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# The complete genome sequence of the Gram-positive bacterium *Bacillus subtilis*

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***Bacillus subtilis* is the best-characterized member of the Gram-positive bacteria. Its genome of 4,214,810 base pairs comprises 4,100 protein-coding genes. Of these protein-coding genes, 53% are represented once, while a quarter of the genome corresponds to several gene families that have been greatly expanded by gene duplication, the largest family containing 77 putative ATP-binding transport proteins. In addition, a large proportion of the genetic capacity is devoted to the utilization of a variety of carbon sources, including many plant-derived molecules. The identification of five signal peptidase genes, as well as several genes for components of the secretion apparatus, is important given the capacity of *Bacillus* strains to secrete large amounts of industrially important enzymes. Many of the genes are involved in the synthesis of secondary metabolites, including antibiotics, that are more typically associated with *Streptomyces* species. The genome contains at least ten prophages or remnants of prophages, indicating that bacteriophage infection has played an important evolutionary role in horizontal gene transfer, in particular in the propagation of bacterial pathogenesis.**

Techniques for large-scale DNA sequencing have brought about a revolution in our perception of genomes. Together with our understanding of intermediary metabolism, it is now realistic to envisage a time when it should be possible to provide an extensive chemical definition of many living organisms. During the past couple of years, the genome sequences of *Haemophilus influenzae*, *Mycoplasma genitalium*, *Synechocystis* PCC6803, *Methanococcus jannaschii*, *M. pneumoniae*, *Escherichia coli*, *Helicobacter pylori*, *Archaeoglobus fulgidus* and the yeast *Saccharomyces cerevisiae* have been published in their entirety<sup>1-8</sup>, and at least 40 prokaryotic genomes are currently being sequenced. Regularly updated lists of genome sequencing projects are available at <http://www.mcs.anl.gov/home/gaasterl/genomes.html> (Argonne National Laboratory, Illinois, USA) and <http://www.tigr.org> (TIGR, Rockville, Maryland, USA).

The list of sequenced microorganisms does not currently include a paradigm for Gram-positive bacteria, which are known to be important for the environment, medicine and industry. *Bacillus subtilis* has been chosen to fill this gap<sup>9,10</sup> as its biochemistry, physiology and genetics have been studied intensely for more than 40 years. *B. subtilis* is an aerobic, endospore-forming, rod-shaped bacterium commonly found in soil, water sources and in association with plants. *B. subtilis* and its close relatives are an important source of industrial enzymes (such as amylases and proteases), and much of the commercial interest in these bacteria arises from their capacity to secrete these enzymes at gram per litre concentrations. It has therefore been used for the study of protein secretion and for development as a host for the production of heterologous proteins<sup>11</sup>. *B. subtilis* (*natto*) is also used in the production of Natto, a traditional Japanese dish of fermented soya beans.

Under conditions of nutritional starvation, *B. subtilis* stops growing and initiates responses to restore growth by increasing metabolic diversity. These responses include the induction of motility and chemotaxis, and the production of macromolecular hydrolases (proteases and carbohydrases) and antibiotics. If these responses fail to re-establish growth, the cells are induced to form chemically, irradiation- and desiccation-resistant endospores. Sporulation involves a perturbation of the normal cell cycle and the differentiation of a binucleate cell into two cell types. The division of the cell into a smaller forespore and a larger mother cell, each with an entire copy of the chromosome, is the first morphological indication of sporulation. The former is engulfed by the latter and differential expression of their respective genomes, coupled to a complex network of interconnected regulatory path-

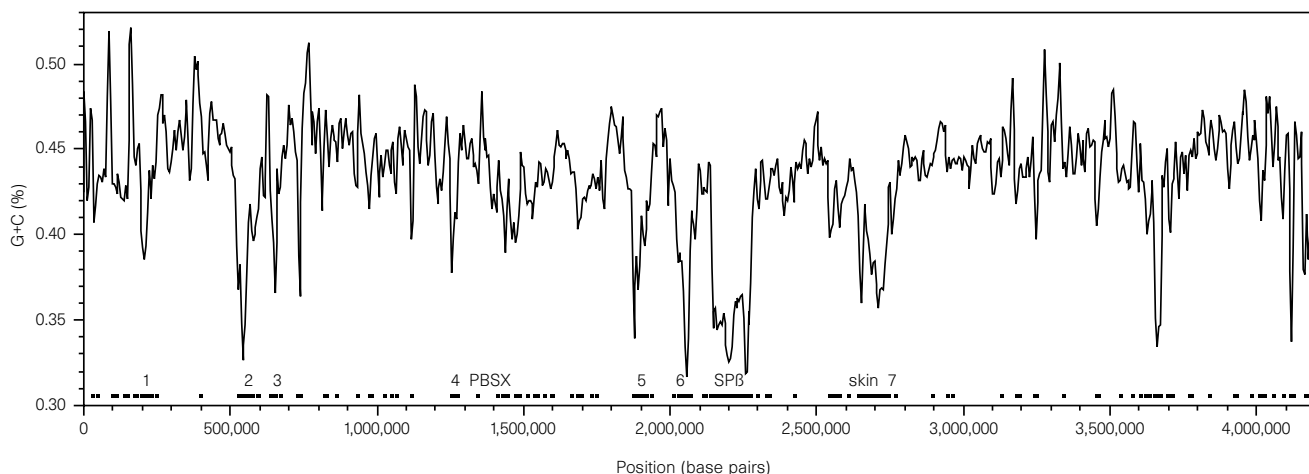
ways and developmental checkpoints, culminates in the programmed death and lysis of the mother cell and release of the mature spore<sup>12</sup>. In an alternative developmental process, *B. subtilis* is also able to differentiate into a physiological state, the competent state, that allows it to undergo genetic transformation<sup>13</sup>.

### General features of the DNA sequence

**Analysis at the replicon level.** The *B. subtilis* chromosome has 4,214,810 base pairs (bp), with the origin of replication coinciding with the base numbering start point<sup>14</sup>, and the terminus at about 2,017 kilobases (kb)<sup>15</sup>. The average G + C ratio is 43.5%, but it varies considerably throughout the chromosome. This average is also different if one considers the nucleotide content of coding sequences, for which G and A (24% and 30%) are relatively more abundant than their counterparts C and T (20% and 26%). A significant inversion of the relative G - C/G + C ratio is visible at the origin of replication, indicating asymmetry of the nucleotide composition between the replication leading strand and the lagging strand<sup>16</sup>. Several A + T-rich islands are likely to reveal the signature of bacteriophage lysogens or other inserted elements (Fig. 1, see below).

We have analysed the abundance of oligonucleotides ('words') in the genome in various ways: absolute number of words in the genomic text, or comparison with the expected count derived from several models of the chromosome (for example, Markov models, or simulated sequences in which previously known features of the genome were conserved<sup>17</sup>). Comparing the experimental data with various models allowed us to define under- and overrepresentation of words in the experimental data set by reference to the model chosen. In general, the dinucleotide bias follows closely what has been described for other prokaryotes<sup>18,19</sup>, in that the dinucleotides most overrepresented are AA, TT and GC, whereas those less represented are TA, AC and GT. Plots of the frequencies of AG, GA, CT and TC in sliding windows along the chromosome show dramatic decreases or increases around the origin and terminus of replication (data not shown). Trinucleotide frequency, directly related to the coding frame, will be discussed below. The distribution of words of four, five and six nucleotides shows significant correlations between the usage of some words and replication (several such oligonucleotides are very significantly overrepresented in one of the strands and underrepresented in the other one).

Setting a statistical cut-off for the significance of duplications at  $10^{-3}$ , we expected duplication by chance of words longer than 24 nucleotides to be rare<sup>20</sup>. In fact, the genome of *B. subtilis* contains a plethora of such duplications, some of them appearing more than



**Figure 1** Distribution of A + T-rich islands along the chromosome of *B. subtilis*, in sliding windows of 10,000 nucleotides, with a step of 5,000 nucleotides. Location of genes from class 3 according to codon usage analysis (see Fig. 4) is indicated

by dots at the bottom of the graph. Known prophages (PBSX, SP $\beta$  and *skin*) are indicated by their names, and prophage-like elements are numbered from 1 to 7.

twice. Among the duplications, we identified, as expected, the ribosomal RNA genes and their flanking regions, but also regions known to correspond to genes comprising long sequence repeats (such as *pks* and *srf*). We also found several regions that were not expected: a 182-bp repetition within the *yyaL* and *yyaO* genes; a 410-bp repetition between the *yxaK* and *yxaL* genes; an internal duplication of 174 bp inside *ycdI*; and significant duplications in the regions involved in the transcriptional control of several genes (such as 118 bp repeated three times between *yxbB* and *yxbC*). Finally, we found several repetitions at the borders of regions that might be involved in bacteriophage integration.

The most prominent duplication was a 190-bp element that was repeated 10 times in the chromosome. Multiple alignment of the ten repeats showed that they could be classified into two subfamilies with six and three copies each, plus a copy of what appears to be a chimera. Similar sequences have also been described in the closely related species *Bacillus licheniformis*<sup>21,22</sup>. A striking feature of these repeats is that they are only found in half of the chromosome, at either side of the origin of replication, with five repeats on each side. Furthermore, with the exception of the most distal repeat at position 737,062, they lie in the same orientation with respect to the movement of the replication fork (Figs 2 and 3). Putative secondary structures conserved by compensatory mutations, as well as an insert in three of the copies, suggest that this element could indicate a structural RNA molecule.

**Analysis at the transcription and translation level.** Over 4,000 putative protein coding sequences (CDSs) have been identified, with an average size of 890 bp, covering 87% of the genome sequence (Fig. 2). We found that 78% of the genes started with ATG, 13% with TTG and 9% with GTG, which compares with 85%, 3% and 14%, respectively, in *E. coli*<sup>8</sup>. Fifteen genes (eight in the predicted CDSs in bacteriophage SPβ) exhibiting unusual start codons (namely ATT and CTG) were also identified through their

similarities to known genes in other organisms or because they had a good GeneMark prediction (see Methods). This has not yet been substantiated experimentally. However, in the case of the gene coding for translation initiation factor 3, the similarity with its *E. coli* counterpart strongly suggests that the initiation codon is ATT, as is the case in *E. coli*.

We have not annotated CDSs that largely or entirely overlap existing genes, although such genes (for example, *comS* inside *srfAA*) certainly exist. It is also likely that some of the short CDSs present in the *B. subtilis* genome have been overlooked. For these reasons and possible sequencing errors, the estimated number of *B. subtilis* CDSs will fluctuate around the present figure of 4,100.

In several cases, in-frame termination codons or frameshifts were confirmed to be present on the chromosome (for example, an internal termination codon in *ywtF*, or the known programmed translational frameshift in *prfB*), indicating that the genes are either non-functional (pseudogenes) or subject to regulatory processes. It will therefore be of interest to determine whether these gene features are conserved in related *Bacillus* species, especially as strain 168 is derived from the Marburg strain that was subjected to X-ray irradiation<sup>23</sup>.

A few regions do not have any identifiable feature indicating that they are transcribed: they could be 'grey holes' of the type described in *E. coli*<sup>24</sup>. Preliminary studies involving all regions of more than 400 bp without annotated CDSs indicated that, of ~300 such regions, only 15% were likely to be really devoid of protein-coding sequences. One of the longest such regions, located between *yjfo* and *yjfn*, is 1,628 bp long. Grey holes seem generally to be clustered near the terminus of replication. However, a grey-hole cluster located at ~600 kb might be related to the temporary chromosome partition observed during the first stages of sporulation, when a segment of about one-third of the chromosome enters the prespore, and remains the sole part of the chromosome in the prespore for a significant transition period<sup>25</sup>.

The codon usage of *B. subtilis* CDSs was analysed using factorial correspondence analysis<sup>17</sup>. We found that the CDSs of *B. subtilis* could be separated into three well-defined classes (Fig. 4). Class 1 comprises the majority of the *B. subtilis* genes (3,375 CDSs), including most of the genes involved in sporulation. Class 2 (188 CDSs) includes genes that are highly expressed under exponential growth conditions, such as genes encoding the transcription and translation machineries, core intermediary metabolism, stress proteins, and one-third of genes of unknown function. Class 3 (537 CDSs) contains a very high proportion of genes of unidentified function (84%), and the members of this class have codons enriched in A + T residues. These genes are usually clustered into groups between 15 and 160 genes (for example, bacteriophage SPβ) and correspond to the A + T-rich islands described above (Fig. 1). When they are of known function, or when their products display similarity to proteins of known function, they usually correspond to functions found in, or associated with, bacteriophages or transposons, as well as functions related to the cell envelope. This includes the region *ycd/ydd/yde* (40 genes that are missing in some *B. subtilis* strains<sup>26</sup>), where gene products showing similarities to bacteriophage and transposon proteins are intertwined. Many of these genes are associated with virulence genes identified in pathogenic Gram-positive bacteria, suggesting that such virulence factors are transmitted horizontally among bacteria at a much higher frequency than previously thought. If we include these A + T-rich regions as possible cryptic phages, together with known bacteriophages or bacteriophage-like elements (SPβ, PBSX and the *skin* element), we find that the genome of *B. subtilis* 168 contains at least 10 such elements (Figs 2 and 3). Annotation of the corresponding regions often reveals the presence of genes that are similar to bacteriophage lytic enzymes, perhaps accounting for the observation that *B. subtilis* cultures are extremely prone to lysis.

The ribosomal RNA genes have been previously identified and

**Table 1 Functional classification of the *Bacillus subtilis* protein-coding genes**

The genes of known function or encoding products similar to known proteins in *B. subtilis* or in other organisms have been classified into functional categories (2,379 genes). The total number of genes in each category is indicated after the category title. Genes are listed in alphabetical order within each category, and their positions (in kilobases) on the *B. subtilis* chromosome are indicated after the gene names. A brief description is given for each gene. In some cases, interacting proteins have been indicated between brackets (for example, histidine kinases and response regulator, phosphatases and their substrates). More detailed and constantly updated information is available in the SubtiList database (see Methods). A preliminary assessment of the significance of sequence similarities was obtained through an automated procedure involving a combination between the BLAST2P probability and the percentage of amino-acid identity. Matches considered significant were re-examined manually. It should be emphasized that functions assigned to 'y' genes are based only on sequence similarity information with the best counterparts in protein databanks. Genes whose products are only similar to other unknown proteins, or not significantly similar to any other proteins in databanks (categories V and VI), were omitted.

**Figure 2** General view of the *B. subtilis* chromosome. Arrows indicate the orientation of transcription. Genes are coloured according to their classification into six broad functional categories (blue, category I; green, category II; red, category III; orange, category IV; purple, category V; pink, category VI; see Table 1). Class 2 CDSs according to codon usage analysis are indicated by oblique hatches, and class 3 CDSs are indicated by vertical hatches. Ribosomal RNA genes are coloured in yellow. Transfer RNA genes are marked by triangles. Other RNA genes are represented as white arrows. Known genes (non-'y' genes) are printed in bold type. Putative transcription termination sites are represented as loops. Known prophages and prophage-like elements are indicated by brown hatches on the chromosome line. The 190-bp element repeated ten times is represented by hatched boxes.

shown to be organized into ten rRNA operons, mainly clustered around the origin of replication of the chromosome (Figs 2 and 3). In addition to the 84 previously identified tRNA genes, by using the Palingol<sup>27</sup> and tRNAscan<sup>28</sup> programs, we propose four putative new tRNA loci (at 1,262 kb, 1,945 kb, 2,003 kb and 2,899 kb), specific for lysine, proline and arginine (UUU, GGG, CCU and UCU anticodons, respectively). The 10S RNA involved in degradation of proteins made from truncated mRNA has been identified (*ssrA*), as well as the RNA component of RNase P (*rnpB*) and the 4.5S RNA involved in the secretion apparatus (*scr*).

There is a strong transcription orientation bias with respect to the movement of the replication fork: 75% of the predicted genes are transcribed in the direction of replication. Plotting the density of coding nucleotides in each strand along the chromosome readily identifies the replication origin and terminus (Fig. 3). To identify putative operons, we followed ref. 29 for describing Rho-independent transcription termination sites. This yielded ~1,630 putative terminators (340 of which were bidirectional). We retained only those that were located less than 100 bp downstream of a gene, or that were considered by the program to be 'very strong' (in order to account for possible erroneous CDSs). This yielded a total of ~1,250 terminators, with a mean operon size of three genes. A similar approach to the identification of promoters is problematical, especially because at least 14 sigma factors, recognizing different promoter sequences, have been identified in *B. subtilis*. Nevertheless, the consensus of the main vegetative sigma factor ( $\sigma^A$ ) appears to be identical to its counterpart in *E. coli* ( $\sigma^{70}$ ): 5'-TTGACA-*n*<sub>17</sub>-TATAAT-3'. Relaxing the constraints of the similarity to sigma-specific consensus sequences led to an extremely high number of false-positive results, suggesting that the consensus-oriented approach to the identification of promoters should be replaced by another approach<sup>17</sup>.

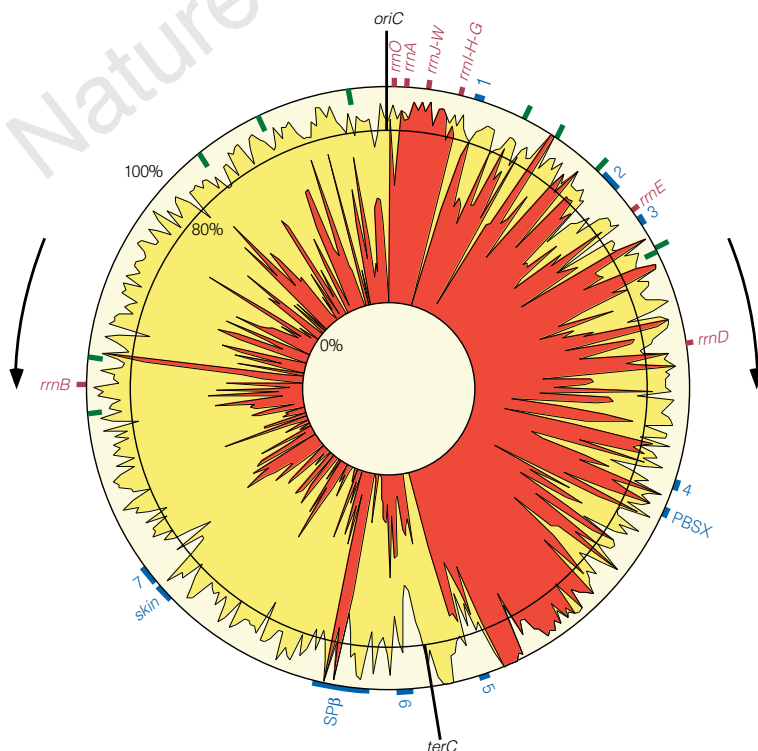
**Classification of gene products**

Genes were classified according to ref. 14, based on the representation of cells as Turing machines in which one distinguishes between the machine and the program (Table 1). Using the BLAST2P software running against a composite protein databank compound of SWISS-PROT (release 34), TREMBL (release 3, update 1) and *B.*

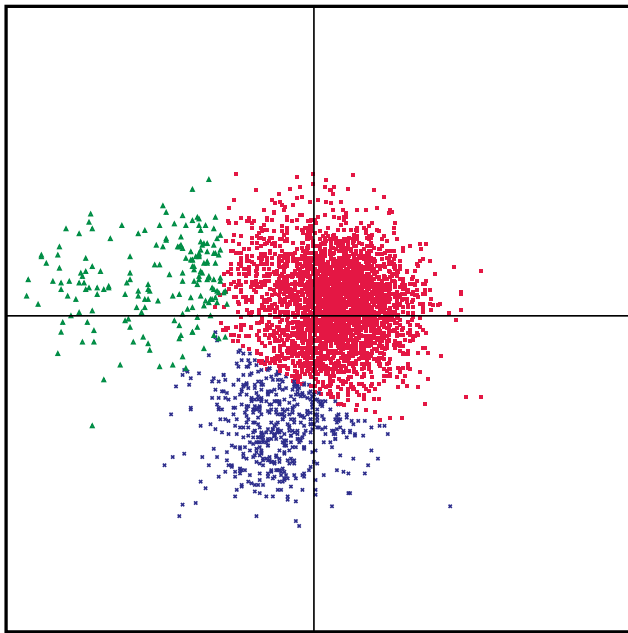
*subtilis* proteins, we assigned at least one significant counterpart with a known function to 58% of the *B. subtilis* proteins. Thus for up to 42% of the gene products, the function cannot be predicted by similarity to proteins of known function: 4% of the proteins are similar only to other unknown proteins of *B. subtilis*; 12% are similar to unknown proteins from some other organism; and 26% of the proteins are not significantly similar to any other proteins in databanks. This preliminary analysis should be interpreted with caution, because only ~1,200 gene functions (30%) have been experimentally identified in *B. subtilis*. We used the 'y' prefix in gene names to emphasize that the function has not been ascertained (2,853 'y' genes, representing 70%).

**Regulatory systems.** Transcription regulatory proteins. Helix-turn-helix proteins form a large family of regulatory proteins found in both prokaryotes and eukaryotes. There are several classes, including repressors, activators and sigma factors. Using BLAST searches, we constructed consensus matrices for helix-turn-helix proteins to analyse the *B. subtilis* protein library. We identified 18 sigma or sigma-like factors, of which nine (including a new one) are of the SigA type. We also putatively identified 20 regulators (among which 18 were products of 'y' genes) of the GntR family, 19 regulators (15 'y' genes) of the LysR family, and 12 regulators (5 'y' genes) of the LacI family. Other transcription regulatory proteins were of the AraC family (11 members, 10 'y'), the Lrp family (7 members, 3 'y'), the DeoR family (6 members, 3 'y'), or additional families (such as the MarR, ArsR or TetR families). A puzzling observation is that several regulatory proteins display significant similarity to aminotransferases (seven such enzymes have been identified as showing similarity to repressors).

**Two-component signal-transduction pathways.** Two-component regulatory systems, consisting of a sensor protein kinase and a response regulator, are widespread among prokaryotes. We have identified 34 genes encoding response regulators in *B. subtilis*, most of which have adjacent genes encoding histidine kinases. Response regulators possess a well-conserved N-terminal phospho-acceptor domain<sup>30</sup>, whereas their C-terminal DNA-binding domains share similarities with previously identified response regulators in *E. coli*, *Rhizobium meliloti*, *Klebsiella pneumoniae* or *Staphylococcus aureus*. Representatives of the four subfamilies recently identified in *E. coli*<sup>31</sup>



**Figure 3** Density of coding nucleotides along the *B. subtilis* chromosome. Yellow stands for the density of coding nucleotides in both strands of the sequence; red indicates the density of coding nucleotides in the clockwise strand (nucleotides involved in genes transcribed in the clockwise orientation). The movement of the replication forks is represented by arrows. Ribosomal RNA operons are indicated by brown boxes. Known prophages and prophage-like elements are represented as blue lines. The 190-bp element repeated ten times is represented by green lines.



**Figure 4** Factorial correspondence analysis of codon usage in the *B. subtilis* CDSs. Red dots, genes from class 1; green triangles, genes from class 2; blue crosses, genes from class 3. Class 2 contains genes coding for the translation and transcription machineries, and genes of the core intermediary metabolism. Class 3 genes correspond to codons strongly enriched in A or T in the wobble position; they generally belong to prophage-like inserts in the genome.

(OmpR, FixJ, CitB and LytR) have been identified in *B. subtilis*. In a fifth subfamily, CheY, the DNA-binding domain is absent. The DNA-binding domain of a single *B. subtilis* response regulator, YesN, shares similarity with regulatory proteins of the AraC family. **Quorum sensing.** The *B. subtilis* genome contains 11 aspartate phosphatase genes, whose products are involved in dephosphorylation of response regulators, that do not seem to have counterparts in Gram-negative bacteria such as *E. coli*. Downstream from the corresponding genes are some small genes, called *phr*, encoding regulatory peptides that may serve as quorum sensors<sup>32</sup>. Seven *phr* genes have been identified so far, including three new genes (*phrG*, *phrI* and *phrK*).

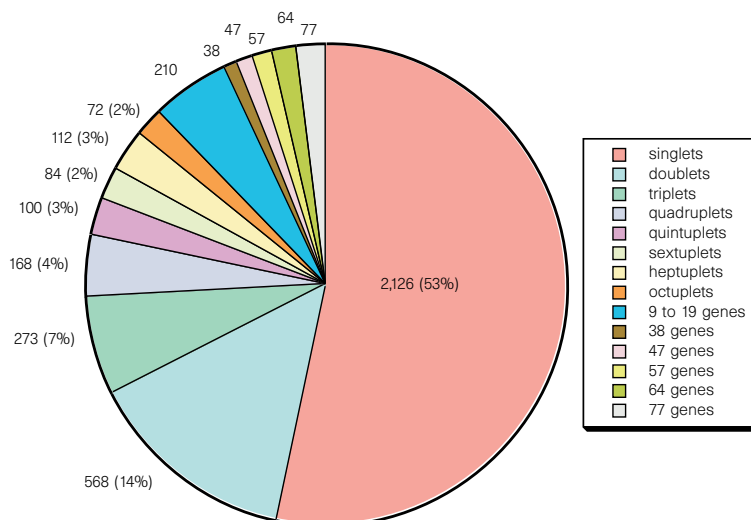
**Protein secretion.** It is known that *B. subtilis* and related *Bacillus* species, in particular *B. licheniformis* and *B. amyloliquefaciens*, have a high capacity to secrete proteins into the culture medium. Several genes encoding proteins of the major secretion pathway have been identified: *secA*, *secD*, *secE*, *secF*, *secY*, *ffh* and *ftsY*. Surprisingly, there is no gene for the SecB chaperone. It is thought that other chaperone(s) and targeting factor(s), such as Ffh and FtsY, may take over the SecB function. Further, although there is only one such gene in *E. coli*, five type I signal peptidase genes (*sipS*, *sipT*, *sipU*, *sipV* and *sipW*) have been found<sup>33</sup>. The *lsp* gene, encoding a type II signal peptidase required for processing of lipo-modified precursors, was also identified. PrsA, located at the outer side of the membrane, is important for the refolding of several mature proteins after their translocation through the membrane.

**Other families of proteins.** ABC transporters were the most frequent class of proteins found in *B. subtilis*. They must be extremely important in Gram-positive bacteria, because they have an envelope comprising a single membrane. ABC transporters will therefore allow such bacteria to escape the toxic action of many compounds. We propose that 77 such transporters are encoded in the genome. In general they involve the interaction of at least three gene products, specified by genes organized into an operon. Other families comprised 47 transport proteins similar to facilitators (and perhaps sometimes part of the ABC transport systems), 18 amino-acid permeases (probably antiporters), and at least 16 sugar transporters belonging to the PEP-dependent phosphotransferase system.

General stress proteins are important for the survival of bacteria under a variety of environmental conditions. We identified 43 temperature-shock and general stress proteins displaying strong similarity to *E. coli* counterparts.

**Missing genes.** Histone-like proteins such as HU and H-NS have been identified in *E. coli*. We found that *B. subtilis* encodes two putative histone-like proteins that show similarity to *E. coli* HU, namely HBSu and YonN, but found no homologue to H-NS. It is known that the *hbs* gene encoding HBSu is essential, but we do not expect the *yonN* gene to be essential because it is present in the SP $\beta$  prophage. IHF is similar to HU, and it is not known whether HBSu plays a similar role to that of IHF in *E. coli*. Similarly, no protein similar to FIS could be found.

Genes encoding products that interact with methylated DNA, such as *seqA* in *E. coli*, involved in the regulation of replication initiation timing, or *mutH*, the endonuclease recognizing the newly synthesized strand during mismatch repair at hemi-methylated



**Figure 5** Gene paralogue distribution in the genome of *B. subtilis*. Each *B. subtilis* protein has been compared with all other proteins in the genome, using a Smith and Waterman algorithm. The baseline is established by making a similar

comparison using 100 independent random shuffles of the protein sequence (Z-score > 13).

GATC sites, are also missing. This is in line with the absence of known methylation in *B. subtilis*, equivalent to Dam methylation in *E. coli*. Similarly, *E. coli sfiA*, encoding an inhibitor of FtsZ action in the SOS response, has no counterpart in *B. subtilis*. In contrast, *B. subtilis* replication initiation-specific genes, such as *dnaB* and *dnaD*, are missing in *E. coli*. The exact counterpart of the *E. coli mukB* gene, involved in chromosome partitioning, does not exist in *B. subtilis*, but genes *spo0J* and *smc* (Smc is weakly similar to MukB), which are suggested to be involved in partitioning of the *B. subtilis* chromosome, are missing in *E. coli*.

Turnover of mRNA is controlled in *E. coli* by a 'degradosome' comprising RNase E. It has a counterpart in *B. subtilis*, but we failed to find a clear homologue of RNase E in this organism. Whether this is related to the role of ribosomal protein S1 as an RNA helicase involved in mRNA turnover in *E. coli* requires further investigation. In particular, a homologue of *rpsA* (S1 structural gene), *yfpD*, might be involved in a structure homologous to the degradosome<sup>34</sup>.

**Structurally unrelated genes of similar function.** Several genes encode products that have similar functions in *E. coli* and *B. subtilis*, but have no evident common structure. This is the case for the helicase loader genes, *E. coli dnaC* and *B. subtilis dnaI*; the genes coding for the replication termination protein, *E. coli tus* and *B. subtilis rtp*; and the division topology specifier genes, *E. coli minE* and *B. subtilis divIVA*. The situation may even be more complex in multisubunit enzymes: *B. subtilis* synthesizes two DNA polymerase III  $\alpha$  chains, one having 3'-5' proofreading exonuclease activity (PolC) and the other without the exonuclease activity (DnaE); in *E. coli*, only the latter exists. *E. coli* DNA polymerase II is structurally related to DNA polymerase  $\alpha$  of eukaryotes, whereas *B. subtilis* YshC is related to DNA polymerase  $\beta$ .

## Metabolism of small molecules

The type and range of metabolism used for the interconversion of low-molecular-weight compounds provide important clues to an organism's natural environment(s) and its biological activity. Here we briefly outline the main metabolic pathways of *B. subtilis* before the reconstruction of these pathways *in silico*, the correlation of genes with specific steps in the pathway, and ultimately the prediction of patterns of gene expression.

**Intermediary metabolism.** It has long been known that *B. subtilis* can use a variety of carbohydrates. As expected, it encodes an Embden–Meyerhof–Parnas glycolytic pathway, coupled to a functional tricarboxylic acid cycle. Further, *B. subtilis* is also able to grow anaerobically in the presence of nitrate as an electron acceptor. This metabolism is, at least in part, regulated by the FNR protein, binding to sites upstream of at least eight genes (four sites experimentally confirmed and four putative sites). A noteworthy feature of *B. subtilis* metabolism is an apparent requirement of branched short-chain carboxylic acids for lipid biosynthesis<sup>35</sup>. Branched-chain 2-keto acid decarboxylase activity exists and may be linked to a variety of genes, suggesting that *B. subtilis* can synthesize and utilize linear branched short-chain carboxylic acids and alcohols.

**Amino-acid and nucleotide metabolism.** Pyrimidine metabolism of *B. subtilis* seems to be regulated in a way fundamentally different from that of *E. coli*, as it has two carbamylphosphate synthetases (one specific for arginine synthesis, the other for pyrimidine). Additionally, the aspartate transcarbamylase of *B. subtilis* does not act as an allosteric regulator as it does in *E. coli*. As in other microorganisms, pyrimidine deoxyribonucleotides are synthesized from ribonucleoside diphosphates, not triphosphates. The cytidine diphosphate required for DNA synthesis is derived from either the salvage pathway of mRNA turnover or from the synthesis of phospholipids and components of the cell wall. This means that polynucleotide phosphorylase is of fundamental importance in nucleic acid metabolism, and may account for its important role in competence<sup>36</sup>. Two ribonucleoside reductases, both of class I, NrdEF type, are encoded by the *B. subtilis* chromosome, in one case

from within the SP $\beta$  genome. In this latter case, the gene corresponding to the large subunit both contains an intron and codes for an intein (V.L., unpublished data). The gene of the small subunit of this enzyme also contains an intron, encoding an endonuclease, as was found for the homologue in bacteriophage T4.

By similarity with genes from other organisms, there appears to be, in addition to genes involved in amino-acid degradation (such as the *roc* operon, which degrades arginine and related amino acids), a large number of genes involved in the degradation of molecules such as opines and related molecules, derived from plants. This is also in line with the fact that *B. subtilis* degrades polygalacturonate, and suggests that, in its biotope, it forms specific relations with plants.

**Secondary metabolism.** In addition to many genes coding for degradative enzymes, almost 4% of the *B. subtilis* genome codes for large multifunctional enzymes (for example, the *srf*, *pps* and *pks* loci), similar to those involved in the synthesis of antibiotics in other genera of Gram-positive bacteria such as *Streptomyces*. Natural isolates of *B. subtilis* produce compounds with antibiotic activity, such as surfactin, fengycin and difficidin, that can be related to the above-mentioned loci. This bacterium therefore provides a simple and genetically amenable model in which to study the synthesis of antibiotics and its regulation. These pathways are often organized in very long operons (for example, the *pks* region spans 78.5 kb, about 2% of the genome). The corresponding sequences are mostly located near the terminus of replication, together with prophages and prophage-like sequences.

## Paralogues and orthologues

It is important to relate intermediary metabolism to genome structure, function and evolution. We therefore compared the *B. subtilis* proteins with themselves, as well as with proteins from known complete genomes, using a consistent statistical method that allows the evaluation of unbiased probabilities of similarities between proteins<sup>37,38</sup>. For *Z*-scores higher than 13, the number of proteins similar to each given protein does not vary, indicating that this cut-off value identifies sets of proteins that are significantly similar.

**Families of paralogues.** Many of the paralogues constitute large families of functionally related proteins, involved in the transport of compounds into and out of the cell, or involved in transcription regulation. Another part of the genome consists of gene doublets (568 genes), triplets (273 genes), quadruplets (168 genes) and quintuplets (100 genes). Finally, about half of the genome is made of genes coding for proteins with no apparent paralogues (Fig. 5). No large family comprises only proteins without any similarity to proteins of known function.

The process by which paralogues are generated is not well understood, but we might find clues by studying some of the duplications in the genome. Several approximate DNA repetitions, associated with very high levels of protein identity, were found, mainly within regions putatively or previously identified as prophages. This is in line with previous observations about PBSX and the *skin* element<sup>39,40</sup>, and suggests that these prophage-like elements share a common ancestor and have diverged relatively recently. In addition, several protein duplications are in genes that are located very close to each other, such as *yukL* and *dhbF* (the corresponding proteins are 65% identical in an overlap of 580 amino acids), *yugJ* and *yugK* (proteins 73% identical), *yxjG* and *yxjH* (proteins 70% identical), and the entire *opuB* operon, which is duplicated 3 kb away (*opuC* operon, yielding ~80% of amino-acid identity in the corresponding proteins).

The study of paralogues showed that, as in other genomes, a few classes of genes have been highly expanded. This argues against the idea of the genome evolving through a series of duplications of ancestral genomes, but rather for the idea of genes as living organisms, subject to evolutionary constraints, some being sub-

mitted to expansion and natural selection, and others to local duplications of DNA regions.

Among paralogue doublets, some were unexpected, such as the three aminoacyl tRNA synthetases doublets (*hisS* (2,817 kb) and *hisZ* (3,588 kb); *thrS* (2,960 kb) and *thrZ* (3,855 kb); *tyrS* (3,036 kb) and *tyrZ* (3,945 kb)) or the two *mutS* paralogues (*mutS* and *yshD*). This latter situation is similar to that found in *Synechocystis*. In the case of *B. subtilis*, the presence of two MutS proteins could indicate that there are two different pathways for long-patch mismatch repair, possibly a consequence of the active genetic transformation mechanism of *B. subtilis*.

**Families of orthologues.** Because *Mycoplasma* spp. are thought to be derived from Gram-positive bacteria similar to *B. subtilis*, we compared the *B. subtilis* genome with that of *M. genitalium*. Among the 450 genes encoded by *M. genitalium*, the products of 300 are similar to proteins of *B. subtilis*. Among the 146 remaining gene products, a further 3 are similar to proteins of other *Bacillus* species, and 9 to proteins of other Gram-positive bacteria; 25 are similar to proteins of Gram-negative bacteria; and 19 are similar to proteins of other *Mycoplasma* spp. This leaves only 90 genes that would be specific to *M. genitalium* and might be involved in the interaction of this organism with its host.

The *B. subtilis* genome is similar in size to that of *E. coli*. Because these bacteria probably diverged more than one billion years ago, it is of evolutionary value to investigate their relative similarity. About 1,000 *B. subtilis* genes have clear orthologous counterparts in *E. coli* (one-quarter of the genome). These genes did not belong either to the prophage-like regions or to regions coding for secondary metabolism (~15% of the *B. subtilis* genome). This indicates that a large fraction of these genomes shared similar functions. At first sight, however, it seems that little of the operon structure has been conserved. We nevertheless found that ~100 putative operons or parts of operons were conserved between *E. coli* and *B. subtilis*. Among these, ~12 exhibited a reshuffled gene order (typically, the arabinose operon is *araABD* in *B. subtilis* and *araBAD* in *E. coli*). In addition to the core of the translation and transcription machinery, we identified other classes of operons that were well conserved between the two organisms, including major integrated functions such as ATP synthesis (*atp* operon) and electron transfer (*cta* and *qox* operons). As well as being well preserved, the murein biosynthetic region was partly duplicated, allowing creation of part of the genes required for the sporulation division machinery<sup>41</sup>. The amino-acid biosynthesis genes differ more in their organization: the *E. coli* genes for arginine biosynthesis are spread throughout the chromosome, whereas the arginine biosynthesis genes of *B. subtilis* form an operon. The same is true for purine biosynthetic genes. Genes responsible for the biosynthesis of coenzymes and prosthetic groups in *B. subtilis* are often clustered in operons that differ from those found in *E. coli*. Finally, several operons conserved in *E. coli* and *B. subtilis* correspond to unknown functions, and should therefore be priority targets for the functional analysis of these model genomes.

Comparison with *Synechocystis* PCC6803 revealed about 800 orthologues. However, in this case the putative operon structure is extremely poorly conserved, apart from four of the ribosomal protein operons, the *groES*–*groEL* operon, *yfnHG* (respectively in *Synechocystis* *rfbFG*), *rpsB*–*tsf*, *ylxS*–*nusA*–*infB*, *asd*–*dapGA*–*ymfA*, *spmAB*, *efp*–*accB*, *grpE*–*dnaK*, *yurXW*. The nine-gene *atp* operon of *B. subtilis* is split into two parts in *Synechocystis*: *atpBE* and *atpIHGFDAC*.

## Conclusion

The biochemistry, physiology and molecular biology of *B. subtilis* have been extensively studied over the past 40 years. In particular, *B. subtilis* has been used to study postexponential phase phenomena such as sporulation and competence for DNA uptake. The genome sequences of *E. coli* and *B. subtilis* provide a means of studying the

evolutionary divergence, one billion years ago, of eubacteria into the Gram-positive and Gram-negative groups. The availability of powerful genetic tools will allow the *B. subtilis* genome sequence data to be exploited fully within the framework of a systematic functional analysis program, undertaken by a consortium of 19 European and 7 Japanese laboratories coordinated by S. D. Ehrlich (INRA, Jouy-en-Josas, France) and by N. Ogasawara and H. Yoshikawa (Nara Institute of Science and Technology, Nara, Japan). □

## Methods

**Genome cloning and sequencing.** An international consortium was established to sequence the genome of *B. subtilis* strain 168 (refs 9, 10, 42). At its peak, 25 European, seven Japanese and one Korean laboratory participated in the program, together with two biotechnology companies. Five contiguous DNA regions totalling 0.94 Mb, and two additional regions of 0.28 and 0.14 Mb, were sequenced by the Japanese partners, while the European partners sequenced a total of 2.68 Mb. A few sequences from strain 168 published previously were not resequenced when long overlaps did not indicate differences.

A major technical difficulty was the inability to construct in *E. coli* gene banks representative of the entire *B. subtilis* chromosome using vectors that have proved efficient for other sources of bacterial DNA (such as bacteriophage or cosmid vectors). This was due to the generally very high level of expression of *B. subtilis* genes in *E. coli*, leading to toxic effects. This limitation was overcome by: cloning into a variety of vectors<sup>9,43,44</sup>; using an *E. coli* strain maintaining low-copy number plasmids<sup>44</sup>; using an integrative plasmid/marker rescue genome-walking strategy<sup>44</sup>; and *in vitro* amplification using polymerase chain reaction (PCR) techniques<sup>45,46</sup>.

Although cloning vectors were used in the early stages as templates for sequencing reactions, they were largely superseded in the later stages by long-range and inverse PCR techniques. To reduce sequencing errors resulting from PCR amplification artefacts, at least eight amplification reactions were performed independently and subsequently pooled. The various sequencing groups were free to choose their own strategy, except that all DNA sequences had to be determined entirely on both strands.

**Sequence annotation and verification.** The sequences were annotated by the groups, and sent to a central depository at the Institut Pasteur<sup>14</sup>. The Japanese sequences were also sent there through the Japanese depository at the Nara Institute of Science and Technology. The same procedures were used to identify CDSs and to detect frameshifts. They were embedded within a cooperative computer environment dedicated to automatic sequence annotation and analysis<sup>39</sup>. In a first step, we identified in all six possible frames the open reading frames (ORFs) that were at least 100 codons in length. In a second step, three independent methods were used: the first method used the GeneMark coding-sequence prediction method<sup>47</sup> together with the search for CDSs preceded by typical translation initiation signals (5'-AAGGAGTG-3'), located 4–13 bases upstream of the putative start codons (ATG, TTG or GTG); the second method used the results of a BLAST2X analysis performed on the entire *B. subtilis* genome against the non-redundant protein database at the NCBI; and the third method was based on the distribution of non-overlapping trinucleotides or hexanucleotides in the three frames of an ORF<sup>48</sup>.

In general, frameshifts and missense mutations generating termination codons or eliminating start codons are relatively easy to detect. We shall devise a procedure for detecting another type of error, GC instead of CG or vice versa, which are much more difficult to identify. It should be noted that putative frameshift errors should not be corrected automatically. The sequences of the flanking regions of a 500-bp fragment centred around a putative error were sent to an independent verification group, which performed PCR amplifications using chromosomal DNA as template, and sequenced the corresponding DNA products.

**Organization and accessibility of data.** The *B. subtilis* sequence data have been combined with data from other sources (biochemical, physiological and genetic) in a specialized database, SubtiList<sup>49</sup>, available as a Macintosh or Windows stand-alone application (4th Dimension runtime) by anonymous FTP at <ftp://ftp.pasteur.fr/pub/GenomeDB/SubtiList>. SubtiList is also accessible through a World-Wide Web server at <http://www.pasteur.fr/Bio/SubtiList.html>,



where it has been implemented on a UNIX system using the Sybase relational database management system. A completely rewritten version of SubtiList is in preparation to facilitate browsing of the information of the whole chromosome. Flat files of the whole DNA and protein sequences in EMBL and FASTA format will be made available at the above ftp address. Another *B. subtilis* genome database is also under development at the Human Genome Center of Tokyo University (<http://www.genome.ad.jp>), and SubtiList will also be available there.

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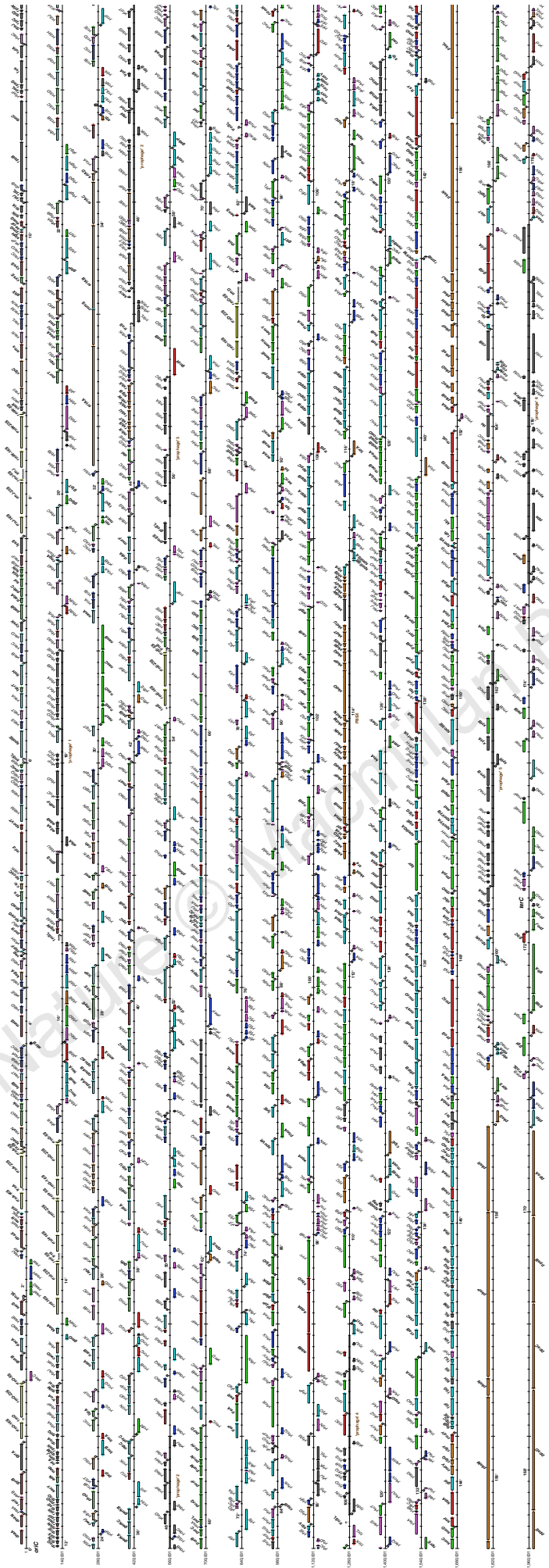
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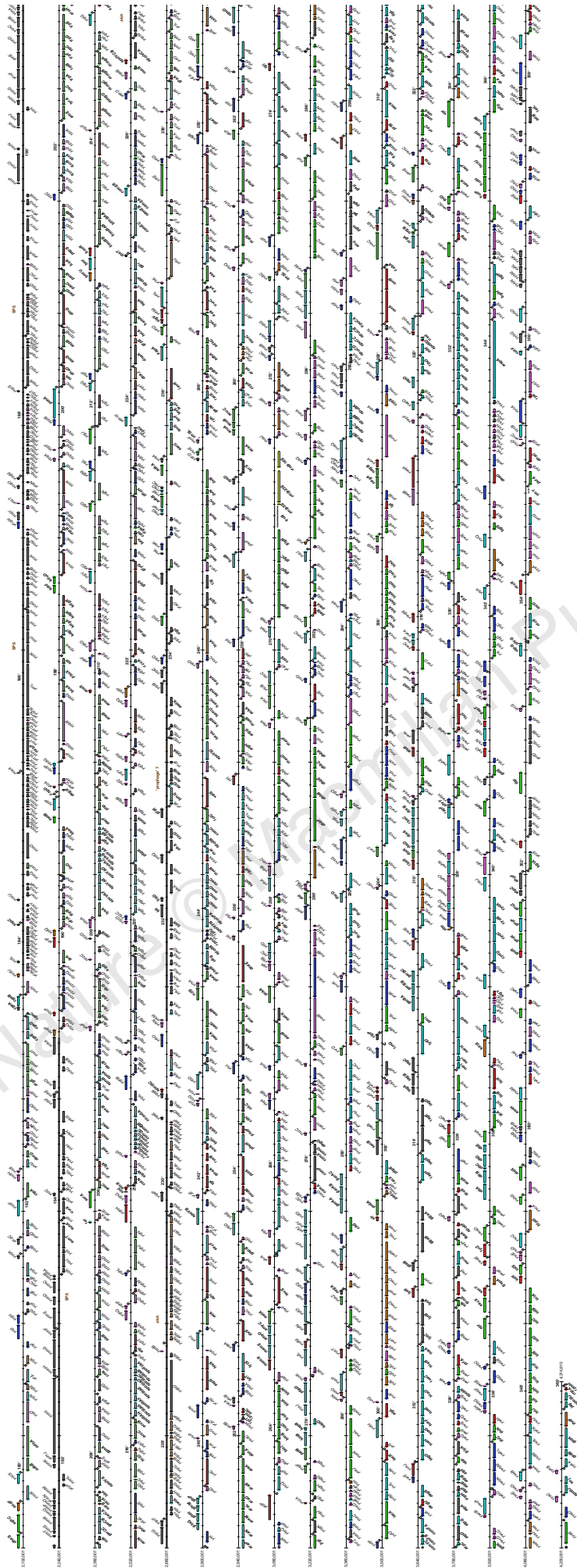








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<i>ywpB</i>	3743	hydroxymyristoyl-(acyl carrier protein) dehydrogenase	<i>yjbT</i>	1245	thiamin biosynthesis	<i>recR</i>	29	DNA repair and genetic recombination
<i>yxjD</i>	4001	3-oxoadipate CoA-transferase	<i>yjbU</i>	1245	thiamin biosynthesis	<i>ruvA</i>	2636	Holliday junction DNA helicase
<i>yxjE</i>	4001	3-oxoadipate CoA-transferase	<i>yjbV</i>	1246	phosphomethylpyrimidine kinase	<i>ruvB</i>	2635	Holliday junction DNA helicase
II.5		METABOLISM OF COENZYMES AND PROSTHETIC GROUPS ..... 99	<i>ykqB</i>	1513	thiamin biosynthesis	<i>sbcD</i>	1143	endonuclease SbcD homologue
<i>bioA</i>	3094	adenosylmethionine-8-amino-7-oxononanoate aminotransferase (biotin biosynthesis)	<i>ykxK</i>	1440	6-pyruvyl tetrahydrobiopterin synthase	<i>yjbP</i>	1659	ATP-dependent DNA helicase
<i>bioB</i>	3091	biotin synthetase (biotin biosynthesis)	<i>ykxL</i>	1440	coenzyme PQQ synthesis	<i>yocI</i>	2095	ATP-dependent DNA helicase
<i>bioD</i>	3091	dethiobiotin synthetase (biotin biosynthesis)	<i>yjbQ</i>	1577	pyrimidine-thiamine biosynthesis	<i>yorkQ</i>	2180	single-strand DNA-specific exonuclease
<i>bioF</i>	3092	8-amino-7-oxononanoate synthase (biotin biosynthesis)	<i>ylnD</i>	1633	uroporphyrin-III C-methyltransferase	<i>yqhH</i>	2549	SNF2 helicase
<i>bioI</i>	3089	cytochrome P450-like enzyme (biotin biosynthesis)	<i>ylnF</i>	1635	uroporphyrin-III C-methyltransferase	<i>yrrC</i>	2808	conjugation transfer protein
<i>bioW</i>	3094	8-carboxyhexanoate-CoA ligase (biotin biosynthesis)	<i>yiol</i>	1642	pantothenate metabolism flavoprotein	<i>yrvE</i>	2825	single-strand DNA-specific exonuclease
<i>dfrA</i>	2296	dihydrofolate reductase (glycine/purine/DNA precursor synthesis, conversion of dUMP to dTMP)	<i>yngH</i>	1954	protein carboxylase	<i>yvwA</i>	3735	SNF2 helicase
<i>dhaS</i>	2100	aldehyde dehydrogenase	<i>yocD</i>	2127	nitroreductase	III.4		DNA PACKAGING AND SEGREGATION ..... 10
<i>dhaA</i>	3291	2,3-dihydro-2,3-dihydroxybenzoate dehydrogenase (2,3-dihydroxybenzoate biosynthesis)	<i>yqgV</i>	2574	5-formyltetrahydrofolate cyclo-ligase	<i>grfA</i>	1935	DNA gyrase-like protein (subunit A)
<i>dhbB</i>	3288	isochorismatase (2,3-dihydroxybenzoate biosynthesis)	<i>yqS</i>	2469	pantothenate kinase	<i>grfB</i>	1933	DNA gyrase-like protein (subunit B)
<i>dhbC</i>	3291	isochorismatase synthase (2,3-dihydroxybenzoate biosynthesis)	<i>yrrL</i>	2796	folate metabolism	<i>grfA</i>	7	DNA gyrase (subunit A)
<i>dhbE</i>	3289	2,3-dihydroxybenzoate-AMP ligase (enterobactin synthetase component E) (2,3-dihydroxybenzoate biosynthesis)	<i>yrrM</i>	2795	caffeoyl-CoA O-methyltransferase	<i>gyrB</i>	5	DNA gyrase (subunit B)
<i>dhbF</i>	3287	involved in 2,3-dihydroxybenzoate biosynthesis	<i>yueD</i>	3265	sepiapterin reductase	<i>hbs</i>	2385	non-specific DNA-binding protein HBSu
<i>folA</i>	87	dihydropterin aldolase (folate biosynthesis)	<i>yueJ</i>	3261	pyrazinamidase/nicotinamidase	<i>smc</i>	1666	chromosome segregation SMC protein homologue
<i>folC</i>	2866	folyl-polyglutamate synthetase (folate biosynthesis)	<i>yueK</i>	3260	nicotinate phosphoribosyltransferase	<i>smf</i>	1682	DNA processing Smf protein homologue
<i>folD</i>	2529	methylene tetrahydrofolate dehydrogenase / methylenetetrahydrofolate cyclohydrolase (purines and amino acids biosynthesis)	<i>yuiG</i>	3293	biotin metabolism	<i>topA</i>	1683	DNA topoisomerase I
<i>folK</i>	87	7,8-dihydro-8-hydroxymethylpterin pyrophosphokinase (dihydrofolate biosynthesis)	<i>yurB</i>	3335	4-hydroxybenzoyl-CoA reductase	<i>topB</i>	476	DNA topoisomerase III
<i>ggt</i>	2004	$\gamma$ -glutamyltranspeptidase (glutathione metabolism)	<i>yurC</i>	3338	4-hydroxybenzoyl-CoA reductase	<i>yopN</i>	2225	HU-related DNA-binding protein
<i>gsaB</i>	943	glutamate-1-semialdehyde aminotransferase	<i>yurD</i>	3338	4-hydroxybenzoyl-CoA reductase	III.5		RNA SYNTHESIS ..... 244
<i>hemA</i>	2878	glutamyl-tRNA reductase (porphyrin biosynthesis)	<i>yutB</i>	3320	lipic acid synthetase	III.5.1		INITIATION ..... 19
<i>hemB</i>	2874	8-aminolevulinic acid dehydratase (porphyrin biosynthesis)	<i>ywaB</i>	3950	quinone biosynthesis	<i>sigA</i>	2601	RNA polymerase major sigma factor ( $\sigma^70$ )
<i>hemC</i>	2876	porphobilinogen deaminase (porphyrin biosynthesis)	<i>ywbE</i>	3796	protoporphyrinogen oxidase	<i>sigB</i>	522	RNA polymerase general stress sigma factor ( $\sigma^32$ )
<i>hemD</i>	2875	uroporphyrinogen III cosynthase (porphyrin biosynthesis)	<i>ywcC</i>	3755	isochorismatase	<i>sigD</i>	1716	RNA polymerase flagella, motility, chemotaxis and autolysis sigma factor ( $\sigma^{54}$ )
<i>hemE</i>	1086	uroporphyrinogen III decarboxylase (porphyrin biosynthesis)	II.6		METABOLISM OF PHOSPHATE ..... 9	<i>sigE</i>	1604	RNA polymerase sporulation mother cell-specific (early) sigma factor ( $\sigma^S$ ) (SpollGB)
<i>hemH</i>	1087	ferrochelatase (porphyrin biosynthesis)	<i>phoA</i>	1018	alkaline phosphatase A	<i>sigF</i>	2443	RNA polymerase sporulation forespore-specific (early) sigma factor ( $\sigma^S$ ) (SpollAC)
<i>hemL</i>	2873	glutamate-1-semialdehyde 2,1-aminotransferase (porphyrin biosynthesis)	<i>phoB</i>	621	alkaline phosphatase III	<i>sigG</i>	1605	RNA polymerase sporulation forespore-specific (late) sigma factor ( $\sigma^S$ ) (SpollIG)
<i>hemN</i>	2630	coproporphyrinogen III oxidase (porphyrin biosynthesis)	<i>phoD</i>	284	phosphodiesterase/alkaline phosphatase	<i>sigH</i>	117	RNA polymerase vegetative and early stationary-phase sigma factor ( $\sigma^70$ ) (SpolH)
<i>hemX</i>	2877	negative effector of the concentration of HemA	<i>phoH</i>	2615	phosphate starvation-induced protein	<i>sigL</i>	3513	RNA polymerase sigma factor ( $\sigma^4$ )
<i>hemY</i>	1088	protoporphyrinogen IX oxidase (porphyrin biosynthesis)	<i>xpaC</i>	36	hydrolysis of 5-bromo-4-chloroindolyl phosphate	<i>sigV</i>	2769	RNA polymerase ECF-type sigma factor ( $\sigma^5$ )
<i>menB</i>	3149	dihydroxynaphthoic acid synthetase (menaquinone biosynthesis)	<i>ybiM</i>	248	alkaline phosphatase	<i>sigW</i>	195	RNA polymerase ECF-type sigma factor ( $\sigma^6$ )
<i>menD</i>	3151	2-succinyl-6-hydroxy-2,4-cyclohexadiene-1-carboxylate synthase / 2-oxoglutarate decarboxylase (menaquinone biosynthesis)	<i>ykoX</i>	1408	alkaline phosphatase	<i>sigX</i>	2414	RNA polymerase ECF-type sigma factor ( $\sigma^7$ )
<i>menE</i>	3148	O-succinylbenzoic acid-CoA ligase (menaquinone biosynthesis)	<i>ykoX</i>	1408	alkaline phosphatase	<i>sigY</i>	3970	RNA polymerase ECF-type sigma factor ( $\sigma^8$ )
<i>menF</i>	3153	menaquinone-specific isochorismatase (menaquinone biosynthesis)	<i>yiaK</i>	1549	phosphate starvation inducible protein	<i>sigZ</i>	2742	RNA polymerase ECF-type sigma factor ( $\sigma^9$ )
<i>moaB</i>	3014	molybdopter precursor biosynthesis	<i>yngC</i>	1947	alkaline phosphatase	<i>spolIC</i>	2701	RNA polymerase sporulation mother cell-specific (late) sigma factor ( $\sigma^S$ ) (C-terminal half)
<i>moaD</i>	1499	molybdopter converting factor (subunit 1)	II.7		METABOLISM OF SULPHUR ..... 8	<i>spolVCB</i>	2652	RNA polymerase sporulation mother cell-specific (late) sigma factor ( $\sigma^S$ ) (N-terminal half)
<i>moaE</i>	1498	molybdopter converting factor (subunit 2)	<i>yisZ</i>	1170	adenylsulfate kinase	<i>xpf</i>	1324	RNA polymerase PoxX sigma factor-like
<i>moaA</i>	1495	molybdopter-guanine dinucleotide biosynthesis	<i>yitA</i>	1171	sulfate adenyltransferase	<i>yhdM</i>	1030	RNA polymerase ECF-type sigma factor
<i>moaB</i>	1498	molybdopter-guanine dinucleotide biosynthesis	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>ykoZ</i>	1411	RNA polymerase sigma factor
<i>moaE</i>	1497	molybdopter biosynthesis protein	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>yiaC</i>	1543	RNA polymerase ECF-type sigma factor
<i>moaB</i>	1496	molybdopter biosynthesis protein	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	III.5.2		REGULATION ..... 213
<i>mtA</i>	2385	GTP cyclohydrolase I (tetrahydrofolate biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>abh</i>	1517	transcriptional regulator of transition state genes (AbrB-like)
<i>nadA</i>	2846	quinolinate synthetase (quinolinate biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>abrB</i>	45	transcriptional pleiotropic regulator of transition state genes ( <i>aprE</i> , <i>comK</i> , <i>ftsAZ</i> , <i>hpr</i> , <i>motAB</i> , <i>npfE</i> , <i>pdpE</i> , <i>rbS</i> , <i>spoOH</i> , <i>spoVG</i> , <i>spoVE</i> , <i>tycA</i> )
<i>nadB</i>	2849	L-aspartate oxidase (quinolinate biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>acoR</i>	883	transcriptional activator of the acetoin dehydrogenase operon ( <i>acoABC</i> )
<i>nadC</i>	2847	nicotinate-nucleotide pyrophosphorylase (NAD/NADP biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>ahrC</i>	2522	transcriptional regulator of arginine metabolism expression ( <i>roc</i> operon)
<i>nadE</i>	338	NH <sub>4</sub> <sup>+</sup> -dependent NAD <sup>+</sup> synthetase (NAD biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>alsR</i>	3711	transcriptional regulator of the $\alpha$ -acetolactate operon ( <i>alsSD</i> )
<i>narA</i>	3772	molybdopter precursor biosynthesis	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>ansR</i>	2456	transcriptional repressor of the <i>ansAB</i> operon ( <i>Xre</i> family)
<i>narX</i>	355	uroporphyrin-III C-methyltransferase (porphyrin biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>araR</i>	3485	transcriptional repressor of the arabinose operon ( <i>araBDLMMNPO</i> )
<i>nifS</i>	2849	required for NAD biosynthesis	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>aziB</i>	2729	transcriptional repressor of the <i>aziBCD</i> operon
<i>pabA</i>	84	p-aminobenzoate synthase glutamine amidotransferase (subunit B) / anthranilate synthase (subunit II) (folate and tryptophan biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>birA</i>	2355	transcriptional repressor of the biotin operon ( <i>bioWAFDBI</i> ) / biotin acetyl-CoA-carboxylase synthetase
<i>pabB</i>	83	p-aminobenzoate synthase (subunit A) (folate biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>bltR</i>	2716	transcriptional regulator of the <i>bltD</i> operon
<i>pabC</i>	85	aminodeoxychorismate lyase (folate biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>bmrR</i>	2495	transcriptional activator of the <i>bmrUR</i> operon
<i>panB</i>	2354	ketopantoate hydroxymethyltransferase (pantothenate biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>ccpA</i>	3044	transcriptional regulator involved in carbon catabolite control
<i>panC</i>	2353	pantothenate synthetase (pantothenate biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>cheB</i>	1711	two-component response regulator-like [CheA] / methyl-accepting chemotaxis proteins-gluamate methylesterase
<i>panD</i>	2352	aspartate 1-decarboxylase (pantothenate biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>cheY</i>	1703	two-component response regulator [CheA] involved in modulation of flagellar switch bias (chemotaxis)
<i>ribA</i>	2429	GTP cyclohydrolase II / 3,4-dihydroxy-2-butanone 4-phosphate synthase (riboflavin biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>citR</i>	1020	transcriptional repressor of the citrate synthase I gene ( <i>citA</i> )
<i>ribB</i>	2429	riboflavin synthase ( $\alpha$ subunit) (riboflavin biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>citT</i>	832	two-component response regulator [CitS]
<i>ribC</i>	1737	riboflavin kinase / FAD synthase (riboflavin biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>codY</i>	1690	transcriptional pleiotropic repressor (expression of <i>srfA</i> , <i>comK</i> , <i>dpp</i> , <i>gabP</i> , <i>hut</i> , <i>ureABC</i> )
<i>ribG</i>	2431	riboflavin-specific deaminase (riboflavin biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>comA</i>	3253	two-component response regulator [ComP] of late competence genes / surfactin production competence transcription factor (CTF), final autoregulatory control switch prior to competence development
<i>ribH</i>	2428	riboflavin synthase ( $\beta$ subunit) (riboflavin biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>comK</i>	1117	transcriptional regulator of late competence operon ( <i>comG</i> ) and surfactin expression ( <i>srfA</i> )
<i>ribT</i>	2427	reductase (riboflavin biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>comQ</i>	3256	transcriptional regulator of late competence operon ( <i>comG</i> ) and surfactin expression ( <i>srfA</i> )
<i>sul</i>	86	dihydropterolate synthase (dihydrofolate biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>ctsR</i>	101	transcriptional repressor of class III stress genes ( <i>clpC</i> , <i>clpP</i> )
<i>thiA</i>	955	synthesis of the pyrimidine moiety of thiamin (thiamin biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>degA</i>	1163	transcriptional activator involved in the degradation of glutamine phosphoribosylpyrophosphate amidotransferase
<i>thiC</i>	3930	thiamine-phosphate pyrophosphorylase (thiamin biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>degU</i>	3644	two-component response regulator [DegS] involved in degradative enzyme and competence regulation ( <i>sacB</i> , <i>degQ</i> , <i>comK</i> )
<i>thiD</i>	3900	phosphomethylpyrimidine kinase (thiamin biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>deoR</i>	4052	transcriptional repressor of the <i>dra</i> / <i>nupC</i> / <i>pdp</i> operon (deoxyribonucleoside)
<i>thiK</i>	3931	hydroxyethylthiazole kinase (thiamin biosynthesis)	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>fnr</i>	3831	transcriptional regulator of anaerobic genes ( <i>narK</i> , <i>narGHJ</i> )
<i>yaal</i>	26	isochorismatase	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>fruR</i>	1507	transcriptional repressor of the fructose operon ( <i>fruRBA</i> )
<i>ydiA</i>	640	thiamin-monophosphate kinase	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>gerE</i>	2904	transcriptional regulator required for expression of late spore coat genes
<i>ydiG</i>	646	molybdopter precursor biosynthesis	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>glcR</i>	3739	transcriptional repressor involved in the expression of the phosphotransferase system
<i>yhaV</i>	1058	coproporphyrinogen III oxidase	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>glcT</i>	1456	transcriptional antiterminal essential for the expression of the <i>ptsGHI</i> operon
<i>yhcB</i>	979	flavodoxin	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>glrR</i>	1877	transcriptional repressor of the glutamine synthetase gene ( <i>glrA</i> )
<i>yhuU</i>	1112	biotin biosynthesis	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>glpP</i>	1001	transcriptional antiterminal and control of mRNA stability of <i>glpD</i>
<i>yhxA</i>	1000	adenosylmethionine-8-amino-7-oxononanoate aminotransferase	<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>glpC</i>	2014	transcriptional activator of the glutamate synthase operon ( <i>gltAB</i> )
			<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>gltR</i>	2725	transcriptional repressor of the glutamate synthase operon ( <i>gltAB</i> )
			<i>yitB</i>	1172	phospho-adenylsulfate sulfotransferase	<i>gntR</i>	4113	transcriptional repressor of the gluconate operon ( <i>gntRKPZ</i> )
			III.1		DNA REPLICATION ..... 22			
			<i>dnaA</i>	2965	initiation of chromosome replication			
			<i>dnaB</i>	2965	initiation of chromosome replication / membrane attachment protein			
			<i>dnaC</i>	4158	replicative DNA helicase			
			<i>dnaD</i>	2345	initiation of chromosome replication			
			<i>dnaE</i>	2994	DNA polymerase III ( $\alpha$ subunit)			
			<i>dnaG</i>	2603	DNA primase			
			<i>dnal</i>	2963	primosome component (helicase loader)			
			<i>dnai</i>	2	DNA polymerase III ( $\beta$ subunit)			
			<i>dnaiX</i>	27	DNA polymerase III ( $\gamma$ and $\tau$ subunits)			
			<i>hoiB</i>	41	DNA polymerase III ( $\delta$ subunit)			
			<i>polA</i>	2975	DNA polymerase I			
			<i>polC</i>	1727	DNA polymerase III ( $\alpha$ subunit)			
			<i>priA</i>	1643	ribosomal replication factor Y			
			<i>rh</i>	1677	ribonuclease H			
			<i>rtp</i>	2018	replication terminator protein			
			<i>ssb</i>	4199	single-strand DNA-binding protein			
			<i>yerF</i>	719	ATP-dependent DNA helicase			
			<i>yerG</i>	721	DNA ligase			
			<i>yocV</i>	2192	DNA ligase			
			<i>yori</i>	2179	DNA polymerase III ( $\alpha$ subunit)			
			<i>yrcP</i>	2311	5'-3' exonuclease			
			<i>ywpH</i>	3740	single-strand DNA-binding protein			
			III.2		DNA RESTRICTION/MODIFICATION AND REPAIR ..... 39			
			<i>adaA</i>	204	methylphosphotriester-DNA alkyltransferase / transcriptional activator of the <i>adaAB</i> operon			

<i>gutR</i>	667	transcriptional activator of the sorbitol dehydrogenase gene ( <i>gutA</i> )	<i>ydeC</i>	562	transcriptional regulator (AraC/XylS family)	III.5.4	TERMINATION.....4	
<i>hpr</i>	1073	transcriptional repressor of sporulation and extracellular proteases genes ( <i>aprE</i> , <i>nprE</i> , <i>sin</i> )	<i>ydeE</i>	564	transcriptional regulator (AraC/XylS family)	<i>nusA</i>	1732	transcription termination
<i>hrcA</i>	2629	transcriptional repressor of class I heat-shock genes ( <i>dnaK</i> , <i>groESL</i> )	<i>ydeF</i>	571	transcriptional regulator (GntR family) / amino-transferase (MocR-like)	<i>nusG</i>	118	transcription antitermination factor
<i>hutP</i>	4040	transcriptional activator of the histidine utilization operon ( <i>hutPHUGM</i> )	<i>ydeL</i>	574	transcriptional regulator (GntR family) / amino-transferase (MocR-like)	<i>rho</i>	3904	transcriptional terminator Rho
<i>iolR</i>	4084	transcriptional repressor of the myo-inositol catabolism operon ( <i>iolABCDEFGHIJ/iolRS</i> )	<i>ydeS</i>	578	transcriptional regulator (TetR/AcrR family)	<i>yqhZ</i>	2529	transcription termination
<i>kdgR</i>	2325	transcriptional repressor of the pectin utilization operon ( <i>kdgRKA</i> )	<i>ydeT</i>	579	transcriptional regulator (ArsR family)			
<i>lacR</i>	3509	transcriptional repressor of the $\beta$ -galactosidase gene ( <i>lacA</i> )	<i>ydeY</i>	583	transcriptional regulator (GntR family) / amino-transferase (MocR-like)			
<i>levR</i>	2765	transcriptional activator of the levansucrase operon ( <i>levDEFGLsacC</i> )	<i>ydfI</i>	589	two-component response regulator [YdfH]			
<i>lexA</i>	1918	transcriptional repressor of the SOS regulon	<i>ydgG</i>	609	transcriptional regulator (MarR family)			
<i>licR</i>	3963	transcriptional regulator (antiterminator) of the lichenan operon ( <i>licBCAH</i> )	<i>ydgJ</i>	613	transcriptional regulator (MarR family)			
<i>licT</i>	4012	transcriptional antiterminator required for substrate-dependent induction and catabolite repression of <i>bglPH</i>	<i>ydhC</i>	616	transcriptional regulator (GntR family)			
<i>lmrA</i>	290	transcriptional repressor of the lincomycin operon ( <i>lmrBA</i> )	<i>ydhI</i>	630	transcriptional regulator (GntR family)			
<i>lrpA</i>	551	transcriptional Lrp-like regulator (repression of <i>glyA</i> transcription and KinB-dependent sporulation)	<i>ydhJ</i>	632	transcriptional regulator (TetR/AcrR family)			
<i>lrpB</i>	552	transcriptional Lrp-like regulator (repression of <i>glyA</i> transcription and KinB-dependent sporulation)	<i>ydhK</i>	908	two-component response regulator [YdhI]			
<i>lrpC</i>	476	transcriptional regulator (Lrp/AsnC family)	<i>ydhL</i>	1027	transcriptional regulator (GntR family) / amino-transferase (MocR-like)			
<i>lytR</i>	3662	attenuator role for <i>lytABC</i> and <i>lytR</i> expression	<i>ydhQ</i>	1033	transcriptional regulator (MerR family)			
<i>lytT</i>	2956	two-component response regulator [LytS] involved in the rate of autolysis	<i>ydhD</i>	1089	transcriptional regulator (TetR/AcrR family)			
<i>msmR</i>	3096	transcriptional regulator (LacI family)	<i>ydhM</i>	1129	transcriptional regulator (LacI family)			
<i>mta</i>	3764	transcriptional activator of multidrug-efflux transfer genes ( <i>mta</i> and <i>bit</i> )	<i>ydhN</i>	1162	transcriptional regulator (AraC/XylS family)			
<i>mtb</i>	2384	hypothan operon RNA-binding attenuation protein (TRAP)	<i>ydhO</i>	1166	transcriptional regulator (GntR family) / amino-transferase (MocR-like)			
<i>paiA</i>	3304	transcriptional repressor of sporulation, septation and degradative enzyme genes ( <i>aprE</i> , <i>nprE</i> , <i>phoA</i> , <i>sacB</i> )	<i>ydhP</i>	1270	transcriptional antiterminator (BglG family)			
<i>paiB</i>	3304	transcriptional repressor of sporulation and degradative enzyme genes	<i>ydhQ</i>	1272	transcription regulation			
<i>phoP</i>	2978	two-component response regulator [PhoR] involved in phosphate regulation ( <i>phoA</i> , <i>phoB</i> , <i>phoD</i> , <i>resABCDE</i> )	<i>ydhR</i>	1308	transcriptional regulator (LacI family)			
<i>pkcA</i>	1781	transcriptional regulator of the polyketide synthase operon ( <i>pkcS</i> )	<i>ydhS</i>	1391	two-component response regulator [YkoH]			
<i>purR</i>	54	transcriptional repressor of the purine operon ( <i>purEKBCLQFMNH</i> )	<i>ydhT</i>	1398	transcriptional regulator (MarR family)			
<i>pyrR</i>	1618	transcriptional attenuation of the pyrimidine operon ( <i>pyrPBCADF</i> ) / uracil phosphoribosyltransferase activity (minor) (pyrimidine biosynthesis)	<i>ydhU</i>	1485	transcriptional regulator (LysR family)			
<i>rbtR</i>	3700	transcriptional repressor of the ribose operon ( <i>rbtRKDACB</i> )	<i>ydhV</i>	1433	transcriptional regulator (MarR family)			
<i>resD</i>	2417	two-component response regulator [ResE] involved in aerobic and anaerobic respiration ( <i>resA</i> , <i>resB</i> , <i>resC</i> , <i>resD</i> )	<i>ydhW</i>	1455	transcriptional regulator (LacI family)			
<i>ribR</i>	3001	transcriptional regulator of riboflavin biosynthesis genes	<i>ydhX</i>	1754	transcriptional regulator (GntR family)			
<i>rocR</i>	4145	transcriptional activator of arginine utilization operons ( <i>rocABC</i> , <i>rocDEF</i> )	<i>ydhY</i>	1923	two-component response regulator (CheY homologue)			
<i>sacT</i>	3906	transcriptional antiterminator involved in positive regulation of <i>sacA</i> and <i>sacP</i>	<i>ydhZ</i>	2045	transcriptional regulator (LysR family)			
<i>sacV</i>	532	transcriptional regulator of the levansucrase gene ( <i>sacB</i> )	<i>ydhA</i>	2058	transcriptional regulator (phage-related) (Xre family)			
<i>sacY</i>	3942	transcriptional antiterminator involved in positive regulation of levansucrase and sucrose synthesis	<i>ydhB</i>	2080	transcriptional regulator (AraC/XylS family)			
<i>senS</i>	959	transcriptional activator of extracellular enzyme genes ( <i>amyE</i> , <i>aprE</i> , <i>nprE</i> )	<i>ydhC</i>	2091	two-component response regulator [YocF]			
<i>sinR</i>	2552	transcriptional regulator of post-exponential-phase responses genes ( <i>aprE</i> , <i>comK</i> , <i>kinB</i> , <i>sigD</i> , <i>spo0A</i> , <i>spoIIA</i> , <i>spoIIE</i> , <i>spoIIG</i> )	<i>ydhD</i>	2097	transcriptional regulator (LysR family)			
<i>slr</i>	3529	transcriptional activator of competence development and sporulation genes	<i>ydhE</i>	2221	transcriptional regulator (phage-related) (Xre family)			
<i>spIA</i>	1461	transcriptional regulator of the spore photoproduct lyase operon ( <i>spIAB</i> )	<i>ydhF</i>	2084	transcriptional regulator (ArsR family)			
<i>spo0A</i>	2518	two-component response regulator [KinC] central for the initiation of sporulation ( <i>spo0A</i> , <i>abrB</i> , <i>kinA</i> , <i>kinB</i> , <i>spoIIA</i> , <i>spoIIE</i> , <i>spoIIG</i> ) (part of phosphorylated Spo0B-P <sub>2</sub> -Spo0A-P)	<i>ydhG</i>	2043	transcriptional regulator			
<i>spo0F</i>	3809	two-component response regulator [KinA, KinB] involved in the initiation of sporulation (part of phosphorylated Spo0F-P <sub>2</sub> -Spo0B-P)	<i>ydhH</i>	2294	transcriptional regulator ( $\sigma$ -dependent)			
<i>spoIID</i>	3748	transcriptional regulator of $\sigma^H$ - and $\sigma^I$ -dependent genes	<i>ydhI</i>	2287	transcriptional regulator (Fur family)			
<i>spoVT</i>	64	transcriptional positive and negative regulator of $\sigma^H$ -dependent genes	<i>ydhJ</i>	2287	transcriptional regulator (PliB family)			
<i>tenA</i>	1242	transcriptional regulator of extracellular enzyme genes ( <i>aprE</i> , <i>nprE</i> , <i>phoA</i> , <i>sacB</i> )	<i>ydhK</i>	2414	negative regulator of $\sigma^H$ activity			
<i>tenI</i>	1243	transcriptional activator of extracellular enzyme genes	<i>ydhL</i>	2698	transcriptional regulator (phage-related) (Xre family)			
<i>tnrA</i>	1397	transcriptional pleiotropic regulator involved in global nitrogen regulation (expression of <i>nrpAB</i> , <i>nasB</i> , <i>gabP</i> , <i>ureABC</i> , <i>glnRA</i> )	<i>ydhM</i>	2657	transcriptional regulator (ArsR family)			
<i>treR</i>	853	transcriptional repressor of the trehalose operon ( <i>trePAR</i> )	<i>ydhN</i>	2591	transcriptional regulator (Fur family)			
<i>xre</i>	1321	transcriptional repressor of PBSX genes	<i>ydhO</i>	2543	transcriptional regulator			
<i>xylR</i>	1891	transcriptional repressor of the xylose operon ( <i>xylAB</i> )	<i>ydhP</i>	2506	transcriptional regulator ( $\sigma$ -dependent)			
<i>yacF</i>	88	transcriptional regulator (nitrogen regulation protein)	<i>ydhQ</i>	2450	transcriptional regulator (Fur family)			
<i>ybbB</i>	185	transcriptional regulator (AraC/XylS family)	<i>ydhR</i>	2755	transcriptional regulator (MerR family)			
<i>ybdD</i>	221	two-component response regulator [YbdK]	<i>ydhS</i>	2748	transcriptional regulator (LysR family)			
<i>ybfI</i>	244	transcriptional regulator (AraC/XylS family)	<i>ydhT</i>	2721	transcriptional regulator (LysR family)			
<i>ybpP</i>	251	transcriptional regulator (AraC/XylS family)	<i>ydhU</i>	2777	transcriptional regulator (TetR/AcrR family)			
<i>ybgA</i>	258	transcriptional regulator (GntR family)	<i>ydhV</i>	2770	anti-sigma factor [ $\sigma^I$ ]			
<i>ycbB</i>	267	two-component response regulator [YcbA]	<i>ydhW</i>	2704	two-component response regulator [YrkQ]			
<i>ycbG</i>	273	transcriptional regulator (LysR family)	<i>ydhX</i>	2918	transcriptional regulator (TetR/AcrR family)			
<i>ycbL</i>	278	two-component response regulator [YcbM]	<i>ydhY</i>	2904	transcriptional regulator (MarR family)			
<i>yccH</i>	296	two-component response regulator [YccG]	<i>ydhZ</i>	3063	transcriptional regulator (AraC/XylS family)			
<i>yceK</i>	320	transcriptional regulator (ArsR family)	<i>ydhA</i>	3008	transcriptional regulator (LysR family)			
<i>ycgK</i>	341	transcriptional regulator (LysR family)	<i>ydhB</i>	3118	transcriptional regulator (GntR family)			
<i>yciA</i>	412	transcriptional regulator (LysR family)	<i>ydhC</i>	3113	two-component response regulator [YtsB]			
<i>ycu</i>	426	two-component response regulator [YciK]	<i>ydhD</i>	3071	transcriptional regulator (DeoR family)			
<i>ycnC</i>	438	transcriptional regulator (TetR/AcrR family)	<i>ydhE</i>	3238	two-component response regulator [YufL]			
<i>ycnF</i>	441	transcriptional regulator (GntR family) / amino-transferase (MocR-like)	<i>ydhF</i>	3221	transcriptional regulator (Lrp/AsnC family)			
<i>ycnK</i>	449	transcriptional regulator (DeoR family)	<i>ydhG</i>	3207	transcriptional regulator (DeoR family)			
<i>ycsO</i>	461	transcriptional regulator (LysR family)	<i>ydhH</i>	3345	transcriptional regulator (GntR family)			
<i>ycxD</i>	406	transcriptional regulator (GntR family) / amino-transferase (MocR-like)	<i>ydhI</i>	3374	transcriptional regulator (MarR family)			
<i>ycaZ</i>	439	transcriptional regulator (ArsR family)	<i>ydhJ</i>	3466	transcriptional regulator (ArsR family)			
<i>ycaY</i>	467	transcriptional antiterminator (BglG family)	<i>ydhK</i>	3488	transcriptional regulator (LysR family)			
<i>ydcG</i>	499	two-component response regulator [YdcF]	<i>ydhL</i>	3567	two-component response regulator [YvcQ]			
<i>ydcN</i>	531	transcriptional regulator (phage-related) (Xre family)	<i>ydhM</i>	3558	transcriptional regulator (LacI family)			
			<i>ydhN</i>	3540	transcriptional regulator (TetR/AcrR family)			
			<i>ydhO</i>	3509	transcriptional regulator (GntR family)			
			<i>ydhP</i>	3496	two-component response regulator [YvtT]			
			<i>ydhQ</i>	3646	transcriptional regulator			
			<i>ydhR</i>	3617	transcriptional regulator (TetR/AcrR family)			
			<i>ydhS</i>	3596	transcriptional regulator (GntR family)			
			<i>ydhT</i>	3385	two-component response regulator [YvcB]			
			<i>ydhU</i>	3394	two-component response regulator [YvcE]			
			<i>ydhV</i>	3409	two-component response regulator [YvrG]			
			<i>ydhW</i>	3945	transcriptional regulator (MarR family)			
			<i>ydhX</i>	3932	transcriptional regulator (LysR family)			
			<i>ydhY</i>	3864	transcriptional regulator (LysR family)			
			<i>ydhZ</i>	3853	transcriptional regulator (LysR family)			
			<i>ydhA</i>	3748	transcriptional regulator (MarR family)			
			<i>ydhB</i>	3723	transcriptional regulator (MarR family)			
			<i>ydhC</i>	3720	transcriptional regulator (Lrp/AsnC family)			
			<i>ydhD</i>	3693	transcriptional regulator			
			<i>ydhE</i>	4109	transcriptional regulator (MarR family)			
			<i>ydhF</i>	4072	two-component response regulator [YxdK]			
			<i>ydhG</i>	3993	two-component response regulator [YxjM]			
			<i>ydhH</i>	3991	transcriptional regulator (LysR family)			
			<i>ydhI</i>	4197	transcriptional regulator (LacI family)			
			<i>ydhJ</i>	4189	transcriptional regulator (MerR family)			
			<i>ydhK</i>	4183	transcriptional regulator (MarR family)			
			<i>ydhL</i>	4180	transcriptional regulator (LysR family)			
			<i>ydhM</i>	4154	two-component response regulator [YvcG]			
			<i>ydhN</i>	4122	transcriptional regulator (GntR family)			
			<i>ydhO</i>					
			<i>ydhP</i>					
			<i>ydhQ</i>					
			<i>ydhR</i>					
			<i>ydhS</i>					
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			<i>ydhC</i>					
			<i>ydhD</i>					
			<i>ydhE</i>					
			<i>ydhF</i>					

<i>lepA</i>	2632	GTP-binding protein	<i>yvE</i>	3515	spore coat polysaccharide biosynthesis	<i>xxdC</i>	1322	PBSX prophage		
<i>tsf</i>	1718	elongation factor Ts	<i>yvB</i>	3384	serine protease Do	<i>xxdD</i>	1323	PBSX prophage		
<i>tufA</i>	133	elongation factor Tu	<i>yvqC</i>	3732	capsular polysaccharide biosynthesis	<i>xxdE</i>	1327	PBSX prophage		
<i>yiaG</i>	1546	GTP-binding elongation factor	<i>yvqD</i>	3732	capsular polysaccharide biosynthesis	<i>xxdF</i>	1328	PBSX prophage		
			<i>yvqE</i>	3731	capsular polysaccharide biosynthesis	<i>xxdG</i>	1329	PBSX prophage		
III.75	TERMINATION	.....	3	<i>ywsC</i>	3700	capsular polyglutamate biosynthesis	<i>xxdH</i>	1330	PBSX prophage	
<i>frr</i>	1720	ribosome recycling factor	<i>ywtA</i>	3698	capsular polyglutamate biosynthesis	<i>xxdI</i>	1331	PBSX prophage		
<i>prfA</i>	3797	peptide chain release factor 1	<i>ywtB</i>	3698	capsular polyglutamate biosynthesis	<i>xxdJ</i>	1331	PBSX prophage		
<i>prfB</i>	3627	peptide chain release factor 2	<i>yxxA</i>	4148	serine protease Do	<i>xxdK</i>	1332	PBSX prophage		
						<i>xxdM</i>	1333	PBSX prophage		
III.8	PROTEIN MODIFICATION	.....	27	IV.2	DETOXIFICATION	.....	68	<i>xxdN</i>	1334	PBSX prophage
<i>amhX</i>	325	amidohydrolase	<i>aadK</i>	2736	aminoglycoside 6-adenyltransferase	<i>xxdO</i>	1334	PBSX prophage		
<i>igt</i>	3593	prolipoprotein diacylglycerol transferase (lipoprotein biosynthesis)	<i>ahpC</i>	4118	alkyl hydroperoxide reductase (small subunit)	<i>xxdP</i>	1338	PBSX prophage		
			<i>ahpF</i>	4119	alkyl hydroperoxide reductase (large subunit) /	<i>xxdQ</i>	1339	PBSX prophage		
<i>map</i>	147	methionine aminopeptidase	<i>bmrU</i>	2493	NADH dehydrogenase	<i>xxdR</i>	1340	PBSX prophage		
<i>pcp</i>	237	pyrrolidone-carboxylate peptidase				<i>xxdS</i>	1340	PBSX prophage		
<i>ppbB</i>	2435	peptidyl-prolyl isomerase	<i>cah</i>	342	cephalosporin C deacetylase	<i>xxdT</i>	1341	PBSX prophage		
<i>prkA</i>	973	serine protein kinase	<i>cypA</i>	2732	cytochrome P450-like enzyme	<i>xxdU</i>	1342	PBSX prophage		
<i>igl</i>	3212	transglutaminase	<i>cypX</i>	3603	cytochrome P450-like enzyme	<i>xxdV</i>	1343	PBSX prophage		
<i>ybdM</i>	224	protein kinase	<i>katA</i>	960	vegetative catalase 1	<i>xxdW</i>	1345	PBSX prophage		
<i>ydiC</i>	642	glycoprotein endopeptidase	<i>katB</i>	4009	catalase 2	<i>xxdX</i>	1345	PBSX prophage		
<i>ydiD</i>	643	ribosomal-protein-alanine N-acetyltransferase	<i>katX</i>	3964	catalase	<i>xxdY</i>	1345	PBSX prophage lytic exoenzyme		
<i>ydiE</i>	643	glycoprotein endopeptidase	<i>ksgA</i>	51	dimethyladenosine transferase (kasugamycin resistance)	<i>xmA</i>	1325	PBSX terminase (small subunit)		
<i>yfkJ</i>	862	protein-tyrosine phosphatase	<i>mmr</i>	3857	methylerythromycin A resistance protein	<i>xmB</i>	1325	PBSX terminase (large subunit)		
<i>yfjG</i>	840	methionine aminopeptidase	<i>padC</i>	3532	beta-lactamase	<i>xrA</i>	1324	PBSX prophage		
<i>yjck</i>	1261	ribosomal-protein-alanine N-acetyltransferase	<i>penP</i>	2048	beta-lactamase	<i>ycaD</i>	304	L-alanyl-D-glutamate peptidase		
<i>ykbB</i>	1528	formylmethionine deformylase	<i>pksS</i>	1859	hydroxylase of the polyketide produced by the	<i>ydcL</i>	530	integrase		
<i>ykyY</i>	1453	Xaa-Pro dipeptidase				<i>ydcM</i>	531	immunity region protein in prophage		
<i>yloP</i>	1651	protein kinase	<i>sodA</i>	2585	superoxide dismutase	<i>yhgE</i>	1090	phage infection protein		
<i>yppP</i>	2287	peptide methionine sulfoxide reductase	<i>sodF</i>	2103	superoxide dismutase	<i>yjbj</i>	1235	lytic transglycosylase		
<i>yqeT</i>	2624	ribosomal protein L11 methyltransferase	<i>tetL</i>	4188	tetracycline resistance leader peptide	<i>yjqB</i>	1318	phage-related replication protein		
<i>yqhT</i>	2539	Xaa-Pro dipeptidase	<i>thdF</i>	4212	thiophen and furan oxidation	<i>ymaC</i>	1863	phage-related protein		
<i>ytel</i>	3020	protease IV	<i>tmrB</i>	339	tunicamycin resistance	<i>ymaH</i>	1867	host factor-1 protein		
<i>ytpJ</i>	3068	Xaa-His dipeptidase	<i>yaaN</i>	36	toxic cation resistance	<i>ymlD</i>	1755	phage-related protein		
<i>yvtA</i>	3105	protein kinase	<i>yde</i>	190	beta-lactamase	<i>ymlE</i>	1756	phage-related protein		
<i>yxtM</i>	3150	prolyl aminopeptidase	<i>ydfO</i>	581	antibiotic resistance protein	<i>ymlL</i>	1914	phage-related replication protein		
<i>yylE</i>	3297	leucyl aminopeptidase	<i>ydlQ</i>	229	beta-lactamase	<i>yobO</i>	2075	phage-related pre-neck appendage protein		
<i>yylE</i>	3791	protein-tyrosine phosphatase	<i>yblX</i>	229	beta-lactamase	<i>yokA</i>	2284	DNA recombinase		
<i>yxaL</i>	4102	serine/threonine protein kinase	<i>ycbI</i>	276	immunity phosphotransferase	<i>yokL</i>	2274	phage-related protein		
			<i>ycbR</i>	283	toxic cation resistance protein	<i>yolB</i>	2272	phage-related protein		
III.9	PROTEIN FOLDING	.....	8	<i>yceC</i>	312	tellurium resistance protein	<i>yomA</i>	2264	holin	
<i>dnaK</i>	2627	class I heat-shock protein (chaperonin)	<i>yceD</i>	312	tellurium resistance protein	<i>yomJ</i>	2248	phage-related immunity protein		
<i>groEL</i>	650	class I heat-shock protein (chaperonin)	<i>yceE</i>	313	tellurium resistance protein	<i>yomP</i>	2243	phage-related protein		
<i>groES</i>	650	class I heat-shock protein (chaperonin)	<i>yceF</i>	314	tellurium resistance protein	<i>yomR</i>	2242	phage-related protein		
<i>tig</i>	2887	trigger factor (prolyl isomerase)	<i>yceH</i>	316	toxic anion resistance protein	<i>yomS</i>	2241	phage-related lytic exoenzyme		
<i>ykkC</i>	1376	chaperonin	<i>yceI</i>	316	toxic anion resistance protein	<i>yqaD</i>	2200	phage-related DNA-binding protein anti-repressor		
<i>ykkD</i>	1376	chaperonin	<i>ycesF</i>	467	lactam utilization protein	<i>yqaZ</i>	2190	phage-related protein		
<i>ykdR</i>	3541	chaperonin	<i>yddD</i>	496	manganese-containing catalase	<i>yqjB</i>	2160	phage-related endodeoxyribonuclease		
<i>yksD</i>	3541	chaperonin	<i>ydyB</i>	581	macrolide glycosyltransferase	<i>yqjC</i>	2700	phage-related protein		
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<i>bbsA</i>	2304	glutathione peroxidase	<i>yetM</i>	790	salicylate 1-monoxygenase	<i>yqam</i>	2694	phage-related protein		
<i>clpC</i>	104	class III stress response-related ATPase (repressor of competence)	<i>yetO</i>	792	cytochrome P450 / NADPH-cytochrome P450 reductase	<i>yqaO</i>	2692	phage-related protein		
<i>clpE</i>	1437	ATP-dependent Clp protease-like	<i>yfjM</i>	836	nitric-oxide synthase	<i>yqaS</i>	2690	phage-related terminase large subunit		
<i>clpP</i>	3645	ATP-dependent Clp protease proteolytic subunit (class III heat-shock protein)	<i>yfnC</i>	804	fosmidycin resistance protein	<i>yqaT</i>	2689	phage-related terminase small subunit		
<i>clpQ</i>	1688	B-type subunit of the 20S proteasome	<i>ygaF</i>	943	thiol-specific antioxidant protein	<i>yqbA</i>	2688	phage-related protein		
<i>clpX</i>	2885	ATP-dependent Clp protease ATP-binding subunit (class III heat-shock protein)	<i>yhgG</i>	1122	monooxygenase	<i>yqbD</i>	2684	phage-related protein		
<i>clpY</i>	1688	ATP-dependent Clp protease-like	<i>yjgY</i>	1169	chlorine peroxidase	<i>yqbE</i>	2683	phage-related protein		
<i>csbB</i>	930	stress response protein	<i>yjgZ</i>	1291	monooxygenase	<i>yqbl</i>	2681	phage-related protein		
<i>csbB</i>	994	major cold-shock protein	<i>yjgK</i>	1292	macrolide glycosyltransferase	<i>yqbl</i>	2681	phage-related protein		
<i>csbC</i>	559	cold-shock protein	<i>yjgA</i>	1366	immunity to bacteriotoxins	<i>yqbk</i>	2680	phage-related protein		
<i>csbD</i>	2307	cold-shock protein	<i>ykbB</i>	1375	N-acetyltransferase	<i>yqblM</i>	2679	phage-related protein		
<i>cstA</i>	2937	carbon starvation-induced protein	<i>ykoY</i>	1410	toxic anion resistance protein	<i>yqbm</i>	2679	phage-related protein		
<i>ctc</i>	59	general stress protein	<i>yndN</i>	1916	fosfomycin resistance protein	<i>yqbN</i>	2677	phage-related protein		
<i>degQ</i>	3256	degradative enzyme production	<i>yocD</i>	2088	immunity to bacteriotoxins	<i>yqbO</i>	2677	phage-related protein		
<i>degR</i>	2308	degradative enzyme production	<i>yokJ</i>	2117	macrolide glycosyltransferase	<i>yqbP</i>	2672	phage-related protein		
<i>dnaI</i>	2625	heat-shock protein (activation of DnaK)	<i>yoiM</i>	2115	superoxide dismutase	<i>yqbQ</i>	2671	phage-related protein		
<i>dps</i>	3136	stress- and starvation-induced gene controlled by	<i>yokD</i>	2281	aminoglycoside N <sup>3</sup> -acetyltransferase	<i>yqdB</i>	2670	phage-related protein		
			<i>yokM</i>	2655	arsenate reductase	<i>yqds</i>	2670	phage-related protein		
<i>gbsA</i>	3186	glycine betaine aldehyde dehydrogenase (osmoprotection)	<i>yqrT</i>	2596	penicillin tolerance	<i>yqdt</i>	2670	phage-related protein		
<i>gbsB</i>	3184	alcohol dehydrogenase (osmoprotection)	<i>yrtP</i>	2776	cytochrome P450 / NADPH-cytochrome P450 reductase	<i>yqaC</i>	2669	phage-related protein		
<i>gpeE</i>	2628	heat-shock protein (activation of DnaK)	<i>ytpB</i>	2736	2-nitropropane dioxygenase	<i>yqcC</i>	2668	phage-related protein		
<i>gsiB</i>	494	general stress protein	<i>ytlI</i>	3017	thiol peroxidase	<i>yqcD</i>	2667	phage-related protein		
<i>gspA</i>	3944	general stress protein	<i>ytnJ</i>	3002	nitrotriacetate monooxygenase	<i>yqcE</i>	2666	phage-related protein		
<i>hit</i>	1076	Hit-like protein involved in cell-cycle regulation	<i>yubB</i>	3195	bacitracin resistance protein (undecaprenol kinase)	<i>yqxG</i>	2666	phage-related lytic exoenzyme		
<i>htgD</i>	4090	class III heat-shock protein (chaperonin)				<i>yqxH</i>	2665	holin		
<i>htrA</i>	1359	serine protease Do (heat-shock protein)	<i>yusI</i>	3366	arsenate reductase	IV.5	TRANSPOSON AND IS	.....	10	
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<i>lonA</i>	2882	Lon-like ATP-dependent protease	<i>yvpT</i>	3543	reticuline oxidase	<i>ydcQ</i>	533	transposon protein		
<i>lonB</i>	2884	Lon-like ATP-dependent protease	<i>ywch</i>	3910	monooxygenase	<i>ydcR</i>	535	transposon protein		
<i>mrqA</i>	3383	metalloregulation DNA-binding stress protein	<i>ywnH</i>	3760	phosphothreonine acetyltransferase	<i>ydcB</i>	537	transposon protein		
<i>rsbR</i>	519	positive regulator of $\sigma^E$ activity (interaction with RsbS)	<i>yxel</i>	4062	penicillin amidase	<i>ydcE</i>	538	transposon protein		
<i>rsbS</i>	520	negative regulator of $\sigma^E$ activity (antagonist of RsbT)	<i>yxeK</i>	4061	monooxygenase	<i>yddH</i>	544	transposon protein		
<i>rsbT</i>	520	positive regulator of $\sigma^E$ activity (switch protein/serine kinase [RsbS])	<i>yxr5</i>	4185	streptothricin acetyl-transferase	<i>yefB</i>	739	site-specific recombinase		
<i>rsbU</i>	521	indirect positive regulator of $\sigma^E$ activity (serine phosphatase [RsbV-P])	IV.3	ANTIBIOTIC PRODUCTION	.....	30	<i>yefC</i>	739	resolvase	
<i>rsbV</i>	522	positive regulator of $\sigma^E$ activity (anti-anti-sigma factor [RsbW])	<i>pksB</i>	1782	involved in polyketide synthesis	<i>yneB</i>	1918	resolvase		
<i>rsbW</i>	522	negative regulator of $\sigma^E$ activity (switch protein/serine kinase [RsbV], anti-sigma factor [ $\sigma^E$ ])	<i>pksC</i>	1783	involved in polyketide synthesis	<i>yocA</i>	2085	transposon-related protein		
<i>rsbX</i>	523	indirect negative regulator of $\sigma^E$ activity (serine phosphatase [RsbS-P])	<i>pksD</i>	1785	involved in polyketide synthesis	IV.6	MISCELLANEOUS	.....	26	
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<i>ydaG</i>	473	general stress protein	<i>pksF</i>	1788	involved in polyketide synthesis	<i>csbA</i>	3614	putative membrane protein		
<i>yfiK</i>	910	surface adhesion	<i>pksG</i>	1789	involved in polyketide synthesis	<i>csbB</i>	36	$\sigma^E$ -transcribed gene		
<i>yjRL</i>	1414	heat-shock protein	<i>pksH</i>	1790	involved in polyketide synthesis	<i>ctaG</i>	1564	function unknown		
<i>yjxA</i>	1381	general stress protein	<i>pksI</i>	1791	involved in polyketide synthesis	<i>eag</i>	1430	small membrane protein		
<i>yjyA</i>	1637	fibrinectin-binding protein	<i>pksJ</i>	1792	involved in polyketide synthesis	<i>ecsC</i>	1079	function unknown		
<i>yloU</i>	1655	alkaline-shock protein	<i>pksK</i>	1794	polyketide synthase	<i>mmgE</i>	2509	function unknown		
<i>ynbA</i>	1875	GTP-binding protein protease modulator	<i>pksL</i>	1808	polyketide synthase	<i>nifZ</i>	3027	NifS protein homologue		
<i>ynzF</i>	1880	$\delta$ -endotoxin	<i>pksM</i>	1821	polyketide synthase	<i>sapB</i>	726	mutant activates alkaline phosphatase during sporulation independently of $\sigma^E$ and $\sigma^H$		
<i>yocK</i>	2097	general stress protein	<i>pksN</i>	1834	polyketide synthase	<i>sbp</i>	1595	small basic protein		
<i>yocM</i>	2098	small heat-shock protein	<i>pksP</i>	1835	polyketide synthase	<i>veg</i>	53	function unknown		
<i>yodU</i>	2151	capsular polysaccharide biosynthesis	<i>pksR</i>	1850	polyketide synthase	<i>yael</i>	102	creatine kinase		
<i>yokG</i>	2279	$\delta$ -endotoxin	<i>pksS</i>	1897	peptide synthetase	<i>ybaL</i>	257	ATP-binding Mrp-like protein		
<i>yppP</i>	2286	capsular polysaccharide biosynthesis	<i>pksT</i>	1982	peptide synthetase	<i>yobU</i>	257	NifS protein homologue		
<i>yxG</i>	3047	general stress protein	<i>pksU</i>	1974	peptide synthetase	<i>yerN</i>	730	pet112-like protein		
<i>yxH</i>	3047	general stress protein	<i>ppeE</i>	1963	peptide synthetase	<i>yhdP</i>	1033	hemolysin		
<i>yxl</i>	3046	general stress protein	<i>sbo</i>	3835	subtilisin A	<i>yhdT</i>	1035	hemolysin		
<i>yxk</i>	3529	capsular polysaccharide biosynthesis	<i>sfp</i>	408	surface production	<i>yheG</i>	1049	calcium-binding protein		
<i>yxlE</i>	3528	capsular polysaccharide biosynthesis	<i>srfAA</i>	377	surface synthesis / competence	<i>yplQ</i>	2295	hemolysin III homologue		
<i>yxlM</i>	3527	capsular polysaccharide biosynthesis	<i>srfAB</i>	387	surface synthesis / competence	<i>yqxC</i>	2523	hemolysin-like		
<i>yveN</i>	3525	capsular polysaccharide biosynthesis	<i>srfAC</i>	398	surface synthesis / competence	<i>yrkA</i>	2720	hemolysin-like		
<i>yveO</i>	3524	exopolysaccharide biosynthesis	<i>srfAD</i>	402	surface synthesis / competence	<i>yrvO</i>	2811	NifS protein homologue		
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<i>yveQ</i>	3522	capsular polysaccharide biosynthesis				<i>yuhV</i>	3357	NifU protein homologue		
<i>yveR</i>	3521	spore coat polysaccharide biosynthesis	<i>yomB</i>	2264	bacteriocin	<i>yurW</i>	3359	NifS protein homologue		
<i>yveT</i>	3519	capsular polysaccharide biosynthesis	<i>yukL</i>	3282	antibiotic synthetase	<i>yutI</i>	3309	NifU protein homologue		
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			<i>ripX</i>	2449	integrase/recombinase	VI	NO SIMILARITY	1053		
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			<i>xxdA</i>	1320	PBSX prophage					
			<i>xxdB</i>	1321	PBSX prophage					