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Genome Maps of *Campylobacter jejuni* and *Campylobacter coli*

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Little information concerning the genome of either *Campylobacter jejuni* or *Campylobacter coli* is available. Therefore, we constructed genomic maps of *C. jejuni* UA580 and *C. coli* UA417 by using pulsed-field gel electrophoresis. The genome sizes of *C. jejuni* and *C. coli* strains are approximately 1.7 Mb, as determined by *Sal*I and *Sma*I digestion (N. Chang and D. E. Taylor, J. Bacteriol. 172:5211–5217, 1990). The genomes of both species are represented by single circular DNA molecules, and maps were constructed by partial restriction digestion and hybridization of DNA fragments extracted from low-melting-point agarose gels. Homologous DNA probes, encoding the *flaAB* and 16S rRNA genes, as well as heterologous DNA probes from *Escherichia coli*, *Bacillus subtilis*, and *Haemophilus influenzae*, were used to identify the locations of particular genes. *C. jejuni* and *C. coli* contain three copies of the 16S and 23S rRNA genes. However, they are not located together within an operon but show a distinct split in at least two of their three copies. The positions of various housekeeping genes in both *C. jejuni* UA580 and *C. coli* UA417 have been determined, and there appears to be some conservation of gene arrangement between the two species.

Pulsed-field gel electrophoresis (PFGE) has facilitated the construction of physical maps of the chromosomes of several pathogenic bacteria. Physical maps for *Pseudomonas aeruginosa* (37, 39, 40), *Haemophilus influenzae* Rd (21, 22), *H. influenzae* type b (4), *Haemophilus parainfluenzae* (14), *Clostridium perfringens* (5), and *Shigella flexneri* (31) have been published. Genome maps of other bacteria, including *Escherichia coli* K-12 (44), *Bacillus subtilis* (32), and *Streptomyces coelicolor* (13), are also available.

In the cases of bacteria such as *E. coli*, *S. coelicolor*, *B. subtilis*, *P. aeruginosa*, and even *H. influenzae*, from which many genes have been cloned, homologous probes have been used to map gene loci. With species for which fewer homologous gene probes are available, it has been necessary to resort to the use of heterologous DNA probes for mapping. Genes encoding general housekeeping functions have been chosen in the hope that enough homology exists at the DNA level for DNA hybridization to be detected under conditions of low stringency. Heterologous DNA probes have proved useful for mapping genes in *C. perfringens* (5).

We recently determined the genome sizes of *Campylobacter jejuni* and *Campylobacter coli* to be 1.7 Mb and constructed a preliminary physical map of *C. jejuni* UA580 (6). *C. jejuni* 81116 was also shown to have a genome size of 1.7 Mb (27). Kim and Chan (16), however, have estimated the size of one *C. jejuni* strain (TGH9011) to be 1.9 Mb by field inversion gel electrophoresis. Nuijten et al. (27) have constructed a genome map of *C. jejuni* 81116 and determined the locations of the flagellar genes (*flaA* and *flaB*) with a homologous DNA probe and those of the 16S rRNA genes with a heterologous DNA probe from a mycoplasma (8). PFGE has also proved useful for comparison of *C. jejuni* and *C. coli* genome DNA for epidemiologic studies (51).

The goal of this study was to construct physical maps of the genomes of *C. jejuni* UA580 and *C. coli* UA417 by using *Sma*I and *Sal*I. Although few genes from *Campylobacter* spp. have been cloned, two available homologous DNA probes, as well as a number of heterologous probes, were used to place genes on the maps.

MATERIALS AND METHODS

Bacterial strains. The *Campylobacter* strains used in this study are listed in Table 1. All organisms were grown on Mueller-Hinton agar (Oxoid Ltd., London, England) in 7% CO_2 at 37°C.

Preparation of DNA. Overnight cell cultures were suspended in TE buffer (50 mM Tris, 5 mM EDTA, pH 8.0), and 200 μl of this suspension was added to 1 ml of melted 1.2% low-melting-point agarose (Bethesda Research Laboratories). This cell-agarose mixture was dispensed into 150-μl molds. DNA blocks were prepared as described previously (44), placed in ESP lysis buffer (0.25 M EDTA [pH 9.0], 0.5% lauryl sarcosine [Sarkosyl NL97; ICN Pharmaceuticals Inc., Irvine, Calif.], 0.5 mg of proteinase K [Sigma Chemical Co., St. Louis, Mo.] per ml), and incubated at 50°C for 48 h.

Restriction endonuclease digestion. The restriction enzymes used were *Nci*I, *Bss*HII, *Sma*I and *Sal*I, which were purchased from Boehringer GmbH, Mannheim, Germany, or Bethesda Research Laboratories Canada, Burlington, Ontario, Canada. Thin slices of the DNA blocks, prepared as described above, were washed three times in a phenylmethylsulfonyl fluoride solution (0.0175 g/100 ml of TE buffer) and then rinsed three times in TE buffer. The DNA slices were equilibrated in 100 μl of the appropriate enzyme buffer, and then restriction digestions were carried out with 40 to 50 U of enzyme in fresh buffer. These reaction mixtures were incubated for 18 h at 37°C.

PFGE. Electrophoresis was performed with a 2015 Pulsaphor unit (LKB Instruments Inc., Rockville, Md.) equipped with a hexagonal electrode (contour-clamped homogeneous electric field). Agarose gels (1%) prepared in 0.05 M TBE buffer (Tris-borate-EDTA running buffer) were run for 24 h at 175 V and 12°C. The pulse times varied from 15 to 35 s. The gels were stained with ethidium bromide and photographed under UV illumination with a Pentax 35-mm camera. Phage λ48.5 and λΔ39 DNA concatemers (Promega)

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TABLE 1. Strains of *Campylobacter* used in this study

UA strain designation[a]	Original strain designation	Species	Source	Reference
UA344	V267	*C. jejuni*	A. D. Pearson	51
UA501	81116	*C. jejuni*	D. G. Newell	50
UA580	NCTC 11168	*C. jejuni*	H. Lior	6
UA695	E7513	*C. jejuni*	L. Mueller	51
UA709	205224	*C. jejuni*	H. Endtz	51
UA417	LCDC C2633	*C. coli*	H. Lior	6
UA578	NCTC 11353	*C. coli*	H. Lior	53
UA585	118114R	*C. coli*	D. Ribeiro	51
UA749	C245	*C. coli*	H. Goosens	51

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were used as molecular size standards. Sizes of fragments were estimated as described previously (6).

DNA blotting and hybridization. Chromosomal DNA fragments from pulsed-field gels were transferred onto nylon membranes (Hybridization transfer membrane; Micro Separation Inc.) as described previously (41). The probes used for mapping included *Campylobacter* chromosomal fragments isolated from low-melting-point agarose as well as various plasmids containing housekeeping genes. These probes were labelled with [α-^{32}P]dATP by either nick translation or random priming as described previously (41). Hybridization was done at 42°C for homologous probes and 37°C for heterologous probes in 50% formamide–5× SSC (1× SSC is 0.15 M NaCl plus 0.015 M sodium citrate)–0.1% sodium dodecyl sulfate–1 mM EDTA–1× Denhardt solution–250 μg of herring sperm DNA per ml. Filters were then washed at 65°C in 2× SSC for 15 to 60 min. Autoradiograms were prepared with Kodak XAR-5 film (Eastman Kodak Co., Rochester, N.Y.) by exposing the nylon membranes for 3 to 5 days at −70°C before development.

RESULTS AND DISCUSSION

Genome sizes of *C. jejuni* and *C. coli* strains. The genome sizes of four strains each of *C. jejuni* and *C. coli* from different geographic sources are shown in Table 2. The *Sma*I and *Sal*I restriction patterns of *C. jejuni* and *C. coli* DNA from different sources have been compared recently (51). The average size for *C. jejuni* strains was 1.709 Mb, and that for *C. coli* strains was 1.703 Mb. These results demonstrate that the genome sizes of *C. jejuni* and *C. coli* strains are fairly consistent, even though the strains originated in different geographic locations. None of the genome sizes approached 1.9 Mb, as has been reported previously for one *C. jejuni* strain (16). *Sma*I restriction fragments of *H. influenzae* Rd, which has a genome size of 1.900 Mb (22), were consistently about 0.2 Mb larger than *C. jejuni* or *C. coli* chromosomes (data not shown). Therefore, the values determined previously for *C. coli* and *C. jejuni* genome sizes (6, 27) appear to be precise estimates for most strains, although we could not rule out the possibility that some strains have larger genome sizes, possibly because of duplication events.

TABLE 2. Genome sizes of *C. jejuni* and *C. coli* strains isolated from various locations

Species	Strain	Geographic origin	Genome size (kb)		
			Determined directly by digestion with:		Avg
			*Sma*I	*Sal*I	
C. jejuni	UA344	United Kingdom	1,702	1,712	1,707
	UA580	Eastern Canada	1,726	1,718.5	1,722
	UA695	Western Canada	1,663	1,720	1,692
	UA709	The Netherlands	1,710	1,720	1,715
Avg for species					1,709
C. coli	UA417	Eastern Canada	1,679	1,697	1,688
	UA578	United States	1,719	1,734.5	1,727
	UA585	Wales	1,686	1,697.5	1,692
	UA749	Belgium	1,712	1,702	1,707
Avg for species					1,703

TABLE 3. Sizes of restriction fragments of *C. jejuni* UA580 and *C. coli* UA417 DNA used to construct maps

Fragment no.	Fragment size (kb)[a]			
	C. jejuni UA580		*C. coli* UA417	
	*Sal*I	*Sma*I	*Sal*I	*Sma*I
1	980 ± 2.8	371 ± 2.9	430 ± 7.3	255 ± 5.8
2	280 ± 6.5	345 ± 2.8	400 ± 5.2	250 ± 2.4
3	220 ± 6.5	316 ± 6.3	344 ± 3.7	240 ± 5.8
4	110 ± 7.1	191 ± 1.3	276 ± 4.3	238 ± 2.4
5	80 ± 4.1	161 ± 0.8	125 ± 3.1	163 ± 4.6
6	48.5 ± 0	141 ± 0.8	97 ± 3.1	143 ± 2.8
7		107 ± 8.4	25 ± 0.7	124 ± 2.3
8		55 ± 4.1		97 ± 2.1
9		39 ± 4.6		85 ± 2.9
10				42 ± 2.1
11				23 ± 1.9
12				13 ± 0.7
13				6 ± 0
Total size	1,718 ± 5.0	1,726 ± 11.8	1,697 ± 6.8	1,679 ± 8.1

[a] Sizes of restriction fragments determined from at least three different gels (mean ± standard deviation).

Construction of physical maps of *C. jejuni* UA580 and *C. coli* UA417. The sizes of *Sal*I and *Sma*I restriction fragments used to construct the genome maps are shown in Table 3. The maps were constructed from partial digestion patterns and from hybridization of overlapping restriction fragments extracted from low-melting-point agarose gels. Both homologous and heterologous DNA probes were used to map positions of genes on the maps. The genomes of *C. jejuni* UA580 (Fig. 1) and *C. coli* UA417 (Fig. 2) consist of single circular molecules.

Separate arrangement of genes for 16S and 23S rRNA in *C. jejuni* UA580 and *C. coli* UA417. It has been shown previously that *C. jejuni* strains contain three copies of 16S rRNA genes (15, 19, 27). This was demonstrated by insertional mutagenesis (19), hybridization of a DNA probe containing a sequence of 16S rRNA genes (16S rDNA) from *Mycoplasma* sp. strain PG50 (8) to restriction fragments of *C. jejuni* 81116 DNA separated by PFGE (27), and hybridization of 5′-end-labelled rRNA to cloned DNA fragments of *C. jejuni* TGH9011 (15).

Chromosomal digests of *C. jejuni* UA580 DNA and *C. coli* UA417 DNA digested with *Sal*I and *Sma*I are shown in Fig. 3. Hybridization of a 16S rRNA gene probe from *C. jejuni* (36) to Southern blots prepared from gels containing these digests (data not shown) confirmed the presence of three copies of 16S rRNA genes in *C. jejuni* UA580 and showed that *C. coli* UA417 also contains three copies. Hybridization

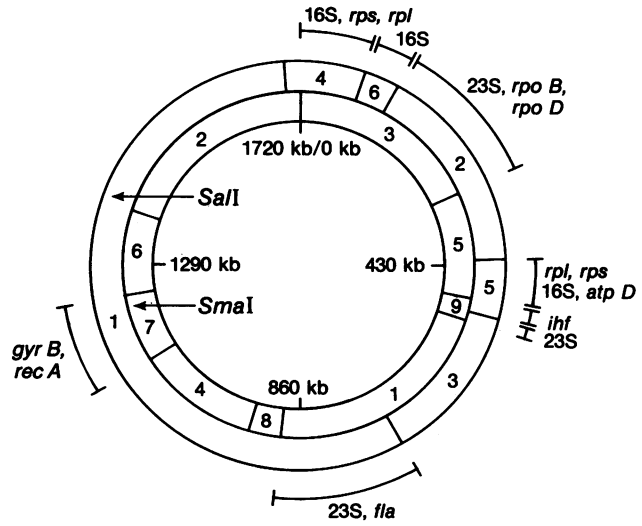

FIG. 1. Physical map of the *C. jejuni* UA580 chromosome. The map was constructed from partial digestion patterns obtained with *Sma*I and *Sal*I and hybridization of ^{32}P-labelled DNA fragments after extraction from low-melting-point agarose. The DNA probes used in mapping are listed in Table 4.

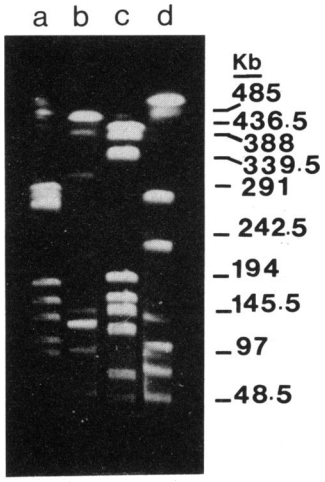

FIG. 3. PFGE of *C. jejuni* UA580 and *C. coli* UA417 chromosomal DNA digested with *Sma*I and *Sal*I. Electrophoresis was carried out with a contour-clamped homogenous electric field system for 24 h at 185 V and 12°C with a pulse time of 20 s in a 1% agarose gel. Shown are *C. coli* UA417 DNA digested with *Sma*I (lane a) or *Sal*I (lane b) and *C. jejuni* UA580 DNA digested with *Sma*I (lane c) or *Sal*I (lane d). The sizes of the λ DNA ladder markers are shown on the right.

experiments with a 23S rRNA gene probe from *E. coli* (49) demonstrated that both species also contain three copies of 23S rDNA (Fig. 4). In *C. jejuni* UA580, at least two of the 23S rRNA genes are located separately from two of the 16S rRNA genes. In only one instance might the 16S and 23S rDNAs be located together; in this case, they would be located where the *Sal*I-6 fragment contains the 16S rDNA and the Δ*Sal*I-2 fragment contains the 23S rDNA. In this case, the *Sal*I restriction site at kb 140 would separate the two rDNAs. Further experiments are necessary to determine whether this is the case or whether all three 16S and 23S rDNA loci are split in *C. jejuni* UA580. *C. coli* UA417 also contains two separate 16S and 23S rRNA genes (Fig. 2). It is possible that the 16S rDNA in *Sma*I-5 and the 23S rDNA in *Sma*I-10 are located together, perhaps separated by the *Sma*I site at coordinate 92.

Positions of rRNA genes in *C. jejuni* 81116. Nuijten et al. (27) mapped the positions of the *flaA* and *flaB* genes and the 16S rRNA genes on *C. jejuni* 81116 (UA501). We wished to

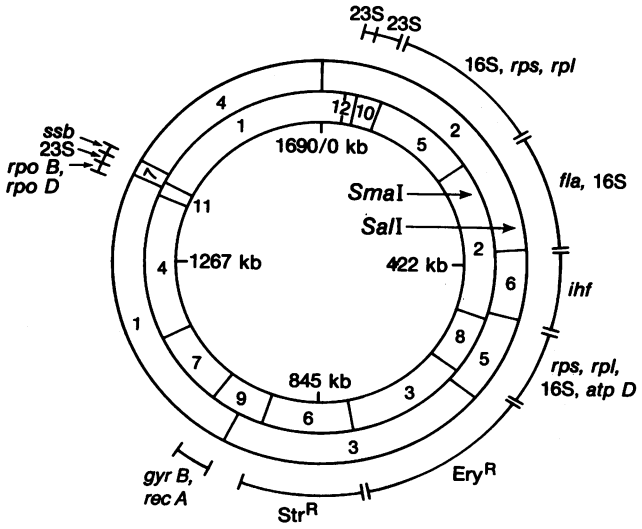

FIG. 2. Physical map of the *C. coli* UA417 chromosome. See the legend to Fig. 1 for details of map construction and Table 4 for probes used. The positions of Str^r and Ery^r markers were mapped by natural transformation of extracted DNA fragments (52).

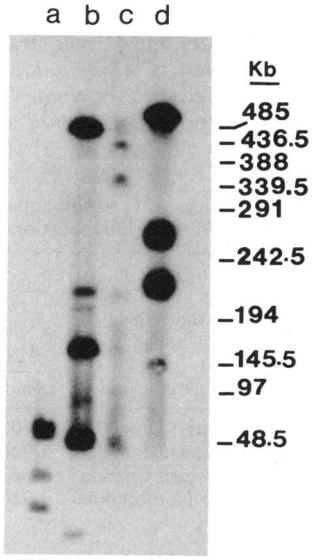

FIG. 4. Southern blot of a contour-clamped homogeneous electric field gel containing *C. coli* UA417 DNA digested with *Sma*I (lane a) or *Sal*I (lane b) and *C. jejuni* UA580 DNA digested with *Sma*I (lane c) or *Sal*I (lane d), separated under PFGE conditions similar to those given in the legend to Fig. 3, and hybridized with ^{32}P-labelled 23S rRNA gene probe from *E. coli* (pCW1) (49). The sizes of λ DNA markers are shown on the right.

TABLE 4. DNA probes used to map gene loci on genomes of *C. jejuni* UA580 and *C. coli* UA417

Gene(s)[a]	Plasmid	Species of origin[b]	Source	Reference(s)
16S rRNA	pAR140	*C. jejuni*	A. Rashtchian	36
flaA flaB	pIVB-300	*C. jejuni*	B. A. M. van der Zeijst	29
23S rRNA	pCW1	*E. coli*	J. Ofengand and C. Weitzmann	49
rplJ rplL	pNO2016	*E. coli*	M. Nomura	34
rpsG rpsL	pNO2005	*E. coli*	M. Nomura	33
ssb	pTL119A-5	*E. coli*	C. Radding	24
ihf	pPLhip-himA-5	*E. coli*	M. Dubow	26
atpD	pBJC505	*E. coli*	S. Cole	47
rpoD	pCUC522	*B. subtilis*	S. Cole	35
rpoB	pRIF2	*H. influenzae*	W. Albritton	4
rec-1[c]	pDJM90	*H. influenzae*	R. J. Redfield	2
gyrB	pRRNOV1	*H. influenzae*	R. J. Redfield	38, 43

[a] For additional information on the genes and their functions, see the text.
[b] Species from which the cloned fragment originated.
[c] *rec-1* is a *recA*-like gene (2).

determine the relative positions of 16S and 23S rDNAs on the *C. jejuni* 81116 (UA501) map. Therefore, the 16S rRNA gene probe from *C. jejuni* and the 23S rRNA gene probe from *E. coli* (Table 4) were hybridized to Southern blots prepared from 81116 DNA digested with *Sal*I, *Nci*I, and *Bss*HII. The *E. coli* 16S rDNA probe hybridized to the same DNA fragments that were found by Nuijten et al. (27) to hybridize to the 16S probe from *Mycoplasma* sp. strain PG50 (8). However, the 23S rDNA probe hybridized to different fragments (Fig. 5). One of the 16S rRNA genes in *Nci*I-9 is located quite separately from the 23S rRNA gene in *Bss*HII-3, whereas the other two 16S and 23S rRNA genes may be located together, separated by a *Nci*I restriction site.

In *E. coli* (1) and *B. subtilis* (25), rRNA genes are closely linked in the order 16S-23S-5S. However, this order and close linkage, although common, are not universal (see reference 18 for a review). Some microorganisms such as *Mycoplasma gallisepticum* contain a single copy of 23S-5S and a separate 16S gene (7). *Mycoplasma hyopneumoniae* contains a single copy of 16S-23S and a separate 5S gene (45). *Pirellula marina*, a planctomycete, contains two separate copies of both 23S-5S and 16S (23), and *Thermus thermophilus* has a similar number and arrangement of rRNA genes (11, 12). There also appears to be no close linkage among the two copies of the 23S and 16S rDNAs and the one copy of the 5S rDNA in *Leptospira interrogans* (9).

Unfortunately, no information regarding the positions of 5S rDNA genes in *C. jejuni* and *C. coli* is yet available. We have been unable to obtain a suitable probe to detect the 5S rRNA gene alone. An *E. coli* 5S rRNA probe (17) did not hybridize to Southern blots prepared from pulsed-field gels of *C. jejuni* or *C. coli* DNA (data not shown). This is probably because the 5S rRNA from *C. jejuni* has less than 65% sequence homology with *E. coli* or other available procaryotic 5S rRNAs (20). Therefore, additional studies are required in order to determine the positions of the 5S rRNA genes with respect to the 23S and 16S rRNA genes.

It is known that individual members of the same genus, such as members of the genus *Mycoplasma*, may have their *rrn* loci arranged differently from one another (18). It is also possible that different strains of the same species have different *rrn* arrangements. *C. jejuni* TGH9011 seemed to have two closely linked 23S-16S loci and a third 23S-16S locus located separately (15), although a more recent study by the same authors using field inversion gel electrophoresis suggested that the three rRNA operons in this strain are not as closely linked as previously proposed (16). Thus, the three different *C. jejuni* strains examined so far appear to have different 23S and 16S rDNA arrangements.

Arrangement of flagellar genes and variation in genome maps. *C. jejuni* and *C. coli* contain two copies of flagellar genes (*flaA* and *flaB*) immediately adjacent to one another (10, 28, 29). The *flaAflaB* genes in *C. jejuni* 81116 are located approximately 300 kb from one 16S rRNA gene and 700 kb from another (Fig. 5). Similarly, flagellar genes in *C. jejuni* UA580 are located about 170 and 700 kb away from the two closest 16S rRNA genes (Fig. 1). These results suggest that the relative locations of flagellar genes and 16S rRNAs are fairly well conserved in these two *C. jejuni* strains. However, their locations with respect to 23S rDNA bear no relationship to one another.

Except for the relationship between the *flaAB* genes and two 16S rDNA copies, there are no obvious similarities in the arrangement of the *flaAB* genes or in that of either 16S or

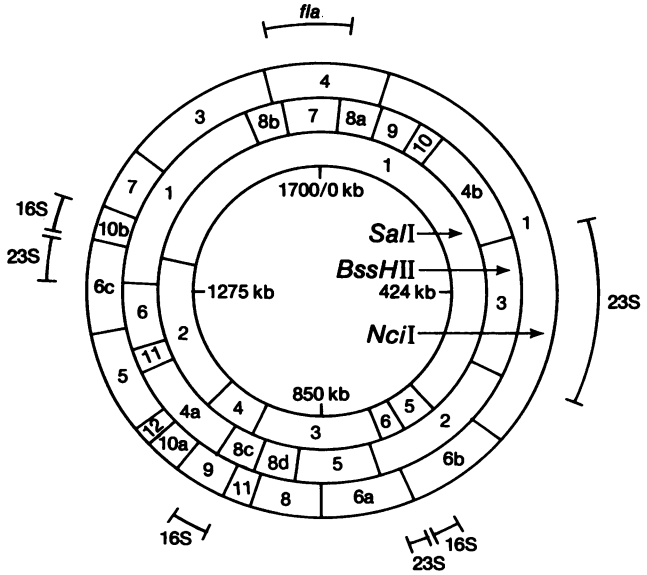

FIG. 5. Physical map of the *C. jejuni* 81116 chromosome, adapted from reference 27 with the addition of 23S rRNA genes by using the pCW1 probe (49).

23S rDNA when *C. jejuni* UA580 and 81116 are compared, although the *SalI* restriction fragments of the two strains have similar sizes (6). Therefore, the situation among *C. jejuni* strains may be similar to that seen among *H. influenzae* b strains, for which genome maps vary widely (4).

Positions of housekeeping genes on *Campylobacter* genomes. Since very few genes from *C. jejuni* and *C. coli* have been cloned, a series of heterologous probes derived from *E. coli*, *B. subtilis*, and *H. influenzae* was used to map the positions of genes for housekeeping functions. Many of these genes did not cross-hybridize, even at low stringency, probably because of differences in base composition, since *C. jejuni* and *C. coli* have a G+C content of about 32.5% (46). On the basis of those that gave positive results (Table 4), we were able to map the positions of several putative genes (Fig. 1 and 2).

We mapped the position of a *recA*-like gene in both *C. jejuni* UA580 and *C. coli* UA417 on the basis of hybridization with the *rec-1* gene from *H. influenzae* (2). However, no homology with either the *E. coli recA* gene (42) or that of *Staphylococcus aureus* (3) was detected.

The gene homologous to the RNA polymerase β subunit (*rpoB*) is located close to the σ^{43} (*rpoD*)-like gene in both *C. jejuni* and *C. coli*. Ribosomal protein genes homologous to an *rplJ rplL* probe, which encode large ribosomal proteins L7/L12 and L10 in *E. coli* (34), hybridized to two regions in both *C. jejuni* and *C. coli*. The same two regions hybridized to a *rpsG rpsL* probe which codes for the S7 and S12 proteins in *E. coli* (33). In the genomes of both *C. jejuni* and *C. coli*, these ribosomal protein genes are associated with a 16S rRNA gene as well as with the ATP synthase gene (*atpD*). Therefore, there appears to be some conservation of gene arrangement between these two *Campylobacter* species.

Integration host factor protein genes (*him hipA*) hybridized to a single DNA fragment in *C. jejuni* and *C. coli*, although these genes are located at two different positions on the *E. coli* map (1). The single-stranded binding protein gene (*ssb*), however, hybridized only with the *C. coli* genome, in which it was located close to a cluster of 23S rRNA and ribosomal protein genes.

Location of DNA gyrase (*gyrB*) gene and possible origin region. The position of *gyrB* was determined by hybridization of a heterologous probe for novobiocin resistance from *H. influenzae* (38, 43). Studies with several species of bacteria (*E. coli*, *Pseudomonas putida*, and *B. subtilis*) have shown that the gene organization patterns in the replication origin region are similar (30) and that the *gyrB* gene is located close to the origin of replication in all three species. In *H. influenzae*, the *nov* (*gyrB*) gene is located close to the *rec-1* gene, and the six ribosomal genes are oriented away from this region, suggesting that it is near the origin of replication (22). The *rec-1* gene is considered to be *recA*-like in *H. influenzae* (2). In both *C. jejuni* UA580 and *C. coli* UA417, the putative *recA* and *gyrB* genes are also located together. It seems reasonable to predict that the origin of replication of the *Campylobacter* species is close to the gene homologous to *gyrB*.

Conclusion. The map of *C. coli* (Fig. 2) appears more complete than that of *C. jejuni* (Fig. 1) because of the existence of streptomycin resistance (Str^r) and erythromycin resistance (Ery^r) mutations in the former species. Natural transformation was used to map the positions of the Ery^r and Str^r markers on the chromosome (52). Both markers probably map to ribosomal protein genes (53). In *E. coli*, the StrA mutation, which results in Str^r, maps to the *rpsL* gene (1). However, the location of the Str^r marker does not correspond to either of the two *rpl* loci identified in *C. coli* UA417.

As more genes from *Campylobacter* species are cloned and sequenced, it will be useful to continue mapping studies of these *Campylobacter* strains, as well as others, to try to determine the degree of conservation of their gene locations. There appears to be a fair degree of variability among the genomes of unrelated isolates of *C. jejuni* and *C. coli* (51). Bacterial genomes that are constantly undergoing genetic exchange via natural transformation, such as those of *Haemophilus* (4) and *Campylobacter* species (48), may be more prone to such genetic rearrangements.

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