MICROBIOLOGICAL REVIEWS, Mar. 1980, p. 57-82
0146-0749/80/01-0057/26$02.00/0
Vol. 44, No. 1

The *Bacillus subtilis* Chromosome

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INTRODUCTION 57
RELATIONSHIP BETWEEN GENETIC AND PHYSICAL DISTANCES IN BACTERIOPHAGE PBS1 TRANSDUCTION 57
SIZE OF THE *B. SUBTILIS* CHROMOSOME 58
ANALYSIS OF THE TRANSFORMATION PROCESS 59
DETAILED *B. SUBTILIS* MAP 60
DETAILED MAP OF THE ORIGIN REGION 61
COMPARISON OF FEATURES OF THE *B. SUBTILIS* AND *ESCHERICHIA COLI* GENETIC MAPS 74
LITERATURE CITED 75

INTRODUCTION

Bacillus subtilis is the most widely studied and thoroughly mapped gram-positive microorganism. Studies have focused on many different aspects of this species, including biochemical and morphological changes during sporulation, germination, and outgrowth; mechanisms of genetic exchange in transformation and transduction; cell wall synthesis and cell growth and division; enzymatic characterization of many catabolic pathways; and a host of others. The isolation and genetic characterization of mutants defective in these processes have played a key role in many of these studies. The ease of transformation with this species was very useful in defining genetic loci, but the limited nature of genetic linkage by transformation made the construction of an uninterrupted transformation linkage map impossible. Other techniques were used in conjunction with transformation that allowed loci to be roughly localized according to their time of replication (21, 45, 213, 214). These investigations allowed a rough framework of loci to be constructed on the assumption that the time of replication of a marker is correlated with its distance from the origin of replication. Bacteriophage PBS1 transduction studies allowed the linkage of large clusters of loci, and recently all the linkage groups have been linked to one another (118).

Previous compilations of the *B. subtilis* map have essentially utilized the framework constructed by time-of-replication studies and have filled in other loci by using transduction and transformation data. No particular effort was made to calibrate these maps by placing loci at correct physical distances from each other. We felt that the application of recent theories of cotransduction frequencies (104, 209) to PBS1 transduction data would allow the construction of a physically calibrated map. Besides its obvious utility to researchers in *B. subtilis*, we felt that such a map could be validly compared to the calibrated linkage map of *Escherichia coli* (10). Such a comparison would be useful to note common features of chromosome organization which have convergently evolved or which have been maintained since the divergence of these species, estimated to have been 1.2 to 1.8 billion years ago (87).

RELATIONSHIP BETWEEN GENETIC AND PHYSICAL DISTANCES IN BACTERIOPHAGE PBS1 TRANSDUCTION

Models have been proposed which relate the frequency of cotransduction of markers to their physical distance from each other on a transducing piece of deoxyribonucleic acid (DNA) (104, 209). The basic features of these models include the possibility that factors other than recombinational events will affect the apparent recombination frequency between any two markers. To be cotransduced, two markers must be contiguous on a single fragment of transducing DNA; as the distance between them increases, their chance of being on the same transducing fragment decreases. Furthermore, as the markers become closer to the ends of the transducing fragment, the size of the pieces of DNA outside of the markers in which crossing-over might occur becomes limited, reducing the number of cotransductants.

The models also make certain assumptions about the transduction process. They assume that recombination is linearly proportional to the length of DNA in which the recombination can occur and that transducing fragments are of uniform length and have random endpoints. None of these assumptions has been verified in the PBS1 transduction system used to compile this map, and there is evidence in some other

transduction systems for violation of these assumptions, e.g., marker-specific effects, nonreciprocal crosses, and preferred endpoints (32, 104). However, the theoretical predictions of the models have shown good agreement with observed distances in bacteriophage P22 transduction in *Salmonella typhimurium* (10, 104). The validity of the *B. subtilis* map constructed by this method will be discussed in more detail later.

Although there are a variety of genetic mapping systems in *B. subtilis*, the PBS1 transduction system has been the key to the generation of a complete, uninterrupted circular map. The large size of the transducing DNA fragment allows cotransduction of markers separated by almost 10% of the chromosome. PBS1 cotransduction values for all available markers were used to calculate a corrected genetic distance between markers by Kemper's formula, $C = (1 - t) + t(\ln t)$ (104), where C is the cotransduction index of the markers and t is the fractional length of the transducing fragment separating the markers. The genetic distance between markers (t) can be converted to physical distance (D), if the average length of the transducing fragment (T) is known, by the formula $D = t(T)$. A plot of the former equation is shown in Fig. 1. An inspection of this plot shows that the cotransduction frequency falls quickly as the physical distance between two markers increases. For example, two markers, A and B, separated by half the length of a transducing fragment ($0.5t$), would show only 15% cotransduction, not 50%. Also, this model predicts that recombination values should not be additive. For example, if marker C is halfway between markers A and B above, it would be $0.25t$ from each and show 60% recombination from each. But the two outside markers, A and B, would show only 85% recombination, not 120%.

An example of the application of this formula is shown in Fig. 2. The recombination values in PBS1 transduction were taken from reported values in the literature, whereas the t value was extrapolated from the formula $C = (1 - t) + t(\ln t)$. As one can see in this chosen example, the sum of the t values of contiguous subintervals closely approximates the calculated t value for the larger intervals. The recombination values, on the other hand, are not additive. We felt that the ability of this formula to convert cotransduction values into t values, which show such additivity, is an important point in determining the validity of this type of analysis. This property of additivity suggests that the t value is a meaningful measurement of physical distance and as such can be used to generate an internally consistent map with loci placed according to their relative physical distances from one another.

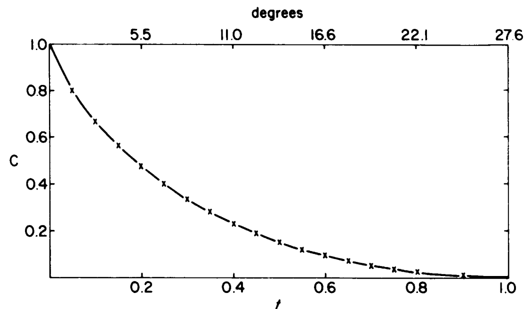


FIG. 1. *Theoretical relationship between markers. This figure is the graph of the equation C = (1 − t) + t(ln t). The variables C and t are defined in the text. Also indicated is the chromosomal distance (in degrees) corresponding to a given t value.*

SIZE OF THE *B. SUBTILIS* CHROMOSOME

The previous arguments support the notion that the map generated by our analysis is internally consistent; i.e., the markers are placed correctly according to their relative physical distances. We next tried to determine a means of calibrating the map by absolute physical distance. The entire distance around the chromosome was determined to be 13.05 times the length of the genetic transducing fragment (T). If the size of the genetic transducing fragment were known, we could multiply it by 13.05 and compare that size with other determined values of the size of the *B. subtilis* chromosome. If T equals the size of the PBS1 genome (190×10^6 daltons [88]), then the chromosome size would equal 2.5×10^9 daltons; if T equals the genome size (150×10^6 daltons [111]) of PBS2 (a virulent derivative of PBS1), then the chromosome size would equal 2.0×10^9 daltons. An independent way to measure T is to measure recombination values between two markers with an addition or deletion of known size between them. This has been essentially accomplished by measuring the cotransduction of the *metB5* and *kauA1* loci in strains either carrying ($C = 18.1\%$; $t = 0.46$) or cured ($C = 77.7\%$, $t = 0.06$) of the SPβ prophage (222). These calculations suggest that SPβ (62×10^6 daltons) is 0.4 times the length of the transducing fragment; therefore, T would equal 155×10^6 daltons, giving a chromosome size of 2×10^9 daltons. These genetic determinations of the chromosome size are in good agreement with the physical determinations (by viscoelastic method, 2.0×10^6 daltons [106]; by renaturation rate, 2.4×10^9 to 2.6×10^9 daltons [11, 56]). These data suggest that T has a physical length

sacQ thr-5 citG cysB

52 (20)

40 (13)

51 (19)

66 (30)

84 (49)

FIG. 2. *PBS1 transduction map of the sacQ-cysB region. The numbers on the line are reported recombination values (×100) for the indicated pairs of loci. The values in parentheses are the calculated t values (×100).*

of approximately 150 × 10^6 daltons, allowing us to assign absolute D values to the intervals determined between markers from C values.

ANALYSIS OF THE TRANSFORMATION PROCESS

A similar analysis of transformation data might provide evidence about the transformation process. The two questions we addressed were: (i) Can we determine a rough estimate of the physical distance between two markers from their cotransformation frequency? and (2) Does the cotransformation of markers in relation to their distance apart follow the theoretical curve predicted for cotransduction?

Two approaches were used in this analysis. The first was to find pairs of markers for which both their cotransformation index and their C value are known. Values were picked that reflected selection of the same marker, and in most cases, the C value and cotransformation index for a pair of markers came from data from the same investigators. These values were converted to t values, using the previously described equation, $C = (1 - t) + t(\ln t)$, and then plotted. Such a plot is shown in Fig. 3. If the Kemper equation describes the relationship between D and C, the points should fall along a line whose slope is the ratio of the size of the transducing fragment to the size of the transforming fragment. It is obvious that the data points have very little correlation. The majority of the points fall near the predicted lines for a ratio of between 10 and 20, suggesting that the transducing fragment is between 10 and 20 times larger than the transforming fragment. One inherent source of error in such a comparison of transformation and transduction is that any markers showing cotransformation will show extremely high (greater than 90%) cotransduction. Therefore, only a small portion of the curve can be examined, and the confidence levels of the C values and cotransformation indices are low, since the number of recombinant colonies will be low in these crosses.

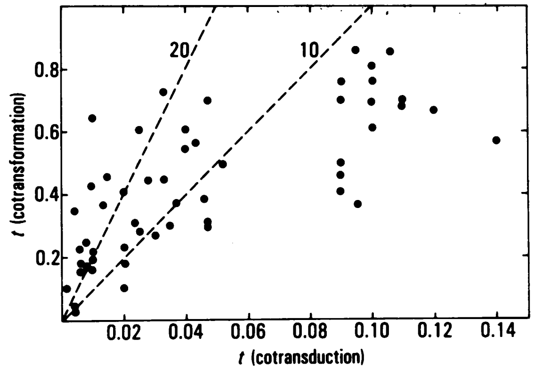


FIG. 3. *Comparison of C and cotransformation values for pairs of loci. Each data point indicates the point corresponding to the ordered pair defined by the calculated t for cotransduction and the calculated t for cotransformation for a single pair of loci. The broken lines are the theoretical lines expected for transducing fragment-transforming fragment size ratios of 10 and 20.*

It is interesting that the data points in Fig. 3 seem to fall into two clusters. An examination of the pairs of markers within the two clusters did not show any obvious reason why they might be clustered. For example, they did not seem to be in any particular map location, nor were they any particular kind of marker, nor were the crosses done by any particular group of workers. By this analysis, the markers in the cluster to the right act as though the ratio of the size of the transducing fragment to the size of the transforming fragment is low, i.e., as though they are transformed by a larger fragment than the other markers or, conversely, transduced by a smaller fragment.

The second approach was to analyze the transformation data for a series of linked markers for which an estimate of D could be made. We felt that the tryptophan operon would be amenable to such an analysis. The six proteins coded by this operon have been well characterized and have an aggregate size of 236,000 daltons (80, 81,

83, 84, 86). If we assume an average amino acid size of 120, these proteins would need approximately 6,000 base pairs of coding DNA. Cloning of this operon from the related species *B. licheniformis* suggests that this estimate is in the correct size range (D. Dubnau, personal communication). A series of mutations extending throughout the *trp* operon have been ordered by transformation, and thus their positions and distances from each other can be approximated (28). A plot was made of the cotransformation of these markers versus their approximated distances from one another (Fig. 4). Also shown are the theoretical curves that would be generated for apparent sizes of genetic transforming DNA of 15-, 30-, or 60-kilobase pairs. The data indicate that the apparent transforming DNA segment is approximately 30,000 base pairs.

The comparison of the transduction and transformation data indicated that the transforming DNA fragment is approximately 1/10 to 1/20 the size of the transducing fragment, or 11 to 22 kilobase pairs, whereas the analysis of the *trp* operon suggests a size of approximately 30 kilobase pairs. Although the figures are quite disparate, they are in the size range of the piece of transforming DNA which is bound to the competent cell, 10 to 20 kilobase pairs (40). The single-stranded DNA piece which is integrated seems to be much smaller, about 4.3 kilobase pairs (39). This analysis indicates that the effective size of the transforming DNA is much larger than the actual size of the integrated piece and is much closer to the size of the piece that binds to the cell. It has also been found that the integration of these small single-stranded regions seems to occur in clusters (39, 40). Our analysis is in agreement with a model that a cluster of single-strand pieces derived from a single bound piece of DNA is integrated contiguously or nearly contiguously.

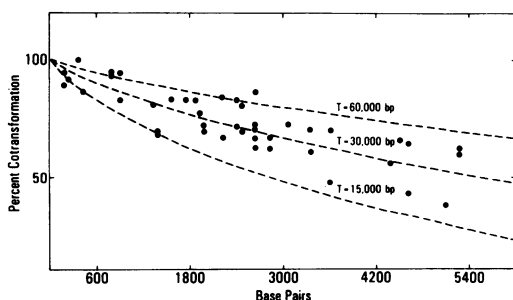


FIG. 4. *Relationship between the cotransformation index and physical distance between loci. Each datum point indicates the point corresponding to the ordered pair defined by the estimated number of base pairs separating two loci and the percent cotransformation of the two loci. The broken lines indicate the theoretical curves expected for transforming-fragment sizes equal to 15,000, 30,000, or 60,000 base pairs.*

DETAILED *B. SUBTILIS* MAP

The *guaA* locus, which is known to be near the origin, was chosen as a reference point and placed at 0° on the circular map. All the other markers were then placed relative to the *guaA* locus. The *citK* and *gltA* loci ended up near 180°. These loci have been shown to be replicated very late and are probably near the terminus of replication (65). Figure 5 shows the placement of selected landmark loci on the map. There are no surprises in terms of their placement with respect to their placement on previous maps. This correspondence is in agreement with the assumption that the physical distances of markers from the origin determine the times of replication of markers, i.e., that the rate of DNA replication is approximately the same at all intervals of the chromosome.

The detailed map is shown in Fig. 6. Sporulation and germination loci are shown on the inner circle, whereas all the other loci are shown on the outer circle. For convenience in locating markers, the map is divided into degree intervals; the positions of markers in Table 1 are given in degrees. Not all of the markers in the origin region (approximately 355 to 15°) are placed on Fig. 6 due to lack of space. A more detailed map of the origin is presented below (see Fig. 7).

We have tried to use the nomenclature that we feel is most generally accepted. Certain loci commonly known by alternate designations are presented in Table 1 with cross-references to their present designations on this map. We have used the designations for the *spo* loci suggested in the review by Piggot and Coote (160). The *rec* nomenclature in *B. subtilis* is particularly confusing. We have attempted to use the designations proposed by Mazza and Gallizi (133), with one exception. We have used the *recE* designation for the *rec-4* mutation of Dubnau and Cirigliano (41), rather than the *recE5* of Doly et al. (38). We feel that this *rec-4* mutation has been commonly identified in the literature as *recE*. In Table 1 no attempt has been made to give original designations for cross-reference purposes, and until a uniform nomenclature is accepted, particular care will be needed to keep this area of *B. subtilis* genetics from further entanglement.

There are a few areas of the map which show questionable linkages and need further comment. The region of the map from *metD* to *metC* (100 to 115°) is one of the most troublesome areas. The reported cotransduction frequencies

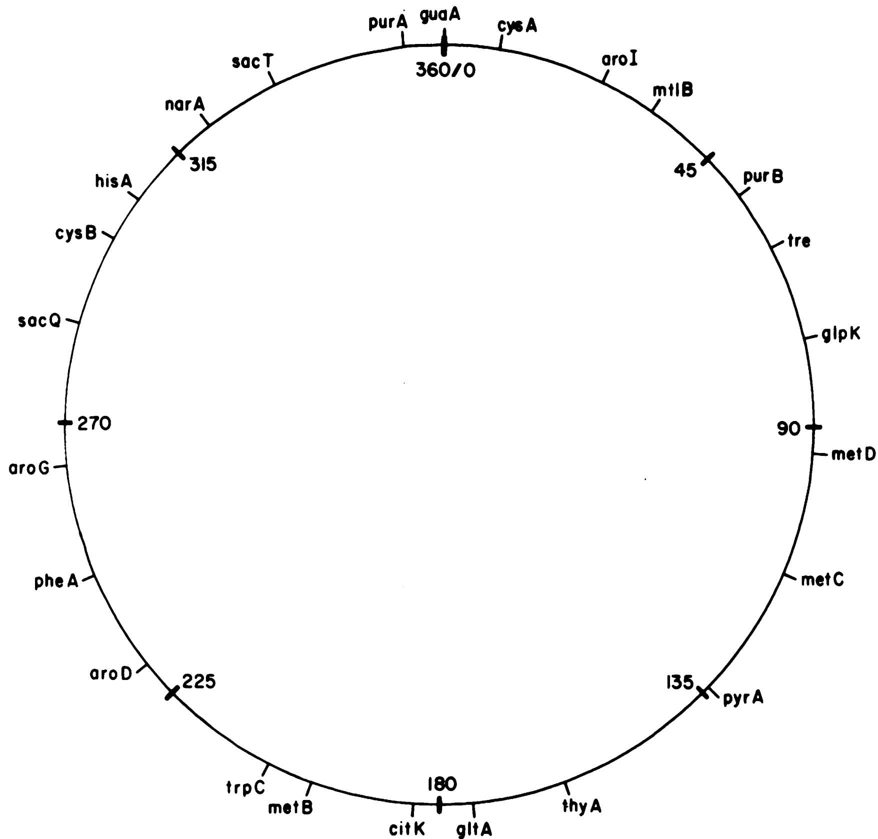


FIG. 5. *Landmark loci of the B. subtilis chromosome.*

and order of markers in this region vary greatly in different reports. There are probably multiple arginine loci in this region which share the same phenotype. The defective prophage, PBS-X, is located in this region and could also play a role in the confused genetics. The general order of markers shown is from data provided by S. Zahler (personal communication).

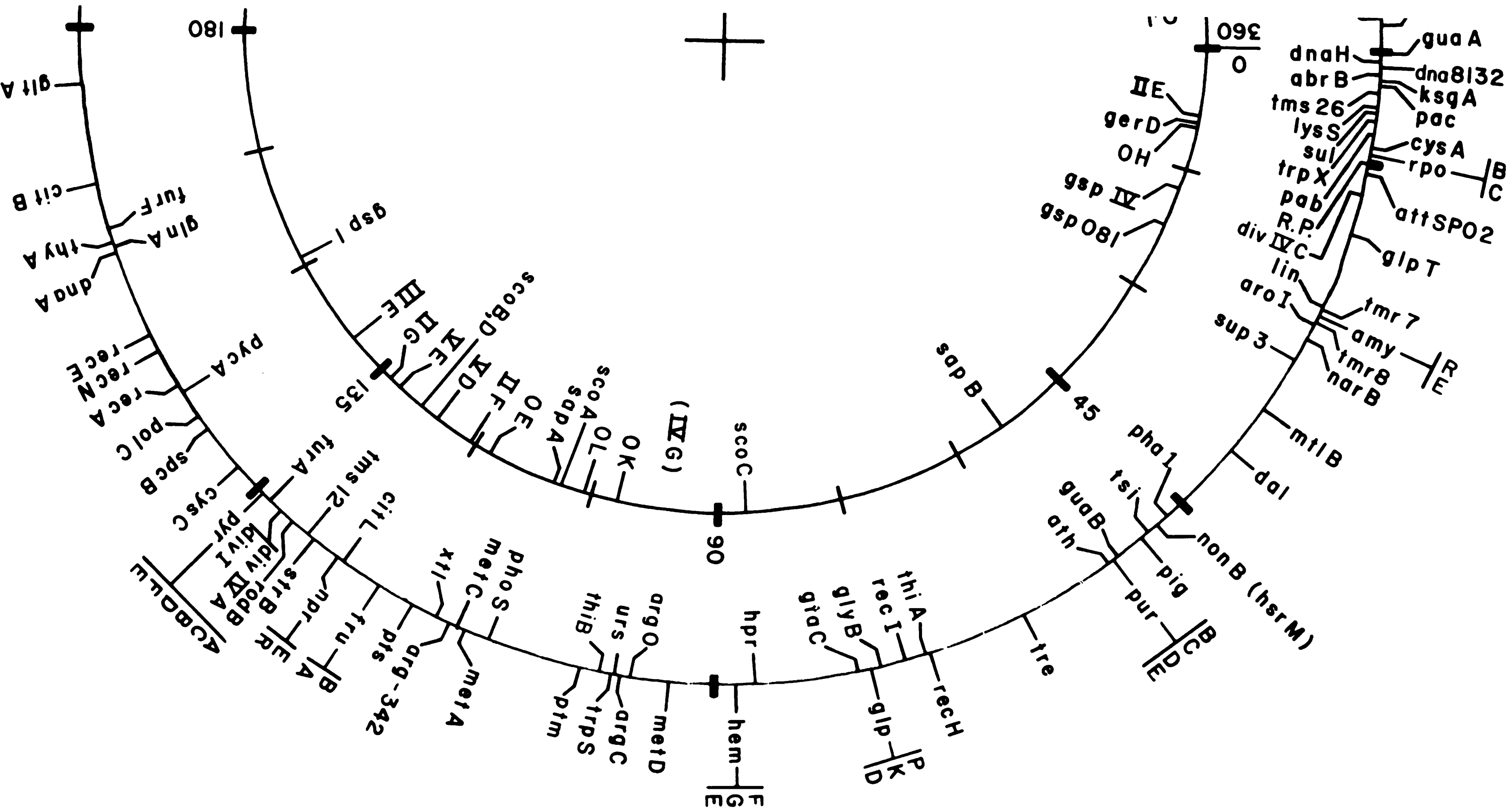
The *citK-gltA* interval (180°) also shows variable linkages. The cotransduction of these two markers can vary from 34 to 66% (Zahler, personal communication). It is interesting that this region of the chromosome also contains a prophage, SPβ. Two of the large silent regions in the *B. subtilis* chromosome, one at 27° and one at 340°, have distances defined by a very limited amount of transduction data, leaving the actual size of the interval open to some question. There were certain markers whose mapping data were either nonexistent or insufficient to place them on the map. These markers are presented in Table 1 along with relevant mapping data. Although the *fla* markers and related loci (*ifm* and *hag*) have been mapped, the data did not seem consistent and the markers were therefore only placed in their general area. Similarly, some sporulation markers are shown localized only to a general area. In this vein, one must remember that during the process of constructing this map two markers might end up adjacent to each other without having been mapped relative to each other. The complexity of the present map precluded identifying such areas with brackets. We have incorporated the data from three-factor transduction and transformation crosses wherever possible to order markers, and we have found that our basic method of map construction usually gave good agreement with such data, but certainly the exact order of some markers could be incorrect.

DETAILED MAP OF THE ORIGIN REGION

The genetics of the region of the chromosome near the origin of replication has been the subject of much study in this laboratory. A detailed map of this area has been recently published (188). We have analyzed the transduction data to construct a calibrated framework for the

nalA
dnaC
purA
recF
novA
dna(ts) A B
360
OJ
S T P A
sac
bsr
hut
E C
fur
azpB
ctrA
ebr
abrA
glyC
narA
div II
rodC
(fla A,B,C)
gtaA
alsR
rna53
gtaB
sacU
estB
azi
uvrA
R B
sac
hisA
smo
cysB
OF
gsp4
315
II D
gerB
hom
citG
tdm
thrA
fumR
ald
aecB
sacQ
div V
ksgB
gerF
II C
gerG
gsp10
III D
gerA
112 A B
bio
G A
aro
alsA
argA
H C
cit
P R
pho
citF
polA
uvrB
dnaB
azlA
aecA
amm
dnaI
att Ø105
270
gerE
IV F
OB
II B (V B)
IV E
III C (IV C)
IV D
spoLl
B C
ilv
div IV B
leu
nic
A C B
D C B A
hem
pheA
recB
azlB
acf
sacL
aroD
asaA
til
ts39
dnaE
225
OG
OA
III A (III B)
IV B (V A)
II A
IV A
gerC
180
ahrB
lys
glyA
mtr
hisH
strC
aspH
rib
ser
aroC
aro
tyrA
recG
aspB
metB
thyB
F B H
trp
E D C F B A
aroE
dnaD
tmp
ilvD
ilvA
SPβ
kauA
citK

FIG. 6. *Detailed map of the B. subtilis chromosome.*



guaA
dna8132
ksgA
pac
cysA
rpo
B
C
attSPO2
glpT
tmr7
amy
R
E
tmr8
narB
dnaH
abrB
tms26
lysS
sul
trpX
pab
R.P.
divIVC
lin
aroI
sup3
mtlB
dal
nonB (hsrM)
360
0
IIE
gerD
OH
gspIV
gsp081
pha1
tsi
pig
pur
B
C
D
E
guaB
ath
45
tre
sapB
recH
thiA
recI
glp
P
K
D
glyB
gtaC
hpr
hem
F
G
E
scoC
90
(IVG)
metD
argO
urs
argC
thiB
trpS
ptm
OK
OL
scoA
sapA
OE
IIF
scoB,D
VD
VE
IIG
IIIE
135
gspI
phoS
metC
metA
xtl
arg-342
pts
citL
fru
B
A
tms12
npr
E
R
strB
furA
rodB
divIVA
divI
pyr
A
C
B
D
F
E
cysC
pycA
spcB
polC
recA
recN
recE
glnA
furF
dnaA
thyA
citB
gltA
180

TABLE 1. *Genetic markers of B. subtilis*

Gene symbol	Mnemonic	Map position[a]	Phenotype, enzyme deficiency, or other characteristic	References[b]
abrA	Antibiotic resistance	325	Partial suppressor of stage 0 mutant phenotypes	A
abrB	Antibiotic resistance	5	Partial suppressor of stage 0 mutant phenotypes	194, 196
absA	Antibiotic sensitivity		Partial suppressor of stage 0 mutant phenotypes, see *abrB*	92, 93
absB	Antibiotic sensitivity		Partial suppressor of stage 0 mutant phenotypes, see *abrB*	92, 93
ace	Acetate	UC	Pyruvate dehydrogenase defect, linked to *pycA*	C
acf	Acriflavine	235	Acriflavine resistance	13, 91
aecA	Aminoethylcysteine	250	Aminoethylcysteine resistance, regulation of aspartokinase II	131, B
aecB	Aminoethylcysteine	290	Aminoethylcysteine resistance, structural gene for aspartokinase II	131, B
ahrA	Arginine hydroxamate		Arginine hydroxamate resistance, linked to *cysA*	68, D
ahrB	Arginine hydroxamate	220	Arginine hydroxamate resistance	68
ald	Alanine	285	L-Alanine dehydrogenase	118
alsA	Acetoin	265	Acetolactate synthase	221
alsR	Acetoin	320	Constitutive acetolactate synthase	221
amm	Ammonia	250	Glutamate requirement	42
amt			3-Aminotyrosine resistance; part of or very close to *tyrA* locus, see *tyrA*	163
amyB	Amylase		Control of amylase synthesis; probably identical to *sacQ* and *pap*, see *sacQ*	175, 189
amyE	Amylase	25	Amylase structural gene, also called *amyA*	219
amyR	Amylase	25	Control of amylase synthesis, also called *amyH*	215, 218
argA	Arginine	260	Arginine requirement	17, 127
argC	Arginine	100	Arginine or citrulline requirement	127, E
argO	Arginine	100	Arginine, ornithine, or citrulline requirement	127, E
arg342	Arginine	115	Arginine-ornithine or citrulline requirement	77
aroA	Aromatic	265	3-Deoxy-D-arabinoheptalosonic-7-phosphate synthase	78, 143
aroB	Aromatic	210	Dehydroquinate synthase	143
aroC	Aromatic	210	Dehydroquinate dehydratase	78, 143
aroD	Aromatic	230	Shikimate dehydrogenase	3, 77, 78
aroE	Aromatic	210	3-Enolpyruvylshikimate-5-phosphate synthase	143, 146
aroF	Aromatic	210	Chorismate synthase	78, 143
aroG	Aromatic	270	Chorismate mutase, isozyme 3	78, 143
aroH	Aromatic	210	Chorismate mutase, isozymes 1 and 2	124, 143
aroI	Aromatic	25	Shikimate kinase	118
aroJ	Aromatic		Tyrosine and phenylalanine, see *hisH*	145
asaA	Arsenate	230	Arsenate resistance	1, 2
aspA	Aspartate		Pyruvate carboxylase, see *pycA*	25, 77
aspB	Aspartate	200	Aspartate aminotransferase	77
aspH	Aspartate	215	Constitutive aspartase	89
ath	Adenine-thiamine	55	Adenine-thiamine requirement	220
attSPβ	Attachment	190	Integration site for phage SPβ	222
attSPO2	Attachment	10	Integration site for phage SPO2	90, 182
attφ3T	Attachment		Integration site for phage φ3T, probably maps between *kauA* and SPβ	207, E
attφ105	Attachment	245	Integration site for phage φ105	158, 173

TABLE 1—*Continued*

Gene symbol	Mnemonic	Map position[a]	Phenotype, enzyme deficiency, or other characteristic	References[b]
azi	Azide	310	Resistance to sodium azide	A
azlA	Azaleucine	250	4-Azaleucine resistance, derepressed leucine biosynthetic enzymes	202
azlB	Azaleucine	240	4-Azaleucine resistance	202, 203
azpA	Azopyrimidine		Resistance to azopyrimidines; alteration of DNA polymerase III, see *polC*	36
azpB	Azopyrimidine	330	Resistance to azopyrimidines	27
bfmA	Branched fatty acid	NM	Lacks branched-chain-keto-acid dehydrogenase	C
bfmB	Branched fatty acid	UC	Requires branched-chain fatty acid, valine, or isoleucine; maps between *strC* and *lys*	C
bioA	Biotin	270	7-Oxo-8-aminopelargonate:7,8-diaminopelargonate aminotransferase	156
bioB	Biotin	270	Biotin synthetase	156
bio112	Biotin	270	Early defect in biotin synthesis	156
bry	Bryamycin		Bryamycin (thiostrepton) resistance, maps in ribosomal protein cluster	67, 182
bsr	Restriction, modification	340	Restriction, modification by *B. subtilis* strain "R"	194
but		NM	5-Bromouracil tolerant	19
catA			Hyperproduction of extracellular proteases, see *hpr*	118
cdd		NM	Deoxycytidine-cytidine deaminase	168
citB	Citric acid cycle	165	Aconitate hydratase	172, 221
citC	Citric acid cycle	260	Isocitrate dehydrogenase	79, 172
citF	Citric acid cycle	255	Succinate dehydrogenase	79, 172
citG	Citric acid cycle	295	Fumarate hydratase	172
citH	Citric acid cycle	260	Malate dehydrogenase	53, A
citK	Citric acid cycle	185	α-Ketoglutarate dehydrogenase complex, enzyme E1	76, 172
citL	Citric acid cycle	125	Lipoamide dehydrogenase (NADH), E3 component of both pyruvate dehydrogenase and α-ketoglutarate dehydrogenase complexes	76
cml	Chloramphenicol		Chloramphenicol resistance, caused by mutations in at least five 50S ribosomal proteins, all mapping in the ribosomal protein cluster, see ribosomal protein cluster	152
crk		NM	Cytidine kinase	168
css	Cysteine		Cysteine sensitivity, see *cysA*	97
ctrA	Cytidine requirement	325	Requirement for cytidine in the absence of ammonium ion	118, 221
cym	Cysteine-methionine		Requirement for cysteine or methionine, see *cysA*	97, 159
cysA	Cysteine	10	Cysteine requirement, serine transacetylase; a complex locus comprised by *css* (cysteine sensitivity), *cym* (cysteine or methionine), *hts* (hydrogen sulfide excretion), and *cysA*	97
cysB	Cysteine	300	Cysteine requirement	42
cysC	Cysteine	140	Cysteine, methionine, sulfite, or sulfide requirement	77, 217
dal	D-Alanine	40	D-Alanine requirement; alanine racemase	44, 48
dck		NM	Deoxycytidine kinase	168
ddd		NM	Deoxycytidine kinase	168
divI	Division	130	Temperature-sensitive cell division, formerly *divD*	198

TABLE 1—*Continued*

Gene symbol	Mnemonic	Map position[a]	Phenotype, enzyme deficiency, or other characteristic	References[b]
divII	Division	320	Temperature-sensitive cell division, formerly *divC*	198
divIVA	Division	130	Minicell production	166
divIVB	Division	245	Minicell production	166
divIVC	Division	15	Minicell production, formerly *divA*	198
divV	Division	285	Temperature-sensitive cell division, formerly *divB*	198
dnaA	DNA	160	DNA synthesis; ribonucleotide reduction, probably not ribonucleotide reductase	9, 15, 98, 133, 167
dnaB	DNA	255	DNA synthesis, initiation of chromosome replication	98, 133, 134
dnaC	DNA	355	DNA synthesis	8, 98, 133
dnaD	DNA	200	DNA synthesis, initiation of chromosome replication	98, 133
dnaE	DNA	230	DNA synthesis	98, 133
dnaF	DNA		DNA synthesis; DNA polymerase III, see *polC*	98, 133
dnaG	DNA	0	DNA synthesis	98, 133
dnaH	DNA	0	DNA synthesis	98, 133, 195
dnaI	DNA	250	DNA synthesis	98, 133
dna(ts)A	DNA	350	DNA synthesis	63, 133
dna(ts)B	DNA	350	DNA synthesis	63, 133
dna8132	DNA	0	DNA synthesis, initiation of chromosome replication	63, 66, 195
dpa	Dipicolinic acid	UC	Requires dipicolinic acid for heat-resistant spores, linked to *pyrA*	12
D-*tyr*	D-Tyrosine		Resistance to D-tyrosine; maps within the *tyrA* locus, see *tyrA*	30
ebr	Ethidium bromide	325	Ethidium bromide resistance	19
efg	Elongation factor G	10	Elongation factor G	4, 43, 107
ery	Erythromycin		Erythromycin resistance, ribosomal protein L22, see *rplV*	191, 192
estB	Esterase	310	Esterase B defect	72
flaA	Flagella	315	Defect in flagellar synthesis	60
flaB	Flagella	315	Defect in flagellar synthesis	60
flaC	Flagella	315	Defect in flagellar synthesis	60
fruA	Fructose	120	Fructose transport	55
fruB	Fructose	120	Fructose-1-phosphate kinase	55
fruC	Fructose	NM	Fructokinase	55
fumR	Fumarase	295	Regulation of fumarate hydratase	A
furA	5-Fluorouracil	135	Resistance to 5-fluorouracil	42
furC	5-Fluorouracil	325	Resistance to 5-fluorouracil in the presence of uracil	F
furE	5-Fluorouracil	325	Resistance to 5-fluorouracil in the presence of uracil	E
furF	5-Fluorouracil	160	Resistance to 5-fluorouracil in the presence of uracil	37
fus	Fusidic acid		Fusidic acid resistance, see *efg*	107
gca	Glucosamine	NM	L-Glutamine-D-fructose-6-phosphate aminotransferase	49
gerA	Germination	295	Germination defective	139, 179
gerB	Germination	315	Germination defective	139, 179
gerC	Germination	210	Germination defective	139, 179
gerD	Germination	10	Germination defective	139, 179
gerE	Germination	255	Germination defective	139, 179
gerF	Germination	305	Germination defective	139, 179
gerG	Germination	300	Germination defective	139, 179
glnA	Glutamine	160	Glutamine synthetase structural gene	22, 37, 47
glpD	Glycerol phosphate	75	Glycerol-3-phosphate dehydrogenase	122
glpK	Glycerol phosphate	75	Glycerol kinase	122

TABLE 1—*Continued*

Gene symbol	Mnemonic	Map position[a]	Phenotype, enzyme deficiency, or other characteristic	References[b]
glpP	Glycerol phosphate	75	Pleiotropic glycerol mutant	122
glpT	Glycerol phosphate	15	Fosfomycin resistant, glycerol phosphate transport defect	120
gltA	Glutamate	175	Glutamate or aspartate requirement, glutamine-2-ketoglutarate aminotransferase	37, 77
glyA	Glycine	210	Glycine requirement	101-103
glyB	Glycine	75	Glycine requirement	66
glyC	Glycine	320	Glycine requirement	27
gsp1	Germination	150	Outgrowth defective	50
gsp4	Germination	320	Outgrowth defective	50
gsp10	Germination	300	Outgrowth defective	50
gsp081	Germination	20	Outgrowth defective	5
gspIV	Germination	20	Outgrowth defective	50
gtaA		310	Glucosylation of teichoic acid, lacks uridine-diphosphate-glucose–poly(glycerolphosphate)α-glucosyltransferase	118, 216
gtaB		310	Glucosylation of teichoic acid	216
gtaC		75	Glucosylation of teichoic acid, lacks phosphoglucomutase	216
guaA	Guanine	0	Inosine-monophosphate dehydrogenase	195, C
guaB	Guanine	50	Guanine requirement	A, C
gutA	Glucitol	NM	D-Glucitol permease	29
gutB	Glucitol	NM	D-Glucitol dehydrogenase	29
gutR	Glucitol	NM	Constitutive synthesis of D-glucitol permease and D-glucitol dehydrogenase	29
hag	Flagella	315	Flagellar antigen, maps in the *flaA,B,C,* region	60, 129
hds		5	Pleiotropic extragenic suppressors of DNA mutations	177
hemA	Heme biosynthesis	245	δ-Aminolevulinate synthase	105
hemB	Heme biosynthesis	245	Porphobilinogen synthase	17
hemC	Heme biosynthesis	245	Porphobilinogen deaminase	17
hemD	Heme biosynthesis	245	Uroporphyrinogen III cosynthase	136
hemE	Heme biosynthesis	90	Uroporphyrinogen decarboxylase	135
hemF	Heme biosynthesis	90	Coproporphyrinogen oxidase	135
hemG	Heme biosynthesis	90	Ferrochelatase	135
hisA	Histidine	305	Histidine requirement, probable location of all histidine enzymes except *hisH*	21, 42, 45, 142
hisH	Histidine	205	Histidinol-phosphate aminotransferase, tyrosine and phenylalanine aminotransferases	145
hom	Homoserine	290	Threonine and methionine requirement, deletion lacking homoserine dehydrogenase	F
hpr	Protease	90	Overproduction of proteases	73
hsrM	Restriction	45	Host restriction, modification (Marburg strain); probably identical to *nonB*	173
hts	Hydrogen sulfide		Excretion of hydrogen sulfide, see *cysA*	97
hut	Histidine utilization	345	Histidine degradation	31, G
ifm	Flagella	UC	Increased flagella and motility, maps near *flaA,B,C* cluster	60
ilvA	Isoleucine-valine	200	Threonine dehydratase	14, 76
ilvB	Isoleucine-valine	250	Condensing enzyme	14, 202

TABLE 1—*Continued*

Gene symbol	Mnemonic	Map position[a]	Phenotype, enzyme deficiency, or other characteristic	References[b]
ilvC	Isoleucine-valine	250	α-Hydroxy-β-ketoacid reductoisomerase	14, 202
ilvD	Isoleucine-valine	200	Dihydroxyacid dehydratase	14
inh	Inhibition by histidine		Inhibition by histidine; probably within *tyrA* locus, see *tyrA*	143, 146
kan	Kanamycin	10	Kanamycin resistance, maps in the ribosomal protein cluster	58
kauA	Keto acid uptake	185	Branched-chain α-keto acid transport	57
kir	Kiromycin		Probable mutation in the structural gene for elongation factor Tu, see *tuf*	181
ksgA	Kasugamycin	5	High-level kasugamycin resistance	193, 195
ksgB	Kasugamycin	280	Low-level kasugamycin resistance	193
ksgC	Kasugamycin	UC	Fumarate hydratase defective, kasugamycin resistance	A
leuA	Leucine	250	α-Isopropylmalate synthase	14, 42, 202, 203
leuB	Leucine	250	Isopropylmalate isomerase	202
leuC	Leucine	250	β-Isopropylmalate dehydrogenase	14, 202, 203
lin	Lincomycin	25	Lincomycin resistance	59, 67
lpm	Lipiarmycin		Lipiarmycin resistance; RNA polymerase, see *rpoC*	184
lys	Lysine	210	Lysine requirement, diaminopimelate decarboxylase	89, 101
lysS	Lysine	5	Lysyl-transfer-RNA synthetase	165
lyt	Lytic	NM	Autolytic enzymes	46
mdh			Malate dehydrogenase, see *citH*	53
metA	Methionine	115	Responds to methionine, cystathionine, or homocysteine	188
metB	Methionine	200	Responds to methionine or homocysteine	7
metC	Methionine	115	Responds to methionine	42
metD	Methionine	95	Responds to methionine	216
mic	Micrococcin		Resistance to micrococcin, see *rplC*	183
mit	Mitomycin	UC	Resistance to mitomycin C, maps near *rplV*	95
mtlB	Mannitol	35	Mannitol-1-phosphate dehydrogenase	118
mtr	5-Methyltryptophan	210	Resistance to 5-methyltryptophan, derepression of the tryptophan biosynthetic pathway	82, 85
nalA	Nalidixic acid	355	Resistance to nalidixic acid	66, 195
narA	Nitrate	320	Inability to use nitrate as a nitrogen source	118, 221
narB	Nitrate	30	Inability to use nitrate as a nitrogen source	118, 221
nea	Neamine		Neamine resistance, see ribosomal protein cluster	59
neo	Neomycin		Neomycin resistance, see ribosomal protein cluster	59, 67
nic	Nicotinic acid	245	Nicotinic acid requirement	75, 101
nonA	Nonpermissive	UC	Permissive for bacteriophages SP10 and φNR2, closely linked to *rfm*	174
nonB	Nonpermissive	45	Permissive for bacteriophages SP10 and φNR2	174
novA	Novobiocin	0	Resistance to novobiocin	67, 195
nprE	Neutral protease	125	Structural gene for neutral protease	197
nprR	Neutral protease	125	Regulatory gene for neutral protease	197
ole	Oleandomycin		Oleandomycin resistance, see ribosomal protein cluster	59, 67
pab	*p*-Aminobenzoic acid	10	*p*-Aminobenzoic acid requirement, subunit A of *p*-aminobenzoate synthase	96

TABLE 1—*Continued*

Gene symbol	Mnemonic	Map position[a]	Phenotype, enzyme deficiency, or other characteristic	References[b]
pac	Pactamycin	5	Resistance to pactamycin	67, 195
pap			Hyperproduction of proteases and amylase, see *sacQ*	189, 212
pfk		NM	Phosphofructokinase	55
pha1		50	Resistance to phage SPO1	118
pheA	Phenylalanine	245	Phenylalanine requirement, prephenate dehydratase	14
phoP	Phosphatase	260	Regulation of alkaline phosphatase and alkaline phosphodiesterase	113, 210
phoR	Phosphatase	260	Regulation of alkaline phosphatase	112, 113, 137
phoS	Phosphatase	110	Constitutive alkaline phosphatase	162
pig	Pigment	50	Sporulation-associated pigment	171
polA	Polymerase	260	DNA polymerase A	53, 110
polC	Polymerase	145	DNA polymerase III, azopyrimidine resistance	9, 36, 126, 169
ptm		105	Pyrithymine resistance	H
pts		120	Phosphoenolpyruvate phosphotransferase	54, 148
purA	Purine	355	Adenine requirement	155
purB	Purine	55	Adenine, guanine, or hypoxanthine requirement	124, 155
purC	Purine	55	Adenine or hypoxanthine requirement	124
purD	Purine	55	Adenine or hypoxanthine requirement	124
purE	Purine	55	Adenine requirement	124
pycA		145	Pyruvate carboxylase	25, 77
pyrA	Pyrimidine	135	Carbamyl phosphate synthetase	164
pyrB	Pyrimidine	135	Aspartate carbamoyl transferase	164
pyrC	Pyrimidine	135	Dihydroorotase	164
pyrD	Pyrimidine	135	Dihydroorotate dehydrogenase	164
pyrE	Pyrimidine	135	Orotate phosphoribosyltransferase, also called *pyrX*	164, I
pyrF	Pyrimidine	135	Orotidine-5′-phosphate decarboxylase	164
pyrG	Pyrimidine	NM	Cytidine-5′-triphosphate synthetase	168
recA	Recombination	145	Genetic recombination and radiation resistance	75, 133
recB	Recombination	245	Genetic recombination and radiation resistance	75, 133
recC	Recombination		Genetic recombination; indirect effect of bacteriophage SPO2 lysogeny, see *attSPO2*	41, 52, 133
recD	Recombination	5	Genetic recombination and radiation resistance	64, 133, 195
recE	Recombination	150	Genetic recombination and radiation resistance, adenosine triphosphate-dependent nuclease	41, 132, 133
recF	Recombination	355	Genetic recombination and radiation resistance	64, 133, 195
recG	Recombination	205	Genetic recombination and radiation resistance	62, 132, 138
recH	Recombination	70	Genetic recombination and radiation resistance, adenosine triphosphate-dependent nuclease	133, 144
recI	Recombination	70	Genetic recombination and radiation resistance	133, 144
recL	Recombination	UC	Genetic recombination and radiation resistance, linked to *cysA*	41, 132, 133
recM	Recombination	5	Genetic recombination and radiation resistance	41, 132, 133
recN	Recombination	150	Genetic recombination and radiation resistance	132, 133, A

TABLE 1—*Continued*

Gene symbol	Mnemonic	Map position[a]	Phenotype, enzyme deficiency, or other characteristic	References[b]
relA		NM	Relaxed RNA synthesis	190
rfm	Rifampin		Rifampin resistance; RNA polymerase, see *rpoB*	61, 185
rib	Riboflavin	210	Riboflavin requirement	102
rna53	RNA synthesis	315	Temperature-sensitive RNA synthesis	170
rodB		130	Cell wall defective	99
rodC		320	Cell wall defective	99
rplA	Ribosomal protein, large	10	Ribosomal protein BL1, chloramphenicol resistance II	152, 153
rplC	Ribosomal protein, large	10	Ribosomal protein BL3, probable micrococcin resistance	153, 183
rplK	Ribosomal protein, large	10	Ribosomal protein BL11, thiostrepton resistance	153, 157, 206
rplL	Ribosomal protein, large	10	Ribosomal protein B12, chloramphenicol resistance VI	152, 153
rplO	Ribosomal protein, large	10	Ribosomal protein BL15, chloramphenicol resistance III	152, 153
rplV	Ribosomal protein, large	10	Ribosomal protein BL22, erythromycin resistance	153, 191
rpoB	RNA polymerase	10	β subunit of RNA polymerase, rifampin resistance	61, 185
rpoC	RNA polymerase	10	β' subunit of RNA polymerase, streptolydigin resistance	62, 185
rpsE	Ribosomal protein, small	10	Ribosomal protein S5, spectinomycin resistance	67, 94, 153
rpsL	Ribosomal protein, small	10	Ribosomal protein S12, streptinomycin resistance	59, 153
rpsT	Ribosomal protein, small	10	Ribosomal protein S20	151, 153
Ribosomal protein cluster			Cluster of ribosomal proteins, including S3, S5, S8, S12, S17, S19, S20, BL1, BL2, BL4, BL5, BL6, BL8, BL12, BL14, BL15, BL16, BL17, BL22, BL23, and BL25.	153
rRNA cluster		15	Probable site of 5 to 7 rRNA gene clusters and many transfer RNA genes	150, 180, J
sacA	Sucrose	335	β-Fructofuranosidase	116, 117
sacB	Sucrose	305	Levansucrase	117
sacL	Sucrose	240	Levanase	109
sacP	Sucrose	335	Sucrose transport	116
sacQ	Sucrose	285	Hyperproduction of levansucrase and proteases	108, 117, 175
sacR	Sucrose	305	Constitutive β-fructofuranosidase production	117
sacS	Sucrose	335	Constitutive β-fructofuranosidase production	117
sacT	Sucrose	335	Constitutive β-fructofuranosidase production	117
sacU	Sucrose	310	Regulatory gene for levansucrase	108, 117, 119, 189
sapA		110	Alkaline phosphatase	162
sapB		55	Alkaline phosphatase	162
scoA		110	Sporulation control	138
scoB		130	Sporulation control	138
scoC		90	Sporulation control	138
scoD		130	Sporulation control	138

TABLE 1—*Continued*

Gene symbol	Mnemonic	Map position[a]	Phenotype, enzyme deficiency, or other characteristic	References[b]
ser	Serine	210	Requirement for serine	82
smo	Smooth	305	Smooth/rough colony morphology	60
spcA	Spectinomycin		Spectinomycin resistance, see *rpsE*	26, 67, 94
spcB	Spectinomycin	140	Spectinomycin resistance	67, 126
spcD	Spectinomycin	UC	Spectinomycin dependence, maps between *cysA* and *purA*	70
spg	Sporangiomycin		Sporangiomycin resistance, 50S ribosome alteration, see ribosomal protein cluster	16
spoCM	Sporulation	355	Stage 0 sporulation, possibly identical to *spo0J*	24
spoL1	Sporulation	230	"Decadent" sporulation	13
spo0A	Sporulation	215	Stage 0 sporulation	160
spo0B	Sporulation	245	Stage 0 sporulation	160
spo0E	Sporulation	120	Stage 0 sporulation	160
spo0F	Sporulation	325	Stage 0 sporulation	160
spo0G	Sporulation	220	Stage 0 sporulation	160
spo0H	Sporulation	10	Stage 0 sporulation	160
spo0J	Sporulation	355	Stage 0 sporulation	160
spo0K	Sporulation	105	Stage 0 sporulation	160
spo0L	Sporulation	105	Stage 0 sporulation	A
spoIIA	Sporulation	210	Stage II sporulation	160
spoIIB	Sporulation	245	Stage II sporulation	160
spoIIC	Sporulation	300	Stage II sporulation	160
spoIID	Sporulation	320	Stage II sporulation	160
spoIIE	Sporulation	10	Stage II sporulation	160
spoIIF	Sporulation	120	Stage II sporulation	160
spoIIG	Sporulation	130	Stage II sporulation	160
spoIIIA	Sporulation	215	Stage III sporulation	160
spoIIIB	Sporulation	215	Stage III sporulation	160
spoIIIC	Sporulation	235	Stage III sporulation	160
spoIIID	Sporulation	295	Stage III sporulation	160
spoIIIE	Sporulation	140	Stage III sporulation	160
spoIVA	Sporulation	210	Stage IV sporulation	160
spoIVB	Sporulation	215	Stage IV sporulation	160
spoIVC	Sporulation	235	Stage IV sporulation	160
spoIVD	Sporulation	235	Stage IV sporulation	160
spoIVE	Sporulation	240	Stage IV sporulation	160
spoIVF	Sporulation	245	Stage IV sporulation	160
spoIVG	Sporulation	95	Stage IV sporulation	160
spoVA	Sporulation	210	Stage V sporulation	160
spoVB	Sporulation	245	Stage V sporulation	160
spoVC	Sporulation	10	Stage V sporulation	160
spoVD	Sporulation	125	Stage V sporulation	160
spoVE	Sporulation	130	Stage V sporulation	160
spoVF	Sporulation	NM	Stage V sporulation	160
sprA		NM	Derepression of homoserine kinase, homoserine dehydrogenase, and the minor threonine dehydratase (*tdm*)	199
sprB		290	Partial suppression of isoleucine requirement allows threonine dehydratase *sprA* mutants to grow in minimal medium, maps near *tdm* locus, see *tdm*	200
ssp1	Ultraviolet repair	NM	Endonuclease excising spore photoproducts	141
std	Streptolydigin		Streptolydigin resistance; RNA polymerase, see *rpoC*	62, 185
strA	Streptomycin		Streptomycin resistance, see *rpsL*	59
strB	Streptomycin	130	Streptomycin resistance	187
strC	Streptomycin	220	Streptomycin resistance	187
sul	Sulfonilamide	10	Sulfonilamide resistance	90, 96

TABLE 1—*Continued*

Gene symbol	Mnemonic	Map position[a]	Phenotype, enzyme deficiency, or other characteristic	References[b]
sup3	Suppressor	30	Suppressor transfer RNA	71
tag		NM	Cell wall synthesis	23
tdm		290	Minor threonine dehydratase	200
thiA	Thiamine	70	Thiamine requirement	101
thiB	Thiamine	100	Thiamine requirement	77
thrA	Threonine	290	Threonine requirement, homoserine kinase	42, 197, 199
thyA	Thymidine	160	Thymidylate synthetase A	7, 147, 208
thyB	Thymidine	200	Thymidylate synthetase B	7, 147, 208
til	Tilerone	230	Tilerone resistance	A
tmp	Trimethoprim	200	Trimethoprim resistance	201
tmr7	Tunicamycin	25	Tunicamycin resistance, hyperproductivity of extracellular α-amylase	149
tmr8	Tunicamycin	25	Tunicamycin resistance	149
tms12		130	Temperature-sensitive cell division	35, A
tms26		5	Temperature-sensitive cell division	35, 194
tolA	Tolerance		Tolerance to bacteriophages, see *abrB*	92, 93
tolB	Tolerance	NM	Tolerance to bacteriophages	92, 93
tre	Trehalose	60	Trehalose	118
trpA	Tryptophan	205	Tryptophan synthase α	6, 84, 205
trpB	Tryptophan	205	Tryptophan synthase β	6, 84, 205
trpC	Tryptophan	205	Indole-3-glycerol-phosphate synthase	6, 84, 205
trpD	Tryptophan	205	Anthranilate phosphoribosyltransferase	6, 84, 205
trpE	Tryptophan	205	Anthranilate synthase	6, 84, 205
trpF	Tryptophan	205	*N*-(5′-Phosphoribosyl)-anthranilate isomerase	84, 205
trpS	Tryptophan	100	Tryptophanyl-transfer-RNA synthase	188
trpX	Tryptophan	10	Glutamine-binding protein common to anthranilate synthase and *p*-aminobenzoate synthase	96
tsi		50	Temperature-sensitive induction of bacteriophage PBS-X	178
tsp	Thiostrepton		Thiostrepton resistance, 50S subunit, maps in ribosomal protein cluster	157
ts39		230	Temperature-sensitive synthesis of phosphatidylethanolamine	121
tuf	Tu factor	10	Elongation factor Tu	43, 181
tyrA	Tyrosine	205	Tyrosine requirement, prephenate dehydrogenase	143, 146
urg		NM	*N*-Glycosidase	128
urs		100	Uracil sensitivity, arginine-specific carbamyl-phosphate synthase	I
uvrA	Ultraviolet repair	310	Excision of ultraviolet-light-induced pyrimidine dimers in DNA	75, 118, 141
uvrB	Ultraviolet repair	250	Excision of ultraviolet-light-induced pyrimidine dimers in DNA	141
vas			Valine sensitivity; maps within threonine dehydratase locus, see *ilvA*	114
xtl		115	Induced PBS-X bacteriophage lack tails	51

[a] Abbreviations: UC, map position not fully defined; NM, not mapped.

[b] References include unpublished data from: (A) J. Hoch, (B) W. Steinberg, (C) E. Freese, (D) S. Baumberg, (E) S. Zahler, (F) C. Anagnostopoulos, (G) S. Fisher, (H) A. Galizzi, (I) R. Switzer, and (J) W. Steinberg and D. Henner.

markers in this region. This area, extending from approximately 355 to 15° of the chromosome, is shown in Fig. 7.

A large portion of the origin region encodes for functions involved in protein synthesis. There is a ribosomal protein cluster in the area of *cysA-attSPO2* whose endpoints are not well defined. At least 21 ribosomal proteins have been mapped to this area by a variety of techniques (153). Individual proteins which are al-

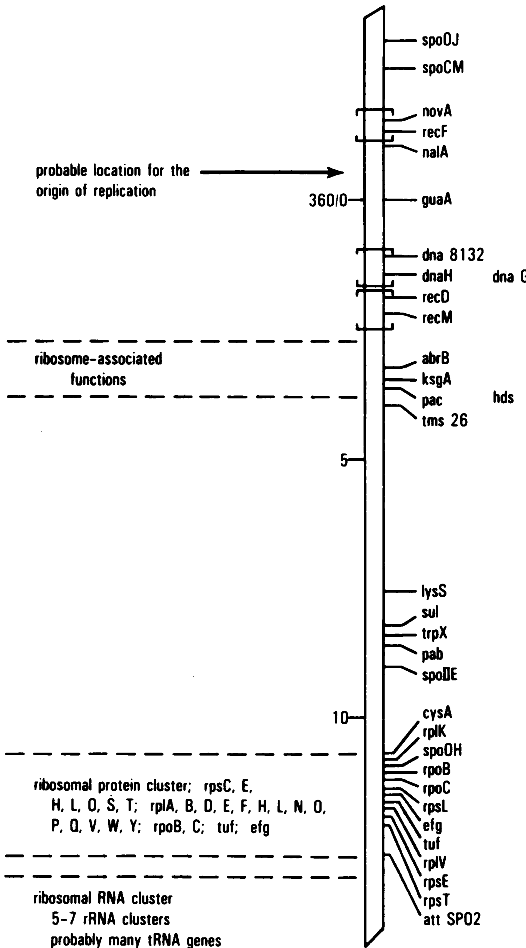


FIG. 7. *Detailed map of the origin region of the B. subtilis chromosome. tRNA, Transfer RNA.*

tered in certain antibiotic-resistant mutants have been mapped by their antibiotic-resistant phenotype, including: BL11, thiostrepton resistance (153, 157, 206); S12, streptomycin resistance (59, 153); BL22, erythromycin resistance (153, 191); S5, spectinomycin resistance (67, 94, 153); BL1, chloramphenicol resistance II; BL12, chloramphenicol resistance VII; and BL15, chloramphenicol resistance III (152, 153). By using electrophoretic and chromatographic differences between ribosomal proteins from different *Bacillus* strains and species, Osawa and colleagues have shown that the genes for ribosomal proteins S3, S5, S8, S12, S17, S19, S20, BL4, BL5, BL6, BL8, BL14, BL16, BL17, BL22, BL23, and BL25 are located in this region (151, 153). Recently the ribosomal proteins of the 30S subunit in *Bacillus* have been numbered to correspond to their counterparts in *E. coli*, and they are now numbered S1, S2, etc. (153). The correspondence of the proteins of the 50S subunit is not established, and the proteins have been designated BL1, BL2, etc. For the genetic designation of these loci, we have followed the convention established in *E. coli* and designated 30S ribosomal protein loci as *rps*, followed by a letter corresponding to the number designation of the protein, and 50S ribosomal protein loci as *rpl* or *rpm* (for proteins 27 and above), with the same lettering designation. Also mapping in this cluster are genes for the two elongation factors G and Tu. These two loci have both been defined directly by temperature-sensitive mutations and by antibiotic resistance mutations (4, 43, 107, 181). The β and β' subunits of ribonucleic acid (RNA) polymerase (RNA nucleotidyltransferase), defined by resistance to rifampin and streptolydigin, respectively, have also been shown to map in this gene cluster (61, 62, 185).

The *abrB* locus is a pleiotropic partial suppressor of many *spoO* mutations, and mutations at this site show electrophoretic alterations in core ribosomal proteins (196). It is not yet clear how mutations in the *abrB* locus cause these electrophoretic alterations, but the cause could possibly be a modifying or processing enzyme of some sort. The *ksgA* locus, although originally mapped to the right of *cysA*, has been recently mapped in this laboratory near the *pac* locus (193; J. A. Hoch, unpublished data). In *E. coli* there are three kasugamycin resistance loci, *ksyA*, *ksgB*, and *ksgC*, whose resistances are attributed to undermethylation of 16S ribosomal RNA (rRNA), alteration of permeability, and alteration of ribosomal protein S2, respectively (69, 186, 215). Although the exact mechanism of kasugamycin resistance is not known in *B. subtilis*, it is likely that this *ksgA* locus is a ribosomal alteration of some kind. The pactamycin resistance locus in this area also has not been well defined, but the mechanism of pactamycin action seems to result in inhibition of formation of the initiation complex of protein synthesis (34). These three loci seem to define a group of genes that have ribosome-associated functions.

The rRNA and transfer RNA genes were localized by density transfer techniques to the early region of the chromosome (150, 180). Chow and Davidson showed by electron microscopic analysis that the SPO2 attachment site is 6,000 base pairs from an rRNA gene cluster which is separated from a second cluster by about 600 base pairs (33). Their data strongly suggest that these two rRNA gene clusters are linked to three to five more rRNA gene clusters. This evidence indicates that there are five to seven rRNA gene clusters distal or proximal to the *attSPO2* site. Restriction analysis of chromosomal DNA shows a tight linkage of many of the transfer RNA genes with rRNA genes (W. Steinberg and

D. Henner, unpublished data). Thus, it is probable that many of the transfer RNA genes are also localized in this ribosomal gene cluster.

COMPARISON OF FEATURES OF THE *B. SUBTILIS* AND *ESCHERICHIA COLI* GENETIC MAPS

A quick glance at either the *B. subtilis* or the *E. coli* genetic map shows a greatly varying gene density in different areas of the chromosome (10). Both chromosomes show clusters that are tightly packed with known loci and silent regions containing no known locus at all. It is possible that this arrangement of loci in some way reflects a functional organization of chromosome structure. It has been suggested that clustered organization in *E. coli* is related to the folded structure of the condensed bacterial nucleoid (10). The silent regions could play a structural role in chromosome organization and might not be available for coding capacity or might not be accessible to the RNA- and protein-synthesizing machinery. It is interesting to note that the largest silent regions in both *E. coli* and *B. subtilis* are near the termini of replication. The presence of these silent regions in both species increases the likelihood that they play an integral role in chromosome organization. With the recent strides in cloning technology, these areas should soon be available for studies to determine whether they are noncoding regions and what their role may be.

An informative way to look at the distribution of genes is a plot of the number of genes per unit of map length. Figure 8 shows such a plot for the *B. subtilis* map. Again, one notes that the majority of genes are arranged in a few large clusters. It was noted for *E. coli* that many of the genes for balanced macromolecular synthesis, such as those for rRNA, transfer RNA, RNA and DNA polymerases, ribosomal proteins, oxidative phosphorylation proteins, etc., are disproportionately located in these very dense clusters (10). A similar situation seems to hold true in *B. subtilis*. The major clusters contain the genes for ribosomal proteins, amino acid pathway enzymes, structural components, and RNA- and DNA-polymerizing functions, whereas the sparser regions seem to have many loci of a rather less essential nature, such as sugar utilization enzymes. The relative paucity of markers on the *B. subtilis* map compared with that of *E. coli* makes the conclusions more tentative, but it seems that in both species the more essential genes are located in the denser clusters.

In *B. subtilis* a large number of developmental loci have been mapped. It has been proposed that one method of control of the developmental process could be an alteration of the structure of

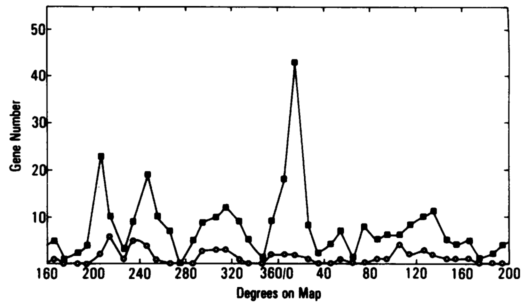


FIG. 8. *Gene density map of the B. subtilis chromosome. The number of genes in each 5° interval of the B. subtilis map is plotted versus the map location. Symbols:* ■, *all loci;* ○, *developmental loci.*

the chromosome, making the developmental genes accessible to the biosynthetic machinery (74). An examination of the distribution of the developmental genes shows that whereas they are clustered to a certain extent, they seem to be clustered within the major vegetative gene clusters (Fig. 8). Thus, their distribution makes the model of alteration of the chromosomal structure seem less likely as a control mechanism.

So far, the comparisons of the *E. coli* and *B. subtilis* maps have shown correspondence of some general features, i.e., a few dense gene clusters involved in important biosynthetic events, the presence of silent regions around the genome, and a very large silent region near the terminus of replication. There are general features in which the chromosomes of the two species differ. *E. coli* has its four major gene clusters distributed symmetrically near the origin of replication, and the hypothesis has been presented that the increased gene dosage of genes located near the origin might play a role in this arrangement (10). In contrast, in *B. subtilis* the major gene clusters seem to be spread more evenly throughout the chromosome. It is interesting to note that in both species the majority of the ribosomal protein genes and rRNA sequences are located near the origin of replication. A second difference in the chromosomal organization of the two species is a lack of symmetry in gene distribution in *B. subtilis* (Fig. 8). A gene density plot in *E. coli* shows a certain degree of symmetry, which, it was speculated, may define two halves of the genome that are organized in a complementary manner, or may be a relict of the evolutionary development of the genome (10). In *B. subtilis* the distribution of presently known loci fails to suggest an axis of symmetry in the genome.

In summary, the *B. subtilis* and *E. coli* chromosomes are similar in that active genes tend to be clustered together, separated by silent re-

gions. On the other hand, the distribution of clusters on the two chromosomes differs greatly between the species suggesting that cluster distribution is not related to chromosome replication and that any general inference to its significance cannot be drawn from studies in a single species.

ACKNOWLEDGMENTS

This review was supported by Public Health Service grants GM 19416 and GM 25891 from the National Institute of General Medical Sciences.

We are grateful for unpublished data supplied by our colleagues.

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