Draft genome sequence of marine-derived *Streptomyces* sp. TP-A0598, a producer of anti-MRSA antibiotic lydicamycins

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**Abstract**

*Streptomyces* sp. TP-A0598, isolated from seawater, produces lydicamycin, structurally unique type I polyketide bearing two nitrogen-containing five-membered rings, and four congeners TPU-0037-A, −B, −C, and −D. We herein report the 8 Mb draft genome sequence of this strain, together with classification and features of the organism and generation, annotation and analysis of the genome sequence. The genome encodes 7,240 ORFs, of which 4,450 ORFs were assigned with COG categories. Also, 66 tRNA genes and one rRNA operon were identified. The genome contains eight gene clusters involved in the production of polyketides and nonribosomal peptides. Among them, a PKS/NRPS gene cluster was assigned to be responsible for lydicamycin biosynthesis and a plausible biosynthetic pathway was proposed on the basis of gene function prediction. This genome sequence data will facilitate to probe the potential of secondary metabolism in marine-derived *Streptomyces*.

**Keywords:** Lydicamycin, TPU-0037, Biosynthetic gene, Polyketide synthase, *Streptomyces*

**Introduction**

Members of the genus *Streptomyces*, Gram-positive filamentous actinomycetes, are an attractive source for bioactive secondary metabolites. Terrestrial surface soil is the most common habitat for *Streptomyces* but a recent survey has disclosed its ubiquitous distribution in marine environments. Marine *Streptomyces* are currently attracting much attention as an untapped resource of novel bioactive compounds useful for drug development [1–3]. In our screening for new anti-MRSA antibiotics, *Streptomyces* sp. TP-A0598 collected from deep sea water was found to produce lydicamycin and its four new congeners of polyketide origin (Fig. 1) [4]. Lydicamycin is characterized by the unprecedented pyrrolidine ring modified by an aminomethyl group to which a polyketide-derived carbon chain with multiple hydroxyl and olefinic functionalities is linked and to the other end of the chain is linked an octalin modified by a tetramic acid. Despite this unique structural feature, biosynthetic genes of lydicamycin have not been reported to date. In this study, we conducted whole genome shotgun sequencing of the strain TP-A0598 to identify the PKS gene cluster for lydicamycin. We herein present the draft genome sequence of *Streptomyces* sp. TP-A0598, together with the description of genome properties and annotation for secondary metabolite genes. The putative lydicamycin biosynthetic gene cluster and a plausible biosynthetic pathway are also reported.

**Organism information**

**Classification and features**

In the course of screening for new bioactive molecules produced by marine microorganisms, *Streptomyces* sp. TP-A0598 was isolated from a seawater sample collected in 2,600 meters off the shore and 321 meters in depth at Namerikawa, Toyama, Japan by a membrane filter method and found to produce lydicamycin and its novel congeners. This strain grew well on Bennett’s, ISP 3, ISP 4, ISP 5 and Yeast starch agars. On ISP 5, ISP 6 and ISP...
7 agars, the growth was poor. The color of aerial mycelia was grayish olive and that of the reverse side was pale yellow on ISP 3 agar. Diffusible pigments were not formed on any agar media that we examined. Strain TP-A0598 formed spiral spore chains and the spores were cylindrical, 0.5 × 0.9 μm in size, having a warty surface [4]. A scanning electron micrograph of this strain is shown in Fig. 2. Growth occurred at 15–37 °C (optimum 30 °C) and pH 5–9 (optimum pH 7). Strain TP-A0598 exhibited growth with 0–7 % (w/v) NaCl (optimum 0 % NaCl). Strain TP-A0598 utilized D-glucose, sucrose, inositol, L-rhamnose, D-mannitol, D-raffinose, D-fructose, L-arabinose, and D-xylene for growth (Table 1) [4]. This strain was deposited in the NBRC culture collection with the registration number of NBRC 110027. The genes encoding 16S rRNA were amplified by PCR using two universal primers, 9 F and 1541R. After purification of the PCR product by AMPure (Beckman Coulter), the sequencing was carried out according to a established methods [5]. Homology search of the sequence by EzTaxon-e [6] indicated the highest similarity (99.93 %, 1465/1466) to *Streptomyces angustmyceticus* NBRC 3934 T (AB184817) [7] as the closest type strain. A phylogenetic tree was reconstructed on the basis of the 16S rRNA gene
sequence together with phylogenetic neighbors that showed over 98.5% similarity (Fig. 3) using ClustalX2 [8] and NJplot [9]. The phylogenetic analysis confirmed that the strain TP-A0598 belongs to the genus *Streptomyces*.

**Chemotaxonomic data**

The whole-cell hydrolysates of strain TP-A0598 contained L-L-diaminopimelic acid, glycine, ribose and madurose. The cellular fatty acids consisted of 21% 14-methylpentadecanoic acid (iso C_{15:0}), 9% 13-methyltetradecanoic acid (iso C_{15:0}), 8% 12-methyltetradecanoic acid (anteiso C_{15:0}) and other minor fatty acids [4].

**Genome sequencing information**

**Genome project history**

In collaboration between Toyama Prefectural University and NBRC, the organism was selected for genome sequencing to elucidate the lydicamycin biosynthetic gene cluster. We successfully accomplished the genome project of *Streptomyces* sp. TP-A0598 as reported in this paper. The draft genome sequence data have been deposited in the INSDC database under the accession number BBNO01000001-BBNO01000020. The project information and its association with MIGS version 2.0 compliance are summarized in Table 2 [10].

**Growth conditions and genomic DNA preparation**

*Streptomyces* sp. TP-A0598 monoisolate was grown on polycarbonate membrane filter (Advantec) on double-diluted ISP 2 agar medium (0.2% yeast extract, 0.5% malt extract, 0.2% glucose, 2% agar, pH 7.3) at 28°C. High quality genomic DNA for sequencing was isolated from the mycelia with an EZ1 DNA Tissue Kit and a Bio Robot EZ1 (Qiagen) according to the protocol for extraction of nucleic acid from Gram-positive bacteria. The size, purity, and double-strand DNA concentration of the genomic DNA were measured by pulsed-field gel electrophoresis, ratio of absorbance values at 260 nm and 280 nm, and Quant-iT PicoGreen dsDNA Assay Kit (Life Technologies) to assess the quality.

**Genome sequencing and assembly**

Shotgun and pair-end libraries were prepared and sequenced using 454 pyrosequencing technology and HiSeq1000 (Illumina) pair-end technology, respectively (Table 2). The 70 Mb shotgun sequences and 702 Mb pair-end sequences were assembled into 20 scaffolds larger than 500 bp using Newbler v2.6, and subsequently finished using GenoFinisher [11].

**Genome annotation**

Coding sequences were predicted by Prodigal [12] and tRNA-scanSE [13]. The gene functions were annotated using an in-house genome annotation pipeline and domains related to PKS and NRPS were searched for using the SMART and PFAM domain databases. PKS and NRPS gene clusters and their domain organizations were

**Table 1** Classification and general features of *Streptomyces* sp. TP-A0598

| MIGS ID | Property | Term | Evidence code* |
|---------|----------|------|----------------|
| Classification | Domain | Bacteria | TAS [16] |
| | Phylum | Actinobacteria | TAS [17] |
| | Class | Actinobacteria | TAS [18] |
| | Order | Actinomycetales | TAS [18–21] |
| | Suborder | Streptomycineae | TAS [19, 20] |
| | Family | Nocardiaceae | TAS [20, 22, 23] |
| | Genus | Streptomyces | TAS [20, 23–25] |
| | Species | Streptomyces sp. | TAS [4] |
| | Strain | TP-A0598 | TAS [4] |
| | Gram stain | Not tested, likely positive | NAS |
| | Cell shape | Branched mycelia | TAS [4] |
| | Motility | Not reported | TAS [4] |
| | Sporulation | Sporulating | TAS [4] |
| | Temperature range | Grows from 15°C to 37°C | IDA |
| | Optimum temperature | 30°C | IDA |
| | pH range | 5–9; 7 | IDA |
| | Carbon source | D-glucose, sucrose, inositol, L-hamnose, D-mannitol, D-raffinose, D-fructose, L-arabinose, D-xylose | TAS [4] |
| | Habit | Marine | TAS [4] |
| | Salinity | Grows from 0% to 7% NaCl | IDA |
| | Oxygen requirement | Aerobic | TAS [4] |
| | Biotic relationship | Free-living | TAS [4] |
| | Pathogenicity | Not reported | TAS [4] |
| | Geographic location | 2,600 meters off the shore at Namerikawa, Toyama, Japan | TAS [4] |
| Sample collection | Not reported | TAS [4] |
| Latitude | Not reported | TAS [4] |
| Longitude | Not reported | TAS [4] |
| Attitude | –321 m | TAS [4] |

*Evidence codes – IDA: Inferred from Direct Assay; TAS: Traceable Author Statement (i.e., a direct report exists in the literature); NAS: Non-traceable Author Statement (i.e., not directly observed for the living, isolated sample, but based on a generally accepted property for the species, or anecdotal evidence). These evidence codes are the Gene Ontology project [26]*
analyzed manually. Similarity search in the NCBI nr database was also used for functional prediction of genes in the lydicamycin biosynthetic gene cluster.

**Genome properties**

The total size of the genome is 8,319,549 bp and the GC content is 71.0 % (Table 3), similar to other genome-sequenced *Streptomyces* members. Of the total 7,344 genes, 7,240 are protein-coding genes and 75 are RNA genes. The classification of genes into COGs functional categories is shown in Table 4. As for the secondary metabolism, *Streptomyces* sp. TP-A0598 has two type I PKS, two type II PKS, two NRPS, and two hybrid PKS/NRPS gene clusters, suggesting the high capacity of production of polyketides and nonribosomal peptides.

**Insights from the genome sequence**

The chemical structure of lydicamycin (Fig. 1) suggests that its carbon skeleton is assembled from eleven malonyl-CoA and six methylmalonyl-CoA precursors by type I PKS pathway. In addition, this pathway should be
combined with NRPS pathway since lydicamycin bears a tetramic acid moiety derived from the condensation of an amino acid to the polyketide chain. We therefore searched for a type I PKS gene cluster consisting of seventeen PKS modules and an NRPS module. A hybrid PKS/NRPS gene cluster in scaffold03 (Table 5, Fig. 4) consists of seventeen PKS modules and one NRPS module (Fig. 5b). According to the assembly line rule [14], the predicted structure of the polyketide arising from this PKS/NRPS hybrid gene cluster was in good accordance with the actual structure of lydicamycin (Fig. 5b). As a starter unit for the polyketide assembly, 4-guanidinobutyryl CoA could be proposed on the basis of annotation of TPA0598_03_00880, TPA0598_03_00650 and TPA0598_03_00700. These genes were predicted to encode amine oxidase, acyl-CoA ligase, and transacylase by comparing the corresponding genes present in the ECO-02301 biosynthetic gene cluster. In the biosynthesis of ECO-02301, 4-aminobutyryl-CoA is supplied from L-arginine by a sequential action of amine oxidase, acyl-CoA ligase, and amidinohydrolase and is transferred to ACP by transacylase (Fig. 5a) [15].

Table 3: Genome statistics

| Attribute                          | Value   | % of Total |
|------------------------------------|---------|------------|
| Genome size (bp)                   | 8,319,549 | 100.0      |
| DNA coding (bp)                    | 7,149,098 | 85.9       |
| DNA G + C (bp)                     | 5,915,420 | 71.0       |
| DNA scaffolds                      | 20      | 100.0      |
| Total genes                        | 7,344   | 100.0      |
| Protein-coding genes               | 7,240   | 98.6       |
| RNA genes                          | 75      | 1.0        |
| Pseudo genes                       | 29      | 0.4        |
| Genes in internal clusters         | 761     | 10.4       |
| Genes with functional prediction   | 3,207   | 43.7       |
| Genes assigned to COGs             | 4,450   | 60.6       |
| Genes with Pfam domains            | 4,543   | 61.9       |
| Genes with signal peptides         | 653     | 8.9        |
| Genes with transmembrane helices   | 1,770   | 24.1       |
| CRISPR repeats                     | 5       | -          |

Table 4: Number of genes associated with general COG functional categories

| Code | Value | % of age | Description                                      |
|------|-------|----------|--------------------------------------------------|
| J    | 196   | 2.70     | Translation                                      |
| A    | 2     | 0.03     | RNA processing and modification                  |
| K    | 519   | 7.17     | Transcription                                    |
| L    | 155   | 2.14     | Replication, recombination and repair            |
| B    | 0     | 0.00     | Chromatin structure and dynamics                 |
| D    | 40    | 0.55     | Cell cycle control, mitosis and meiosis          |
| V    | 127   | 1.75     | Defense mechanisms                               |
| T    | 210   | 2.91     | Signal transduction mechanisms                   |
| M    | 192   | 2.65     | Cell wall/membrane biogenesis                    |
| N    | 0     | 0.00     | Cell motility                                    |
| U    | 34    | 0.47     | Intracellular trafficking and secretion          |
| O    | 138   | 1.91     | Posttranslational modification, protein turnover, chaperones |
| C    | 271   | 3.74     | Energy production and conversion                 |
| G    | 318   | 4.39     | Carbohydrate transport and metabolism            |
| E    | 424   | 5.86     | Amino acid transport and metabolism              |
| F    | 105   | 1.45     | Nucleotide transport and metabolism              |
| H    | 161   | 2.22     | Coenzyme transport and metabolism                |
| I    | 187   | 2.58     | Lipid transport and metabolism                   |
| P    | 177   | 2.44     | Inorganic ion transport and metabolism           |
| Q    | 141   | 1.95     | Secondary metabolites biosynthesis, transport and catabolism |
| R    | 631   | 8.72     | General function prediction only                 |
| S    | 422   | 5.83     | Function unknown                                 |
| -    | 2,790 | 38.50    | Not in COGs                                     |

The total is based on the total number of protein coding genes in the genome.
genes for an amine oxidase (TPA0598_03_00880), an acyl-CoA ligase (TPA0598_03_00650), and a transacylase (TPA0598_03_00700) are present in the surrounding region of the PKS cluster but an amidinohydrolase gene responsible for the hydrolysis of the guanidine residue to the primary amine is lacking (Fig. 5a, Table 5). After the 4-guanidinobutyryl starter is loaded onto ACP of TPA0598_03_00840, the polyketide chain is extended by eight PKSs and a glycine is added to the polyketide terminus by an NRPS module (Fig. 5b), followed by the formation of an octalin and a tetramic acid ring (Fig. 5c). It was not possible to assign a gene responsible for the

Table 5 Open reading frames in the lydicamycin biosynthetic gene cluster

| orf (locus tag) | size (aa) | proposed function | BLAST search |
|----------------|----------|-------------------|--------------|
| TPA0598_03_00650 | 473      | acyl-CoA ligase    | hypothetical protein, Streptomyces sp. FxanaC1, WP_018093236 |
| TPA0598_03_00660 | 929      | LuxR family transcriprional regulator | LuxR family transcriprional regulator, Streptomyces sp. FxanaC1, WP_026170289 |
| TPA0598_03_00670 | 274      | unknown           | hypothetical protein, Saccharopolyspora azurea, EHY88948 |
| TPA0598_03_00680 | 632      | two-component system histidine kinase | hypothetical protein, Streptomyces sp. FxanaC1, WP_018093233 |
| TPA0598_03_00690 | 218      | two-component system response regulator | LuxR family transcriprional regulator, Streptomyces sp. FxanaC1, WP_018093232 |
| TPA0598_03_00700 | 336      | transacylase      | ACP S-malonyltransferase, Streptomyces sp. FxanaC1, WP_026170288 |
| TPA0598_03_00710 | 123      | unknown           | hypothetical protein, Streptomyces sp. FxanaC1, WP_018093229 |
| TPA0598_03_00720 | 64       | unknown           | hypothetical protein, JCGZ_17256, Jatropha curcas, KDP45649 |
| TPA0598_03_00730 | 80       | unknown           | putative protein-disulfide isomerase, Xanthomonas gardneri, EGD16922 |
| TPA0598_03_00740 | 3,598    | PKS               | polyketide synthase, Streptomyces rapamycinicus, AGPS7755 |
| TPA0598_03_00750 | 7,054    | PKS               | Beta-ketoacyl synthase, Streptomyces violaceusniger, AEM87320 |
| TPA0598_03_00760 | 3,548    | PKS               | Beta-ketoacyl synthase, Streptomyces violaceusniger, AEM87320 |
| TPA0598_03_00770 | 1,846    | PKS               | Beta-ketoacyl synthase, Streptomyces iranensis, CDR09758 |
| TPA0598_03_00780 | 5,648    | PKS               | polyketide synthase type I, Streptomyces aizunensis, AAX09191 |
| TPA0598_03_00790 | 3,662    | PKS               | hypothetical protein, Streptomyces sp. FxanaC1, WP_018091594 |
| TPA0598_03_00800 | 3,265    | PKS               | hypothetical protein, Streptomyces sp. PRh5, EXU66032 |
| TPA0598_03_00810 | 270      | unknown           | hypothetical protein, Streptomyces sp. FxanaC1, WP_018091596 |
| TPA0598_03_00820 | 1,031    | NRPS              | hypothetical protein, Streptomyces sp. FxanaC1, WP_018091598 |
| TPA0598_03_00830 | 300      | unknown           | hypothetical protein, Streptomyces sp. FxanaC1, WP_018091598 |
| TPA0598_03_00840 | 1,923    | PKS               | hypothetical protein, Streptomyces sp. FxanaC1, WP_018091599 |
| TPA0598_03_00850 | 429      | cytochrome P450   | cytochrome P450, Streptomyces sp. FxanaC1, WP_026169967 |
| TPA0598_03_00860 | 260      | unknown           | membrane protein, Saccharopolyspora rectivirgula, KEH45939 |
| TPA0598_03_00870 | 253      | type-II thioesterase | hypothetical protein, Streptomyces sp. FxanaC1, WP_018091603 |
| TPA0598_03_00880 | 551      | amine oxidase     | amine oxidase, Streptomyces sp. FxanaC1, WP_026169968 |
| TPA0598_03_00890 | 344      | transcriprional regulator | hypothetical protein, Streptomyces sp. FxanaC1, WP_018091605 |
| TPA0598_03_00900 | 496      | amidase           | hypothetical protein, Streptomyces sp. FxanaC1, WP_018091606 |

*encoded in complementary strand, %Identity/similarity

Fig. 4 Genetic map of lydicamycin biosynthetic gene cluster
Fig. 5 Proposed lydicamycin synthetic pathway. 

a. starter synthesis compared with that of ECO-02301; 
b. chain elongation; 
c. cyclization and modification yielding final products.
Table 6 Proposed mechanism to produce lydicamycin congeners

| congener          | substrate of m3 AT<sub>m</sub> | m1T ER | CYP450          |
|-------------------|--------------------------------|--------|-----------------|
| lydicamycin       | methylmalonyl-CoA              | active | involved        |
| TPU-0037-A        | malonyl-CoA                   | active | involved        |
| TPU-0037-B        | methylmalonyl-CoA              | inactive| uninvolved      |
| TPU-0037-C        | malonyl-CoA                   | active | uninvolved      |
| TPU-0037-D        | methylmalonyl-CoA              | active | uninvolved      |

cyclization of the guanidino precursor into a pyrrolidine ring. A cytochrome P450 (TPA0598_03.00850) would be responsible for the hydroxylation of the octalin carbon at C-8 (Fig. 5c). Production of deoxy- and demethylcongeners suggests that substrate recognition by the AT domain in module3 (second module of TPA0598_03_00740) and the ER domain in module11 (first module of TPA0598_03_00780) is likely not strict (Table 6).

Conclusions

The 8 Mb draft genome of *Streptomyces* sp. TP-A0598, a producer of lydicamycins isolated from seawater, has been deposited at GenBank/ENA/DDBJ under accession number BBNO00000000. We successfully identified the PKS/NRPS hybrid cluster for lydicamycin biosynthesis and proposed a plausible biosynthetic pathway. In addition, the genome of strain TP-A0598 contained seven orphan PKS or NRPS gene clusters but secondary metabolites from these orphan clusters have not been isolated yet. The genome sequence information disclosed in this study will be utilized for the investigation of additional new bioactive compounds from this strain and will also serve as a valuable reference for evaluation of the metabolic potential in marine-derived *Streptomyces*.

Abbreviations

AT<sub>m</sub>: Adenylation domain whose substrate is glycine; ACP: Acyl carrier protein domain; AT: Acyltransferase domain whose substrate is malonyl-CoA; AT<sub>n</sub>: AT whose substrate is methylmalonyl-CoA; C: Condensation domain; CoA: Coenzyme A; CYP450: Cytochrome P450; DH: Dehydratase domain; dh: Inactive DH; ER: Enoylreductase domain; ISP: International System for Prokaryotic Gene Recognition and Translation Initiation Site Identification; PKS: Polyketide synthase; NRPS: Nonribosomal peptide synthetase; T: Thiolation domain; TE: Thioesterase domain.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

HK identified the lydicamycin-biosynthetic gene cluster and drafted the manuscript. NM annotated the genome sequence. AH carried out the genome sequencing. NF organized the genome sequencing. YI designed this study and edited the manuscript. All authors read and approved the final manuscript.

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