

Genomic sequence of a Lyme disease spirochaete, *Borrelia burgdorferi*

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The genome of the bacterium *Borrelia burgdorferi* B31, the aetiologic agent of Lyme disease, contains a linear chromosome of 910,725 base pairs and at least 17 linear and circular plasmids with a combined size of more than 533,000 base pairs. The chromosome contains 853 genes encoding a basic set of proteins for DNA replication, transcription, translation, solute transport and energy metabolism, but, like *Mycoplasma genitalium*, it contains no genes for cellular biosynthetic reactions. Because *B. burgdorferi* and *M. genitalium* are distantly related eubacteria, we suggest that their limited metabolic capacities reflect convergent evolution by gene loss from more metabolically competent progenitors. Of 430 genes on 11 plasmids, most have no known biological function; 39% of plasmid genes are paralogues that form 47 gene families. The biological significance of the multiple plasmid-encoded genes is not clear, although they may be involved in antigenic variation or immune evasion.

In the mid-1970s, a geographic clustering of an unusual rheumatoid arthritis-like condition was reported in Connecticut¹. That cluster of cases focused attention on the syndrome that is now called Lyme disease. It was subsequently realized that a similar disorder had been known in Europe since the beginning of this century. Lyme disease is characterized by some or all of the following manifestations: an initial erythematous annular rash, flu-like symptoms, neurological complications, and arthritis in about 50% of untreated patients². In the United States, the disease occurs primarily in northeastern and midwestern states, and in western parts of California and Oregon. These regions coincide with the ranges of various species of *Ixodes* ticks, the primary vector of Lyme disease. Lyme disease is now the most common tick-transmitted illness in the United States, and has been reported in many temperate parts of the Northern Hemisphere.

It was not until the early 1980s that a new spirochaete, *Borrelia burgdorferi*³, was isolated and cultured from the midgut of *Ixodes* ticks, and subsequently from patients with Lyme disease^{4,5}. Analysis of genetic diversity among individual *Borrelia* isolates has defined a closely related cluster containing at least 10 tick-borne species of Lyme disease agents, called '*B. burgdorferi* (*sensu lato*)'. *B. burgdorferi* resembles most other spirochaetes in that it is a highly specialized, motile, two-membrane, spiral-shaped bacterium that lives primarily as an extracellular pathogen. *Borrelia* is fastidious and difficult to culture *in vitro*, requiring a specially enriched media and low oxygen tension⁶.

One of the most striking features of *B. burgdorferi* is its unusual genome, which includes a linear chromosome approximately one megabase in size⁷⁻¹⁰ and numerous linear and circular plasmids¹¹⁻¹³, with some isolates containing up to 20 different plasmids. The plasmids have a copy number of approximately one per chromosome^{10,14}, and different plasmids often appear to share regions of homologous DNA^{13,15,16}. Long-term culture of *B. burgdorferi* results in the loss of some plasmids, changes in protein expression profiles,

and a loss in the ability of the organism to infect laboratory animals, suggesting that the plasmids encode important proteins involved in virulence¹⁷⁻¹⁹.

Because of its importance as a pathogen of humans and animals, and the value of complete genome sequence information for understanding its life cycle and advancing drug and vaccine development, we sequenced the genome of *B. burgdorferi* type strain (B31), using the random sequencing method previously described²⁰⁻²⁴. Here we summarize the results from sequencing, assembly and analysis of the linear chromosome and 11 plasmids.

Chromosome analysis

The linear chromosome of *B. burgdorferi* has 910,725 base pairs (bp) and an average G+C content of 28.6%. Base pair one represents the first double-stranded base pair that we observed at the left telomere. Previous genome characterizations agree with the nucleotide sequence of the large chromosome^{10,25-28}. The 853 predicted coding sequences (open reading frames; ORFs) have an average size of 992 bp, similar to that observed in other prokaryotic genomes, with 93% of the *B. burgdorferi* genome representing

Figure 1 Linear representations of the *B. burgdorferi* B31 chromosome and plasmids. The location of predicted coding regions colour-coded by biological role, RNA genes, and tRNAs is indicated. Arrows represent the direction of transcription for each predicted coding region. Numbers associated with tRNA symbols represent the number of tRNAs at a locus. Numbers associated with GES represent the number of membrane-spanning domains according to the Goldman, Engelman and Steitz scale as calculated by TopPred⁴⁹. Only proteins with five or more GES are indicated. Members of paralogous gene families are identified by family number. Transporter abbreviations: mal, maltose; P, gly and bet, proline, glycine, betaine; gly, glycerol; aa, amino acid; E, glutamate; fru, fructose; glu, glucose; s/p, spermidine/putrescine; pan, pantothenate; Pi, phosphate; lac, lactate; rib, ribose; ?, unknown.

coding sequence. Biological roles were assigned to 59% of the 853 ORFs using the classification scheme adapted from Riley²⁹ (Fig. 1), 12% of ORFs matched hypothetical coding sequences of unknown function from other organisms, and 29% were new genes. The average relative molecular mass (M_r) of the chromosome-encoded proteins in *B. burgdorferi* is 37,529 ranging from 3,369 to 254,242, values similar to those observed in other bacteria including *Haemophilus influenzae*²⁰ and *Mycoplasma genitalium*²¹. The median isoelectric point (pI) for all predicted proteins is 9.7.

Analysis of codon usage in *B. burgdorferi* reveals that all 61 triplet codons are used. When both AU- and GC-containing codons specify a single amino acid, there is a marked bias (from 2-fold to more than 20-fold, depending on the amino acid) in the use of AU-rich codons. The most frequently used codons are AAA (Lys, 8.1%), AAU (Asn, 5.9%), AUU (Ile, 5.9%), UUU (Phe, 5.7%), GAA (Glu, 5.0%), GAU (Asp, 4.2%) and UUA (Leu, 4.2%). The most common amino acids are Ile (10.6%), Leu (10.3%), Lys (10.2%), Ser (7.8%) and Asn (7.2%). The high value for Lys is in agreement with the median calculated isoelectric point of 9.7.

Plasmid analysis

Analysis of the nucleotide sequence and Southern analyses on *B. burgdorferi* DNA indicate that, in addition to the large linear chromosome, isolate B31 contains linear plasmids of the following approximate sizes: 56 kilobase pairs (kbp) (lp56), 54 kbp (lp54), four plasmids of 28 kbp (lp28-1, lp28-2, lp28-3 and lp28-4), 38 kbp (lp38), 36 kbp (lp36), 25 kbp (lp25) and 17 kbp (lp17); and circular plasmids of the following sizes: 9 kbp (cp9), 26 kbp (cp26) and five or six homologous plasmids of 32 kbp (cp32). These include all of the plasmids previously identified in this strain, but comparisons with other B31 cultures suggest that this isolate may have lost one 21 kbp linear and one or two 32 kbp circular plasmids during growth in culture since its original isolation^{11-14,19,30}. The sequences of all plasmids were assembled as part of this project. However, the assembled sequences of the cp32 and related lp56 plasmids could not be determined with a high degree of confidence because of DNA sequence similarity among them ($\geq 99\%$ in several regions of

3,000–5,000 bp per plasmid)^{13,16} (Table 1). Improved assembly strategies are being tested to achieve closure on these plasmids (G. Sutton, unpublished). Plasmid lp17 is identical to that of lp16.9 from Barbour *et al.*¹⁵.

The 11 plasmids we have described contain a total of 430 putative ORFs with an average size of 507 bp; plasmid G+C content ranges from 23.1% to 32.3%. Only 71% of plasmid DNA represents predicted coding sequences, a value significantly lower than that on the chromosome. This indicates that average intergenic distances are greater in the plasmids than in the chromosome, and that many potential ORFs contain authentic frameshifts or stops (see E29, for example), suggesting that they are decaying genes not encoding functional proteins. Of the 430 plasmid ORFs, only 70 (16%) could be identified and these include membrane proteins such as OspA-D, decorin-binding proteins, the VlsE lipoprotein recombination cassette, and the purine ribonucleotide biosynthetic enzymes GuaA and GuaB. We found that 100 ORFs (23%) match other hypothetical proteins from plasmids in this and related strains of *B. burgdorferi*^{15,16,31}; 10 ORFs (2.3%) match hypothetical proteins from species other than *Borrelia*; and 250 ORFs (58%) have no database match.

We found that 47 paralogous gene families containing from 2 to 12 members account for 39% (169 ORFs) of the plasmid-encoded genes with no known biological role (Fig. 1). Parologue families 32 and 50, typified by previously identified *B. burgdorferi* plasmid genes cp32 orfC and cp8.3 orf2, respectively, have some similarities to proteins involved in replication, segregation and control of copy number in other bacterial systems^{16,31}. Previous studies have reported examples of plasmid gene duplication, but the extent of

Table 2 Gene identification numbers are listed with the prefix BB as in Fig. 2. Each gene identified is listed in its functional role category (adapted from Riley²⁹). The percentage of similarity and a two-letter abbreviation for genus and species for the best match are also shown. An expanded version of this table with additional information is available on the World-Wide Web at <http://www.tigr.org/tdb/mdb/bbdb/bbdb.htm>. Abbreviations of gene names are: Ac, acetyl; BP, binding protein; biosyn, biosynthesis; cello, cellobiose; CPDase, carboxypeptidase; Dcase, decarboxylase; DHase, dehydrogenase; flgr, flagellar/flagellum; fru, fructose; GBP, glycine, betaine, L-proline; glu, glucose; Kase, kinase; mal, maltose; MC-methyl-accepting chemotaxis; MTase, methyltransferase; NAG, N-acetylglucosamine; OH, hydroxy; OP, oligopeptide; P, phosphate; PPTase, phosphotransferase; PPase, phosphatase; prt, protein; put, putative; RDase, reductase; RG, ribose/galactose; SAM, S-adenosyl-methionine; Sase, synthetase/synthase; SP, spermidine/putrescine; ss, single-stranded; sub, subunit; Tase, transferase.

Abbreviation of genus and species are: Ah, *Aeromonas hydrophila*; Ar, *Agrobacterium radiobacter*; Al, *Alteromonas* sp.; Ab, *Anabaena* sp.; An, *Anacystis nidulans*; At, *Arabidopsis thaliana*; Av, *Azotobacter vinelandii*; Bf, *Bacillus firmus*; Bl, *Cacillus licheniformis*; Bm, *Bacillus megaterium*; Bs, *Bacillus stearothermophilus*; Bc, *Bacillus subtilis*; Bb, *Borrelia burgdorferi*; Bc, *Borrelia coriaceae*; Bh, *Borrelia hermsii*; Ba, *Buchnera aphidicola*; Ca, *Clostridium acetobutylicum*; Cl, *Clostridium longisporum*; Cp, *Clostridium perfringens*; Cg, *Corynebacterium glutamicum*; Cb, *Coxiella burnetii*; Cp, *Cyanophora paradoxa*; Dd, *Dictyostelium discoideum*; Ec, *Escherichia coli*; Eh, *Entamoeba histolytica*; Ec, *Enterobacter cloacae*; El, *Enterococcus faecalis*; Eh, *Enterococcus hirae*; Ha, *Haemophilus aegyptius*; Hi, *Haemophilus influenzae*; Hp, *Helicobacter pylori*; Hs, *Homo sapiens*; La, *Lactobacillus acidophilus*; Ll, *Lactococcus lactis*; Li, *Leptospira interrogans serovar Iai*; Mj, *Methanococcus jannaschii*; Mb, *Methanosarcina barkeri*; Ml, *Mycobacterium leprae*; Mt, *Mycobacterium tuberculosis*; Mc, *Mycoplasma capricolum*; Mg, *Mycoplasma genitalium*; Mh, *Mycoplasma hominis*; Mh, *Mycoplasma hyorhinis*; Mm, *Mycoplasma mycoides*; Mp, *Mycoplasma pneumoniae*; Mx, *Mycococcus xanthus*; Ng, *Neisseria gonorrhoeae*; Nm, *Neisseria meningitidis*; Os, *Odontella sinensis*; Pt, *Paramecium tetraurelia*; Pa, *Pediococcus acidilactici*; Pf, *Plasmodium falciparum*; Pg, *Porphyromonas gingivalis*; Pv, *Proteus vulgaris*; Pa, *Pseudomonas aeruginosa*; Pm, *Pseudomonas mevalonii*; Pp, *Pseudomonas putida*; Rm, *Rhizobium meliloti*; Rc, *Rhodobacter capsulatus*; Rs, *Rhodobacter sphaeroides*; Rp, *Rickettsia prowazekii*; Sc, *Saccharomyces cerevisiae*; Sc, *Salmonella choleraesuis*; St, *Salmonella typhimurium*; Sh, *Serpulina hydysenteriae*; Sd, *Shigella dysenteriae*; So, *Spinacia oleracea*; Sc, *Staphylococcus carnosus*; Se, *Staphylococcus epidermidis*; Sp, *Streptococcus pyogenes*; Sc, *Streptomyces coelicolor*; Ss, *Sulfolobus solfataricus*; Syn, *Synechococcus* sp.; Sp, *Synechocystis* PCC6803; Tt, *Thermoanaerobacterium thermosaccharolyticum*; Tb, *Thermophilic bacterium RT8.B4*; Tt, *Thermoproteus tenax* virus; Tm, *Thermotoga maritima*; Tat, *Thermus aquaticus thermophilus*; Ta, *Thermus aquaticus*; Td, *Treponema denticola*; Tp, *Treponema pallidum*; Ta, *Triticum aestivum*; Tb, *Trypanosoma brucei* mitochondrion; Vc, *Vibrio cholerae*; Vp, *Vibrio parahaemolyticus*; Zm, *Zymomonas mobilis*.

Table 1 Genome features in *Borrelia burgdorferi*

| | |
|--|------------------------|
| Chromosome | 910,725 bp (28.6% G+C) |
| Coding sequences (93%) | |
| RNAs (0.7%) | |
| Intergenic sequence (6.3%) | |
| 853 coding sequences | |
| 500 (59%) with identified database match | |
| 104 (12%) match hypothetical proteins | |
| 249 (29%) with no database match | |
| Plasmids | |
| cp9 | 9,386 bp (23.6% GC) |
| cp26 | 26,497 bp (26.3% GC) |
| lp17 | 16,828 bp (23.1% GC) |
| lp25 | 24,182 bp (23.3% GC) |
| lp28-1 | 26,926 bp (32.3% GC) |
| lp28-2 | 29,771 bp (31.5% GC) |
| lp28-3 | 28,605 bp (25.1% GC) |
| lp28-4 | 27,329 bp (24.4% GC) |
| lp36 | 36,834 bp (26.8% GC) |
| lp38 | 38,853 bp (26.1% GC) |
| lp54 | 53,590 bp (28.1% GC) |
| Coding sequences (71%) | |
| Intergenic sequence (29%) | |
| 430 coding sequences | |
| 70 (16%) with identified database match | |
| 110 (26%) match hypothetical proteins | |
| 250 (58%) with no database match | |
| Ribosomal RNA | Chromosome coordinates |
| 16S | 444581–446118 |
| 23S | 438590–441508 |
| 5S | 438446–438557 |
| 23S | 435334–438267 |
| 5S | 435201–435312 |
| Stable RNA | |
| tmRNA | 46973–47335 |
| mpB | 750816–751175 |
| Transfer RNA | |
| 34 species (8 clusters, 14 single genes) | |

*The telomeric sequences of the nine linear plasmids assembled as part of this study were not determined; estimation of the number of missing terminal nucleotides by restriction analysis suggests that less than 1,200 bp is missing in all cases. Comparisons with previously determined sequences of lp 16.9 and one terminus of lp28-1 indicate that 25, 60 and 1,200 bp are missing, respectively.

this redundancy has become even more apparent with the complete sequence of these 11 plasmids from isolate B31. Moreover, a preliminary search of 221 putative ORFs from the cp32s and lp56 indicates that at least 50% display $\geq 70\%$ amino-acid similarity to ORFs from the other 11 plasmids presented here (data not shown). Although plasmid-encoded genes have been implicated in infectivity and virulence^{17–19}, the biological roles of most of these genes are not known. The significance of the large number of paralogous plasmid-encoded genes is not understood. These proteins may be expressed differentially in tick and mammalian hosts, or may undergo homologous recombination to generate antigenic variation in surface proteins. This hypothesis is supported by the identification of 63 plasmid-encoded putative membrane lipoproteins (Fig. 1).

Several copies of a putative recombinase/transposase similar to IS891-like transposases were identified in the *B. burgdorferi* plasmids. Linear plasmid 28-2 contains one full-length copy of this gene. Although no inverted repeats were found on either side of the transposase, there is a putative ribosome-binding site several nucleotides upstream of the apparent start codon, and a stem-loop structure ($-27 \text{ kcal mol}^{-1}$) 195 bp downstream of the stop codon in an area with no ORFs. This transposase might represent a functional gene important for the frequent DNA rearrangements that presumably occur in *Borrelia* plasmids. There are other partial or nearly complete copies of the transposase gene that contain frame-destroying mutations elsewhere in the genome: two copies on lp17, one on lp36, one on lp38, one on lp28-3, two on lp28-1, and one near the right end of the large linear chromosome.

Origin of replication

The replication mechanism for the linear chromosome and plasmids in *B. burgdorferi* is not yet known. Replication possibly begins at the termini, as has been proposed for the poxvirus hairpin telomeres³², or may begin from a single origin somewhere along the length of the linear replicon. Of the genes on the linear chromosome, 66% are transcribed away from the centre of the chromosome (Fig. 1), similar to the transcriptional bias observed for the genomes of *M. genitalium*²¹ and *M. pneumoniae*³³. It has been suggested that bacterial genes are optimally transcribed in the same direction as that in which replication forks pass over them, particularly for highly transcribed genes^{34,35}.

Given the transcriptional bias observed in *B. burgdorferi*, it seems likely that the origin of replication is near the centre of the chromosome. Because bacterial chromosomal replication origins are usually near *dnaA*³⁶, it is intriguing to note that this gene (BB437) lies almost exactly at the centre of the linear *B. burgdorferi* chromosome^{10,27}. A centrally initiated, bi-directional replication fork would be equidistant from the two chromosome ends, and replication would traverse the rRNA genes in the same direction as transcription.

An analysis of GC skew, $(G - C)/(G + C)$ calculated in 10-kilobase (kb) windows across the chromosome, shows a clear break at

the putative origin of replication. The GC-skew values are uniformly negative from 0 to 450 kb (minus strand), and uniformly positive (plus strand) from 450 kb to the end of the chromosome (Fig. 2). Additional evidence for the location of the origin of replication comes from our discovery of an octamer, TTGTTTTT, whose skewed distribution in the plus versus the minus strand of the chromosome matches the GC skew (Fig. 2). The biological significance of this octamer has not yet been determined, although it may be analogous to the Chi site in *Escherichia coli* that is implicated in *recBCD* mediated recombination. No GC skew was observed in any of the plasmids, although the heptamer ATTTTTT displays a skewed distribution in the plus versus the minus strand of lp28-4 that changes at the approximate midpoint of the plasmid (not shown).

Transcription and translation

Genes encoding the three subunits (α , β , β') of the core RNA polymerase were identified in *B. burgdorferi* along with σ^{70} and two alternative σ factors, σ^{54} and *rpoS*. The role and specificity of each of these σ factors in transcription regulation in *B. burgdorferi* are not known. The *nusA*, *nusB* and *rho* genes, which are involved in transcription elongation and termination, were also identified.

A region of the genome with a significantly higher G + C content (43%), located between nucleotides 434,000 and 447,000, contains the rRNA operon. As previously reported, the rRNA operon in *B. burgdorferi* contains a 16S rRNA–Ala-tRNA–Ile-tRNA–23S rRNA–5S rRNA–23S rRNA–5S rRNA^{37,38}. All of the genes are present in the same orientation, except for that encoding Ile tRNA. Four unrelated genes, encoding 3-methyladenine glycosylase, hydrolyase and two with no database match, are also present in the rRNA operon. Three of these genes are transcribed in the same direction as the rRNAs.

We identified in the chromosome 31 tRNAs with specificity for all 20 amino acids (Fig. 1). These are organized into 7 clusters plus 13 single genes. All tRNA synthetases are present except glutaminyl tRNA-synthetase. A single glutamyl tRNA synthetase probably aminoacylates both tRNA^{Glu} and tRNA^{Gln} with glutamate followed by transamidation by Glu-tRNA amidotransferase, a heterotrimeric enzyme present in *B. burgdorferi* and several Gram-positive bacteria and archaea³⁰. The lysyl-tRNA synthetase (LysS) in *B. burgdorferi* is a class I type that has no resemblance to any known bacterial or eukaryotic LysS, but is most similar to LysS from the archaea⁴⁰.

Replication, repair and recombination

The complement of genes in *B. burgdorferi* involved in DNA replication is smaller than in *E. coli*, but similar to that in *M. genitalium*²¹. Three ORFs have been identified with high homology to four of the ten polypeptides in the *E. coli* DNA polymerase III: α , β and γ , and τ . In *E. coli*, the γ and τ proteins are produced by programmed ribosomal frameshifting. This observation suggests that DNA replication in *B. burgdorferi*, like that in *M. genitalium*, is accomplished with a restricted set of genes. *B. burgdorferi* has one

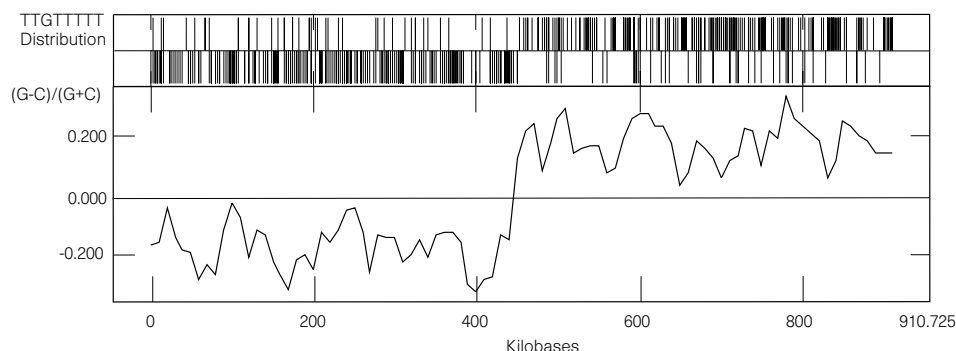


Figure 2 Distribution of TTGTTTTT and GC skew in the *B. burgdorferi* chromosome. Top, distribution of the octamer TTGTTTTT. The lines in the top panel represent the location of this octamer in the plus strand of the sequence, and those in the second panel represent the location of this oligomer in the minus strand of the sequence. Bottom, GC skew.

type I topoisomerase (*topA*) and two type II topoisomerases (gyrase and topoisomerase IV) for DNA topology management and chromosome segregation, despite its linear chromosomal structure. This suggests that topoisomerase IV may be required for more than the separation of circular DNAs during segregation.

The DNA repair mechanisms in *B. burgdorferi* are similar to those in *M. genitalium*. DNA excision repair can presumably occur by a pathway involving endonuclease III, PolI and DNA ligase. The genes for two of three DNA mismatch repair enzyme (*mutS*, *mutL*) are

present. The apparent absence of *mutH* is consistent with the lack of GATC (*dam*) methylation in strain B31 (S. Casjens, unpublished). Also present are genes for the repair of ultraviolet-induced DNA damage (*uvrA*, *uvrB*, *uvrC* and *uvrD*) (Table 2).

B. burgdorferi has a complete set of genes to perform homologous recombination, including *recA*, *recBCD*, *sbcC*, *sbcD*, *recG*, *ruvAB* and *recJ*. 3'-Exonuclease activity associated with *sbcB* in *E. coli* may be encoded by *exoA* (exodeoxynuclease III). Although *recA* is present, we found no evidence for *lexA*, which encodes the repressor that

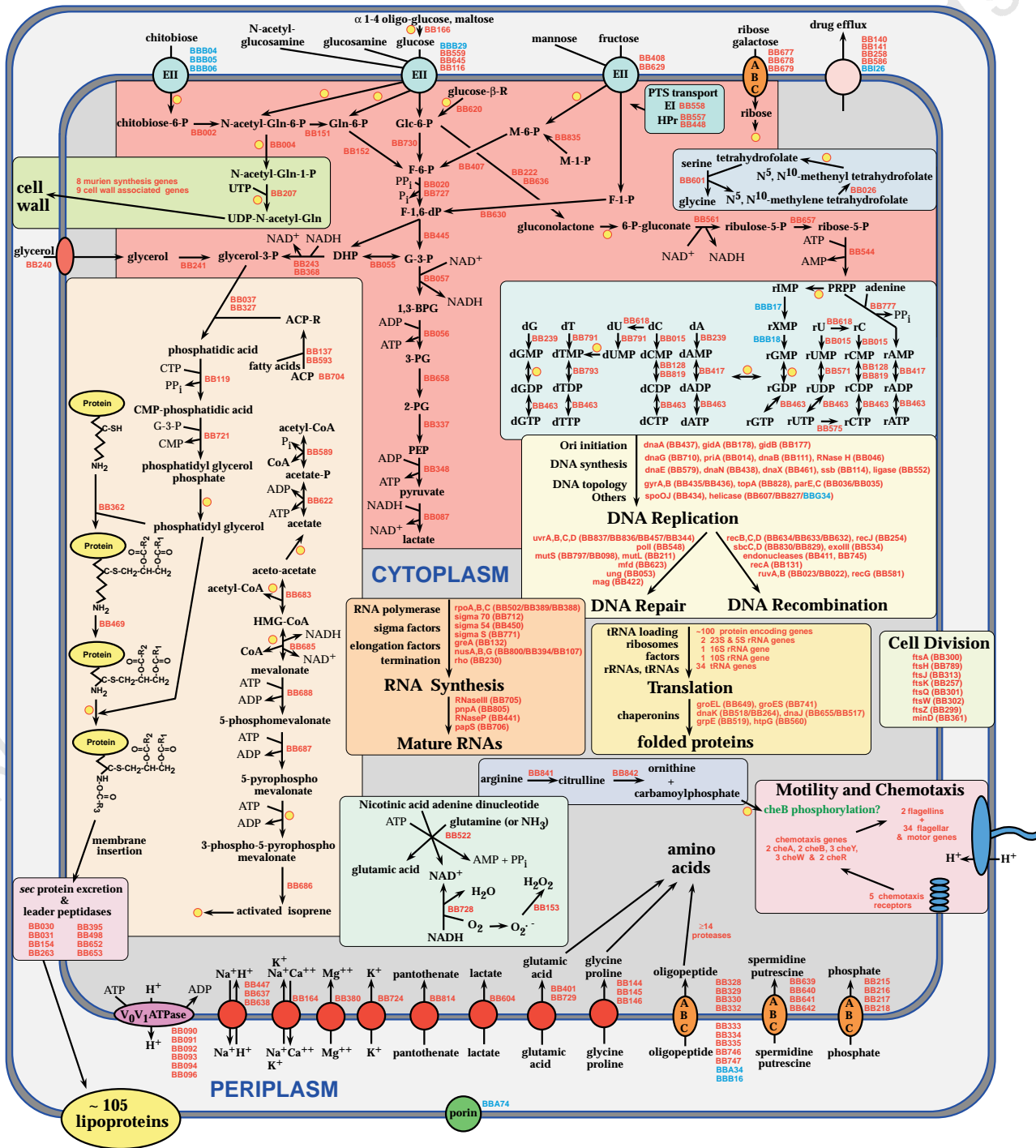


Figure 3 Solute transport and metabolic pathways in *B. burgdorferi*. A schematic diagram of a *B. burgdorferi* cell providing an integrated view of the transporters and the main components of the metabolism of this organism, as deduced from the genes identified in the genome. The ORF numbers correspond to those listed

in Table 2 (red indicates chromosomal and blue indicates plasmid ORFs). Presumed transporter specificity is indicated. Yellow circles indicate: places where particular uncertainties exist as to the substrate specificity, subcellular location or direction of catalysis: or expected activities that were not found.

regulates SOS genes in *E. coli*. No genes encoding DNA restriction or modification enzymes are present.

Biosynthetic pathways

The small genome size of *B. burgdorferi* is associated with an apparent absence of genes for the synthesis of amino acids, fatty acids, enzyme cofactors, and nucleotides, similar to that observed with *M. genitalium*²¹ (Fig. 3, Table 2). The lack of biosynthetic pathways explains why growth of *B. burgdorferi* *in vitro* requires serum-supplemented mammalian tissue-culture medium. This is also consistent with previous biochemical data indicating that *Borrelia* lack the ability to elongate long-chain fatty acids, such that the fatty-acid composition of *Borrelia* cells reflects that present in the growth medium⁶.

Transport

The linear chromosome of *B. burgdorferi* contains 46 ORFs and the plasmids contain 6 ORFs that encode transport and binding proteins (Fig. 3, Table 2). These gene products contribute to 16 distinct membrane transporters for amino acids, carbohydrates, anions and cations. The distribution of transporters between the four categories of functions in this section is similar to that observed in other heterotrophs (such as *Haemophilus influenzae*, *M. genitalium* and *H. pylori*), with most being dedicated to the import of organic compounds.

There are marked similarities between the transport capacity of *B.*

burgdorferi and *M. genitalium*. Both genomes have a limited number of recognizable transporters, so it is not clear how they can sustain diverse physiological reactions. Several of the identified transporters in both genomes exhibit broad substrate specificity, exemplified by the oligopeptide ABC transporter (*opp* operon) or the glycine, betaine, L-proline transport system (*proVWX*). Therefore, these organisms probably compensate for their restricted coding potential by producing proteins that can import a wide variety of solutes. This is important because *B. burgdorferi* is unable to synthesize any amino acids *de novo*. We were unable to identify any transport systems for nucleosides, nucleotides, NAD/NADH or fatty acids, although they are likely to be present.

Glucose, fructose, maltose and disaccharides seem to be acquired by the phosphoenolpyruvate:phosphotransferase system (PTS). The two nonspecific components, enzyme 1 (*ptsI*) and Hpr (*ptsH*), are associated in one operon with an apparently glucose-specific, phosphohistidine-sugar phosphotransferase enzyme IIA (*crr*). Separate from this operon are four permeases (enzyme IIBC), *fruA* in two copies (fructose), *ptsG* (glucose) and *malX* (glucose/maltose) (Fig. 3, Table 2). The fructose-specific enzyme IIA is induced in the ORF with IIBC (*fruA*), as has been observed in *M. genitalium*⁴¹. Ribose may be imported by an ATP-binding cassette transporter (*rbsAC*). The *rbsAC* genes are transcribed in an operon with a methyl-accepting chemotaxis protein that may respond to β -galactosides, suggesting that movement of the organisms towards sugars may be coupled to the transport process.

Energy metabolism

The limited metabolic capacity of *B. burgdorferi* is similar to that found in *M. genitalium* (Fig. 3, Table 2). Genes encoding all of the enzymes of the glycolytic pathway were identified. Analysis of the metabolic pathway suggests that *B. burgdorferi* uses glucose as a primary energy source, although other carbohydrates, including glycerol, glucosamine, fructose and maltose, may be used in glycolysis. Pyruvate produced by glycolysis is converted to lactate, consistent with the microaerophilic nature of *B. burgdorferi*. Generation of reducing power occurs through the oxidative branch of the pentose pathway. None of the genes encoding proteins of the tricarboxylic acid cycle or oxidative phosphorylation were identified. The similarity in metabolic strategies of two distantly related, obligate parasites, *M. genitalium* and *B. burgdorferi*, suggests convergent evolutionary gene loss from more metabolically competent, distant progenitors.

Addition of *N*-acetylglucosamine (NAG) to culture medium is required for growth of *B. burgdorferi*⁶. NAG is incorporated into the cell wall, and may also serve as an energy source. The cp26 plasmid encodes a PTS cellobiose transporter homologue that could have specificity for the structurally similar compound chitobiose (di-*N*-acetyl-D-glucosamine). A gene product on the chromosome with sequence similarity to chitobiose (BB2) may convert chitobiose to NAG. *B. burgdorferi* can metabolize NAG to fructose-6-phosphate, which then can enter the glycolytic cycle through the action of *N*-acetylglucosamine-6-phosphate deacetylase and glucosamine-6-phosphate isomerase. NAG is the primary constituent of chitin, which makes up the tick cuticle⁶, and may be a source of carbohydrate for *B. burgdorferi* when it is associated with its tick host.

The parallels between *B. burgdorferi* and *M. genitalium* appear to extend to other aspects of their metabolism. Both organisms lack a respiratory electron transport chain, so ATP production must be accomplished by substrate-level phosphorylation. Consequently, membrane potential is established by the reverse reaction of the V_1V_0 -type ATP synthase, here functioning as an ATPase to expel protons from the cytoplasm (Fig. 3, Table 2). The ATP synthase genes in *B. burgdorferi* appear to be transcribed as part of a seven-gene operon. They are not typical of those usually found in eubacteria, more closely resembling the eukaryotic vacuolar (*V*-type) and archaeal (*A*-type) H^+ -translocating ATPases⁴², both in size

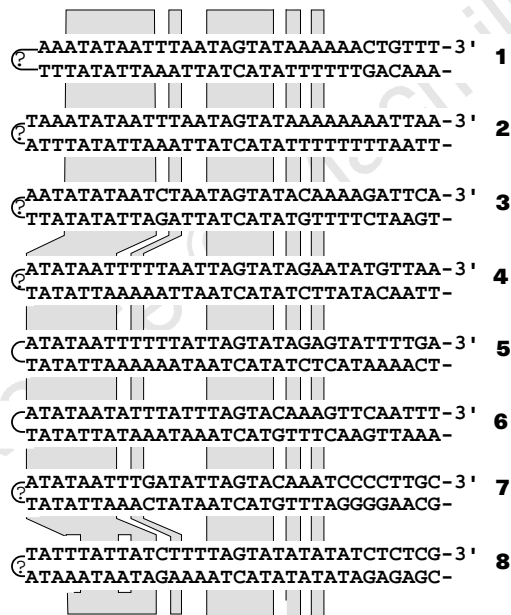


Figure 4 Telomere nucleotide sequences from *Borrelia* species. Nucleotide sequences are shown for known *Borrelia* telomeres as indicated: 1, *B. burgdorferi* Sh-2-82 chromosome left end; 2, *B. burgdorferi* B31 chromosome left end; 3, *B. afzelii* R-IP3 chromosome right end; 4, *B. burgdorferi* B31 chromosome right end; 5, *B. burgdorferi* B31 plasmid lp17 left end; 6, *B. burgdorferi* B31 plasmid lp17 right end; 7, *B. hermsii* plasmids bp7E and pb21E right ends; 8, *B. burgdorferi* B31 plasmid lp28-1 right end. In each case the telomere is at the left. Question marks (?) indicate locations where S1 nuclease was used to open terminal hairpins during the sequence determinations. Stippled areas highlight regions that appear to have been most highly conserved among these telomeres; no strong sequence conservation has been found near the right of the terminal 26 bp among the different sequences listed, except between the chromosomal left ends from strains B31 and Sh-2-82 (see text). The telomeric sequences of the strain B31 chromosome were determined in this report; the others are from references 14, 28, 30, 45, 46.

and sequence similarity, than the bacterial F_1F_0 ATPases. Genome analysis of *Treponema pallidum*, the pathogenic spirochaete that causes syphilis, has also revealed the presence of a V_1V_0 -type ATP synthase (C. M. F. *et al.*, manuscript in preparation), suggesting that this may be a feature of spirochaetes.

Regulatory systems

Although the expression of *Borrelia* genes varies according to the current host species, temperature, host body location and other local factors, control of gene expression appears to differ from more well studied eubacteria. A typical set of homologues of heat-shock response genes is present (*groES*, *groEL*, *grpE*, *dnaJ*, *hslU*, *hslV*, *dnaK* and *htpG*), and *B. burgdorferi* is known to have such a response; however, it lacks the σ -32 that controls their transcription in *E. coli*. Only a few homologues to other eubacterial regulatory proteins are present, including only two response-regulator two-component systems.

Motility and chemotaxis

Like other spirochaetes, *B. burgdorferi* has periplasmic flagella that are inserted at each end of the cell and extend towards the middle of the cell body. The unique flagella allow the organism to move through viscous solutions, an ability that is presumed to be important in its migration to distant tissues following deposition in the skin layers⁴³. Proteins involved in motility and chemotaxis are encoded by 54 genes, more than 6% of the *B. burgdorferi* chromosome, most of which are arranged in eight operons containing between 2 and 25 genes.

B. burgdorferi contains several copies of the chemotaxis genes (*cheR*, *cheW*, *cheA*, *cheY* and *cheB*) downstream of the methyl-accepting chemotaxis proteins. Other eubacteria also have duplications of some *che* genes, but those genes in *B. burgdorferi* are the most redundant set yet found. *B. burgdorferi* lacks recognizable virulence factors; thus, its ability to migrate to distant sites in the tick and mammalian host is probably dependent on a robust chemotaxis response. Multiple chemotaxis genes may provide redundancy in this system in order to meet such challenges or, alternatively, these genes may be differentially expressed under varied physiological conditions. Another speculative possibility is that the flagellar motors at the two ends of the *B. burgdorferi* cell are different and require different *che* systems. In support of this idea is the observation that one of the motor switch genes, *fliG*, is also present in two copies.

Membrane protein analysis

Much of the previous work on *B. burgdorferi* has focused on outer-surface membrane genes because of their potential importance in bacterial detection and vaccination. Nearly all *Borrelia* membrane proteins have been found to be typical bacterial lipoproteins. A search of *B. burgdorferi* ORFs for a consensus lipobox in the first 30 amino acids identified 105 putative lipoproteins, representing more than 8% of coding sequences. This contrasts with a total of only 20 putative lipoproteins in the 1.67-million base pair *H. pylori* genome (1.3% of coding sequences)²³. The periplasmic binding proteins involved in transport of amino acids/peptides and phosphate in *B. burgdorferi* are candidate lipoproteins, suggesting that they may be anchored to the outer surface of the cytoplasmic membrane as in Gram-positive bacteria, rather than localized in the periplasmic space.

In better-characterized eubacteria, prolipoprotein diacylglycerol transferase (*lgt*), prolipoprotein signal peptidase (*lsp*), and apolipoprotein:phospholipid *N*-acyl transferase (*lnt*) are required for post-translational processing and addition of lipids to the amino-terminal cysteine. Genes for the first two of the enzymes (*lgt* and *lsp*) are present in the *B. burgdorferi* genome, but the gene for *lnt* was not identified, although biochemical evidence argues for all three activities in *B. burgdorferi*⁴⁴. The sequence similarity of an *lnt*

homologue in *B. burgdorferi* may be too low to be identified using our search methods, or its activity may be present in a new enzyme. In *E. coli* the Sec protein export system moves lipoproteins through the inner membrane, and *Borrelia* carries a complete set of these protein-secretion gene homologues (*secA/D/E/F/Y* and *tth*; only the non-essential *secB* is missing).

Analysis of telomeres

The two chromosomal telomeres of strain B31 have similar 26-bp inverted terminal sequences (Fig. 4). We found no other similarity between the two ends, and these 26-bp sequences are very similar to the previously characterized *Borrelia* telomeres. Terminal restriction fragments from both B31 chromosomal termini were shown to exhibit snapback kinetics (data not shown), strongly indicating that both terminate in covalently closed hairpins, like previously characterized *Borrelia* telomeres^{28,45,46}.

The left chromosomal telomere of strain B31 is identical to the previously characterized left telomere of strain Sh-2-82 (ref. 28), except for a 31 bp insertion in B31 26 bp from the end. The right-most 7,454 bp contains surprisingly few ORFs, given the ORF density elsewhere on the chromosome. The function of this region is unknown, but it contains several unusual features. The right terminal 900 bp contains considerable homology to the left ends of lp17 and lp28-3. The region between 3,600 bp and 8,000 bp from the right end also contains several areas with similarity to plasmid sequences, including a portion of the transposase-like gene approximately 4,500 bp from the right end. The spacing between the two conserved motifs (ATATAAT and TAGTATA) in the right 26-bp terminal repeat is the same as most previously known plasmid telomeres but different from the previously known chromosomal telomeres. These findings support the idea that the right end of the *Borrelia* chromosome has historically exchanged telomeres with the linear plasmids²⁸.

Conclusions

The *B. burgdorferi* genome sequence will provide a new starting point for the study of the pathogenesis, prevention and treatment of Lyme disease. With the exception of a small number of putative virulence genes (haemolysins and drug-efflux proteins), this organism contains few, if any, recognizable genes involved in virulence or host-parasite interactions, suggesting that *B. burgdorferi* differs from better-studied eubacteria in this regard. It will be interesting to determine the role of the multi-copy plasmid-encoded genes, as previous work has implicated plasmid genes in infectivity and virulence. The completion of the genome sequence from a second spirochaete, *Treponema pallidum* (C.M.F. *et al.*, manuscript in preparation) will allow for the identification of genes specific to each species and to this bacterial phylum, and will provide further insight into prokaryotic diversity. □

Methods

Cell lines. A portion of a low-passage subculture of the original Lyme-disease spirochaete tick isolate⁴ was obtained from A. Barbour. The type strain of *B. burgdorferi* (ATCC 35210)³, B31, was derived from this isolate by limiting dilution cloning⁵. Cells were grown in Barbour-Stoenner-Kelly medium II (BSKII)⁶, omitting the additions of antibiotics and gelatin, in tightly closed containers at 33–34 °C. Cells were subcultured three or fewer times *in vitro* between successive rounds of infection in C3H/HeJ mice to minimize loss of infectivity and plasmid content^{17,18}. After four successive transfers of infection in mice, a primary culture of B31, established from infected ear tissue, was expanded to 2.51 by four successive subcultures. All available evidence indicates that the B31 line used for preparation of genomic DNA was probably clonal, as genetic heterogeneity was undetectable by several criteria including macro-restriction analysis (S. Casjens, unpublished data) and plasmid analysis of clonal derivatives of the B31 line¹³.

Sequencing. The *B. burgdorferi* genome was sequenced by a whole-genome random sequencing method previously applied to other microbial genomes^{20–24}.

An approximately 7.5-fold genome coverage was achieved by generating 19,078 sequences from a small insert plasmid library with an average edited length of 505 bases. The ends of 69 large insert lambda clones were sequenced to obtain a genome scaffold; 50% of the genome was covered by at least one lambda clone. Sequences were assembled using TIGR Assembler as described^{20–24}, resulting in a total of 524 assemblies containing at least two sequences, which were clustered into 85 groups based on linking information from forward and reverse sequence reads. All *Borrelia* sequences that had been mapped were searched against the assemblies in an attempt to delineate which were derived from the various elements of the *B. burgdorferi* genome. Some contigs were also located on the existing physical map by Southern analysis. Sequence and physical gaps for the chromosome were closed as described^{20–24}. At the completion of the project, less than 3% of the chromosome had single-fold coverage. The linear chromosome of *B. burgdorferi* has covalently closed hairpin structures at its termini that are similar to those reported for linear plasmids in this organism¹¹. The telomeric sequences (106 and 72 bp, respectively, from the left and right ends) were obtained after nicking the terminal loop with S1 nuclease and amplifying terminal sequences by ligation-mediated polymerase chain reaction (PCR) as described²⁸. The unknown terminal sequence was determined in both directions on four independent plasmid clones of the amplified DNA from each telomere. A minimum amount of S1 nuclease was used and, because of their sequence similarity to other *Borrelia* telomeres, it is likely that few, if any, nucleotides were lost from the B31 chromosomal telomeres in this process.

Identification of ORFs. Coding regions (ORFs) were identified using compositional analysis using an interpolated Markov model based on variable-length oligomers⁴⁷. ORFs of >600 bp were used to train the Markov model, as well as *B. burgdorferi* ORFs from GenBank. Once trained, the model was applied to the complete *B. burgdorferi* genome sequence and identified 953 candidate ORFs. ORFs that overlapped were visually inspected, and in some cases removed. Non-overlapping ORFs that were found between predicted coding regions and >30 amino acids in length were retained and included in the final annotation. All putative ORFs were searched against a non-redundant amino-acid database as described^{20–24}. ORFs were also analysed using 527 hidden Markov models constructed for several conserved protein families (PFAM v2.0) using HMMER⁴⁸. Families of paralogous genes were constructed by pairwise searches of proteins using FASTA. Matches that spanned at least 60% of the smaller of the protein pair were retained and visually inspected. A total of 94 paralogous gene families containing 293 genes were identified (Fig. 1).

Identification of membrane-spanning domains (MSDs). TopPred⁴⁹ was used to identify potential MSDs in proteins. A total of 526 proteins containing at least one putative MSD were identified, of which 183 were predicted to have more than one MSD. The presence of signal peptides and the probable position of a cleavage site in secreted proteins were detected using Signal-P as described²³; 189 proteins were predicted to have a signal peptide. Lipoproteins were identified by scanning for a lipobox in the first 30 amino acids of every protein. A consensus sequence relaxed from that used for *H. pylori*²³ was defined for the purpose of this search based on known or putative *B. burgdorferi* lipoprotein consensus sequences.

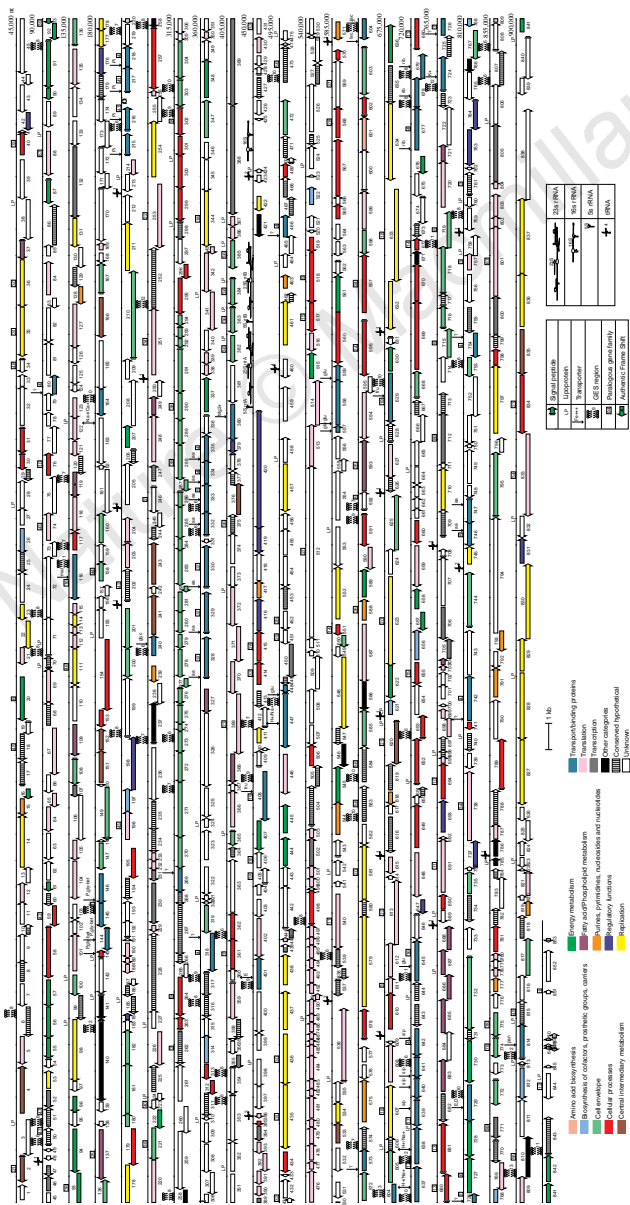
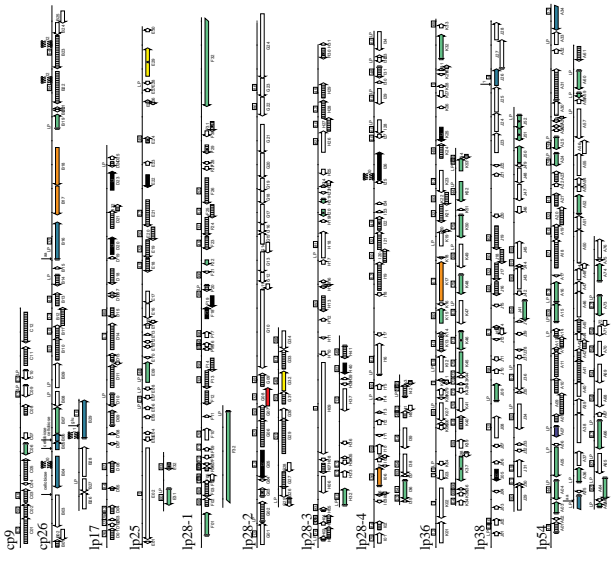
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Correspondence and requests for materials should be sent to C.M.F. (e-mail: gbb@tigr.org). The annotated genome sequence and gene family alignments are available on the World-Wide Web at <http://www.tigr.org/tldb/mdb/bbdb/bbdb.html>. Sequences have been deposited with GenBank under the following accession numbers: AE00783 (chromosome); AE00784 (lp28-3); AE00785 (lp25); AE00786 (lp28-2); AE00787 (lp38); AE00788 (lp36); AE00789 (lp28-4); AE00790 (lp54); AE00791 (cp9); AE00792 (cp26); AE00793 (lp17); and AE00794 (lp28-1).



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Table 2. Identification of *B. burgdorferi* genes

| BB# | Identification (Species) | Accession | Gene | Product | Accession | Product | Accession | Product |
|--|---|-----------|--------|---|-----------|---------|---|---------|
| Amino acid biosynthesis | | | | | | | | |
| <i>Serine family</i> | | | | | | | | |
| BB601 | serine OMTase (glyA) (Eo) | 73 | BBH20 | outer membrane porin (omp23), put (Eb) | 74 | BB291 | flg basal-body rod prt (flgB) (Eb) | 100 |
| Biosynthesis of acetate, prosthete group, and carrier | | | | | | | | |
| <i>Folate</i> | | | | | | | | |
| BB605 | methyltetrahydrofolate DHase (fdD) (Ee) | 61 | BBH21 | outer membrane porin (omp23), put (Eb) | 74 | BB292 | flg basal-body rod prt (flgC) (Eb) | 100 |
| <i>Heme and porphyrin</i> | | | | | | | | |
| BB197 | protoporphyrinogen oxidase q put (Ee) | 58 | BBE09 | prt p23 (Eb) | 93 | BB294 | flg basal-body rod prt (flgE) (Eb) | 100 |
| BB468 | oxygen-independent coproporphyrinogen III oxidase, put (Ee) | 51 | BBE19 | outer surface prt C (ospC) (Eb) | 100 | BB295 | flg basal-body rod prt (flgF) (Eb) | 100 |
| <i>Monoamine and ubiquinone</i> | | | | | | | | |
| BB514 | cotransyl-LTPase (copE) (Eo) | 57 | BBE07 | outer surface prt, put (Eb) | 45 | BB274 | flg biosyn prt (flgG) (Eb) | 100 |
| <i>Penicillins</i> | | | | | | | | |
| BB512 | penicillinase (pbp1b) (Eo) | 53 | BBE10 | glutamate racemase (murI) (Eo) | 56 | BB275 | flg biosyn prt (flgH) (Eb) | 100 |
| <i>Pyridoxine</i> | | | | | | | | |
| BB768 | pyridoxal kinase (pdxK) (So) | 47 | BBE25 | N-acetylmethyl-L-alanine amide q put (Ee) | 53 | BB276 | flg biosyn prt (flgI) (Eb) | 100 |
| <i>Thiamine</i> | | | | | | | | |
| BB621 | 4-methyl-5-(b-CH ₂ thiazole)nonoF biosyn prt (thiJ) (Eo) | 58 | BBE26 | N-acetylmethyl-L-alanine amide q put (Ee) | 53 | BB147 | flg filament 41 kDa core prt (flgE) (Eb) | 100 |
| <i>Pyridine nucleotides</i> | | | | | | | | |
| BB522 | NH ₂ dep NAD+ Sase (Pc) | 65 | BBE27 | penicillin-BP (pbp3) (Ng) | 52 | BB668 | flg filament outer layer prt (flgA) (Eb) | 99 |
| Cell envelope | | | | | | | | |
| <i>Membranes, lipoproteins, and porins</i> | | | | | | | | |
| BB382 | basal membrane prt B (bmpB) (Eb) | 100 | BBE28 | penicillin-BP (pbp1) (Nm) | 52 | BB294 | flg hook assembly prt (flgD) (Eb) | 100 |
| BB383 | basal membrane prt A (bmpA) (Eb) | 100 | BBE29 | penicillin-BP (pbp2) (Hi) | 52 | BB295 | flg hook prt (flgE) (Eb) | 100 |
| BB384 | basal membrane prt C (bmpC) (Eb) | 100 | BBE30 | phospho-N-acetylmethyl-pentapeptidease (mraY) (Eb) | 100 | BB181 | flg hook-associated prt (flgK) (Eb) | 99 |
| BB385 | basal membrane prt D (bmpD) (Eb) | 100 | BBE31 | rod shape-determining prt (mreB-1) (Eo) | 73 | BB149 | flg hook-associated prt 2 (flgJ) (Eb) | 99 |
| BB108 | basal membrane prt (Tp) | 50 | BBE32 | rod shape-determining prt (mreB-2) (Hi) | 61 | BB132 | flg hook-associated prt 3 (flgL) (Eb) | 99 |
| BB319 | exported prt (trnS:b) (Tp) | 50 | BBE33 | serinotype D-ala-D-ala CPDase (dal) (Hi) | 55 | BB275 | flg hook-basal body complex prt (flgC) (Eb) | 58 |
| BB347 | fibronectin fibrinogen-BP, put (Sp) | 53 | BB472 | UDP-N-acetyl-1-carboxymethylase (murA) (Eo) | 59 | BB292 | flg hook-basal body complex prt (flgE) (Eb) | 100 |
| BB442 | inner membrane prt (Hi) | 63 | BBE36 | UDP-N-acetylmethyl-L-alanine DHase (murE) (Ee) | 55 | BB293 | flg motor rotation prt B (mreB) (Eb) | 100 |
| BB395 | lipoprotein LA7 (Eb) | 100 | BBE37 | UDP-N-acetylmethyl-L-alanine DHase (murE) (Hi) | 53 | BB294 | flg motor rotation prt A (mreA) (Eb) | 100 |
| BB605 | membrane-associated prt p23 (Eb) | 100 | BBE38 | UDP-N-acetylmethyl-L-glutamate DHase (murD) (Ee) | 52 | BB277 | flg motor-attach prt (flgM) (Eb) | 100 |
| BB753 | membrane opening prt, put (So) | 49 | BBE39 | UDP-N-acetylmethyl-L-glutamate-2,3-diaminopimelate DHase (murF) (Eb) | 100 | BB278 | flg motor-attach prt (flgN) (Eb) | 100 |
| BB795 | outer membrane prt (Ng) | 48 | BBE40 | UDP-N-acetylmethyl-L-glutamate-2,3-diaminopimelate DHase (murF) (Hi) | 53 | BB221 | flg motor-attach prt (flgO-1) (Tq) | 54 |
| BB167 | outer membrane prt (trnS) (Tp) | 48 | BBE41 | UDP-N-acetylmethyl-L-glutamate-2,3-diaminopimelate DHase (murF) (Eb) | 100 | BB290 | flg motor-attach prt (flgO-2) (Eb) | 100 |
| BB735 | rare lipoprt A (flpA) (Hi) | 53 | BBE42 | UDP-N-acetyl-coenzyme-N-acetylmethyl-pentapeptide q pyrophosphoryl-uracil-dependent NAATase (murG) (Ee) | 58 | BB272 | flg P-ring prt (flg) (A,F) | 51 |
| BB10 | surface-coated membrane prt 1 (flp1) (Hi) | 45 | BBE43 | antigen, R55, put (Eb) | 48 | BB279 | flg prt (flg) (Eb) | 100 |
| BB158 | ss prt (Eb) | 60 | BBE44 | antigen, R55, put (Eb) | 48 | BB282 | flg prt (flg) (Eb) | 99 |
| <i>Surface polysaccharides, lipopolysaccharides and antigens</i> | | | | | | | | |
| BB424 | decorin BP A (dcpA) (Eb) | 94 | BBE45 | antigen, R55, put (Eb) | 48 | BB283 | flg prt (flg) (Eb) | 100 |
| BB425 | decorin BP B (dcpB) (Eb) | 100 | BBE46 | antigen, R55, put (Eb) | 48 | BB284 | flg prt (flg) (Eb) | 100 |
| BB436 | lipoprotein (Eb) | 54 | BBE47 | antigen, R55, put (Eb) | 52 | BB285 | flg prt (flg) (Eb) | 100 |
| BB459 | lipoprotein (Eb) | 100 | BBE48 | antigen, R55, put (Eb) | 49 | BB286 | flg prt (flg) (Eb) | 100 |
| BB462 | lipoprotein (Eb) | 100 | BBE49 | antigen, R55, put (Eb) | 49 | BB287 | flg prt (flg) (Eb) | 100 |
| BB474 | outer membrane porin (omp23) (Eb) | 100 | BBE50 | immunogenic prt P37 (Eb) | 99 | BB288 | flg prt (flg) (Eb) | 100 |
| BB415 | outer surface prt A (ospA) (Eb) | 99 | BBE51 | immunogenic prt P37, put (Eb) | 97 | BB289 | flg prt (flg) (Eb) | 100 |
| BB416 | outer surface prt B (ospB) (Eb) | 99 | BBE52 | immunogenic prt P37, put (Eb) | 71 | BB290 | flg prt (flg) (Eb) | 100 |
| BB403 | outer membrane prt (Eb) | 100 | BBE53 | immunogenic prt P37, put (Eb) | 49 | BB291 | flg prt (flg) (Eb) | 100 |
| BB452 | outer membrane prt (Eb) | 100 | BBE54 | immunogenic prt P37, put (Eb) | 63 | BB292 | flg prt (flg) (Eb) | 100 |
| BB405 | s1 prt (Eb) | 100 | BBE55 | immunogenic prt P37, put (Eb) | 49 | BB293 | flg prt (flg) (Eb) | 100 |
| BB404 | s2 prt (Eb) | 100 | BBE56 | immunogenic prt P37, put (Eb) | 49 | BB294 | flg prt (flg) (Eb) | 100 |
| BB460 | surface lipoprt P27 (Eb) | 81 | BBE57 | immunogenic prt P37, put (Eb) | 49 | BB295 | flg prt (flg) (Eb) | 100 |
| <i>Cell division</i> | | | | | | | | |
| BB409 | outer surface prt D (ospD) (Eb) | 100 | BBE58 | immunogenic prt P37, put (Eb) | 49 | BB296 | flg prt (flg) (Eb) | 100 |
| BB450 | outer membrane prt, put (Eb) | 61 | BBE59 | immunogenic prt P37, put (Eb) | 63 | BB297 | flg prt (flg) (Eb) | 100 |
| BB451 | vbE1 prt, put (Eb) | 62 | BBE60 | immunogenic prt P37, put (Eb) | 49 | BB298 | flg prt (flg) (Eb) | 100 |
| BB452 | vbE1 prt, put (Eb) | 55 | BBE61 | immunogenic prt P37, put (Eb) | 49 | BB299 | flg prt (flg) (Eb) | 100 |
| Cellular processes | | | | | | | | |
| <i>General</i> | | | | | | | | |
| BB424 | decorin BP A (dcpA) (Eb) | 94 | BBE62 | immunogenic prt P37, put (Eb) | 49 | BB300 | flg prt (flg) (Eb) | 100 |
| BB425 | decorin BP B (dcpB) (Eb) | 100 | BBE63 | immunogenic prt P37, put (Eb) | 49 | BB301 | flg prt (flg) (Eb) | 100 |
| BB436 | lipoprotein (Eb) | 54 | BBE64 | immunogenic prt P37, put (Eb) | 49 | BB302 | flg prt (flg) (Eb) | 100 |
| BB459 | lipoprotein (Eb) | 100 | BBE65 | immunogenic prt P37, put (Eb) | 49 | BB303 | flg prt (flg) (Eb) | 100 |
| BB462 | lipoprotein (Eb) | 100 | BBE66 | immunogenic prt P37, put (Eb) | 49 | BB304 | flg prt (flg) (Eb) | 100 |
| BB474 | outer membrane porin (omp23) (Eb) | 100 | BBE67 | immunogenic prt P37, put (Eb) | 49 | BB305 | flg prt (flg) (Eb) | 100 |
| BB415 | outer surface prt A (ospA) (Eb) | 99 | BBE68 | immunogenic prt P37, put (Eb) | 49 | BB306 | flg prt (flg) (Eb) | 100 |
| BB416 | outer surface prt B (ospB) (Eb) | 99 | BBE69 | immunogenic prt P37, put (Eb) | 49 | BB307 | flg prt (flg) (Eb) | 100 |
| BB403 | outer membrane prt (Eb) | 100 | BBE70 | immunogenic prt P37, put (Eb) | 49 | BB308 | flg prt (flg) (Eb) | 100 |
| BB452 | outer membrane prt (Eb) | 100 | BBE71 | immunogenic prt P37, put (Eb) | 49 | BB309 | flg prt (flg) (Eb) | 100 |
| BB405 | s1 prt (Eb) | 100 | BBE72 | immunogenic prt P37, put (Eb) | 49 | BB310 | flg prt (flg) (Eb) | 100 |
| BB404 | s2 prt (Eb) | 100 | BBE73 | immunogenic prt P37, put (Eb) | 49 | BB311 | flg prt (flg) (Eb) | 100 |
| BB460 | surface lipoprt P27 (Eb) | 81 | BBE74 | immunogenic prt P37, put (Eb) | 49 | BB312 | flg prt (flg) (Eb) | 100 |
| <i>Surface polysaccharides, lipopolysaccharides and antigens</i> | | | | | | | | |
| BB424 | decorin BP A (dcpA) (Eb) | 94 | BBE75 | immunogenic prt P37, put (Eb) | 49 | BB313 | flg prt (flg) (Eb) | 100 |
| BB425 | decorin BP B (dcpB) (Eb) | 100 | BBE76 | immunogenic prt P37, put (Eb) | 49 | BB314 | flg prt (flg) (Eb) | 100 |
| BB436 | lipoprotein (Eb) | 54 | BBE77 | immunogenic prt P37, put (Eb) | 49 | BB315 | flg prt (flg) (Eb) | 100 |
| BB459 | lipoprotein (Eb) | 100 | BBE78 | immunogenic prt P37, put (Eb) | 49 | BB316 | flg prt (flg) (Eb) | 100 |
| BB462 | lipoprotein (Eb) | 100 | BBE79 | immunogenic prt P37, put (Eb) | 49 | BB317 | flg prt (flg) (Eb) | 100 |
| BB474 | outer membrane porin (omp23) (Eb) | 100 | BBE80 | immunogenic prt P37, put (Eb) | 49 | BB318 | flg prt (flg) (Eb) | 100 |
| BB415 | outer surface prt A (ospA) (Eb) | 99 | BBE81 | immunogenic prt P37, put (Eb) | 49 | BB319 | flg prt (flg) (Eb) | 100 |
| BB416 | outer surface prt B (ospB) (Eb) | 99 | BBE82 | immunogenic prt P37, put (Eb) | 49 | BB320 | flg prt (flg) (Eb) | 100 |
| BB403 | outer membrane prt (Eb) | 100 | BBE83 | immunogenic prt P37, put (Eb) | 49 | BB321 | flg prt (flg) (Eb) | 100 |
| BB452 | outer membrane prt (Eb) | 100 | BBE84 | immunogenic prt P37, put (Eb) | 49 | BB322 | flg prt (flg) (Eb) | 100 |
| BB405 | s1 prt (Eb) | 100 | BBE85 | immunogenic prt P37, put (Eb) | 49 | BB323 | flg prt (flg) (Eb) | 100 |
| BB404 | s2 prt (Eb) | 100 | BBE86 | immunogenic prt P37, put (Eb) | 49 | BB324 | flg prt (flg) (Eb) | 100 |
| BB460 | surface lipoprt P27 (Eb) | 81 | BBE87 | immunogenic prt P37, put (Eb) | 49 | BB325 | flg prt (flg) (Eb) | 100 |
| Cellular processes | | | | | | | | |
| <i>General</i> | | | | | | | | |
| BB424 | decorin BP A (dcpA) (Eb) | 94 | BBE88 | immunogenic prt P37, put (Eb) | 49 | BB326 | flg prt (flg) (Eb) | 100 |
| BB425 | decorin BP B (dcpB) (Eb) | 100 | BBE89 | immunogenic prt P37, put (Eb) | 49 | BB327 | flg prt (flg) (Eb) | 100 |
| BB436 | lipoprotein (Eb) | 54 | BBE90 | immunogenic prt P37, put (Eb) | 49 | BB328 | flg prt (flg) (Eb) | 100 |
| BB459 | lipoprotein (Eb) | 100 | BBE91 | immunogenic prt P37, put (Eb) | 49 | BB329 | flg prt (flg) (Eb) | 100 |
| BB462 | lipoprotein (Eb) | 100 | BBE92 | immunogenic prt P37, put (Eb) | 49 | BB330 | flg prt (flg) (Eb) | 100 |
| BB474 | outer membrane porin (omp23) (Eb) | 100 | BBE93 | immunogenic prt P37, put (Eb) | 49 | BB331 | flg prt (flg) (Eb) | 100 |
| BB415 | outer surface prt A (ospA) (Eb) | 99 | BBE94 | immunogenic prt P37, put (Eb) | 49 | BB332 | flg prt (flg) (Eb) | 100 |
| BB416 | outer surface prt B (ospB) (Eb) | 99 | BBE95 | immunogenic prt P37, put (Eb) | 49 | BB333 | flg prt (flg) (Eb) | 100 |
| BB403 | outer membrane prt (Eb) | 100 | BBE96 | immunogenic prt P37, put (Eb) | 49 | BB334 | flg prt (flg) (Eb) | 100 |
| BB452 | outer membrane prt (Eb) | 100 | BBE97 | immunogenic prt P37, put (Eb) | 49 | BB335 | flg prt (flg) (Eb) | 100 |
| BB405 | s1 prt (Eb) | 100 | BBE98 | immunogenic prt P37, put (Eb) | 49 | BB336 | flg prt (flg) (Eb) | 100 |
| BB404 | s2 prt (Eb) | 100 | BBE99 | immunogenic prt P37, put (Eb) | 49 | BB337 | flg prt (flg) (Eb) | 100 |
| BB460 | surface lipoprt P27 (Eb) | 81 | BBE100 | immunogenic prt P37, put (Eb) | 49 | BB338 | flg prt (flg) (Eb) | 100 |
| Cellular processes | | | | | | | | |
| <i>General</i> | | | | | | | | |
| BB424 | decorin BP A (dcpA) (Eb) | 94 | BBE101 | immunogenic prt P37, put (Eb) | 49 | BB339 | flg prt (flg) (Eb) | 100 |
| BB425 | decorin BP B (dcpB) (Eb) | 100 | BBE102 | immunogenic prt P37, put (Eb) | 49 | BB340 | flg prt (flg) (Eb) | 100 |
| BB436 | lipoprotein (Eb) | 54 | BBE103 | immunogenic prt P37, put (Eb) | 49 | BB341 | flg prt (flg) (Eb) | 100 |
| BB459 | lipoprotein (Eb) | 100 | BBE104 | immunogenic prt P37, put (Eb) | 49 | BB342 | flg prt (flg) (Eb) | 100 |
| BB462 | lipoprotein (Eb) | 100 | BBE105 | immunogenic prt P37, put (Eb) | 49 | BB343 | flg prt (flg) (Eb) | 100 |
| BB474 | outer membrane porin (omp23) (Eb) | 100 | BBE106 | immunogenic prt P37, put (Eb) | 49 | BB344 | flg prt (flg) (Eb) | 100 |
| BB415 | outer surface prt A (ospA) (Eb) | 99 | BBE107 | immunogenic prt P37, put (Eb) | 49 | BB345 | flg prt (flg) (Eb) | 100 |
| BB416 | outer surface prt B (ospB) (Eb) | 99 | BBE108 | immunogenic prt P37, put (Eb) | 49 | BB346 | flg prt (flg) (Eb) | 100 |
| BB403 | outer membrane prt (Eb) | 100 | BBE109 | immunogenic prt P37, put (Eb) | 49 | BB347 | flg prt (flg) (Eb) | 100 |
| BB452 | outer membrane prt (Eb) | 100 | BBE110 | immunogenic prt P37, put (Eb) | 49 | BB348 | flg prt (flg) (Eb) | 100 |
| BB405 | s1 prt (Eb) | 100 | BBE111 | immunogenic prt P37, put (Eb) | 49 | BB349 | flg prt (flg) (Eb) | 100 |
| BB404 | s2 prt (Eb) | 100 | BBE112 | immunogenic prt P37, put (Eb) | 49 | BB350 | flg prt (flg) (Eb) | 100 |
| BB460 | surface lipoprt P27 (Eb) | 81 | BBE113 | immunogenic prt P37, put (Eb) | 49 | BB351 | flg prt (flg) (Eb) | 100 |
| Cellular processes | | | | | | | | |
| <i>General</i> | | | | | | | | |
| BB424 | decorin BP A (dcpA) (Eb) | 94 | BBE114 | immunogenic prt P37, put (Eb) | 49 | BB352 | flg prt (flg) (Eb) | 100 |
| BB425 | decorin BP B (dcpB) (Eb) | 100 | BBE115 | immunogenic prt P37, put (Eb) | 49 | BB353 | flg prt (flg) (Eb) | 100 |
| BB436 | lipoprotein (Eb) | 54 | BBE116 | immunogenic prt P37, put (Eb) | 49 | BB354 | flg prt (flg) (Eb) | 100 |
| BB459 | lipoprotein (Eb) | 100 | BBE117 | immunogenic prt P37, put (Eb) | 49 | BB355 | flg prt (flg) (Eb) | 100 |
| BB462 | lipoprotein (Eb) | 100 | BBE118 | immunogenic prt P37, put (Eb) | 49 | BB356 | flg prt (flg) (Eb) | 100 |
| BB474 | outer membrane porin (omp23) (Eb) | 100 | BBE119 | immunogenic prt P37, put (Eb) | 49 | BB357 | flg prt (flg) (Eb) | 100 |
| BB415 | outer surface prt A (ospA) (Eb) | 99 | BBE120 | immunogenic prt P37, put (Eb) | 49 | BB358 | flg prt (flg) (Eb) | 100 |
| BB416 | outer surface prt B (ospB) (Eb) | 99 | BBE121 | immunogenic prt P37, put (Eb) | 49 | BB359 | flg prt (flg) (Eb) | 100 |
| BB403 | outer membrane prt (Eb) | 100 | BBE122 | immunogenic prt P37, put (Eb) | 49 | BB360 | flg prt (flg) (Eb) | 100 |
| BB452 | outer membrane prt (Eb) | 100 | BBE123 | immunogenic prt P37, put (Eb) | 49 | BB361 | flg prt (flg) (Eb) | 100 |
| BB405 | s1 prt (Eb) | 100 | BBE124 | immunogenic prt P37, put (Eb) | 49 | BB362 | flg prt (flg) (Eb) | 100 |
| BB404 | s2 prt (Eb) | 1 | | | | | | |

| | | | | | |
|--------|--|--|-------|--|-----|
| lp28-2 | | <i>ATP-proton motive force interconversion</i> | BB575 | CTP Sase (pyrG) {Mj} | 71 |
| BBG08 | stage 0 sporulation prt J (spoOJ) {Bb} | 66 | BB094 | V-type ATPase, sub A (atpA) {Mb} | 64 |
| | | | BB093 | V-type ATPase, sub B (atpB) {Mb} | 62 |
| | | | BB092 | V-type ATPase, sub D (atpD) {Mj} | 51 |
| | | | BB096 | V-type ATPase, sub E (atpE) {Mj} | 54 |
| | | | BB091 | V-type ATPase, sub I (atpI) {Eh} | 53 |
| | | | BB090 | V-type ATPase, sub K (atpK) {Mj} | 54 |
| | | <i>Electron transport</i> | | | |
| | | | BB061 | thioredoxin (trxA) {Ec} | 59 |
| | | | BB515 | thioredoxin RDase (trxB) {Bb} | 99 |
| | | <i>Fermentation</i> | | | |
| | | | BB622 | acetate kinase (ackA) {Ec} | 63 |
| | | | BB589 | P AcTase (pta) {Tt} | 65 |
| | | <i>Glycolysis</i> | | | |
| | | | BB337 | enolase (eno) {Bs} | 79 |
| | | | BB445 | fructose-bisP aldolase (fba) {Ec} | 80 |
| | | | BB730 | glucose-6-P isomerase (pgi) {Pf} | 62 |
| | | | BB057 | glyceraldehyde 3-P DHase (gap) {Bb} | 99 |
| | | | BB630 | 1-phosphofructoKase (fruK) {Hi} | 52 |
| | | | BB056 | phosphoglycerate Kase (pgk) {Bb} | 99 |
| | | | BB658 | phosphoglycerate mutase (gpmA) {Ec} | 79 |
| | | | BB348 | pyruvate Kase (pyk) {Bs} | 62 |
| | | | BB727 | pyroP-fructose 6-P 1-PPTase (pfk) {Eh} | 65 |
| | | | BB020 | pyroP-fructose 6-P 1-PPTase, sub (pfpB) {Bb} | 100 |
| | | | BB055 | trioseP isomerase {Bb} | 100 |
| | | <i>Pentose phosphate pathway</i> | | | |
| | | | BB222 | glucose-6-P 1-DHase, put {As} | 48 |
| | | | BB636 | glucose-6-P 1-DHase (zwf) {Hi} | 64 |
| | | | BB561 | phosphogluconate DHase (gnd) {Sd} | 71 |
| | | | BB657 | ribose 5-P isomerase (rpi) {Mj} | 61 |
| | | <i>Sugars</i> | | | |
| | | | BB407 | mannose-6-P isomerase (manA) {Ec} | 54 |
| | | | BB444 | nucleotide sugar epimerase {Vc} | 69 |
| | | | BB676 | phosphoglycolate PCase (gph) {Hi} | 50 |
| | | | BB207 | UTP-glucose-1-P uridylylTase (gtaB) {Bs} | 63 |
| | | | BB545 | xylulokinase (xylB) {Bs} | 43 |
| | | Fatty acid and phospholipid metabolism | | | |
| | | <i>General</i> | | | |
| | | | BB037 | 1-acyl-sn-glycerol-3-P AcTase (plsC) {Bb} | 100 |
| | | | BB685 | 3-OH-3-methylglutaryl-CoA RDase (mvaA) {Pm} | 52 |
| | | | BB683 | 3-OH-3-methylglutaryl-CoA Sase (At) | 53 |
| | | | BB109 | Ac-CoA C-AcTase (fadA) {Hi} | 67 |
| | | | BB704 | acyl carrier prt {Syn} | 65 |
| | | | BB721 | CDP-diaclylglycerol-glycerol-3-P 3-phosphatidylTase {Bs} | 55 |
| | | | BB327 | glycerol-3-P O-acylTase, put {So} | 50 |
| | | | BB368 | glycerol-3-P DHase, NAD(P) ⁺ (gpsA) {Bs} | 54 |
| | | | BB137 | long-chain-fatty-acid CoA ligase {Syn} | 54 |
| | | | BB593 | long-chain-fatty-acid CoA ligase {Syn} | 56 |
| | | | BB688 | mevalonate Kase {Mj} | 51 |
| | | | BB686 | mevalonate pyroP DCase {Sc} | 52 |
| | | | BB119 | phosphatidate cytidylTase (cdsA), AFS{Ec} | 61 |
| | | | BB249 | phosphatidylTase {Hp} | 52 |
| | | | BB687 | phosphomevalonate Kase, put {Sc} | 53 |
| | | Purines, pyrimidines, nucleosides, nucleotides | | | |
| | | <i>Nucleotide and nucleoside interconversion</i> | | | |
| | | | BB417 | adenylate kinase (adk) {Bs} | 64 |
| | | | BB128 | cytidylate kinase (cmk-1) {Bs} | 58 |
| | | | BB819 | cytidylate kinase (cmk-2) {Mj} | 57 |
| | | | BB463 | nucleoside-diP kinase (ndk) {Bs} | 70 |
| | | | BB793 | thymidylate kinase (tmk) {Mj} | 59 |
| | | | BB571 | uridylylate kinase (smbA) {Mj} | 54 |
| | | <i>Purine ribonucleotide biosynthesis</i> | | | |
| | | | BB544 | phosphoribosyl pyroP Sase (prs) {Mp} | 59 |
| | | <i>cp26</i> | | | |
| | | | BBB18 | GMP Sase (guaA) {Bb} | 100 |
| | | | BBB17 | IMP DHase (guaB) {Bb} | 100 |
| | | <i>Pyrimidine ribonucleotide biosynthesis</i> | | | |
| | | | BB575 | CTP Sase (pyrG) {Mj} | 71 |
| | | <i>Salvage of nucleosides and nucleotides</i> | | | |
| | | | BB777 | adenine phosphoribosylTase (apt) {Ta} | 63 |
| | | | BB618 | cytidine deaminase (cdd) {Mp} | 61 |
| | | | BB239 | deoxyguanosine/deoxyadenosine kinase(I) sub 2 (dck) {La} | 59 |
| | | | BB375 | pfs prt (pfs-1) {Ec} | 64 |
| | | | BB588 | pfs prt (pfs-2) {Hi} | 59 |
| | | | BB791 | thymidine kinase (tdk) {Bs} | 47 |
| | | | BB015 | uridine kinase (udk) {Bb} | 100 |
| | | <i>Chaperones</i> | | | |
| | | | BB741 | chaperonin (groES) {Pg} | 77 |
| | | | BB602 | chaperonin, put {Cb} | 72 |
| | | | BB519 | grpE prt (grpE) {Bb} | 100 |
| | | | BB295 | heat shock prt (hslU) {Bb} | 100 |
| | | | BB296 | heat shock prt (hslV) {Bb} | 100 |
| | | | BB649 | heat shock prt (groEL) {Bb} | 100 |
| | | | BB517 | heat shock prt (dnaJ-1) {Bb} | 100 |
| | | | BB655 | heat shock prt (dnaJ-2) {Ca} | 59 |
| | | | BB264 | heat shock prt 70 (dnaK-1) {Bb} | 61 |
| | | | BB518 | heat shock prt 70 (dnaK-2) {Bb} | 100 |
| | | | BB560 | heat shock prt 90 (htpG) {Bb} | 100 |
| | | <i>Detoxification</i> | | | |
| | | | BB153 | superoxide dismutase (sodA) {Hi} | 68 |
| | | | BB690 | neutrophil activating prt (napA) {Hi} | 57 |
| | | | BB179 | thiophene and furan oxidation prt (thdF) {Bb} | 100 |
| | | <i>Protein and peptide secretion</i> | | | |
| | | | BB154 | preprt translocase sub (secA) {Bb} | 100 |
| | | | BB395 | preprt translocase sub (secE) {Bl} | 62 |
| | | | BB498 | preprt translocase sub (secY) {Sc} | 64 |
| | | | BB362 | prolipopt diacylglyceryl Tase (lgt) {Ec} | 56 |
| | | | BB652 | prt-export membrane prt (secD) {Ec} | 63 |
| | | | BB653 | prt-export membrane prt (secF) {Hi} | 63 |
| | | | BB030 | signal peptidase I (lepB-1) {Bs} | 51 |
| | | | BB031 | signal peptidase I (lepB-2) {Syn} | 57 |
| | | | BB263 | signal peptidase I (lepB-3) {St} | 57 |
| | | | BB469 | signal peptidase II (lsp) {Sc} | 60 |
| | | | BB694 | signal recognition particle prt (fth) {Bs} | 70 |
| | | | BB610 | trigger factor (tig) {Hi} | 50 |
| | | <i>Transformation</i> | | | |
| | | | BB591 | competence locus E, put {Bs} | 54 |
| | | | BB798 | competence prt F, put {Hi} | 52 |
| | | Central intermediary metabolism | | | |
| | | <i>General</i> | | | |
| | | | BB241 | glycerol kinase (glpK) {Ec} | 74 |
| | | | BB243 | glycerol-3-P DHase, anaerobic (glpA) {Hi} | 52 |
| | | | BB376 | SAM Sase (metK) {Bs} | 72 |
| | | <i>Amino sugars</i> | | | |
| | | | BB152 | glucosamine-6-P isomerase (nagB) {Hi} | 79 |
| | | | BB151 | N-Acglucosamine-6-P deAcase (nagA) {Hi} | 54 |
| | | <i>Degradation of polysaccharides</i> | | | |
| | | | BB620 | -glucosidase, put {Syn} | 58 |
| | | | BB002 | -N-Achexosaminidase, put {As} | 54 |
| | | <i>Phosphorus compounds</i> | | | |
| | | | BB533 | phnP prt (phnP) {Ec} | 48 |
| | | <i>Polysaccharides - (cytoplasmic)</i> | | | |
| | | | BB166 | 4- -glucanoTase (malQ) {Syn} | 55 |
| | | | BB004 | phosphoglucomutase (femD) {Mj} | 52 |
| | | | BB835 | phosphomannomutase (cpsG) {Hi} | 57 |
| | | Energy metabolism | | | |
| | | <i>Aerobic</i> | | | |
| | | | BB728 | NADH oxidase, water-forming (nox) {Sh} | 59 |
| | | <i>Amino acids and amines</i> | | | |
| | | | BB841 | arginine deiminase (arcA) {Cp} | 75 |
| | | | BB842 | ornithine carbamoylTase (arcB) {Ng} | 74 |
| | | <i>Anaerobic</i> | | | |
| | | | BB016 | glpE prt (glpE) {Hi} | 53 |
| | | | BB087 | L-lactate DHase (ldh) {Bs} | 72 |
| | | <i>Salvage of nucleosides and nucleotides</i> | | | |
| | | | BB647 | ferric uptake regulation prt (fur) {Sp} | 48 |
| | | | BB198 | guanosine-3',5'-bis(diP) 3'-pyrophosphohydrolase (spoT) {Ec} | 61 |
| | | | BB737 | histidine phosphoKase/PPase, put {Ml} | 49 |
| | | | BB176 | methanol DHase regulator (moxR) {Bb} | 99 |
| | | | BB416 | pheromone shutdown prt (traB) {Ef} | 61 |
| | | | BB042 | P transport system regulatory prt (phoU) {Pa} | 57 |
| | | | BB379 | prt Kase C1 inhibitor (pkcl) {Bb} | 100 |
| | | | BB419 | response regulatory prt (rrp-1) {Syn} | 57 |
| | | | BB763 | response regulatory prt (rrp-2) {Ec} | 67 |
| | | | BB764 | sensory transduction histidine Kase, put {Bs} | 60 |
| | | | BB420 | sensory transduction histidine Kase, put {Syn} | 61 |
| | | | BB693 | xyllose operon regulatory prt (xylR-1) {Th.} | 48 |
| | | | BB831 | xyllose operon regulatory prt (xylR-2) {Syn} | 51 |
| | | <i>Regulatory functions</i> | | | |
| | | <i>General</i> | | | |
| | | | BB184 | carbon storage regulator (csrA) {Hi} | 63 |
| | | | BB647 | ferric uptake regulation prt (fur) {Sp} | 48 |
| | | | BB198 | guanosine-3',5'-bis(diP) 3'-pyrophosphohydrolase (spoT) {Ec} | 61 |
| | | | BB737 | histidine phosphoKase/PPase, put {Ml} | 49 |
| | | | BB176 | methanol DHase regulator (moxR) {Bb} | 99 |
| | | | BB416 | pheromone shutdown prt (traB) {Ef} | 61 |
| | | | BB042 | P transport system regulatory prt (phoU) {Pa} | 57 |
| | | | BB379 | prt Kase C1 inhibitor (pkcl) {Bb} | 100 |
| | | | BB419 | response regulatory prt (rrp-1) {Syn} | 57 |
| | | | BB763 | response regulatory prt (rrp-2) {Ec} | 67 |
| | | | BB764 | sensory transduction histidine Kase, put {Bs} | 60 |
| | | | BB420 | sensory transduction histidine Kase, put {Syn} | 61 |
| | | | BB693 | xyllose operon regulatory prt (xylR-1) {Th.} | 48 |
| | | | BB831 | xyllose operon regulatory prt (xylR-2) {Syn} | 51 |
| | | <i>Replication</i> | | | |
| | | <i>Degradation of DNA</i> | | | |
| | | | BB411 | endonuclease precursor (nucA) {As} | 53 |
| | | <i>DNA replication, restriction, modification, recombination, and repair</i> | | | |
| | | | BB422 | 3-methyladenine DNA glycosylase (mag) {At} | 56 |
| | | | BB827 | ATP-dep helicase (hrpA) {Ec} | 61 |
| | | | BB437 | chromosomal replication init prt (dnaA) {Bb} | 100 |
| | | | BB435 | DNA gyrase, sub A (gyrA) {Bs} | 67 |
| | | | BB436 | DNA gyrase, sub B (gyrB) {Bb} | 99 |
| | | | BB344 | DNA helicase (uvrD) {Ec} | 55 |
| | | | BB552 | DNA ligase (lig) {Ta} | 56 |
| | | | BB211 | DNA mismatch repair prt (mutL) {Hi} | 55 |
| | | | BB797 | DNA mismatch repair prt (mutS) {Hi} | 57 |
| | | | BB098 | DNA mismatch repair prt, put {Syn} | 51 |
| | | | BB548 | DNA polymerase I (polA) {Hi} | 61 |
| | | | BB579 | DNA polymerase III, sub (dnaE) {Ec} | 62 |
| | | | BB438 | DNA polymerase III, sub (dnaN) {Bb} | 100 |
| | | | BB461 | DNA polymerase III, sub / (dnaX) {Bs} | 61 |
| | | | BB710 | DNA primase (dnaG) {Bs} | 56 |
| | | | BB581 | DNA recombinase (recG) {Syn} | 60 |
| | | | BB828 | DNA topoisomerase I (topA) {Syn} | 64 |
| | | | BB035 | DNA topoisomerase IV (parC) {Bb} | 58 |
| | | | BB036 | DNA topoisomerase IV (parE) {Bb} | 56 |
| | | | BB745 | endonuclease III (nth) {Syn} | 59 |
| | | | BB837 | excinuclease ABC, sub A (uvrA) {Ec} | 4 |
| | | | BB836 | excinuclease ABC, sub B (uvrB) {Ec} | 71 |
| | | | BB457 | excinuclease ABC, sub C (uvrC) {Syn} | 57 |
| | | | BB534 | exodeoxyribonuclease III (exoA) {Bs} | 67 |
| | | | BB632 | exodeoxyribonuclease V, chain | |

| | | | | | | | |
|-------------------------------------|--|-----|---|-----|---|---|-----|
| | (recD) [Ec] | 54 | BB833 isoleucyl-tRNA Sase (ileS) [Sc] | 66 | BB703 ribosomal prt L32 (rpmF) [Bs] | 62 | |
| BB633 | exodeoxyribonuclease V, chain (recB) [Hi] | 51 | BB251 leucyl-tRNA Sase (leuS) [Bs] | 70 | BB396 ribosomal prt L33 (rpmG) [Bs] | 76 | |
| BB634 | exodeoxyribonuclease V, chain (recC) [Hi] | 51 | BB659 lysyl-tRNA Sase [Mj] | 54 | BB440 ribosomal prt L34 (rpmH) [Bb] | 100 | |
| BB829 | exonuclease SbcD (sbcD) [Ec] | 55 | BB587 methionyl-tRNA Sase (metG) [Sc] | 67 | BB189 ribosomal prt L35 (rpmI) [Ba] | 74 | |
| BB830 | exonuclease SbcC (sbcC) [Ec] | 52 | BB514 phenylalanyl-tRNA Sase, sub (pheT) [Bb] | 100 | BB499 ribosomal prt L36 (rpmJ) [Bs] | 89 | |
| BB177 | glucose-inhibited div prt B (gidB) [Bb] | 99 | BB513 phenylalanyl-tRNA Sase, sub (pheS) [Bb] | 100 | BB127 ribosomal prt S1 (rpsA) [Ec] | 55 | |
| BB178 | glucose-inhibited div prt A (gidA) [Bb] | 100 | BB402 prolyl-tRNA Sase (proS) [Sc] | 65 | BB123 ribosomal prt S2 (rpsB) [Pa] | 79 | |
| BB022 | Holliday junction DNA helicase (ruvB) [Bb] | 100 | BB226 seryl-tRNA Sase (serS) [Bs] | 62 | BB484 ribosomal prt S3 (rpsC) [Hi] | 71 | |
| BB023 | Holliday junction DNA helicase (ruvA) [Bb] | 100 | BB720 threonyl-tRNA Sase (thrZ) [Bs] | 67 | BB615 ribosomal prt S4 (rpsD) [Hi] | 63 | |
| BB014 | primosomal prt N (priA) [Bb] | 100 | BB005 tryptophanyl-tRNA Sase (trsA) [Cl] | 65 | BB495 ribosomal prt S5 (rpsE) [Bs] | 77 | |
| BB131 | recA prt (recA) [Bb] | 100 | BB370 tyrosyl-tRNA Sase (tyrS) [Bs] | 62 | BB115 ribosomal prt S6 (rpsF) [Os] | 50 | |
| BB607 | rep helicase, ss DNA-dep ATPase (rep) [Hi] | 61 | BB738 valyl-tRNA Sase (valS) [Bs] | 67 | BB386 ribosomal prt S7 (rpsG) [Sc] | 75 | |
| BB111 | replicative DNA helicase (dnaB) [Ec] | 58 | <i>Degradation of proteins, peptides, and glycopeptides</i> | | | BB492 ribosomal prt S8 (rpsH) [Syn] | 66 |
| BB114 | ss DNA-BP (ssb) [Syn] | 62 | BB608 aminoacyl-histidine dipeptidase (pepD) [Hi] | 55 | BB338 ribosomal prt S9 (rpsI) [Hi] | 71 | |
| BB254 | ss-DNA-specific exonuclease (recJ) [Hi] | 52 | BB366 aminopeptidase I (yscI) [Bb] | 100 | BB477 ribosomal prt S10 (rpsJ) [Bb] | 100 | |
| BB623 | transcription-repair coupling factor (mfd) [Hi] | 60 | BB069 aminopeptidase II [Bs] | 57 | BB501 ribosomal prt S11 (rpsK) [Hi] | 77 | |
| BB053 | uracil DNA glycosylase (ung) [Hi] | 68 | BB611 ATP-dep Clp protease proteolytic component (clpP-1) [Hi] | 79 | BB387 ribosomal prt S12 (rpsL) [An] | 89 | |
| <i>lp28-2</i> | | | BB757 ATP-dep Clp protease proteolytic component (clpP-2) [Hi] | 67 | BB500 ribosomal prt S13 (rpsM) [Op] | 76 | |
| BBG32 | replicative DNA helicase, put [Bs] | 59 | BB369 ATP-dep Clp protease, sub A (clpA) [Ec] | 56 | BB491 ribosomal prt S14 (rpsN) [Bs] | 72 | |
| <i>lp25</i> | | | BB612 ATP-dep Clp protease, sub X (clpX) [Ec] | 75 | BB804 ribosomal prt S15 (rpsO) [Ti] | 77 | |
| BBE29 | adenine specific DNA MTase, put [Hp] | 57 | BB834 ATP-dep Clp protease, sub C (clpC) [Pp] | 67 | BB695 ribosomal prt S16 (rpsP) [Bs] | 70 | |
| Transcription | | | BB253 ATP-dep protease LA (lon-1) [Bb] | 100 | BB487 ribosomal prt S17 (rpsQ) [Mc] | 76 | |
| <i>General</i> | | | BB613 ATP-dep protease LA (lon-2) [Hi] | 65 | BB113 ribosomal prt S18 (rpsR) [Bs] | 78 | |
| BB052 | spoU prt (spoU) [Ec] | 54 | BB359 carboxyl-terminal protease (ctp) [Syn] | 65 | BB482 ribosomal prt S19 (rpsS) [Bb] | 99 | |
| <i>Degradation of RNA</i> | | | BB203 Lambda CII stability-governing prt (hflK) [Ec] | 56 | BB233 ribosomal prt S20 (rpsT) [Bb] | 100 | |
| BB805 | polyribonucleotide nucleotidylTase (pnpA) [Bs] | 68 | BB204 Lambda CII stability-governing prt (hflC) [Ec] | 56 | BB256 ribosomal prt S21 (rpsU) [Mx] | 68 | |
| BB046 | ribonuclease H (rnhB) [Hi] | 66 | BB248 oligoendopeptidase F (pepF) [Li] | 58 | BB516 rRNA methylase (yacO) [Mc] | 66 | |
| BB705 | ribonuclease III (rnc) [Bs] | 62 | BB067 peptidase, put [Sc] | 56 | <i>tRNA modification</i> | | |
| BB441 | ribonuclease P prt component (rnpA) [Bb] | 100 | BB104 periplasmic serine protease DO (htrA) [Hi] | 60 | BB821 2-methylthio-N6-isopentyladenosine tRNA modification enzyme (miaA) [Ec] | 53 | |
| <i>DNA-dependent RNA polymerase</i> | | | BB430 proline dipeptidase (pepQ) [Hi] | 49 | BB084 AT (nifS) [Syn] | 61 | |
| BB502 | DNA-directed RNA polymerase (rpoA) [Bs] | 64 | BB769 sialoglycoprotease (gcp) [Hi] | 60 | BB343 glu-tRNA amidoTase, sub C (gatC) [Bs] | 56 | |
| BB389 | DNA-directed RNA polymerase (rpoB) [Bb] | 97 | BB627 vacuolar X-prolyl dipeptidyl aminopeptidase I (pepX) [Ml] | 55 | BB341 glu-tRNA amidoTase, sub B (gatB) [Bs] | 63 | |
| BB388 | DNA-directed RNA polymerase (rpoC) [Ec] | 71 | <i>Nucleoproteins</i> | | | BB342 glu-tRNA amidoTase, sub A (gatA) [Bs] | 61 |
| BB771 | RNA polymerase sigma factor (rpoS) [Pa] | 61 | BB232 hbbU prt [Bb] | 100 | BB064 methionyl-tRNA formylTase (fmt) [Ec] | 56 | |
| BB712 | RNA polymerase sigma-70 factor (rpoD) [Bb] | 100 | <i>Protein modification</i> | | | BB787 peptidyl-tRNA hydrolase (pth) [Bb] | 100 |
| BB450 | RNA polymerase sigma-54 factor (ntrA) [Av] | 57 | BB105 methionine aminopeptidase (map) [Bs] | 68 | BB012 pseudouridylylase Sase I (hisT) [Bb] | 100 | |
| <i>Transcription factors</i> | | | BB065 polypeptide deformylase (def) [Syn] | 67 | BB021 SAM: tRNA ribosylTase-isomerase [Bb] | 96 | |
| BB107 | N utilization substance prt B (nusB) [Ec] | 62 | BB648 serine/threonine kinase, put [Pf] | 51 | BB809 tRNA-guanine transglycosylase (tgt) [Zm] | 60 | |
| BB800 | N-utilization substance prt A (nusA) [Bs] | 62 | <i>Ribosomal proteins: synthesis and modification</i> | | | BB698 tRNA (guanine-N1)-MTase (trmD) [Mg] | 68 |
| BB394 | transcription antitermination factor (nusG) [Ec] | 64 | BB392 ribosomal prt L1 (rplA) [Bs] | 71 | BB803 tRNA pseudouridine 55 Sase (truB) [Ec] | 57 | |
| BB132 | transcription elongation factor (greA) [Ec] | 56 | BB481 ribosomal prt L2 (rplB) [Bb] | 99 | <i>Translation factors</i> | | |
| BB355 | transcription factor, put [Mx] | 47 | BB478 ribosomal prt L3 (rplC) [Bb] | 99 | BB088 GTP-B membrane prt (lepA) [Hi] | 76 | |
| BB230 | transcription termination factor Rho (rho) [Bb] | 100 | BB479 ribosomal prt L4 (rplD) [Bb] | 100 | BB196 peptide chain release factor 1 (prfA) [Hi] | 73 | |
| <i>RNA processing</i> | | | BB490 ribosomal prt L5 (rplE) [Hi] | 80 | BB074 peptide chain release factor 2 (prfB) [Sc] | 70 | |
| BB706 | polynucleotide adenylylTase (papS) [Bs] | 57 | BB493 ribosomal prt L6 (rplF) [Sc] | 72 | BB121 ribosome releasing factor (frr) [Mt] | 68 | |
| Translation | | | BB390 ribosomal prt L7/L12 (rplL) [Sc] | 75 | BB169 translation initiation factor 1 (infA) [Ec] | 87 | |
| <i>General</i> | | | BB112 ribosomal prt L9 (rplI) [Ec] | 57 | BB801 translation initiation factor 2 (infB) [Bs] | 73 | |
| BB590 | dimethyladenosine Tase (ksgA) [Bs] | 61 | BB391 ribosomal prt L10 (rplJ) [Bs] | 61 | BB190 translation initiation factor 3 (infC) [Pv] | 72 | |
| BB802 | ribosome-B factor A (rbfA) [Bs] | 62 | BB393 ribosomal prt L11 (rplK) [Tm] | 73 | BB691 translation elongation factor G (fus-2) [Tm] | 67 | |
| <i>Amino acyl tRNA synthetases</i> | | | BB339 ribosomal prt L13 (rplM) [Hi] | 72 | BB214 translation elongation factor P (efp) [Ec] | 56 | |
| BB220 | alanyl-tRNA Sase (alaS) [Ec] | 62 | BB488 ribosomal prt L14 (rplN) [Tm] | 79 | BB476 translation elongation factor TU (tuf) [Bb] | 100 | |
| BB594 | arginyl-tRNA Sase (argS) [Mj] | 55 | BB497 ribosomal prt L15 (rplO) [Bs] | 68 | BB122 translation elongation factor TS (tsf) [Hi] | 57 | |
| BB101 | asparaginylyl-tRNA Sase (asnS) [Ec] | 73 | BB485 ribosomal prt L16 (rplP) [Syn] | 81 | BB540 translation elongation factor G (fus-1) [Tm] | 68 | |
| BB446 | aspartyl-tRNA Sase (aspS) [Ec] | 66 | BB503 ribosomal prt L17 (rplQ) [Ec] | 63 | Transport and binding proteins | | |
| BB599 | cysteinyl-tRNA Sase (cysS) [Hi] | 58 | BB494 ribosomal prt L18 (rplR) [Bs] | 69 | <i>General</i> | | |
| BB372 | glutamyl-tRNA Sase (gluX) [Rm] | 63 | BB699 ribosomal prt L19 (rplS) [Ec] | 74 | BB573 ABC transporter, ATP-BP [Bs] | 53 | |
| BB371 | glycyl-tRNA Sase (glyS) [Ta] | 68 | BB188 ribosomal prt L20 (rplT) [Ec] | 70 | BB742 ABC transporter, ATP-BP [Syn] | 57 | |
| BB135 | histidyl-tRNA Sase (hisS) [Mj] | 59 | BB778 ribosomal prt L21 (rplU) [Ec] | 58 | BB466 ABC transporter, ATP-BP [Hi] | 74 | |
| | | | BB483 ribosomal prt L22 (rplV) [Bb] | 100 | BB754 ABC transporter, ATP-BP [Bi] | 60 | |
| | | | BB480 ribosomal prt L23 (rplW) [Bb] | 100 | BB080 ABC transporter, ATP-BP [Mj] | 63 | |
| | | | BB489 ribosomal prt L24 (rplX) [Ec] | 64 | BB269 ATP-BP (yJxH-1) [Bb] | 100 | |
| | | | BB780 ribosomal prt L27 (rpmA) [Hi] | 82 | BB726 ATP-BP (yJxH-2) [Bb] | 54 | |
| | | | BB350 ribosomal prt L28 (rpmB) [Ec] | 62 | <i>lp38</i> | | |
| | | | BB486 ribosomal prt L29 (rpmC) [Bs] | 65 | BBJ26 ABC transporter, ATP-BP [Mj] | 62 | |
| | | | BB496 ribosomal prt L30 (rpmD) [Bs] | 60 | <i>Amino acids, peptide, and amines</i> | | |
| | | | BB229 ribosomal prt L31 (rpmE) [Bs] | 69 | BB729 glutamate transporter (gluTP) [Bs] | 55 | |
| | | | | | BB401 glutamate transporter, put [Bs] | 53 | |
| | | | | | BB146 GBP ABC transporter, ATP-BP | | |

| | | | | | | | | |
|---|---|----|--|--|-----|-------------------------------------|--|-----|
| | (proV) {Sc} | 71 | | {Mg} | 56 | BB586 | femA prt (femA) {Se} | 47 |
| BB145 | GBP ABC transporter, permease prt (proW) {Ec} | 66 | BB557 | phosphocarrier prt HPr (ptsH-2) {Hi} | 69 | BB141 | membrane fusion prt (mtrC) {Hi} | 47 |
| BB144 | GBP ABC transporter, BP (proX) {Ec} | 43 | BB558 | phosphoenolpyruvate-prt PPase (ptsI) {Sc} | 65 | BB126 | multidrug-efflux transporter {Hp} | 55 |
| BB334 | OP ABC transporter, ATP-BP (oppD) {Bs} | 75 | BB408 | PTS system, fru-specific IIABC (fruA-1) {Ec} | 65 | lp25 | | |
| BB335 | OP ABC transporter, ATP-BP (oppF) {Bs} | 80 | BB629 | PTS system, fru-specific IIABC (fruA-2) {Ec} | 68 | BBE22 | pyrazinamidase/nicotinamidase (pncA) {Mt} | 56 |
| BB332 | OP ABC transporter, permease prt (oppB-1){Ec} | 68 | BB559 | PTS system, glu-specific IIA (crr) {Bb} | 100 | <i>Transposon-related functions</i> | | |
| BB747 | OP ABC transporter, permease prt (oppB-2){Bs} | 54 | BB645 | PTS system, glu-specific IIBC (ptsG) {Sc} | 67 | lp38 | | |
| BB333 | OP ABC transporter, permease prt (oppC-1){Hi} | 64 | BB116 | PTS system, mal/glu-specific IIABC (malX) {Ec} | 56 | BBJ05 | transposase-like prt, put {Bb} | 89 |
| BB746 | OP ABC transporter, permease prt (oppC-2){Bs} | 52 | BB677 | RG ABC transporter, ATP-BP (mgIA) {Mg} | 68 | lp36 | | |
| BB328 | OP ABC transporter, periplasmic BP (oppA-1) {Bb} | 74 | BB678 | RG ABC transporter, permease prt (rbsC-1) {Mg} | 51 | BBK25 | transposase-like prt, put {Bb} | 80 |
| BB329 | OP ABC transporter, periplasmic BP (oppA-2) {Bb} | 94 | BB679 | RG ABC transporter, permease prt (rbsC-2) {Mp} | 52 | lp28-1 | | |
| BB330 | OP ABC transporter, periplasmic BP (oppA-3) {Bb} | 81 | cp26 | | | BBF18 | transposase-like prt, put {Bb} | 96 |
| BB642 | SP ABC transporter, ATP-BP (potA) {Ec} | 69 | BBB04 | PTS system, cello-specific IIC (celB) {Bs} | 62 | BBF19 | transposase-like prt, put {Bb} | 96 |
| BB641 | SP ABC transporter, permease prt (potB) {Ec} | 65 | BBB05 | PTS system, cello-specific IIA (celC) {Bs} | 61 | lp28-2 | | |
| BB640 | SP ABC transporter, permease prt (potC) {Ec} | 63 | BBB06 | PTS system, cello-specific IIB (celA) {Bs} | 73 | BBG05 | transposase-like prt {Bb} | 99 |
| BB639 | SP ABC transporter, periplasmic BP (potD) {Ec} | 53 | BBB29 | PTS system, glu-specific IIBC, put {Ec} | 70 | lp28-3 | | |
| lp54 | | | <i>Cations</i> | | | BBH40 | transposase-like prt, put {Bb} | 57 |
| BBA34 | OP ABC transporter, periplasmic BP (oppA-4) {Bc} | 66 | BB724 | K ⁺ transport prt (ntpJ) {Eh} | 60 | lp17 | | |
| cp26 | | | BB380 | Mg ²⁺ transport prt (mgtE) {Bb} | 100 | BBD20 | transposase-like prt, put {Bb} | 99 |
| BBB16 | OP ABC transporter, periplasmic BP (oppA) {Bb} | 78 | BB164 | Na ⁺ /Ca ⁺ exchange prt, put {Mj} | 59 | BBD23 | transposase-like prt, put {Bb} | 88 |
| <i>Anions</i> | | | BB447 | Na ⁺ /H ⁺ antiporter (napA) {Eh} | 57 | Unknown | | |
| BB218 | P ABC transporter, ATP-BP (pstB) {Pa} | 74 | BB637 | Na ⁺ /H ⁺ antiporter (nhaC-1) {Bf} | 48 | BB528 | aldose RDase, put {Bs} | 57 |
| BB216 | P ABC transporter, permease prt (pstC) {Ec} | 58 | BB638 | Na ⁺ /H ⁺ antiporter (nhaC-2) {Hi} | 50 | BB684 | carotenoid biosyn prt, put {Ss} | 58 |
| BB217 | P ABC transporter, permease prt (pstA) {Syn} | 63 | <i>Other</i> | | | BB671 | chemotaxis operon prt (cheX) {Bb} | 99 |
| BB215 | P ABC transporter, periplasmic P-BP (pstS) {Syn} | 48 | BB451 | chromate transport prt, put {Mj} | 58 | BB250 | dedA prt (dedA) {Ec} | 54 |
| <i>Carbohydrates, organic alcohols, and acids</i> | | | Other categories | | | BB168 | dnaK suppressor, put {Ec} | 53 |
| BB240 | glycerol uptake facilitator (glpF) {Bs} | 57 | <i>Adaptations and atypical conditions</i> | | | BB508 | GTP-BP {Tp} | 59 |
| BB604 | L-lactate permease (lctP) {Ec} | 57 | BB237 | acid-inducible prt (act206) {Rm} | 45 | BB219 | gufA prt {Mx} | 54 |
| BB318 | methylgalactoside ABC transporter, ATP-BP (mgIA) {Hi} | 54 | BB786 | general stress prt (ctc) {Bs} | 51 | BB421 | hydrolase {Hi} | 58 |
| BB814 | pantothenate permease (panF) {Ec} | 63 | BB785 | stage V sporulation prt G {Bm} | 74 | BB524 | inositol monoPPase {Hs} | 47 |
| BB448 | phosphocarrier prt HPr (ptsH-1) | | BB810 | virulence factor mviN prt (mviN) {Hi} | 51 | BB454 | lipopolysaccharide biosyn-related prt {Mj} | 49 |
| | | | <i>Colicin-related functions</i> | | | BB702 | lipopolysaccharide biosyn-related prt {Hi} | 62 |
| | | | BB766 | colicin V production prt, put {Hi} | 52 | BB045 | P115 prt {Mh} | 53 |
| | | | BB546 | outer membrane integrity prt (tolA) {Hi} | 44 | BB336 | P26 {Bb} | 100 |
| | | | <i>Drug and analog sensitivity</i> | | | BB363 | periplasmic prt {Bb} | 100 |
| | | | BB140 | acriflavine resistance prt (acrB) {Hi} | 53 | BB033 | small prt (smpB) {Rp} | 70 |
| | | | BB258 | bacitracin resistance prt (bacA) {Ec} | 56 | BB297 | smg prt {Bb} | 100 |
| | | | | | | BB443 | spolI-associated prt (jag) {Bs} | 56 |
| | | | | | | lp54 | | |
| | | | | | | BBA76 | thy1 prt (thy1) {Dd} | 68 |
| | | | | | | lp28-4 | | |
| | | | | | | BBI06 | pfs prt (pfs) {Ec} | 59 |
| | | | | | | cp9 | | |
| | | | | | | BB009 | rev prt (rev) {Bb} | 62 |
| | | | | | | BB010 | rev prt (rev) {Bb} | 66 |