

Whole-genome sequence of a novel, mangrove-derived streptomycete, *Streptomyces malaysiense* strain MUSC 136^T

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Abstract: Since the discovery of streptomycin from *Streptomyces griseus* in the early 1940s, streptomycetes from various environments have been studied thoroughly for the ability to produce bioactive compounds including antibacterial, antioxidant, anticancer, antifungal as well as immunomodulatory properties. Previously identified as a novel strain from a mangrove forest in Malaysia, *Streptomyces malaysiense* MUSC 136^T was selected for genome sequencing to explore its genomic potential. The genomic size comprises of 7,963,326 bp with a G+C content of 72.2% and a total of 6,614 protein-coding genes. As an attempt to investigate the types of biosynthetic gene cluster present in the MUSC 136^T, the whole genome sequence was analyzed with a bioinformatics tool, antibiotics & Secondary Metabolite Analysis Shell (antiSMASH). Using the “strict” prediction method, a total of seven biosynthetic gene clusters which displayed similarity of more than 80% to known gene clusters including ectoine, geosmin as well as desferrioxamine. Apart from emphasizing the importance of streptomycetes from unique environments like mangrove forest, the current study serves as a foundation for future studies on the role of specific genes present in biosynthetic gene clusters which enables the exploitation of MUSC 136^T to synthesize important and valuable compounds.

Keywords: *Streptomyces*; cancer; cytotoxic; mangrove; genome; MUSC 136^T; actinobacteria

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Short Introduction

Ubiquitous in nature, streptomycetes have growth advantages compared to other microbes, given that their unique life cycle and ability to form spores when conditions are not favorable for growth^[1–8]. Additionally, these filamentous microbes can produce compounds of various structures possessing bioactivities such as antioxidant, anticancer, antibacterial, and so forth^[1,9–20]. The discovery of bioactive streptomycetes from unique environments like the deep sea, cave, and mangrove forest has proven successful^[21–33]. During a screening program for bioactive Actinobacteria (including those belonging to genus *Streptomyces*) in Malaysia, *Streptomyces malaysiense* MUSC 136^T was recovered from a mangrove forest in Tanjung Lumpur location on the East Coast of Peninsular Malaysia^[34,35]. The polyphasic study on the strain showed that its 16S rRNA gene showed high

similarities with other members of *Streptomyces* genus, including *Streptomyces misionensis* NBRC 13063^T (99.6%), *Streptomyces phaeoluteichromatogenes* NRRL 5799^T (99.6%), and *Streptomyces rutgersensis* NBRC 12819^T (98.9%). Nonetheless, DNA-DNA hybridization (DDH) results demonstrated that the strain is indeed a novel strain belonging to this genus as its values are well below the recommended delineation value (i.e., 70%) when compared to three of the selected type strains (DDH value ranged from 22.7–47.5%)^[35,36]. The type strain for MUSC 136^T is available at two culture collection centres with the accession of (=DSM 100712^T=MCCC 1K01246^T). In our previous study, fermentative extracts of MUSC 136^T exhibited potent cytotoxic activities against several human colon cancer cell lines, with cell survival recorded to be less than 50% (extract dose: 400 µg/ml)^[35]. In turn, these results prompted further mining into its genomic sequence, particularly the detection of

gene clusters related to bioactive compounds production.

Data description

Whole genomic DNA of MUSC 136^T was extracted using a commercial kit, MasterpureTM DNA purification kit (Epicentre, Illumina Inc., Madison, WI, USA) before RNase treatment (Qiagen, USA)^[37–40]. DNA library was constructed with Nextera DNA Sample Preparation kit (Nextera, USA), while the library quality was evaluated by Bioanalyzer 2100 high sensitivity DNA kit (Agilent Technologies, Palo Alto, CA). Paired-end sequencing was performed on Illumina MiSeq platform with MiSeq Reagent Kit 2 (2 × 250 bp; Illumina Inc., Madison, WI, USA)^[41,42]. After trimming, the paired-end reads were *de novo* assembled on CLC Genomics Workbench version 7 (CLC bio, Denmark), which resulted in 235 contigs and a N₅₀ contig size of approximately 123,175 bp. The genome size of MUSC 136^T comprised 7,963,326 bp, with an average coverage of 95.0-fold and G+C content of 72.2%. The genome sequence of MUSC 136^T has been deposited at DDBJ/EMBL/GenBank under accession of LBDA02000000. The version described in this paper is the second version.

Table 1. General genomic features of *Streptomyces malaysiense* MUSC 136^T.

<i>Streptomyces malaysiense</i> MUSC 136 ^T	
Genome size (bp)	7,963,326
Contigs	235
Contigs N ₅₀ (bp)	123,175
G+C content %	72.2
Genome coverage	95.0x
Protein coding genes	6,614
tRNA	67
rRNA (5S, 16S, 23S)	1, 1, 1

The assembled genome was annotated using Rapid Annotation using Subsystem Technology (RAST) and NCBI Prokaryotic Genome Annotation Pipeline

(PGAP)^[43,44]. Prodigal (Version 2.6) was used to perform gene prediction, while ribosomal RNA (rRNA) and transfer RNA (tRNA) were predicted using RNAmmer and tRNAscan SE version 1.21, respectively^[45–47]. This analysis revealed 6,614 protein-coding genes, along with a total of 67 tRNA and three rRNA genes. Based on RAST annotation, most of the protein-coding genes were shown to be involved in amino acids and derivatives metabolism (9.47%), followed by carbohydrates metabolism (7.19%) and protein metabolism subsystems (4.60%) (Figure 1). Further analysis of antibiotics & Secondary Metabolite Analysis Shell (antiSMASH) detected the presence of 36 biosynthetic gene clusters in MUSC 136^T genome using “strict” detection settings (version 5.1.1)^[48,49]. Among these biosynthetic gene clusters, seven of them displayed more than 80% similarities to known gene clusters related to terpene, lantipeptide, ectoine, thiopeptide, and siderophore production. Besides being an important drug to treat iron overload, the potential use of the siderophore, desferrioxamine, in combatting chronic diseases like neurodegenerative diseases and cancer were also examined over these years^[50–53]. Complementing previous findings from chemical profiling studies, MUSC 136^T indeed produces desferrioxamine, which is suggested to be responsible for the cytotoxicity observed against colon cancer cell lines^[35]. As a matter of fact, iron metabolism has been implicated as a potential therapeutic target in cancer treatment as cancer cells typically have higher iron requirements compared to healthy, normal cells^[54–60]. By reducing the availability of iron, it is possible to reduce oxidative damage, which is often seen in colorectal cancer, while at the same time preventing colon cancer cell growth and survival. With the identification of biosynthetic gene cluster responsible for desferrioxamine within the genome of MUSC 136^T, future works involving modification of gene expression to enhance the production of this valuable compound as well as other pharmaceutically important compounds like ectoine as cytoprotectant against radiation and inflammation^[61–70] as well as lantipeptides which can act as potent antibiotics to prevent deadly infectious diseases^[71–81].

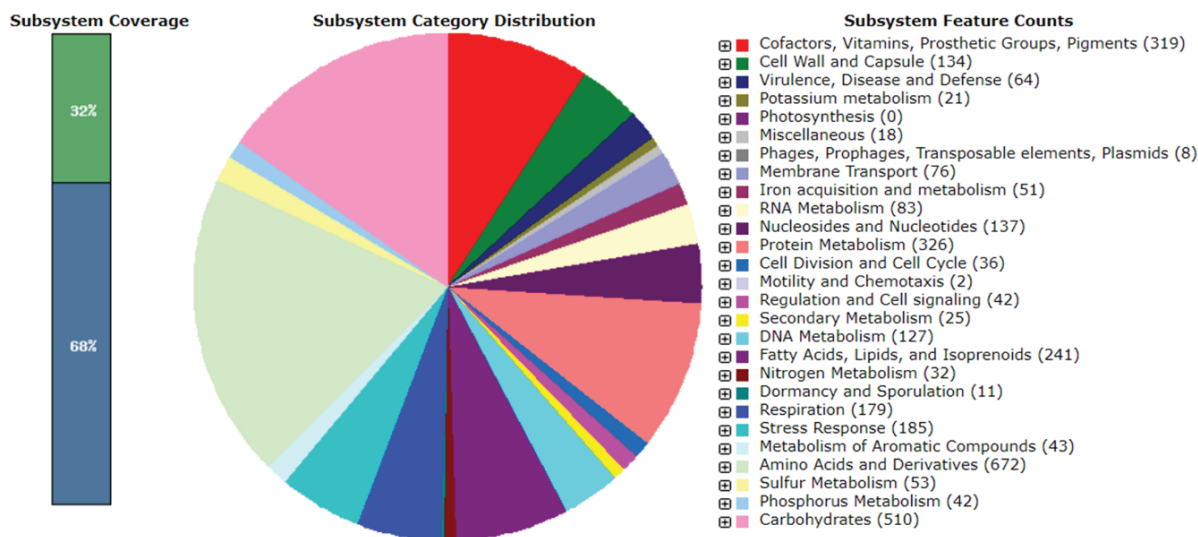


Figure 1. Subsystem category distribution of *Streptomyces malaysiense* MUSC 136^T (based on RAST annotation server).

Conflict of Interest

The authors declare that there is no conflict of interest in this work.

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