https://doi.org/10.15407/microbiolj85.03.012

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SEQUENCES SIMILAR TO THE *lan*-CLUSTER (*STREPTOMYCES CYANOGENUS* S136) WERE FOUND IN THE GENOMES OF OTHER STREPTOMYCETES

The aim *of the work is to identify strains of streptomycetes in the genomes of which there are nucleotide sequences similar to the gene cluster determining the synthesis of landomycin A (lan-cluster) and establish the level of similarity of their primary structures and organizations.* ***Methods.*** *Information on the sequences of the lan-cluster of Streptomyces cyanogenus S136 and chromosomal DNAs of S. cyanogenus S136, Streptomyces laculatispora NRRL B-24909, and Streptomyces griseoluteus JCM 4765 and their annotations are presented in the GenBank database on the NSBI server. A computerized analysis of the nucleotide sequences of streptomycetes was done using the program BLASTN from the server NSBI.* ***Results****. The localization of the lan-cluster in the terminal region of the S. cyanogenus S136 genome has been shown. The nucleotide sequences similar to the lan-cluster sequence of S. cyanogenus S136 were found in the genomes of two strains (S. laculatispora NRRL B-24909 and S. griseoluteus JCM 4765). Streptomycetes (S. cyanogenus S136, S. laculatispora NRRL B-24909, and S. griseoluteus JCM 4765) are not genetically related strains.* ***Conclusions****. There are newly found probable lan-clusters in the genomes of two streptomycetes strains (S. laculatispora NRRL B-24909 and S. griseoluteus JCM 4765). Landomycin clusters of three strains are organized according to the same scheme. The clusters of lan-genes are present in the genomes of genetically unrelated streptomycetes.*

Keywords*: streptomycetes, landomycin cluster, nucleotide sequence, BLASTN analysis.*

Landomycins are compounds belonging to the large subgroup of anguacycline antibiotics that have an antitumor and antibacterial effect. More than two dozen landomycins (A to Z) have been identified [1—5]. As a rule, antibiotic molecules consist of an aglycone moiety and oligosaccharide chains. For example, the landomycin A molecule contains a hexasaccharide formed from four D-olivose residues and two L-rhodinose residues [2, 4]. It was found that, among the studied landomycins, landomycin A has the highest antitumor activity [2, 4, 5].

Citation: Polishchuk L.V., Lukyanchuk V.V. Sequences Similar to the *lan*-Cluster (*Streptomyces cyanogenus* S136) Were Found in the Genomes of Other Streptomycetes. *Microbiological journal.* 2023 (3). P. 12—21. https://doi.org/10.15407/microbiolj85.03.012

Landomycin A is the major component of a complex of landomycins produced by the wild-type strain *S. cyanogenus* S136 [1]. To date, the nucleotide sequences of both the cluster of biosynthetic genes (BGC), which determines the synthesis of landomycin A (*lan*-cluster), and the genomic DNA of the producer strain of the antibiotic *S. cyanogenus* S136 have been determined [1, 6]. However, many laboratories around the world are intensively searching for new producers of landomycin antibiotics [7]. Screening is performed by various methods, including bioinformatics, as there is a significant opportunity to identify probable silent BGCs that determine antibiotic production [8, 9].

The **aim** of the study was to identify new strains of streptomycetes, in the genomes of which there are nucleotide sequences similar to the *lan*-cluster sequence of *S. cyanogenus* S136, and to elucidate the level of their similarity.

Materials and methods. Information on the primary structure of chromosomal DNAs of strains (*S. cyanogenus* S136, *S. laculatispora* NRRL B-24909, and *S. griseoluteus* JCM 4765), genes, and the *lan*-cluster are freely available in the GenBank database at the National Center for Biotechnology Information [www.ncbi.nlm.nih.gov/nucleotide/].

The primary structure of the chromosomal DNA of *S. cyanogenus* S136 strain and its annotation were deposited in the GenBank database under access number NZ_CP071839.1, 8773899 bp [6]. The sequence of *S. cyanogenus* S136 *lan*-cluster and its organization are presented in GenBank under access number AF080235 (34644 bp) [10]. Information on the primary structure of *S. laculatispora* NRRL B-24909 chromosome is placed in the GenBank database under the number JAFMPZ000000000.1, 7316151 bp. The nucleotide sequence of the genomic DNA of *S. griseoluteus* JCM 4765 is deposited in the GenBank database under the number SRRU00000000.1, 6843455 bp.

Computerized analysis of streptomycete nucleotide sequences was done using the program BLASTN [www.ncbi.nlm.nih.gov/blast] on the NCBI server.

Sequences of five genes that determine conserved proteins of *S. laculatispora* NRRL B-24909 (J1C73_08925, J1C73_28375, J1C73_24225, J1C73_33975, and J1C73_33605) and *S. griseoluteus* JCM 4765 (GCM10017776_44380, GCM10017776_25830, GCM10017776_39780, GCM10017776_50280, and GCM10017776_58060) were used for dendrogram construction.

Results. Wild- type strain *S. cyanogenus* S136 was isolated in 1985 from a sample of Indian mountain soil [1]. The strain was found to synthesize a landomycin complex in which landomycin A is a major component [1, 10]. The primary structure of the streptomycete *lan*-cluster has been established, and its organization has been determined [10] (Fig. 1). Transformants of *Streptomyces lividans* and *Streptomyces coelicolor* containing *S. cyanogenus* S136 *lan*-cluster have been shown to produce trace amounts of landomycins [10]. It is possible to consider that the *lan*-cluster contains a complete set of genes that provide synthesis of landomycin A.

Comparative analysis of the chromosome sequence of *S. cyanogenus* S136 (NZ_CP071839.1) and the *lan*-cluster sequence (AF080235.1) revealed the emplacement of *lan*-genes on the genome map of the strain. The cluster is localized on the sequence 6643294 bp — 6677929 bp (genes from S1361_RS29860 to S1361_RS30030). Thus, the *lan*-cluster of *S. cyanogenus* S136, like most BGCs encoding the synthesis of secondary metabolites, is localized in the terminal zone of the chromosome [12]. As previously established, in many BGCs, among the genes required for metabolite production, some «additional» genes are localized (products of which are not involved in the synthesis of this compound, but they may be important for cell viability) [13]. For example, in the *crt*-cluster of *Streptomyces albidoflavus* strain J1074 (CP004370.1), among biosynthetic genes, there is an «additional» gene XNR_5687, which

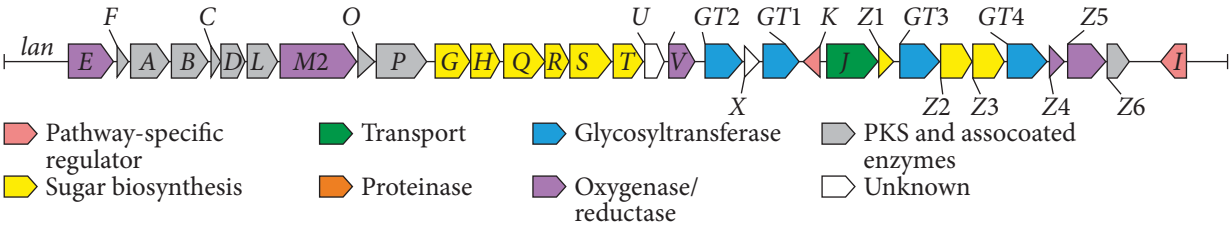

Fig. 1. Scheme of the *lan*-cluster organization of *S. cyanogenus* S136 [11]

encodes a transmembrane protein (Lysine exporter protein). In the *lnd*-cluster of *Streptomyces globisporus* 1912-4Crt (QWFA01000010.1), there is a gene D3105_03425, which determines tRNA-Thr. In the *lan*-cluster, for example, the «additional» gene S1361_RS29915 encodes a protein of the epsilon subunit of the multisubunit enzyme acyl-CoA carboxylase.

It is currently reported that, in addition to the strain *S. cyanogenus* S136, the synthesis of landomycin was detected in the strain *S. globisporus* 1912 [14, 15]. Moreover, a metagenomic clone that produces landomycin E has been made [16]. All this indicates the possibility of the existence of other streptomycetes containing clusters of genes for the synthesis of landomycin. Various screening (microbiological, genetic engineering, and bioinformatical) methods for finding landomycin producers are currently being developed and used [7].

The main task was to identify strains of streptomycetes whose genomes contain sequences similar to the sequence of landomycin BGC in *S. cyanogenus* S136 and to determine the degree of similarity of their primary structures and their organization.

NCBI databases were analyzed using the BLASTN program to screen for streptomycete strains that contain probable *lan*-clusters in their genomes. A number of streptomycetes strains were identified; those genomes contain sequences with significant indicators of their similarity to the *lan*-cluster of *S. cyanogenus* S136 sequence (Table 1). Sequences similar to those of the *lan*-cluster of *S. cyanogenus* S136 are represented as many disparate fragments in the genomes of *Streptomyces* sp. CB00271, *Streptomyces venezuelae* ATCC 15068, *Streptomyces* sp. CS090A, and a number of others. For example, 64 such fragments, localized from 407226 bp up to 8363864 bp in the genome of *S. venezuelae* ATCC 15068, were found (Table 1).

Two strains (*S. laculatispora* NRRL B-24909 and *S. griseoluteus* JCM 4765) were selected for further study. The probable BGC of *S. laculatispora* NRRL B-24909 was localized in fragment (5447 bp — 40361 bp) of contig JAFMPZ010000093.1, and the probable *lan*-cluster of *S. griseoluteus* JCM 4765 was localized in fragment (204953 bp — 239648 bp) of contig SRRU01000006.1.

Table 1. **Indicators of similarity of fragment sequences of streptomycetes to the sequence of *lan*-cluster of *S. cyanogenus* S136 (Query sequence)**

Strain of streptomycetes (Subject sequence)	Indicators of similarity of sequences
S. laculatispora NRRL B-24909 JAFMPZ010000093.1	Qc = 84% I = 86.88%
S. griseoluteus JCM 4765 SRRU01000006.1	Qc = 88% I = 82.66%
Streptomyces sp. CB00271 NZ_CP061072.1	Qc = 65% I = 79.26% *
S. venezuelae ATCC 15068 NZ_CP029194.1	Qc = 59% I = 81.19% *
Streptomyces sp. CS090A NZ_KZ819159.1	Qc = 60% I = 75.73% *

Qc — Query coverage, I — Identity; * — Total indicators of similarity of a set of fragments.

It is shown that these sequences of *S. laculatispora* NRRL B-24909 and *S. griseoluteus* JCM 4765 not only have a significant degree of similarity to the primary structure of the *lan*-cluster of *S. cyanogenus* S136 but are also organized according to the same scheme (Tables 1, 2).

Some genes, such as *lan*GT3, *lan*Z2, and *lan*K, are special only to the *lan*-cluster, but not to the *lnd*-cluster as demonstrated previously [10, 11, 15, 16]. Genes similar to *lan*GT3, *lan*Z2, and *lan*K were found in the genomes of *S. griseoluteus* JCM 4765 (E5082_18205, E5082_18220, E5082_18250) and *S. laculatispora* NRRL B-24909 (JIC73_05270, JIC73_05250, JIC73_05255) (Table 2). In addition, genes E5082_18260 and J1C73_05215, as well as the *lan*I gene of *S. cyanogenus* S136, have been shown to have a terminal localization upstream of the *lanZ6* gene in the *lan*-cluster of *S. griseoluteus* strains JCM 4765 and *S. laculatispora* NRRL B-24909.

The nucleotide sequences of BGCs from the three streptomycetes were shown to have similar molecular sizes. The molecular size of the *S. cyanogenus* S136 *lan* cluster is 34,636 bp; the sizes of the probable BGCs of *S. griseoluteus* JCM 4765 and *S. laculatispora* NRRL B-24909 are 34696 bp and 34915 bp, respectively.

A synteny of probable BGCs of *S. griseoluteus* JCM 4765and *S. laculatispora* NRRL B-24909 and the *lan*-cluster of *S. cyanogenus* S136 was detected. It was shown that both probable BGCs consist of 35 genes, of which 5 are «ballast» genes (Table 2). A greater similarity was found between the sequence of *S. cyanogenus* S136 *lan*-cluster and the BGC *S. griseoluteus* JCM 4765 sequence rather than to the primary structure of *S. laculatispora* NRRL B-24909 cluster (Table 1). In addition, the primary structures of all genes of *S. laculatispora* NRRL B-24909 BGC are less similar to the sequences of analogous genes in the *lan*-cluster of *S. cyanogenus* S136 compared to the genes of *S. griseoluteus* JCM 4765 BGC (Table 2).

A number of strains of *S. griseoluteus* are known for their ability to synthesize polyketide metabolites with antibacterial and antitumor activity, in particular griseolutein, U-77863, and U-77864 [17, 18]. The synthesis of metabolites with anti-MRSA activity by strains of *S. laculatispora* has been reported [19].

The International Committee on the Reconciliation of Approaches to Bacterial Systematics recommended using the primary structure of genomic DNA studies in the hierarchical classification, in addition to the results of traditional phenotypic and serological studies [20—22]. For a long time, the primary structure of 16S rRNA was considered the «gold standard» in determining the genetic affinity of streptomycetes [23], but later the Committee recommended using a number of essential genes for the hierarchical classification of a number of «housekeeping genes» (*rpo*B, *atp*D, *trp*B, *ric*A, and *hrp*A) [21, 24]. The genome sequences of *S. laculatispora* NRRL B-24909 and *S. griseoluteus* JCM 4765 are currently not fully defined (as whole genome shotgun sequences). For example, the 16S rRNA sequence of *S. griseoluteus* JCM 4765 is partially established.

On the other hand, scientists have proposed to determine the genetic consanguinity by the similarity of the nucleotide sequences of five genes that determine conservative proteins (the so-called «molecular signatures») that are specific only to members of the genus *Streptomyces*. Such classical «molecular signatures» are encoded by the genes of the strain *S. coelicolor* A3 (2) SCO1634, SCO2919, SCO4335, SCO3300, and SCO3544 [6, 25]. We used in our research the structures of *S. griseoluteus* JCM 4765 and *S. laculatispora* NRRL B-24909, analogous to the «molecular signatures» of *S. coelicolor* A3(2).

United sequences of five genes of *S. laculatispora* NRRL B-24909 (J1C73_08925, J1C73_28375, J1C73_24225, J1C73_33975, J1C73_33605) and *S. griseoluteus* JCM 4765 (GCM10017776_44380, GCM10017776_25830, GCM10017776_39780, GCM10017776_50280, GCM10017776_58060) were used for construction dendrograms.

Table 2. **Similarity indicators of analogous genes* sequences of streptomycetes BGC**

lad-cluster genes *S. cyanogenus* S136 (Query sequence)	Strains of streptomycetes (Subject sequence)	
	Contig *S. laculatispora* NRRL B-24909 NZ_JAFMPZ010000093.1	Contig *S. griseoluteus* JCM 4765 NZ_SRRU01000006.1
S1361_RS29865 (*lanE*)	J1C73_RS05385 Qc = 100%, I = 92.12%	E5082_RS18100 Qc = 100%, I = 98.05%
S1361_RS29870 (*lanF*)	J1C73_RS05380 Qc = 100%, I = 93.03	E5082_RS18105 Qc = 100%, I = 99.09%
S1361_RS29875 (*lanA*)	J1C73_RS05375 Qc = 100%, I = 93.07%	E5082_RS18110 Qc = 100%, I = 99.05%
S1361_RS29880 (*lanB)*	J1C73_RS05370 Qc = 99%, I = 89.66%	E5082_RS18115 Qc = 100%, I = 98.77%
S1361_RS29885 (*lanC*)	J1C73_RS05365 Qc = 100%, I = 90.74	E5082_RS18120 Qc = 100%, I = 98.52%
S1361_RS29890 (*lanD*)	J1C73_RS05360 Qc = 100%, I = 93.13%	E5082_RS18125 Qc = 100%, I = 99.24%
S1361_RS29895 (*lanL*)	J1C73_RS05355 Qc = 100%, I = 90.49%	E5082_RS18130 Qc = 100%, I = 98.22%
S1361_RS29900 (*lanM*)	J1C73_RS05350 Qc = 100%, I = 84.70%	E5082_RS18135 Qc = 100%, I = 97.09%
S1361_RS29905 (*lanO)*	J1C73_RS05345 Qc = 100%, I = 89.69%	E5082_RS18140 Qc = 100%, I = 97.92%
S1361_RS29910 *(lanP*)	J1C73_RS05340 Qc = 99%, I = 89.14%	E5082_RS18145 Qc = 100%, I = 97.90%
S1361_RS29915 **	J1C73_RS05335 Qc = 100%, I = 71.31%	E5082_RS18150 Qc = 100%, I = 85.65%
S1361_RS29920 (*lanG*)	J1C73_RS05330 Qc = 100%, I = 91.85%	E5082_RS18155 Qc = 100%, I = 98.78%
S1361_RS29925 (*lanH*)	J1C73_RS05325 Qc = 100%, I = 93.07%	E5082_RS18160 Qc = 100%, I = 98.57%
S1361_RS29930 (*lan*Q)	1C73_RS05320 Qc = 100%, I = 92.57%	E5082_RS18165 Qc = 100%, I = 98.24%
S1361_RS29935 (*lanR*)	J1C73_RS05315 Qc = 100%, I = 89.81%	E5082_RS18170 Qc = 100%, I = 98.68%
S1361_RS29940 *(lanS*)	J1C73_RS05310 Qc = 99%, I = 91.44%	E5082_RS18175 Qc = 100%, I = 98.90%
S1361_RS29945 (*lanT*)	J1C73_RS05305 Qc = 99%, I = 87.62%	E5082_RS18180 Qc = 100%, I = 98.24%
S1361_RS29950 ** (*lanU*)	J1C73_RS05300 Qc = 100%, I = 85.19%	E5082_RS18185 Qc = 77%, I = 93.37%
S1361_RS29955 (*lanV*)	J1C73_RS05295 Qc = 99%, I = 87.53%	E5082_RS18190 Qc = 100%, I = 98.16%
S1361_RS29960 **	J1C73_RS05290 Qc = 100%, I = 87.85%.	E5082_RS18195 Qc = 100%, I = 98.75%
S1361_RS29965 (*lanGT2*)	J1C73_RS05285 Qc = 100%, I = 91.18%	E5082_RS18200 Qc = 100%, I = 98.48%
S1361_RS29970 **(*lanX*)	J1C73_RS05280 Qc = 100%, I = 87.05	E5082_RS18205 Qc = 100%, I = 99.28%

lad-cluster genes *S. cyanogenus* S136 (Query sequence)	Strains of streptomycetes (Subject sequence)	
	Contig *S. laculatispora* NRRL B-24909 NZ_JAFMPZ010000093.1	Contig *S. griseoluteus* JCM 4765 NZ_SRRU01000006.1
S1361_RS29975 (*lanGT1*)	J1C73_RS05275 Qc = 100%, I = 89.94%	E5082_RS18210 Qc = 100%, I = 98.64%
S1361_RS29980 *(lanK*)	J1C73_RS05270 Qc = 100%, I = 93.61%	E5082_RS18215 Qc = 100%, I = 99.31%
S1361_RS29985 (*lanJ*)	J1C73_RS05265 Qc = 100%, I = 89.47%	E5082_RS18220 Qc = 100%, I = 98.33%
S1361_RS29990 (*lanZ1*)	J1C73_RS05260 Qc = 100%, I = 87.50%	E5082_RS18225 Qc = 100%, I = 98.09%
S1361_RS29995 (*lanGT3*)	J1C73_RS05255 Qc = 98%, I = 86.75%	E5082_RS18230 Qc = 100%, I = 98.58%
S1361_RS30000 (*lanZ2*)	J1C73_RS05250 Qc = 98%, I = 86.12%	E5082_RS18235 Qc = 100%, I = 97.77%
S1361_RS30005 (*lanZ3*)	J1C73_RS05245 Qc = 98%, I = 83.89%	E5082_RS18240 Qc = 100%, I = 98.16%
S1361_RS30010 (*lanGT4*)	J1C73_RS05240 Qc = 98%, I = 90.35%	E5082_RS18245 Qc = 100%, I = 97.93%
S1361_RS30015 (*lanZ4*)	J1C73_RS05235 Qc = 98%, I = 88.50%	E5082_RS18250 Qc = 100%, I = 98.29%
S1361_RS30020 (*lanZ5*)	J1C73_RS05230 Qc = 98%, I = 87.52%	E5082_RS18255 Qc = 100%, I = 97.91%
S1361_RS30025 (*lanZ6*)	J1C73_RS05225 Qc = 98%, I = 80.25%	E5082_RS18260 Qc = 99%, I = 96.62%
S1361_RS30030**	J1C73_RS05220 Qc = 100%, I = 78.01%	E5082_RS18265 Qc = 100%, I = 95.48%
S1361_RS30035 *(lanI)*	J1C73_RS05215 Qc = 99%, I = 86.13%	E5082_RS18270 Qc = 100%, I = 98.40%

Qc — Query coverage, I — identity, * — by analogous genes in the article, we mean BGC genes whose products perform the same functions, ** — genes whose products do not participate in the metabolite synthesis («ballast»).

As previously demonstrated, the strain *S. cyanogenus* S136 is genetically related to the strain *S. reticuli* TUE45 (LN997842.1) [6]. Using BLASTN analysis of the Database, it was found that *S. laculatispora* NRRL B-24909 is most genetically related to *Streptomyces* sp. CEV 2-1 (NZ_RJUV00000000.1) and *Streptomyces* sp. ADI92-24 (NZ_RPGT00000000.1) (Fig. 2), whereas *S. griseoluteus* JCM 4765 — to *Streptomyces* sp. SID1328 (NZ_WWKH00000000.1) and *S. bauhiniae* BvO16 (NZ_SRRT00000000.1) (Fig. 3).

Streptomycete strains, known producers of landomycin, have been isolated from soil samples from different ecological niches on different continents of the planet, including the mountains of India (*S. cyanogenus* S136), the lake coast in Armenia (*S. globisporus* 1912), and the Arizona desert (uncultivated streptomycete) [10, 15, 16]. Strains of streptomycetes with the probable landomycin BGCs were isolated from soils. There was revealed *S. griseoluteus* JCM 4765 in soil taken on the outskirts of Tokyo, Japan [26]. S. *laculatispora* NRRL B-24909 was isolated from soil taken on a hay meadow in Great Britain [26–28].

Of importance is the obtained result on the spreading of *lan*-clusters among genetically un-

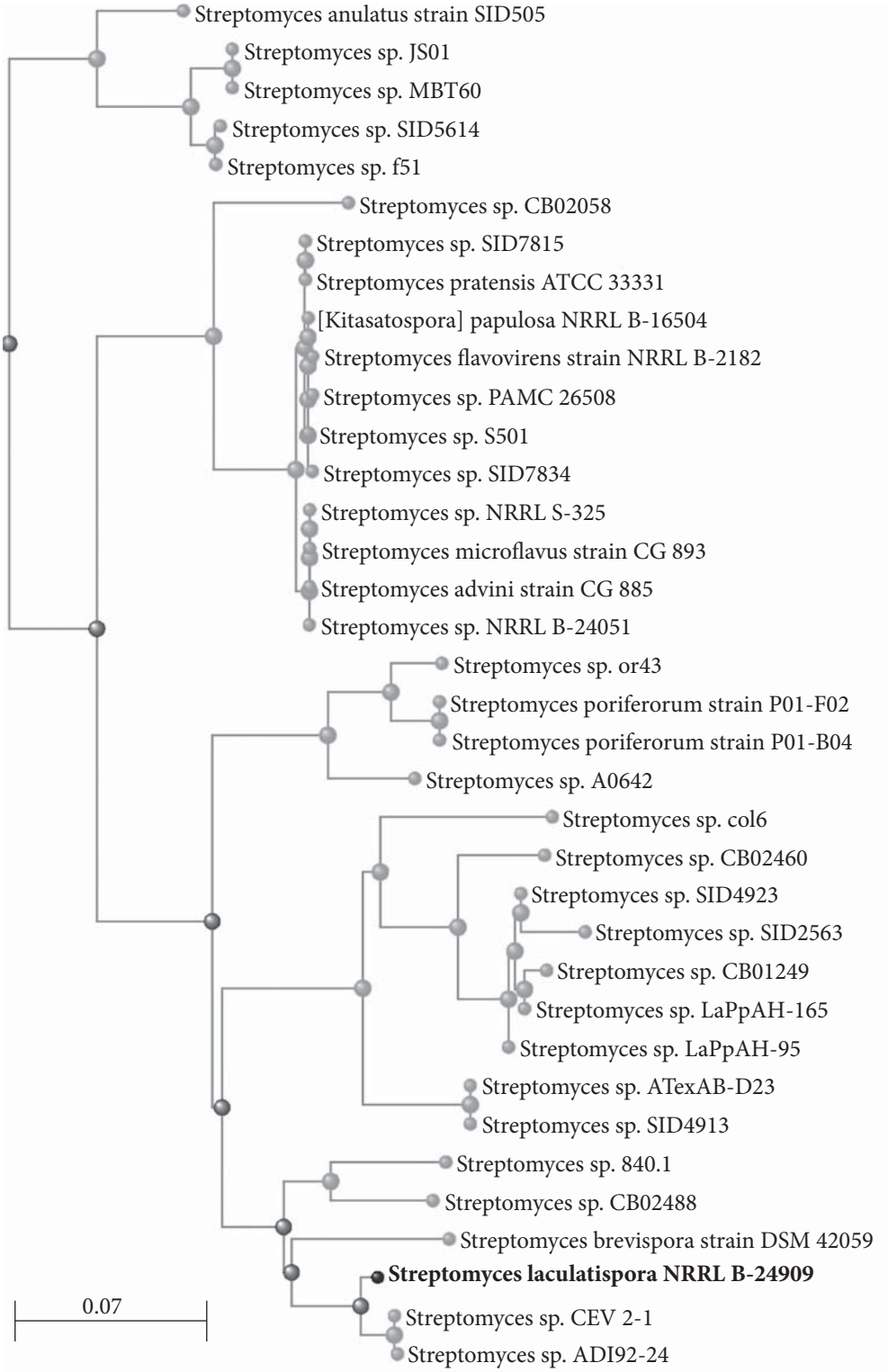

Fig. 2. Tree of genetic consanguinity of *Streptomyces* species built on the basis of similarity to *S. laculatuspora* NRRL B-24909 sequences of five genes that code conservative proteins

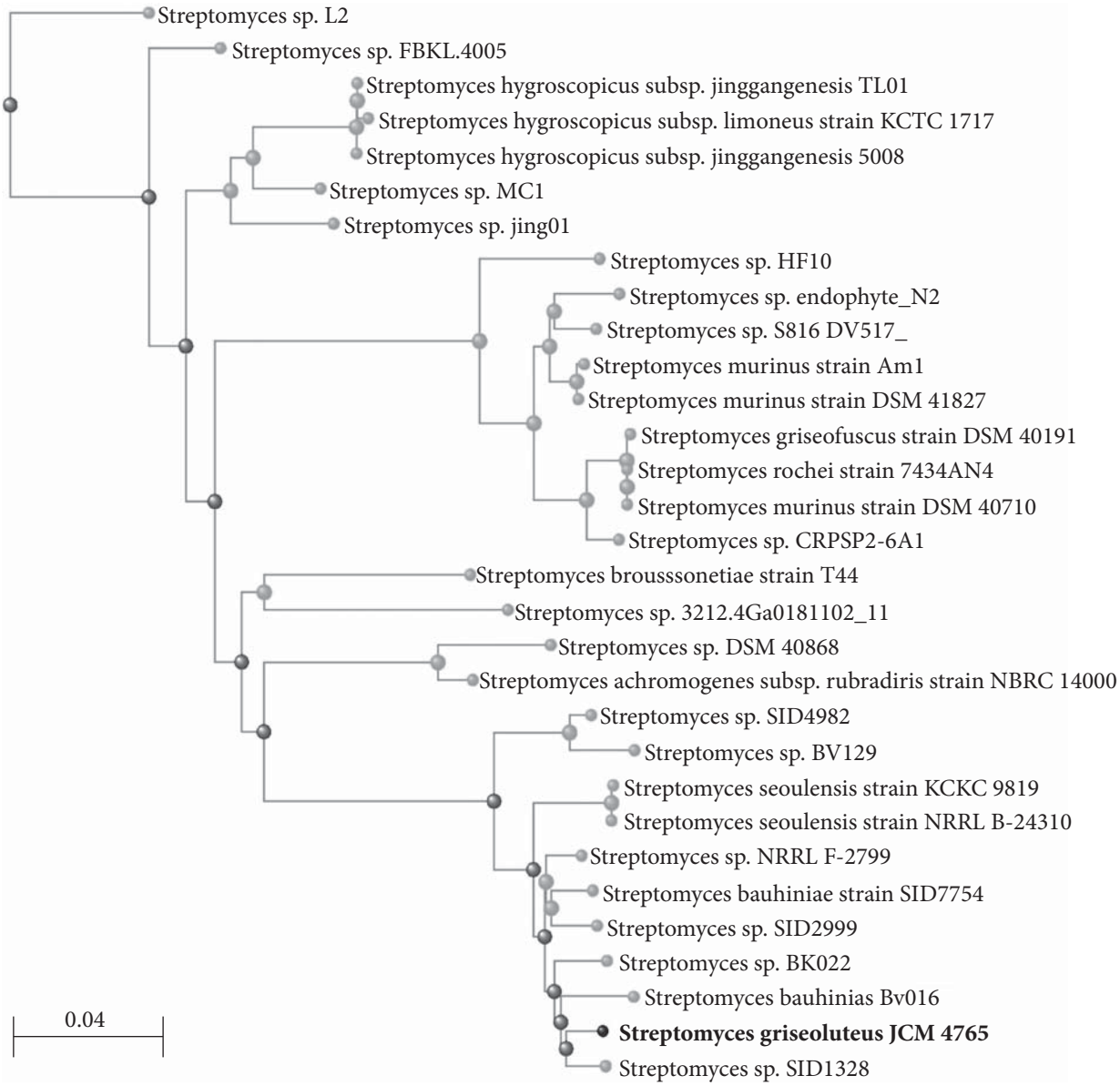

Fig. 3. Tree of genetic consanguinity of *Streptomyces* species built on the basis of similarity to *S. griseoluteus* NRRL B-24909 sequences of five genes that code conservative proteins

related streptomycetes that exist in different conditions on different continents. Thus, it is possible to hope that other streptomycetes that not only have probable landomycin clusters but are also able to synthesize landomycins will be isolated as well.

Conclusions. Two probable landomycin BGCs have been found in the genomes of strains *S. griseoluteus* JCM 4765 and *S. laculatispora* NRRL B-24909. Landomycin clusters of three strains are organized according to the same scheme. Clusters of *lan* genes that determine the synthesis of antibiotic landomycin A are present in the genomes of genetically unrelated streptomycetes *S. cyanogenus* S136, *S. griseoluteus* JCM 4765, and *S. laculatispora* NRRL B-24909.

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Received 16.05.2023

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ПОСЛІДОВНОСТІ, ПОДІБНІ ДО *lan*-КЛАСТЕРА (*STREPTOMYCES CYANOGENUS* S136), ВИЯВЛЕНІ В ГЕНОМАХ ІНШИХ СТРЕПТОМІЦЕТІВ

Метою роботи є виявити штами стрептоміцетів, у геномах яких є нуклеотидні послідовності, подібні до кластера генів, що визначають синтез ландоміцину А (*lan*-кластер), та встановити рівень подібності їхніх первинних структур і організацій. **Методи.** Інформація про послідовності *lan*-кластера і хромосом штамів ДНК *Streptomyces cyanogenus* S136, *S. laculatispora* NRRLB-24909 та *S. griseoluteus* JCM 4765 та їх анотації представлено в базі даних GenBank на сервері NSBI. Комп'ютеризований аналіз нуклеотидних послідовностей стрептоміцетів проводили за допомогою програми BLASTN із сервера NSBI. **Результати.** Показано локалізацію *lan*-кластера в термінальній області генома *S. cyanogenus* S136. Нуклеотидні послідовності, подібні до послідовності *lan*-кластера *S. cyanogenus* S136 виявлено в геномах двох штамів (*S. laculatispora* NRRLB-24909 і *S. griseoluteus* JCM 4765). Стрептоміцети *S. cyanogenus* S136, *S. laculatispora* NRRLB-24909 і *S. griseoluteus* JCM 4765 не є генетично спорідненими штамами. **Висновки.** В геномах штамів стрептоміцетів *S. laculatispora* NRRLB-24909 та *S. griseoluteus* JCM 4765 виявлено вірогідні кластери генів, що детермінують синтез антибіотика ландоміцину А. Ландоміцинові кластери трьох штамів організовано за однаковою схемою. Показано існування *lan*-кластерів в геномах генетично неспоріднених штамів стрептоміцетів.

***Ключові слова**: стрептоміцети, кластер генів біосинтезу ландоміцину, нуклеотидна послідовність, BLASTN аналіз.*