and interaction studies. *J Bacteriol* 2008; **190**: 2161-2171
14 **Oh JD**, Kling-Backhed H, Giannakis M, Xu J, Fulton RS, Fulton LA, Cordum HS, Wang C, Elliott G, Edwards J, Mardis ER, Engstrand LG, Gordon JI. The complete genome sequence of a chronic atrophic gastritis Helicobacter pylori strain: evolution during disease progression. *Proc Natl Acad Sci USA* 2006; **103**: 9999-10004
15 **Enroth H**, Kraaz W, Engstrand L, Nyren O, Rohan T. Helicobacter pylori strain types and risk of gastric cancer: a case-control study. *Cancer Epidemiol Biomarkers Prev* 2000; **9**: 981-985
16 **Baltrus DA**, Amieva MR, Covacci A, Lowe TM, Merrell DS, Ottemann KM, Stein M, Salama NR, Guillemin K. The complete genome sequence of Helicobacter pylori strain G27. *J Bacteriol* 2009; **191**: 447-448
17 **Covacci A**, Censini S, Bugnoli M, Petracca R, Burroni D, Macchia G, Massone A, Papini E, Xiang Z, Figura N. Molecular characterization of the 128-kDa immunodominant antigen of Helicobacter pylori associated with cytotoxicity and duodenal ulcer. *Proc Natl Acad Sci USA* 1993; **90**: 5791-5795
18 **Censini S**, Lange C, Xiang Z, Crabtree JE, Ghiara P, Borodovsky M, Rappuoli R, Covacci A. cag, a pathogenicity island of Helicobacter pylori, encodes type I-specific and disease-associated virulence factors. *Proc Natl Acad Sci USA* 1996; **93**: 14648-14653
19 **El-Etr SH**, Mueller A, Tompkins LS, Falkow S, Merrell DS. Phosphorylation-independent effects of CagA during interaction between Helicobacter pylori and T84 polarized monolayers. *J Infect Dis* 2004; **190**: 1516-1523
20 **Guillemin K**, Salama NR, Tompkins LS, Falkow S. Cag pathogenicity island-specific responses of gastric epithelial cells to Helicobacter pylori infection. *Proc Natl Acad Sci USA* 2002; **99**: 15136-15141
21 **Amieva MR**, Vogelmann R, Covacci A, Tompkins LS, Nelson WJ, Falkow S. Disruption of the epithelial apical-junctional complex by Helicobacter pylori CagA. *Science* 2003; **300**: 1430-1434
22 **Akopyanz N**, Bukanov NO, Westblom TU, Kresovich S, Berg DE. DNA diversity among clinical isolates of Helicobacter pylori detected by PCR-based RAPD fingerprinting. *Nucleic Acids Res* 1992; **20**: 5137-5142
23 **Han FC**, Ng HC, Ho B. Stability of randomly amplified polymorphic DNA fingerprinting in genotyping clinical isolates of Helicobacter pylori. *World J Gastroenterol* 2003; **9**: 2021-2024
24 **Burucoa C**, Lhomme V, Fauchere JL. Performance criteria of DNA fingerprinting methods for typing of Helicobacter pylori isolates: experimental results and meta-analysis. *J Clin Microbiol* 1999; **37**: 4071-4080
25 **van der Ende A**, Rauws EA, Feller M, Mulder CJ, Tytgat GN, Dankert J. Heterogeneous Helicobacter pylori isolates from members of a family with a history of peptic ulcer disease. *Gastroenterology* 1996; **111**: 638-647
26 **Roma-Giannikou E**, Karameris A, Balatsos B, Panayiotou J, Manika Z, Van-Vliet C, Rokkas T, Skandalis N, Kattamis C. Intrafamilial spread of Helicobacter pylori: a genetic analysis. *Helicobacter* 2003; **8**: 15-20
27 **Raymond J**, Thiberge JM, Kalach N, Bergeret M, Dupont C, Labigne A, Dauga C. Using macro-arrays to study routes of infection of Helicobacter pylori in three families. *PLoS One* 2008; **3**: e2259
28 **Kang J**, Huang S, Blaser MJ. Structural and functional divergence of MutS2 from bacterial MutS1 and eukaryotic MSH4-MSH5 homologs. *J Bacteriol* 2005; **187**: 3528-3537
29 **Pinto AV**, Mathieu A, Marsin S, Veaute X, Ielpi L, Labigne A, Radicella JP. Suppression of homologous and homeologous recombination by the bacterial MutS2 protein. *Mol Cell* 2005; **17**: 113-120
30 **Bjorkholm B**, Sjolund M, Falk PG, Berg OG, Engstrand L, Andersson DI. Mutation frequency and biological cost of antibiotic resistance in Helicobacter pylori. *Proc Natl Acad Sci USA* 2001; **98**: 14607-14612
31 **Falush D**, Kraft C, Taylor NS, Correa P, Fox JG, Achtman M, Suerbaum S. Recombination and mutation during long-term gastric colonization by Helicobacter pylori: estimates of clock rates, recombination size, and minimal age. *Proc Natl Acad Sci USA* 2001; **98**: 15056-15061
32 **Karnholz A**, Hoefler C, Odenbreit S, Fischer W, Hofreuter D, Haas R. Functional and topological characterization of novel components of the comB DNA transformation competence system in Helicobacter pylori. *J Bacteriol* 2006; **188**: 882-893
33 **Aras RA**, Kang J, Tschumi AI, Harasaki Y, Blaser MJ. Extensive repetitive DNA facilitates prokaryotic genome plasticity. *Proc Natl Acad Sci USA* 2003; **100**: 13579-13584
34 **Suerbaum S**, Achtman M. Evolution of Helicobacter pylori: the role of recombination. *Trends Microbiol* 1999; **7**: 182-184
35 **Suerbaum S**, Smith JM, Bapumia K, Morelli G, Smith NH, Kunstmann E, Dyrek I, Achtman M. Free recombination within Helicobacter pylori. *Proc Natl Acad Sci USA* 1998; **95**: 12619-12624
36 **Pupo GM**, Lan R, Reeves PR, Baverstock PR. Population genetics of Escherichia coli in a natural population of native Australian rats. *Environ Microbiol* 2000; **2**: 594-610
37 **Lan R**, Reeves PR. Intraspecies variation in bacterial genomes: the need for a species genome concept. *Trends Microbiol* 2000; **8**: 396-401
38 **Salama N**, Guillemin K, McDaniel TK, Sherlock G, Tompkins L, Falkow S. A whole-genome microarray reveals genetic diversity among Helicobacter pylori strains. *Proc Natl Acad Sci USA* 2000; **97**: 14668-14673
39 **Falush D**, Wirth T, Linz B, Pritchard JK, Stephens M, Kidd M, Blaser MJ, Graham DY, Vacher S, Perez-Perez GI, Yamaoka Y, Megraud F, Otto K, Reichard U, Katzowitsch E, Wang X, Achtman M, Suerbaum S. Traces of human migrations in Helicobacter pylori populations. *Science* 2003; **299**: 1582-1585
40 **Linz B**, Balloux F, Moodley Y, Manica A, Liu H, Roumagnac P, Falush D, Stamer C, Prugnolle F, van der Merwe SW, Yamaoka Y, Graham DY, Perez-Trallero E, Wadstrom T, Suerbaum S, Achtman M. An African origin for the intimate association between humans and Helicobacter pylori. *Nature* 2007; **445**: 915-918
41 **Gressmann H**, Linz B, Ghai R, Pleissner KP, Schlapbach R, Yamaoka Y, Kraft C, Suerbaum S, Meyer TF, Achtman M. Gain and loss of multiple genes during the evolution of Helicobacter pylori. *PLoS Genet* 2005; **1**: e43
42 **Atherton JC**, Cao P, Peek RM Jr, Tummuru MK, Blaser MJ, Cover TL. Mosaicism in vacuolating cytotoxin alleles of Helicobacter pylori. Association of specific vacA types with cytotoxin production and peptic ulceration. *J Biol Chem* 1995; **270**: 17771-17777
43 **Letley DP**, Atherton JC. Natural diversity in the N terminus of the mature vacuolating cytotoxin of Helicobacter pylori determines cytotoxin activity. *J Bacteriol* 2000; **182**: 3278-3280
44 **Ji X**, Fernandez T, Burroni D, Pagliaccia C, Atherton JC, Reyrat JM, Rappuoli R, Telford JL. Cell specificity of Helicobacter pylori cytotoxin is determined by a short region in the polymorphic midregion. *Infect Immun* 2000; **68**: 3754-3757
45 **Rhead JL**, Letley DP, Mohammadi M, Hussein N, Mohagheghi MA, Eshagh Hosseini M, Atherton JC. A new Helicobacter pylori vacuolating cytotoxin determinant, the intermediate region, is associated with gastric cancer. *Gastroenterology* 2007; **133**: 926-936
46 **Basso D**, Zambon CF, Letley DP, Stranges A, Marchet A, Rhead JL, Schiavon S, Guariso G, Ceroti M, Nitti D, Rugge M, Plebani M, Atherton JC. Clinical relevance of Helicobacter pylori cagA and vacA gene polymorphisms. *Gastroenterology* 2008; **135**: 91-99
47 **Tummuru MK**, Cover TL, Blaser MJ. Cloning and expression of a high-molecular-mass major antigen of Helicobacter

pylori: evidence of linkage to cytotoxin production. *Infect Immun* 1993; **61**: 1799-1809

48 **Cover TL**, Glupczynski Y, Lage AP, Burette A, Tummuru MK, Perez-Perez GI, Blaser MJ. Serologic detection of infection with cagA+ Helicobacter pylori strains. *J Clin Microbiol* 1995; **33**: 1496-1500

49 **Censini S**, Lange C, Xiang Z, Crabtree JE, Ghiara P, Borodovsky M, Rappuoli R, Covacci A. cag, a pathogenicity island of Helicobacter pylori, encodes type I-specific and disease-associated virulence factors. *Proc Natl Acad Sci USA* 1996; **93**: 14648-14653

50 **Odenbreit S**, Puls J, Sedlmaier B, Gerland E, Fischer W, Haas R. Translocation of Helicobacter pylori CagA into gastric epithelial cells by type IV secretion. *Science* 2000; **287**: 1497-1500

51 **Kutter S**, Buhrdorf R, Haas J, Schneider-Brachert W, Haas R, Fischer W. Protein subassemblies of the Helicobacter pylori Cag type IV secretion system revealed by localization and interaction studies. *J Bacteriol* 2008; **190**: 2161-2171

52 **Rohde M**, Puls J, Buhrdorf R, Fischer W, Haas R. A novel sheathed surface organelle of the Helicobacter pylori cag type IV secretion system. *Mol Microbiol* 2003; **49**: 219-234

53 **Kwok T**, Zabler D, Urman S, Rohde M, Hartig R, Wessler S, Misselwitz R, Berger J, Sewald N, Konig W, Backert S. Helicobacter exploits integrin for type IV secretion and kinase activation. *Nature* 2007; **449**: 862-866

54 **Backert S**, Ziska E, Brinkmann V, Zimny-Arndt U, Fauconnier A, Jungblut PR, Naumann M, Meyer TF. Translocation of the Helicobacter pylori CagA protein in gastric epithelial cells by a type IV secretion apparatus. *Cell Microbiol* 2000; **2**: 155-164

55 **Selbach M**, Moese S, Hauck CR, Meyer TF, Backert S. Src is the kinase of the Helicobacter pylori CagA protein in vitro and in vivo. *J Biol Chem* 2002; **277**: 6775-6778

56 **Stein M**, Rappuoli R, Covacci A. Tyrosine phosphorylation of the Helicobacter pylori CagA antigen after cag-driven host cell translocation. *Proc Natl Acad Sci USA* 2000; **97**: 1263-1268

57 **Higashi H**, Yokoyama K, Fujii Y, Ren S, Yuasa H, Saadat I, Murata-Kamiya N, Azuma T, Hatakeyama M. EPIYA motif is a membrane-targeting signal of Helicobacter pylori virulence factor CagA in mammalian cells. *J Biol Chem* 2005; **280**: 23130-23137

58 **Stein M**, Bagnoli F, Halenbeck R, Rappuoli R, Fantl WJ, Covacci A. c-Src/Lyn kinases activate Helicobacter pylori CagA through tyrosine phosphorylation of the EPIYA motifs. *Mol Microbiol* 2002; **43**: 971-980

59 **Higashi H**, Tsutsumi R, Muto S, Sugiyama T, Azuma T, Asaka M, Hatakeyama M. SHP-2 tyrosine phosphatase as an intracellular target of Helicobacter pylori CagA protein. *Science* 2002; **295**: 683-686

60 **Saadat I**, Higashi H, Obuse C, Umeda M, Murata-Kamiya N, Saito Y, Lu H, Ohnishi N, Azuma T, Suzuki A, Ohno S, Hatakeyama M. Helicobacter pylori CagA targets PAR1/MARK kinase to disrupt epithelial cell polarity. *Nature* 2007; **447**: 330-333

61 **Tammer I**, Brandt S, Hartig R, Konig W, Backert S. Activation of Abl by Helicobacter pylori: a novel kinase for CagA and crucial mediator of host cell scattering. *Gastroenterology* 2007; **132**: 1309-1319

62 **Poppe M**, Feller SM, Romer G, Wessler S. Phosphorylation of Helicobacter pylori CagA by c-Abl leads to cell motility. *Oncogene* 2007; **26**: 3462-3472

63 **Suzuki M**, Mimuro H, Suzuki T, Park M, Yamamoto T, Sasakawa C. Interaction of CagA with Crk plays an important role in Helicobacter pylori-induced loss of gastric epithelial cell adhesion. *J Exp Med* 2005; **202**: 1235-1247

64 **Palli D**, Masala G, Del Giudice G, Plebani M, Basso D, Berti D, Numans ME, Ceroti M, Peeters PH, Bueno de Mesquita HB, Buchner FL, Clavel-Chapelon F, Boutron-Ruault MC, Krogh V, Saieva C, Vineis P, Panico S, Tumino R, Nyren O, Siman H, Berglund G, Hallmans G, Sanchez MJ, Larranaga N, Barricarte A, Navarro C, Quiros JR, Key T, Allen N, Bingham S, Khaw KT, Boeing H, Weikert C, Linseisen J, Nagel G, Overvad K, Thomsen RW, Tjonneland A, Olsen A, Trichoupoulou A, Trichopoulos D, Arvaniti A, Pera G, Kaaks R, Jenab M, Ferrari P, Nesi G, Carneiro F, Riboli E, Gonzalez CA. CagA+ Helicobacter pylori infection and gastric cancer risk in the EPIC-EURGAST study. *Int J Cancer* 2007; **120**: 859-867

65 **Oleastro M**, Monteiro L, Lehours P, Megraud F, Menard A. Identification of markers for Helicobacter pylori strains isolated from children with peptic ulcer disease by suppressive subtractive hybridization. *Infect Immun* 2006; **74**: 4064-4074

66 **Wang G**, Ge Z, Rasko DA, Taylor DE. Lewis antigens in Helicobacter pylori: biosynthesis and phase variation. *Mol Microbiol* 2000; **36**: 1187-1196

67 **Yamaoka Y**, Kita M, Kodama T, Imamura S, Ohno T, Sawai N, Ishimaru A, Imanishi J, Graham DY. Helicobacter pylori infection in mice: Role of outer membrane proteins in colonization and inflammation. *Gastroenterology* 2002; **123**: 1992-2004

68 **Han FC**, Gong M, Ng HC, Ho B. Identification of H pylori strain specific DNA sequences between two clinical isolates from NUD and gastric ulcer by SSH. *World J Gastroenterol* 2003; **9**: 1747-1751

69 **Giannakis M**, Chen SL, Karam SM, Engstrand L, Gordon JI. Helicobacter pylori evolution during progression from chronic atrophic gastritis to gastric cancer and its impact on gastric stem cells. *Proc Natl Acad Sci USA* 2008; **105**: 4358-4363

70 **Dong Q**, O'Sullivan M, Nami A, Dowling P, Murphy G, Buckley M, O'Morain C. A genetic locus of Helicobacter pylori inversely associated with gastric intestinal metaplasia. *FEMS Immunol Med Microbiol* 2005; **44**: 243-249

71 **Lehours P**, Dupouy S, Bergey B, Ruskone-Foumestraux A, Delchier JC, Rad R, Richy F, Tankovic J, Zerbib F, Megraud F, Menard A. Identification of a genetic marker of Helicobacter pylori strains involved in gastric extranodal marginal zone B cell lymphoma of the MALT-type. *Gut* 2004; **53**: 931-937

72 **Lehours P**, Menard A, Dupouy S, Bergey B, Richy F, Zerbib F, Ruskone-Fourmestraux A, Delchier JC, Megraud F. Evaluation of the association of nine Helicobacter pylori virulence factors with strains involved in low-grade gastric mucosa-associated lymphoid tissue lymphoma. *Infect Immun* 2004; **72**: 880-888

73 **El-Omar EM**, Oien K, Murray LS, El-Nujumi A, Wirz A, Gillen D, Williams C, Fullarton G, McColl KE. Increased prevalence of precancerous changes in relatives of gastric cancer patients: critical role of H pylori. *Gastroenterology* 2000; **118**: 22-30

74 **Veres G**, Pehlivanoglu E. Helicobacter pylori infection in pediatrics. *Helicobacter* 2007; **12** Suppl 1: 38-44

75 **Schwarz S**, Morelli G, Kusecek B, Manica A, Balloux F, Owen RJ, Graham DY, van der Merwe S, Achtman M, Suerbaum S. Horizontal versus familial transmission of Helicobacter pylori. *PLoS Pathog* 2008; **4**: e1000180

76 **Konno M**, Yokota S, Suga T, Takahashi M, Sato K, Fujii N. Predominance of mother-to-child transmission of Helicobacter pylori infection detected by random amplified polymorphic DNA fingerprinting analysis in Japanese families. *Pediatr Infect Dis J* 2008; **27**: 999-1003

77 **Salama NR**, Gonzalez-Valencia G, Deatherage B, Aviles-Jimenez F, Atherton JC, Graham DY, Torres J. Genetic analysis of Helicobacter pylori strain populations colonizing the stomach at different times postinfection. *J Bacteriol* 2007; **189**: 3834-3845

78 **Bjorkholm B**, Lundin A, Sillen A, Guillemin K, Salama N, Rubio C, Gordon JI, Falk P, Engstrand L. Comparison of genetic divergence and fitness between two subclones of Helicobacter pylori. *Infect Immun* 2001; **69**: 7832-7838

79 **Kraft C**, Stack A, Josenhans C, Niehus E, Dietrich G, Correa P, Fox JG, Falush D, Suerbaum S. Genomic changes during

chronic Helicobacter pylori infection. *J Bacteriol* 2006; **188**: 249-254
80 **Gressmann H**, Linz B, Ghai R, Pleissner KP, Schlapbach R, Yamaoka Y, Kraft C, Suerbaum S, Meyer TF, Achtman M. Gain and loss of multiple genes during the evolution of Helicobacter pylori. *PLoS Genet* 2005; **1**: e43
81 **Israel DA**, Salama N, Krishna U, Rieger UM, Atherton JC, Falkow S, Peek RM Jr. Helicobacter pylori genetic diversity within the gastric niche of a single human host. *Proc Natl Acad Sci USA* 2001; **98**: 14625-14630
82 **Fox JG**. The non-H pylori helicobacters: their expanding role in gastrointestinal and systemic diseases. *Gut* 2002; **50**: 273-283
83 **O'Rourke JL**, Grehan M, Lee A. Non-pylori Helicobacter species in humans. *Gut* 2001; **49**: 601-606
84 **Mikkonen TP**, Karenlampi RI, Hanninen ML. Phylogenetic analysis of gastric and enterohepatic Helicobacter species based on partial HSP60 gene sequences. *Int J Syst Evol Microbiol* 2004; **54**: 753-758
85 **Eppinger M**, Baar C, Linz B, Raddatz G, Lanz C, Keller H, Morelli G, Gressmann H, Achtman M, Schuster SC. Who ate whom? Adaptive Helicobacter genomic changes that accompanied a host jump from early humans to large felines. *PLoS Genet* 2006; **2**: e120
86 **Suerbaum S**, Josenhans C, Sterzenbach T, Drescher B, Brandt P, Bell M, Droge M, Fartmann B, Fischer HP, Ge Z, Horster A, Holland R, Klein K, Konig J, Macko L, Mendz GL, Nyakatura G, Schauer DB, Shen Z, Weber J, Frosch M, Fox JG. The complete genome sequence of the carcinogenic bacterium Helicobacter hepaticus. *Proc Natl Acad Sci USA* 2003; **100**: 7901-7906
87 **Baar C**, Eppinger M, Raddatz G, Simon J, Lanz C, Klimmek O, Nandakumar R, Gross R, Rosinus A, Keller H, Jagtap P, Linke B, Meyer F, Lederer H, Schuster SC. Complete genome sequence and analysis of Wolinella succinogenes. *Proc Natl Acad Sci USA* 2003; **100**: 11690-11695
88 **Eppinger M**, Baar C, Raddatz G, Huson DH, Schuster SC. Comparative analysis of four Campylobacterales. *Nat Rev Microbiol* 2004; **2**: 872-885
89 **Fouts DE**, Mongodin EF, Mandrell RE, Miller WG, Rasko DA, Ravel J, Brinkac LM, DeBoy RT, Parker CT, Daugherty SC, Dodson RJ, Durkin AS, Madupu R, Sullivan SA, Shetty JU, Ayodeji MA, Shvartsbeyn A, Schatz MC, Badger JH, Fraser CM, Nelson KE. Major structural differences and novel potential virulence mechanisms from the genomes of multiple campylobacter species. *PLoS Biol* 2005; **3**: e15
90 **Gundogdu O**, Bentley SD, Holden MT, Parkhill J, Dorrell N, Wren BW. Re-annotation and re-analysis of the Campylobacter jejuni NCTC11168 genome sequence. *BMC Genomics* 2007; **8**: 162
91 **Parkhill J**, Wren BW, Mungall K, Ketley JM, Churcher C, Basham D, Chillingworth T, Davies RM, Feltwell T, Holroyd S, Jagels K, Karlyshev AV, Moule S, Pallen MJ, Penn CW, Quail MA, Rajandream MA, Rutherford KM, van Vliet AH, Whitehead S, Barrell BG. The genome sequence of the food-borne pathogen Campylobacter jejuni reveals hypervariable sequences. *Nature* 2000; **403**: 665-668
92 **Dailidiene D**, Dailide G, Ogura K, Zhang M, Mukhopadhyay AK, Eaton KA, Cattoli G, Kusters JG, Berg DE. Helicobacter acinonychis: genetic and rodent infection studies of a Helicobacter pylori-like gastric pathogen of cheetahs and other big cats. *J Bacteriol* 2004; **186**: 356-365

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