Comparative Whole Genome Sequence Analysis of the Carcinogenic Bacterial Model Pathogen Helicobacter felis

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Abstract

The gram-negative bacterium Helicobacter felis naturally colonizes the gastric mucosa of dogs and cats. Due to its ability to persistently infect laboratory mice, H. felis has been used extensively to experimentally model gastric disorders induced in humans by H. pylori. We determined the 1.67 Mb genome sequence of H. felis using combined Solexa and 454 pyrosequencing, annotated the genome, and compared it with multiple previously published Helicobacter genomes. About 1,063 (63.6%) of the 1,671 genes identified in the H. felis genome have orthologues in H. pylori, its closest relative among the fully sequenced Helicobacter species. Many H. pylori virulence factors are shared by H. felis: these include the gamma-glutamyl transpeptidase GGT, the immunomodulator NapA, and the secreted enzymes collagenase and HtrA. Helicobacter felis lacks a Cag pathogenicity island and the vacuolating cytotoxin VacA but possesses a complete comB system conferring natural competence. Remarkable features of the H. felis genome include its paucity of transcriptional regulators and an extraordinary abundance of chemotaxis sensors and restriction/modification systems. Helicobacter felis possesses an episomally replicating 6.7-kb plasmid and harbors three chromosomal regions with deviating GC content. These putative horizontally acquired regions show homology and synteny with the recently isolated H. pylori plasmid pHPPC4 and homology to Campylobacter bacteriophage genes (transposases, structural, and lytic genes), respectively. In summary, the H. felis genome harbors a variety of putative mobile elements that are unique among Helicobacter species and may contribute to this pathogen’s carcinogenic properties.

Key words: Helicobacter felis, comparative genomics, genome sequence analysis, horizontal gene transfer, mobile elements, bacteriophage.

Helicobacter felis is a close relative of the human gastric bacterial pathogen H. pylori, the causative agent of gastritis and gastric ulcers (Marshall and Warren 1984) and known risk factor for gastric adenocarcinoma and gastric lymphoma (Parsonnet et al. 1991, 1994). Helicobacter felis was originally isolated from cats (Lee et al. 1990). Its ability to persistently colonize laboratory mice was discovered in 1990 (Lee et al. 1990) and was subsequently exploited to generate convenient and highly reproducible mouse models of Helicobacter-induced chronic active gastritis (Lee et al. 1990, 1993), gastric atrophy (Fox et al. 2000), lymphoma (Enno et al. 1995, 1998), and adenocarcinoma (Fox et al. 2002). It remains the most broadly used strain for modeling gastric pathology associated with virulent Helicobacter infection to date (Houghton et al. 2004; Sayi et al. 2009; Craig et al. 2010a, 2010b; Toller, Altmeier, et al. 2010; Toller, Hitzler, et al. 2010). Whereas fully annotated whole genome sequence information is now available for seven H. pylori isolates (Tomb et al. 1997; Alm et al. 1999; Oh et al. 2006; Giannakis et al. 2008; Baltrus et al. 2009; Farnbacher et al. 2010; Fischer et al. 2010), one strain each of H. hepaticus (Suerbaum et al. 2003), H. mustelae (O’Toole et al. 2010), and H. acinonychis (Eppinger et al. 2006) and for numerous other related species of the Campylobacterales family (Parkhill et al. 2000; Baar et al. 2003), the H. felis genome had not been sequenced to date. Due to its carcinogenic...
properties and complement of virulence factors that are suspected to differ from those of *H. pylori*, the genome sequence information of *H. felis* is expected to generate novel insights into the molecular pathogenesis of this model organism.

The genome sequence of *H. felis* CS1 (ATCC 49179) was determined at the Wellcome Trust Sanger Institute using a combination of 454 pyrosequencing (which generated a total number of 345,320 reads, 47 contigs, 54 × genome coverage) and Solexa sequencing (28.4 million reads, 900 × genome coverage). The average read lengths were 388 bp (454) and 54 bp (Solexa). The combined 454 and Solexa sequencing data were joined to generate a draft sequence based on the assembly scaffold information; gaps between contigs were closed by a single round of polymerase chain reaction-based finishing/gap closure. The resulting final *H. felis* genome assembly revealed a 1,672,681 bp genome that includes a 6,700 bp episomally replicating plasmid. The genome of *H. felis* is comparable in size to the sequenced *H. pylori* genomes (1.59–1.67 Mb) is slightly larger than the *H. mustelae* and *H. acinonychis* genomes (1.58 and 1.55 Mb) but smaller than the *H. hepaticus* genome (1.8 Mb). Its GC content of 44.51% is higher than that determined for *H. pylori* (39%) but well within the range of Campylobacter species generally (30.6–48.5%). Coding sequence predictions made by Orpheus, Glimmer2, and EasyGene software identified 1,671 genes and 1 pseudogene in a coding area of 92%, placing *H. felis* squarely in the range determined for other *Helicobacter* species (1,403–1,875 genes) and Campylobacter species (1,403–2,046 genes). The average length of an *H. felis* gene is 921 bp (0.998 genes per kb). We detected 35 tRNA genes using tRNAscan-SE (Lowe and Eddy 1997). The existence of a previously identified *H. felis* plasmid could be confirmed (see below) (De Ungria et al. 1998). The *H. felis* genome sequence was annotated using Artemis software (Rutherford et al. 2000) version 12 and visualized with DNA Plotter; protein domains and patterns were marked up using Pfam and Prosite (Bateman et al. 2004). Annotation was transferred from the previously annotated *H. pylori* P12 and *H. mustelae* genomes (Fischer et al. 2010; O’Toole et al. 2010) to orthologous genes and then manually curated using FASTA and Blast results. Orthologous proteins were identified as reciprocal best matches using FASTA; all-against-all FASTA searches were performed, and reciprocal best matches were defined if the top hit covered at least 80% of the length of both sequences with at least 60% identity for both proteins. Of the 1,671 genes, 83% could be annotated with high confidence using these criteria. The fully annotated genome is publicly available at GenBank (accession number FQ670179). All genes were assigned to COG categories using the integrated microbial (IMB) genomes tool (Markowitz et al. 2009); annotated genes are color coded according to COG category (fig. 1).

### Helicobacter felis Factors Involved in Colonization, Motility, Chemotaxis, Virulence, and Natural Competence

*Helicobacter felis* shares numerous features with other *Helicobacter* species that facilitate colonization of the gastric acidic environment and are required for motility and chemotaxis (fig. 1 and table 1). The *H. felis* genome harbors a complete urease gene cluster (*ureABIFE*) which in *H. pylori* is essential for gastric colonization (Karita et al. 1995) (fig. 1). In line with the requirement for nickel as a cofactor of urease, the orthologue of the *H. pylori* nickel transporter NixA and another predicted high-affinity nickel transport protein are encoded directly downstream of the urease gene cluster. An additional *ureA,B2* operon is present in *H. felis*, as was reported for *H. mustelae* (O’Toole et al. 2010), where *UreA2* and *UreB2* are known to be expressed under conditions of nickel limitation (Stoof et al. 2008). The *H. felis* genome harbors at least 40 motility/chemotaxis-related genes encoded by the *fla*, *flg*, *fli*, and *fli* gene families (table 1), which in *H. pylori* and other flagellated bacteria are involved in the regulation, secretion, and assembly of the flagellum (O’Toole et al. 2000). *Helicobacter felis* further possesses an extraordinary number of chemotaxis genes. At least 20 predicted methyl-accepting inner membrane chemotaxis proteins (MCPs) are present in the *H. felis* genome, many of which share homology with the *Bacillus subtilis* MCPs *TlpA* (present in 5 copies in the *H. felis* genome), *TlpB* (6 copies), and *TlpC* (3 copies) and tend to be clustered together on the chromosome (fig. 1). In other organisms, the binding of chemotacticants such as urea, bicarbonate, or amino acids to MCPs is transduced to the autophosphorylating kinase CheA via CheW. CheA donates a phosphoryl group from a histidine residue to an aspartate of CheY, which then interacts with switching proteins to change the direction of flagellar motor rotation. *cheA*, *W*, and *Y* orthologues are each present in one copy in the *H. felis* genome. Three additional chemotaxis genes share homology with the *B. subtilis* CheV protein (termed CheV, V1, and V2 in *H. felis*). Like *H. pylori*, *H. felis* lacks *cheB* and *cheR*, which in other bacteria are responsible for modulating the chemotactic response by addition and removal of methyl groups to/from MCPs. The abundance of predicted MCP-like chemotaxis sensors in *H. felis*, especially in comparison to other Campylobacter species (*H. pylori*: 4, *H. hepaticus*: 9, *C. jejuni*: 10), is striking and suggests an elaborate spatial orientation in a diverse habitat.

Apart from a type III secretion system that exports the flagellar subunit components across both membranes (encoded in *H. felis* by predicted orthologues of the *H. pylori* genes *flhA*, *B* and *flhH, I, P, Q, R*), the *H. felis* genome harbors only one additional secretion system. The *comB* regulon encoding the type IV secretion components *comB2, 3, 4, 6, 8, 9, 10* is required for natural competence of *H. pylori* (Hofreuter et al. 1998, 2003; Karnholz et al. 2000).
and its orthologues are expected to encode the identical function in *H. felis*. Whereas the *comB* components of *H. pylori* are organized in only two operons encoding *comB2-4* and *comB6-10*, respectively, the *H. felis* orthologues are dispersed across the genome in three operons (fig. 1). A second *H. pylori*-specific type IV secretion system, encoded by the *Cag* pathogenicity island, is clearly absent in the *H. felis* genome, as is the vacuolating cytotoxin VacA (Montecucco et al. 2001). Other virulence-associated genes of *H. pylori*, in contrast, are present in *H. felis* and typically share a high degree of similarity. An *H. pylori* virulence factor involved in immunomodulation, NapA (Satin et al. 2000), is present in *H. felis*, as are three enzymes recently implicated in *H. pylori* virulence—a collagenase, the secreted serine protease HtrA and the gamma-glutamyl transpeptidase GGT (Gong et al. 2010; Hoy et al. 2010). The cytolethal distending toxin shared by *H. hepaticus* and *C. jejuni* lacks an orthologue in *H. felis*. The *H. felis* genome encodes a total of 52 outer membrane proteins belonging to the Hor, Hop, Hof, and Hom gene families. Orthologues of the Sab and Bab adhesins could not be identified in the *H. felis* genome.

All *Helicobacter* genomes sequenced so far share several features that set the *Helicobacter* genus apart from other enteropathogenic bacteria; one striking characteristic is the scarcity of transcriptional regulators. We could identify only three sigma factors, $\sigma^{{\text{rpaN}}}$, $\sigma^{{\text{rpoD}}}$, and $\sigma^{{\text{FliA}}}$. $\sigma^{{\text{FliA}}}$, as well as the anti-sigma factor FlgM of *H. felis* contribute to the regulation of the fla/flf/flg/flh motility regulon. The CstA regulator of the “stringent response” to carbon starvation is present in the *H. felis* genome. Two-component systems consisting of a membrane histidine kinase sensor protein and a cytoplasmic DNA-binding response regulator are represented in the *H. felis* genome by only two sensors and two response regulators (in addition to the aforementioned CheA/Y system regulating chemotaxis), which all share high homology with their orthologues in other *Helicobacter* genomes. Additional transcriptional regulators identified in the *H. felis* genome include the ferric uptake regulator (Fur), a main regulator of iron acquisition, the nickel-responsive repressor NikR and the carbon storage regulator CsrA. Like other bacterial pathogens colonizing environments limited in ferric and ferrous iron, *H. felis* possesses a number of iron uptake and storage systems. In addition to Fur, the *H. felis* genome encodes orthologues of the *Escherichia coli* Fec and Feo siderophore-mediated iron uptake systems; multiple copies of *frp* genes encoding

**Fig. 1.**—Circular genome atlas of *Helicobacter felis* CS1. Rings from outside to inside: 1, Selected *H. felis* orthologues of *H. pylori* factors associated with virulence, colonization, natural competence, and chemotaxis. 2, Nucleotide coordinates in bp. 3, open reading frame (ORF) distribution, plus strand. 4, ORF distribution, negative strand. ORFs are color coded based on COG classifications. Abbreviations: B2-10, comB2-10; coll., collagenase.
Table 1
Genes with Functions in Colonization, Motility, Chemotaxis, Natural Competence, and Virulence in the *Helicobacter felis* Genome, Compared with *H. pylori*

| Trait                        | *Helicobacter pylori* Locus | Orthologous *H. felis* System | Role in Colonization/Virulence |
|------------------------------|-----------------------------|-------------------------------|-------------------------------|
| Type IV secretion            | Cag PAI                     | Absent                        | Severe inflammation and secretion elevated gastric cancer risk |
| Urease production            | ComB                        | ComB2,3,4,6,8,9,10 present   | Required for natural competence |
|                              | Urease gene cluster         | UreABEFGH present             | Required for acid resistance and gastric colonization |
|                              |                             | additional UreAB cluster present |                                   |
| Vacuolating cytotoxin        | VacA                        | Absent                        | Vacuolization, cytotoxicity, T-cell inhibition |
| Neutrophil activation        | NapA                        | NapA present                  | Neutrophil activation, Th1 polarization |
| Gamma-glutamyl transpeptidase| GGT                         | GGT present                   | Oxidative DNA damage, colonization |
| Outer membrane proteins      | Hop, Hor, Hof, Hom          | Hop, Hor, Hof, Hom             | Binding to various glycosylated host cell surface proteins |
| Motility                     | Fla, Flg, Flh, Fli          | FlaABG; FlgBCE2GG2H1KLM; FlrADEFGHILMPPQRSTWW2Y; FlhABF | Regulation, assembly, and function of flagella |
| Secreted serine protease     | HtrA                        | Present                       | E-cadherin cleavage; access to intercellular space |
| Cytolethal distending toxin  | Absent                      | csl1-3 in *H. hepaticus*; DNase activity |
| Sigma factors                | $\sigma^{54}$, $\sigma^{70}$, $\sigma^{28}$ | $\sigma^{28}$, $\sigma^{70}$, $\sigma^{28}$/fliA | Very few $\sigma$ factors present |
| DNA repair recombination     | RecA, AddA,B                | RecA,N present; AddB present | Required for gastric colonization |
| Collagenase                  | Present                     | RecB,C,D,G absent; mutS present |                                                                      |
| Iron uptake                  | Feo, Fec, Frm, Fur, TonB, ExbB, ExbD | FeoA,B, FeaA, 2xFpb, 2xTonB, ferritin, SodB, Fur, ExbB2,D,D2 | Required for gastric colonization |
|                             |                             |                               | Iron uptake likely critical for early colonization and persistence |

Comparative Analysis of Sequenced and Annotated Helicobacter Genomes

Of the 1,671 genes identified in the *H. felis* genome, 1,033 are predicted to have orthologues in *H. pylori* P12 (61.8%), 1,048 have orthologues in *H. pylori* B8 (62.7%), 1,029 have orthologues in *H. acinonychis* (61.6%), 946 genes have orthologues in *H. mustelae* (56.6%), and 940 have orthologues in *H. hepaticus* (56.2%). A circular plot comparing the *H. felis* genome with these five *Helicobacter* genomes is shown in figure 2 along with GC content and GC skew maps. The genes that are *H. felis*-specific, that is, not shared with these representatives of the other sequenced *Helicobacter* species (purple ring, fig. 2A), are enriched for very few gene classes. Genes encoding restriction/modification systems are particularly overrepresented among *H. felis*-specific genes. The *H. felis* genome encodes eight complete restriction/modification systems as well as methyltransferases for which no matching restriction endonuclease could be identified; several of the complete systems and most of the adenine methyltransferases lack orthologues in the other *Helicobacter* genomes (annotated in red, fig. 2A). The number of restriction/modification systems is thus quite variable across the *Helicobacter* genus, with *H. pylori* encoding at least 11 and *H. hepaticus* encoding only 2 complete systems (Tomb et al. 1997; Suerbaum et al. 2003).

Other classes of *H. felis*-specific genes include additional copies of the chemotaxis sensors *tbpA, B, and C* mentioned earlier and transposases encoded by putative insertion elements (annotated in fig. 2A). As indicated above, *H. felis* possesses a plasmid of 6,712 bp that shares no homology with the plasmids characterized in *H. pylori* (fig. 2B). The plasmid encodes five predicted proteins, two of which—a putative murein transglycosylase and an N-acetylmuramoyl-L-alanine amidase—are peptidoglycan-modifying enzymes with predicted autolytic activity. A replication initiation protein A (RepA) is not encoded by the plasmid; seven chromosome-encoded full-length copies of *repA* (*Hfelis* 200, 16140, 16300, and 16400) may compensate for the plasmid's *repA* deficiency and may regulate its replication in trans. Of the seven *repA* gene copies, two are encoded on two of three putative mobile elements (fig. 2C and D), which differ in GC content from the rest of the genome (fig. 2A). Region 1 (~8 kb in length, positions 1596300–1604640) shows homology and synteny with an *H. pylori* plasmid isolated from a gastric cancer patient in Peru, pHPC4. Two genes of
region I encode an ABC-transporter-like multidrug resistance protein and a mersacidin-modifying enzyme (fig. 2C), which introduces lanthionin rings into lantibiotics such as mersacidin. Both genes show >70% similarity with their H. pylori homologues encoded on pHPPC4 (accession number CP002075). pHPPC4 in turn shares sequence homology with many other H. pylori plasmids (pHel4, pHp69, pHpAG1, pHpG27, pHpP12), which in contrast to pHPPC4 lack both the multidrug resistance and mersacidin-modifying enzyme genes. Despite the fact that region I harbors a repA gene, we have no evidence that the region replicates episomally. A second region, region II (29.8 kb in length, positions 4000–33757, fig. 2C), harbors elements with extensive homology to Campylobacter bacteriophage genes. At least eight region II-encoded phagic structural and morphogenesis proteins and resolvases share a high degree of homology (but no synteny) with Campylobacter jejuni and hominis phage sequences. Several of the bacteriophage genes (Hfelicis0290, 0350, 0450, 0460, 0610) have homologues in either H. hepaticus and/or H. bilis, indicating that the sequenced strains of these two murine pathogens may also harbor prophages. Interestingly, region II is flanked by two IS605 transposases (Hfelicis0370 and Hfelicis0630), one of which is >60% identical to chromosomally encoded transposases of H. pylori. Region III (9.5 kb in length, positions 1624000–1633500, fig. 2D), in contrast, neither bears resemblance to prophages of Campylobacter (despite sharing homology with nonphagic, chromosomally encoded Campylobacter genes) nor do the mobilization and replication initiation proteins encoded by region III resemble their functional counterparts on H. pylori plasmids. Again, we could not find evidence for episomal replication of region III, indicating that this region may represent an integrated, no longer autonomously replicating plasmid derived from Campylobacter.

In summary, the sequence of H. felis reaffirmed many known characteristics of the Helicobacter genus such as the general paucity of transcriptional regulators and the abundance of restriction/modification systems and chemotaxis sensors. Our evidence for the existence of at least one H. felis prophage makes it unique among Helicobacter species, which in contrast to Campylobacter and with the exception of H. acinonychis, are not known to harbor phages. Efforts are currently under way to establish the genetic tools to manipulate H. felis and will hopefully allow us to dissect experimentally which virulence factors are required for gastric carcinogenesis and lymphomagenesis induced in animal models by this interesting bacterial pathogen.

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