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The identification of the replicative helicase loader gene *dciA* within the *Helicobacter pylori* genome challenges current replication initiation models for this bacterium

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Abstract

At the onset of bacterial chromosome replication initiation, replicative helicases are loaded onto DNA, a process requiring helicase loaders. While organisms documented as lacking a helicase loader are rare, the human pathogen *Helicobacter pylori* is a notable exception. Here, relying mainly on genomic synteny and AlphaFold, I demonstrate that the well-documented helicase loader gene *dciA* is present in the *H. pylori* genome and co-localizes with the *uvrC* gene (excinuclease ABC subunit C), which highlights the limitations of the usual methodology used to identify *dciA*. I then provide evidence showing that this finding seriously challenges the two main current chromosome replication initiation models in this bacterium. Given that virulent strains of *H. pylori* pose a significant threat to human health, contributing to various gastric and non-gastric disorders, including certain cancers, I conclude that a deeper understanding of replication initiation in *H. pylori* could facilitate the development of more effective therapeutic strategies.

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Introduction

In bacteria, at the onset of chromosome replication initiation, replicative helicases are loaded onto the DnaA-oriC nucleoprotein platform with the assistance of helicase loaders, such as DnaC in *Escherichia coli* (Arias-Palomo et al., 2013) and DnaI in *Bacillus subtilis* (Velten et al., 2003). These latter are derived from mobile elements and have replaced, in a few bacterial orders, the ancestral and widespread unrelated replicative helicase loader gene *dciA* (Brézellec et al., 2016). Bacteria lacking both *dnaC*/*dnaI* and *dciA* are uncommon and generally exhibit small genomes or host-associated lifestyles (Brézellec et al., 2016). Nevertheless, Brézellec and collaborators showed that in two bacterial orders, *Cellvibrionales* and *Oceanospirillales*, the lambdoid phage genes *λO* and *λP* (the latter encoding the λ phage replicative helicase loader) could have substituted for *dciA* (Brézellec et al., 2017). In the same vein, in *Vibrionales*, *dciA* could also have been frequently replaced by two viral genes (Tominaga et al., 2024). To date, however, *Helicobacter pylori* is the only extensively studied bacterium that appears to lack the ancestral helicase loader gene *dciA* or phage gene counterparts (Blaine et al., 2023).

While it's presumed that *Helicobacter pylori* has lost the ancestral replicative helicase loader gene *dciA*, the unique features of its replicative helicase (HpDnaB) point to a different scenario. HpDnaB exhibits profound differences from classical bacterial replicative helicases. First, HpDnaB differs from canonical DnaB by having a large two-helix insertion, termed HPI, in its C-terminal ATPase domain. This insertion spans 34 amino acid residues (residues 400–433) when compared to *Escherichia coli* DnaB (Stelter et al., 2012). Second, while classical bacterial replicative helicases display a hexameric architecture, HpDnaB forms head-to-head double hexamers, *i.e.*, a dodecameric architecture (Stelter et al., 2012). This leads me to hypothesize that *dciA* is still present in the *H. pylori* genome, but that it has co-evolved with HpDnaB, obscuring its typical Pfam domain signature (DUF721/PF0528) upon which its identification relies.

Using genomic synteny, HHpred, and AlphaFold, I demonstrate here that *dciA* is present in the *H. pylori* genome and that it co-localizes with the *uvrC* gene (excinuclease ABC subunit C), see Figure 1. I then discuss the implications of this finding.

Materials and methods

Strains of *Helicobacter pylori*

A large number of *Helicobacter pylori* strains have been sequenced and annotated. In this study, I focused on strains 26695 (ATCC 700392) (Tomb et al., 1997) and G27 (Baltrus et al., 2009).

Softwares

I used the HHpred tool via its web server (https://toolkit.tuebingen.mpg.de/tools/hhpred). HHpred allows protein domain and structure prediction; it utilizes pairwise alignment of Hidden Markov models (HMMs) to perform sensitive protein sequence searching (Gabler et al., 2020).

I used AlphaFold's results stored in the UniProt database. AlphaFold is an artificial intelligence (AI) program developed by DeepMind for protein structure prediction (Jumper et al., 2021).

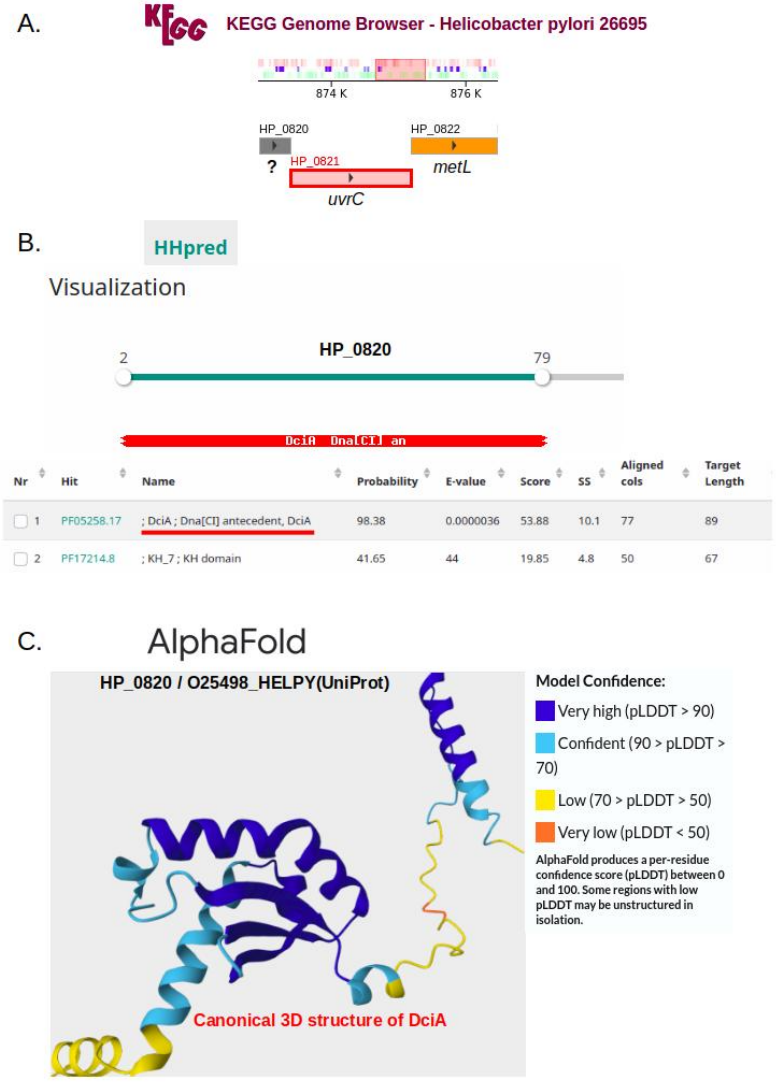

Figure 1 - It is presumed that *Helicobacter pylori* has lost the ancestral replicative helicase loader gene *dciA*. Using genomic synteny (see part A of the image), HHpred (see part B of the image), and AlphaFold (see part C of the image), I demonstrate that *dciA* is present in the *H. pylori* genome and that it co-localizes with the *uvrC* gene (excinuclease ABC subunit C). This finding significantly challenges the two current models of replication initiation in this bacterium. **A**. Many species in *Campylobacterales*, the order including *H. pylori*, show genomic co-localization of the *dciA* and *uvrC* genes. In *H. pylori* strain ATCC 700392 / 26695, *uvrC* (HP_0821) is surrounded by two genes: HP_0820, which encodes a protein annotated as 'predicted coding region HP0820', and HP_0822 (*metL*), encoding a protein annotated as homoserine dehydrogenase. **B**. I reannotated the protein encoded by HP_0820 using HHpred (with default parameters) against Pfam-A_37 (the latest Pfam release). HHpred analysis indicates that this protein contains the DciA-characteristic Pfam domain, *i.e*. PF05258/DUF721. This domain spans residues 2 to 79, with a probability of 0.986, indicating near-certain homology (see HHpred documentation). **C**. I focused on the AlphaFold-predicted structure of the protein encoded by HP_0820 (referred to as O25498_HELPY in UniProt) and observed the presence of the canonical DciA domain structure, which consists of one alpha helix, followed by two beta sheets, a third alpha helix, and a final beta sheet. Therefore, I concluded that HP_0820 is the *dciA* gene**.**

Results

Genomic co-localization of the *dciA* and *uvrC* genes is a feature of numerous *Campylobacterales*

To investigate the presence of *dciA* in the *H. pylori* genome, I began by examining its genomic context in *dciA*-hosting *Campylobacterales* species, the order to which *H. pylori* belongs. I aimed to leverage the genes frequently located near *dciA* to identify it in *H. pylori*. To achieve this, I utilized both the UniProt (UniProt Consortium, 2024) and KEGG (Kanehisa et al., 2024) databases, as detailed below.

To manage the substantial number of *Campylobacterales* proteomes, I concentrated on *Campylobacterales* 'reference proteomes' from UniProt. These proteomes offer a representative cross-section of taxonomic diversity and encompass model organisms and species of biomedical/biotech interest. UniProt contains 77 *Campylobacterales* reference proteomes, see Supplemental file 1 (query in 'Proteomes': (taxonomy_id:213849) AND (proteome_type:1), where '213849' is the 'Taxon ID' for *Campylobacterales* and '1' indicates 'reference proteome').

As shown in (Blain et al., 2022), DciA homologs across different phyla have low conservation in their primary amino acid sequences; consequently, tools such as BLASTP only retrieve very closely related homologs. DciA is therefore typically identified by its Pfam domain signature, DUF721/PF0528. Consequently, I searched the 77 previously identified reference proteomes for DciA-containing proteins using the following UniProt query: (taxonomy_id:213849) AND duf721 AND (keyword:KW-1185), where 'KW-1185' denotes 'reference proteome'. UniProt returned 49 results, corresponding to 46 bacteria, see Supplemental file 2. Of these, 43 contained a single DciA protein, while 3 (*Malaciobacter halophilus*, *Candidatus Campylobacter infans*, and *Helicobacter apodemus*) contained two.

Table 1 - Each line represents a *dciA* gene. The 'Organism' column indicates the species to which *dciA* belongs. The 'UniProt ID' column refers to the UniProt ID of the considered *dciA* gene. The 'Genomic context' column indicates the KEGG annotation of the proteins expressed by the two genes located adjacent to *dciA* on the considered genome, with *dciA* referred to by its ordered locus name. As can be seen, the *uvrC* gene (in bold) is the most frequently located gene adjacent to *dciA*. Note that *Malaciobacter halophilus* and *Candidatus Campylobacter infans* host two *dciA* genes, while *Helicobacter enhydrae* expresses one DciA protein linked to two different KEGG loci.

Organism	*dciA* Ordered locus name	UniProt ID
Aliarcobacter butzleri	Abu_0923	A8ETA9
Arcobacter nitrofigilis	508	D5V0A6
Malaciobacter halophilus	1117	A0A2N1J241 A0A2N1J4B3
Poseidonibacter parvus	1683	A0A1P8KND2
Campylobacter iguaniorum	669	A0A076FH25
Candidatus Campylobacter infans	1960	A0A7H9CJ49 A0A7H9CKE6
Campylobacter curvus	1995	A7GX63
Campylobacter jejuni	284	Q0P909
Campylobacter lari	284	B9KFL2
Helicobacter enhydrae		A0A1B1U6Z8 A0A1B1U6Z8
Helicobacter bizzozeronii		F8KQE8
Helicobacter hepaticus		Q7VK74
Wolinella succinogenes		Q7MR76
Hydrogenimonas sp		A0A3G9GU81
Sulfurimonas lithotrophica		A0A5P8P2C0
Sulfurimonas marina		A0A7M1AWW5
Candidatus Sulfurimonas marisnigri		A0A7S7RQV3
Sulfurimonas aquatica		A0A975AYP7
Sulfurimonas autotrophica		E0UQ91
Sulfurospirillum deleyianum		D1B011
Nitratifractor salsuginis		E6X0A3
Sulfurovum lithotrophicum	285	A0A7U4RQ57

When available, UniProt entries include a cross-reference link to KEGG, a database that provides genomic maps of numerous species, allowing one to trace back from a protein to the genomic location of its encoding gene. Of the 49 previously identified DciA proteins, 24 are linked to KEGG, corresponding to 22 bacterial species, see Supplemental file 3. These include *Malaciobacter halophilus* and *Candidatus Campylobacter infans*, which, as previously mentioned, harbor two *dciA* genes. Of these 24 *dciA* genes, 17 appear to be co-localized with *uvrC* (encoding the excinuclease ABC subunit C), see Table below. Interestingly, among these 17 *dciA* genes, two belong to the genus *Helicobacter*, namely *Helicobacter bizzozeronii* (strain CIII-1) and *Helicobacter hepaticus* (strain ATCC 51449 / 3B1).

In summary, co-localization of *dciA* and *uvrC* is a feature of numerous *Campylobacterales*.

In *H. pylori*, *uvrC* co-localizes with *dciA*

Among the 77 *Campylobacterales* species previously identified (see previous section), two correspond to *H. pylori*: *H. pylori* strain ATCC 700392 / 26695 and *H. pylori* strain G27. Both strains appeared to lack DciA (no DUF721 annotated protein). Given that *dciA* has been shown to co-localize with *uvrC* in numerous *Campylobacterales* (see previous section), I examined the genomic context of *uvrC* in both *H. pylori* strains.

In *H. pylori* strain ATCC 700392 / 26695 and *H. pylori* strain G27, *uvrC* is identified as UVRC_HELPY and UVRC_HELPG, respectively, and is encoded by the genes HP_0821 and HPG27_780, respectively. Using the KEGG link provided by UniProt to trace the protein back to its gene, *uvrC* appears to be located on the direct strand at positions 873393 to 875177 (https://www.genome.jp/dbget-bin/www_bget?hpy:HP_0821) and 844372 to 846156 (https://www.genome.jp/dbget-bin/www_bget?hpg:HPG27_780), respectively. Adjacent to *uvrC* on the same strand, I identified the genes HP_0820 (https://www.kegg.jp/entry/T00008:HP_0820) and HPG27_779 (https://www.kegg.jp/entry/T00777:HPG27_779) at positions 872931 to 873392 and 843910 to 844371, respectively, encoding proteins of 153 amino acids with the following primary sequences:

MEQNIFSLLIQKKSYKKLETLLKLKKLKVFMPLSLQENLLFIFIKDSKLLFAFKDIWASKEFNQR FAKEISHFLNTQGHAYGFDGLNGLEILGYVPKDALKKSNFYAPIKKQARFFRPSALGLFHNPIKDA RLHECFEKARALIHYQRSFFEE

and

MEQNIFSLLIQKKSYKKLETLLKLKKLKVFMPLSLQENLLFIFIKDSKLLFAFKDLWASKEFNQR FAKEISHFLNTQGHAYGFDGLNGLEILGYVPKDALKKANFYAPIKKQARFFRPSALGLFHNPIKDA RLHECFEKARALIHYQRSFFEE

respectively, see part A of Figure 1 for HP_0820/O25498_HELPY.

In UniProt, HP_0820 and HPG27_779 encode the proteins O25498_HELPY and B5Z7I5_HELPG, respectively, which are described as uncharacterized proteins with neither InterPro nor Pfam annotations. These two proteins share 99% sequence identity and differ by two amino acid mismatches

I began by reannotating these proteins using HHpred. Running HHpred (with default parameters) against Pfam-A_37 (the latest Pfam release, June 2024, containing 21979 families), I found that both O25498_HELPY and B5Z7I5_HELPG harbor the Pfam PF05258/DUF721 domain with a probability of 0.986, see Supplemental files 4 and 5, see part B of Figure 1 for HP_0820/O25498_HELPY. This domain spans residues 2 to 79. According to the HHpred documentation, a probability exceeding 0.95 indicates near-certain homology.

Subsequently, I examined the AlphaFold-predicted structures of O25498_HELPY (https://www.uniprot.org/uniprotkb/O25498/entry#structure) and B5Z7I5_HELPG (https://www.uniprot.org/uniprotkb/B5Z7I5/entry#structure), as provided (if available) within the UniProt protein entries. Both structures show very high or high confidence for most residues, with the N-terminal alpha-helix and the linker region exhibiting lower confidence. I then observed that these two AlphaFold structures contained the canonical structural DciA domain architecture, which consists of one alpha helix, followed by two beta sheets, a third alpha helix, and a final beta sheet (Chan-Yao-Chong et al., 2020).

I therefore concluded that HP_0820 and HPG27_779 are the *dciA* genes of *H. pylori* strains ATCC 700392 / 26695 and G27, respectively.

Discussion

Despite the apparent absence of *dciA* from the *H. pylori* genome (Blaine et al., 2023), the unique characteristics of its replicative helicase (HpDnaB), when compared to other bacterial replicative helicases (Stelter et al., 2012), prompt me to propose that *dciA* is still present but has co-evolved with HpDnaB, making it difficult to detect. To test this hypothesis, I decided to use 'genomic synteny', which assumes that during evolution, while genomes can change, some gene arrangements are preserved.

With the growing availability of proteome and genome data, I narrowed my focus to the 77 *Campylobacterales* species, the order to which *H. pylori* belongs, available as 'reference proteomes' in UniProt (UniProt Consortium, 2024). These 77 *Campylobacterales* proteomes include, in particular, those of two *Helicobacter pylori* strains: ATCC 700392 / 26695 and G27. Identifying DciA using the standard DciA Pfam domain signature method, I found that 46 of the 77 *Campylobacterales* proteomes host a DciA protein. To trace back from proteins to their encoding genes, I relied, when available, on cross-referencing links to KEGG (Kanehisa et al., 2024), a database hosting genomic maps of many species. Among the aforementioned 46 species, 22 are stored in KEGG, offering the opportunity to examine the genomic context of *dciA*. I then observed that, frequently, *dciA* is found to co-localize with the *uvrC* gene, *i.e.*, the excinuclease ABC subunit C gene (see Results section 'Genomic co-localization of the *dciA* and *uvrC* genes is a feature of numerous *Campylobacterales*'). Interestingly, this pattern is observed in particular in two close relatives of *Helicobacter pylori*, namely *Helicobacter bizzozeronii* (strain CIII-1) and *Helicobacter hepaticus* (strain ATCC 51449 / 3B1).

I then returned to *H. pylori* to examine the genomic context of its *uvrC* gene. As previously mentioned, two *Helicobacter pylori* strains are stored in UniProt as 'reference proteomes', namely *Helicobacter pylori* strain ATCC 700392 / 26695 and *Helicobacter pylori* strain G27. I focus here only on *Helicobacter pylori* strain ATCC 700392 / 26695, as similar results are obtained for the other strain (see Results section).

The ordered locus name of the *uvrC* gene in *H. pylori* strain ATCC 700392 / 26695 is HP_0821. Adjacent to HP_0821, I identified a gene, HP_0820, located on the same strand, encoding a 153-amino-acid-long protein stored as O25498_HELPY in UniProt, see part A of Figure 1. The UniProt 'Family & Domains' section provides no annotation for O25498_HELPY. This result indicates that the InterProScan tool (Blum et al., 2025) failed to detect any domain in O25498_HELPY when queried against its integrated member database signatures (e.g., Pfam, PROSITE, etc.). I then submitted HP_0820 to HHpred (Gabler et al., 2020), a profile-profile comparison tool for remote homology detection, which identified the DciA-characteristic Pfam DUF721 domain (probability > 0.95) in HP_0820, see part B of Figure 1. This was further supported by AlphaFold's 3D prediction (Jumper et al., 2021) of HP_0820, which revealed the presence of the canonical DciA domain structure, see part C of Figure 1.

Taken together, my results strongly suggest that the proteins encoded by HP_0820 in *H. pylori* strain ATCC 700392 / 26695 and HPG27_780 in *H. pylori* strain G27 are homologous to DciA (see Results section 'In *H. pylori*, *uvrC* co-localizes with *dciA*'). This finding significantly challenges the two current models of chromosome replication initiation in *H. pylori*, as explained below.

The first model suggests that *H. pylori* encodes a gene, HP_0897, which putatively functions as a replicative helicase operator/loader (Verma et al., 2016; Kumar et al., 2019). In UniProt, HP_0897 corresponds to a protein with ID O25557_HELPY. When submitted to HHpred, analysis revealed that HP_0897 harbors the Pfam DUF721 domain, albeit with a reduced probability (0.884) compared to HP_0820. A visual examination of the HP_0897 AlphaFold structure indicates that, similar to HP_0820, it exhibits the canonical DciA domain structure. The presence of this domain likely explains HP_0897's interaction with the replicative helicase DnaB, mirroring the behavior of DciA in several well-studied bacteria (*Caulobacter crescentus* (Ozaki et al., 2022), *Mycobacterium*

tuberculosis (Mann et al., 2017), *Pseudomonas aeruginosa* (Brézellec et al., 2016), and *Vibrio cholerae* (Marsin et al., 2021)). Interestingly, HP_0820 also interacts with DnaB in *Helicobacter pylori* (Häuser et al., 2014). However, a significant difference exists between HP_0820 and HP_0897: HP_0820, but not HP_0897, is an essential gene (Salama et al., 2004), a key characteristic of DciA (Blaine et al., 2022). Nevertheless, while focusing on the growth of knockouts in rich media is one way to identify essential genes, gene persistence is another approach to assess a gene's essentiality (Fang et al., 2005). I thus investigated the gene persistence of both HP_0820 and HP_0897. KEGG currently stores 61 complete *H. pylori* genomes (including strains ATCC 700392 / 26695 and G27). Using the KEGG DBsearch function (which performs a BLASTP of a protein query against the database of all genes stored in KEGG), HP_0820 was found to be persistent—meaning it is present in all 61 *H. pylori* strains examined (see Supplemental file 6)—whereas HP_0897 is not. Specifically, HP_0897 is found in only 45 out of the 61 strains (see Supplemental file 7). In conclusion, HP_0897 is neither essential in *H. pylori* strain ATCC 700392 / 26695 nor persistent in the set of 61 *H. pylori* strains examined, unlike HP_0820. Taken together, these results strongly suggestthat DciA/HP_0820, rather than HP_0897, assists *H. pylori* DnaB at the onset of chromosome replication initiation.

The second model, originally proposed prior to the discovery of HP_0897 (Blaine et al., 2023), posits that *H. pylori* DnaB can self-load onto DNA without requiring a 'dedicated' helicase loader, a hypothesis supported by a study demonstrating HpDnaB's ability to bypass DnaC in *E. coli* and function as an active replicative helicase (Soni et al., 2005). However, experiments carried out in the DciA-containing bacterium *Vibrio cholerae* El Tor strain E7946 showed that *V. cholerae* DnaB can load itself onto DNA *in vitro*, and that *V. cholerae* DciA stimulates this function, resulting in increased DNA unwinding (Marsin et al., 2021). Therefore, the ability to self-load onto DNA might be a common feature of replicative helicases in DciA-containing organisms.

Overall, my work convincingly suggests that *dciA* is present in the *Helicobacter pylori* genome and likely functions as a replicative helicase loader, significantly challenging current models of chromosome replication initiation for this organism. Furthermore, it highlights the limitations of the current methodology used to identify DciA. Moreover, as pointed out by Radford et al. (2023), in the development of novel antibiotics, DNA replication remains a largely underexplored area, even though replisomal proteins are clearly attractive therapeutic targets. This potential can only be realized if the proteins involved in chromosome replication are well-characterized. My work suggests that this criterion is now likely met for *Helicobacter pylori*.

Numerous questions remain to be addressed to fully elucidate replication initiation in *Campylobacterales*. While fruitful in the case of *H. pylori*, my hypothesis that DciA has co-evolved with HpDnaB, leading to the loss of its classical Pfam domain signature, requires further verification across the entire *Campylobacterales* order. Alternatively, as previously shown, *dciA* might have been repeatedly replaced by phage helicase loaders. Both possibilities warrant further investigation.

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Conflict of interest disclosure

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Data, scripts, code and supplementary information availability

Supplementary information is available online (https://doi.org/10.5281/zenodo.17592664; Brézellec, 2025).

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