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NOTE

Analysis of a draft genome sequence of *Kitasatospora cheerisanensis* KCTC 2395 producing bafilomycin antibiotics

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Kitasatospora cheerisanensis **KCTC 2395, producing bafilomycin antibiotics belonging to plecomacrolide group, was isolated from a soil sample at Mt. Jiri, Korea. The draft genome sequence contains 8.04 Mb with 73.6% G+C content and 7,810 open reading frames. All the genes for aerial mycelium and spore formations were confirmed in this draft genome. In phylogenetic analysis of MurE proteins (UDP-*N*-acetylmuramyl-$_{L}$-alanyl-$_{D}$-glutamate:DAP ligase) in a conserved *dcw* (division of cell wall) locus, MurE proteins of *Kitasatospora* species were placed in a separate clade between MurEs of *Streptomyces* species incorporating $_{LL}$-diaminopimelic acid (DAP) and MurEs of *Saccharopolyspora erythraea* as well as *Mycobacterium tuberculosis* ligating *meso*-DAP. From this finding, it was assumed that *Kitasatospora* MurEs exhibit the substrate specificity for both $_{LL}$-DAP and *meso*-DAP. The bafilomycin biosynthetic gene cluster was located in the left subtelomeric region. In 71.3 kb-long gene cluster, 17 genes probably involved in the biosynthesis of bafilomycin derivatives were deduced, including 5 polyketide synthase (PKS) genes comprised of 12 PKS modules.**

Keywords: draft genome, *Kitasatospora*, MurE, polyketide synthase, bafilomycin

Kitasatospora cheerisanensis KCTC 2395 (=YC75) was isolated from a soil sample from Cheeri-San (Mt. Jiri) in the process of screening biological control agents for the phytopathogenic fungus (Chung *et al.*, 1999). Later, the antifungal metabolites produced by this strain were confirmed as bafilomycin derivatives including bafilomycin C1-amide belonging to plecomacrolide group (Moon *et al.*, 2003). The genus *Kitasatospora* is a genus of Actinomycetales having different content of *meso*-diaminopimelic acid (DAP) and galactose in whole-cell lysate from the closely related *Streptomyces* (Omura *et al.*, 1982). The genome sequence of *K. setae* NBRC 14216 (KM-6054) was firstly reported among this genus group (Ichikawa *et al.*, 2010).

The genome sequence of *K. cheerisanensis* KCTC 2395 was determined by a combination of the Illumina GAIIX 100 bp paired-end library, Roche 454 Titaium 8-kb paired-end library and PacBio 10 kb library. The draft genome was assembled with CLC genomic workbench 6.5 and SMART Analysis 2.0. Resulted contigs were scaffolded using GS Assembler 2.6 (Roche Diagnostics). The final assembly provided total 5 scaffolds containing 178 contigs, and the assembled draft genome was deposited at DDBJ/EMBL/GenBank under the accession JNBY00000000 as a bioproject PRJNA209102 (Hwang *et al.*, 2014).

The draft genome of *K. cheerisanensis* consists of 8,035,179 bp with 73.6% G+C content. The comparative analysis of the genome draft showed a homology as high as 85.8% with the complete genome of *K. setae* NBRC 14216 (KM-6054) by the analysis of average nucleotide identity by BLASTn. The MUMmer sequence alignment (Delcher *et al.*, 2003) of whole genome from *K. cheerisanensis* and *K. setae* showed little differences without any significant inversion or deletion, even though there were few gaps in gene synteny (Fig. 1).

The found ORFs (open reading frames) were 7,810 CDSs (coding domain sequences) with 9 rRNA operons and 72 tRNA genes (Table 1). The annotation of each CDS was made by homology search against the COG (cluster of orthologous groups of proteins) and SEED databases (Tatusov *et al.*, 1997, 2000; Disz *et al.*, 2010). The 885 genes were assumed to be involved in information storage and processing, and another 987 genes were identified to participate in cellular processes. The most abundant 1,748 genes encoded the proteins for cell metabolism, but the other 1,084 genes were poorly characterized ones (Table 2).

As in *Streptomyces* strains, all *bld* genes (*bldA*, *bldB*, *bldC*, *bldD*, *bldG*, *bldH*, *bldK*, *bldM*, *bldN*, and *amfC*) required for the formation of aerial mycelium (Claessen *et al.*, 2006; den Hengst *et al.*, 2010) were found in the draft genome (Table 3). It was already known that BldH (AdpA homolog) regulated by *bldA* is an important intermediate transcription regulator in Bld cascade (Chater and Chandra, 2006). Typically UUA codon which can be recognized by *bldA* tRNA was well conserved in *bldH* gene (KCH_28450). Further, all *whi* genes regulating sporulation (*whiA*, *whiB*, *whiD*, *whiE*, *whiG*, *whiH*, *whiI*, *sigF*, *sigN*, and *crgA*) were identified (den Hengst *et al.*, 2010).

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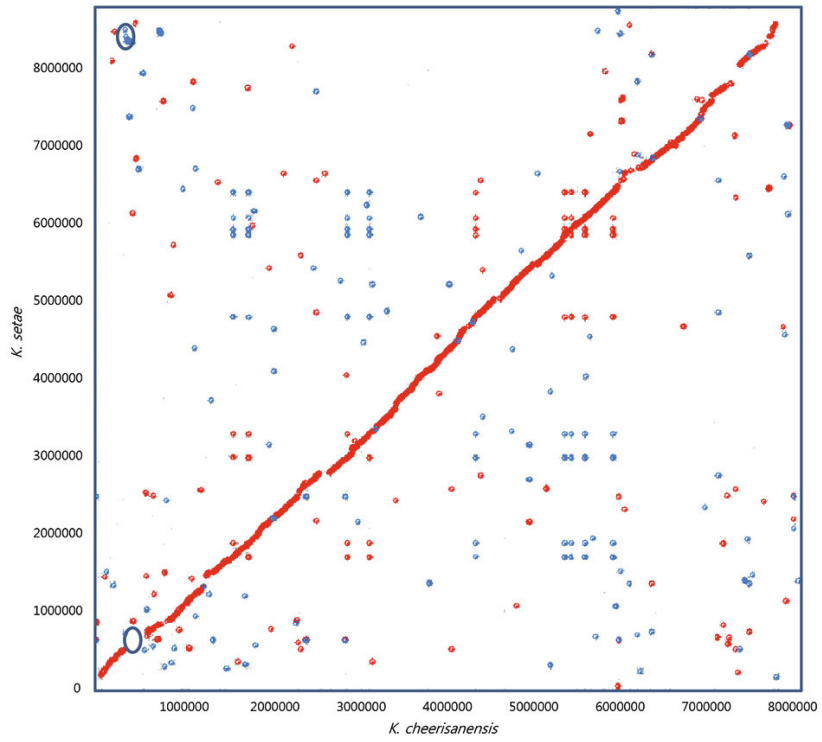

Fig. 1. Whole genome alignment of *K. cheerisanensis* KCTC 2395 and *K. setae* KM-6054 by MUMmer. The red dots are the sequences having the same direction, and blue dots mean the inverted sequences. The location of the bafilomycin biosynthetic gene cluster was marked as circle. This gene cluster in *K. cheerisanensis* is located at left subtelomeric region, but *K. setae* has it at right subtelomeric region.

Table 1. Comparison of genome data of *K. cheerisanensis* KCTC 2395 and other actinomycetes

Strain	Genome type	Total length (bp)	(G+C) content (%)	No. of CDS	No. of rRNA operons	No. of tRNA genes	Reference
K. cheerisanensis KCTC 2395	Draft	8,035,179	73.5	7,810	9	72	This work
K. setae NBRC 14216	Complete	8,783,278	74.2	7,569	9	64	Ichikawa *et al.* (2010)
S. coelicolor A3(2)	Complete	8,667,507	72.1	7,825	6	63	Bentley *et al.* (2002)
S. avermitilis M-4605	Complete	9,025,608	70.7	7,574	6	68	Omura *et al.* (2001)
S. cattleya NRRL 8057	Complete	6,283,062	72.9	5,779	6	64	Barbe *et al.* (2011)
S. griseus IFO 13350	Complete	8,545,929	72.2	7,138	6	66	Ohnishi *et al.* (2008)
S. scabiei 87.22	Complete	10,148,695	71.5	8,746	6	75	Bignell *et al.* (2010)
S. erythraea NRRL 23338	Complete	8,212,805	71.1	7,197	4	50	Oliynyk *et al.* (2007)

Table 2. COG (cluster of orthologous groups of proteins) distribution of ORFs (open reading frames) found in a draft genome of *K. cheerisanensis* KCTC 2395

Category	Group	Function	Number of ORF
Information storage and processing	J	translation, ribosomal structure and biogenesis	207
	K	transcription	529
	L	DNA replication, recombination and repair	149
Cellular processes	D	cell division and chromosome partitioning	39
	O	posttranslational modification, protein turnover, chaperones	152
	M	cell envelope, biogenesis, outer membrane	240
	N	cell motility and secretion	8
	P	inorganic ion transport and metabolism	181
	T	signal transduction mechanisms	367
Cell metabolism	C	energy production and conversion	259
	G	carbohydrate transport and metabolism	368
	E	amino acid transport and metabolism	407
	F	nucleoside transport and metabolism	120
	H	coenzyme metabolism	205
	I	lipid metabolism	249
	Q	secondary metabolites biosynthesis, transport and catabolism	140
Others	R	general function prediction only	669
	S	function unknown	415
Total			4,704

Table 3. **Gene list for aerial mycelium and spore formation in *K. cheerisanensis* KCTC 2395 and *K. setae* KM-6054**

Function	Gene	*K. cheerisanensis*	*K. setae* KM-6054
Aerial mycelium	*bldA*	KCH_t00590	KSE_t0069
	bldB	KCH_16500	KSE_16220
	bldC	KCH_41250	KSE_41620
	bldD	KCH_13680	KSE_13950
	bldG	KCH_36150	KSE_35840
	bldH	KCH_28450	KSE_26930
	bldKA-KE	KCH_47870~KCH_47920	KSE_48250~KSE_48290
	bldM	KCH_32550	KSE_31060
	bldN	KCH_34450	KSE_33690
	amfC	KCH_43270	KSE_43740
Spore formation	*whiA*	KCH_55700	KSE_55390
	whiB	KCH_30810	KSE_29410
	whiD	KCH_32560	KSE_31070
	whiE	KCH_73470~KCH_73550	KSE_72410~KSE_72480
	whiG	KCH_52450	KSE_52540
	whiH	KCH_54200	KSE_54050
	whiI	KCH_55410	KSE_55090
	sigF	KCH_37950	KSE_37310
	sigN	KCH_37960	KSE_37320
	crgA	KCH_39800	KSE_39340

The genus *Kitasatospora* and *Streptomyces* are chemotaxonomically different in the cell wall composition. The peptidoglycan of *Streptomyces* contains only LL-DAP, whereas *Kitasatospora* has *meso*-DAP as well as LL-DAP in its cell wall (Omura *et al.*, 1981; Takahashi *et al.*, 1983). Two *murE* genes in draft genome of *K. cheerisanensis* were identified, as in most of *Streptomyces* genomes (Table 4). Differently from *K. setae* containing three *dapF* gene for diaminopimelate epimerase producing *meso*-DAP, one *dapF* gene (KCH_53750) was present in draft genome of *K. cheerisanensis*, similarly to the most genomes of *Streptomyces* species (Table 4). Ichikawa *et al.* (2010) previously suggested that the presence of *meso*-DAP in whole cell lysate is probably attributed to the third DapF protein (KSE_32630) which showed the close relatedness with DapF proteins of bacteria incorporating *meso*-DAP in cell wall. However this proposal could be more complicated due to the draft genome of *K. cheerisanensis* that includes two *murE* genes and one *dapF*, as likely as *Streptomyces* species. It might be far-fetched in the point that *meso*-DAP is a biosynthetic intermediate for L-lysine pathway. Further we found another *murE* gene in *K. setae* genome sequence (KSE_08470) showing high similarity with the additional *murE* gene of other actinomycetes.

Table 4. **Comparison of genes involved in the incorporation of diaminopimelic acid into peptidoglycan of *K. cheerisanensis* KCTC 2395 and other actinomycetes**

Strain	*murE* gene		*dapF* gene
	dcw locus	additional	
K. cheerisanensis KCTC 2395	KCH_21600	KCH_08750	KCH_53750
K. setae NBRC 14216	KSE_21280	KSE_08470	KSE_32600, KSE_32630, KSE_53750
S. coelicolor A3(2)	SCO_2089	SCO_1212	SCO_5793
S. avermitilis M-4605	SAV_6117	SAV_7125	SAV_2473, SAV_3161
S. cattleya NRRL 8057	SCAT_1206	SCAT_0326	SCAT_4565
S. griseus IFO 13350	SGR_5416	SGR_0186	SGR_1727
S. scabiei 87.22	SCAB-67961	SCAB_78601	SCAB_24751
S. erythraea NRRL 23338	SACE_5856	SACE_3574	SACE_1753

The main *murE* gene (KCH_21600) coding for UDP-*N*-acetylmuramyl-L-alanyl-D-glutamate: DAP ligase was located in a long conserved *dcw* (division of cell wall) locus. The second *murE* gene (KCH_08750) was neighboring the genes for glutamate/glutamine metabolism. Even though the main *murE* genes in a *dcw* locus encode polypeptides larger than 500 amino acids, much shorter proteins possessing around 400 amino acids were produced from the second *murE* genes. Further no significant similarity (about 10–15%) was found between the main MurEs and the second MurEs.

Based on the crystal structures of MurE proteins (Smith, 2006; Basavannacharya *et al.*, 2010; Shanmugam and Natarajan, 2012; McGroty *et al.*, 2013), it has been revealed that those are composed of 3 domains; N-terminal (A) domain binding with UDP portion, the middle (B) domain binding with peptides of UDP-*N*-acetylmuramyl-L-alanyl-D-glutamate (UAG) as well as ATP, and C-terminal (C) domain binding with DAP. Since the additional MurE proteins of actinomycetes did not contain A domain and further C domain is not complete, it is uncertain whether these MurEs exhibit the biological function in peptidoglycan biosynthesis or not.

Assuming that the second MurEs of actinomycetes are nonfunctional, the selection of diamino acids (LL-DAP, *meso*-DAP or L-Lys) as the third amino acid in peptidoglycan biosynthesis could be made by the main MurE proteins. It has been already known that the genus *Streptomyces* contains LL-DAP, the genus *Saccharopolyspora* and the genus *Mycobacterium* have *meso*-DAP, and the genus *Kitasatospora* possesses both LL-form and *meso*-form as their cell wall

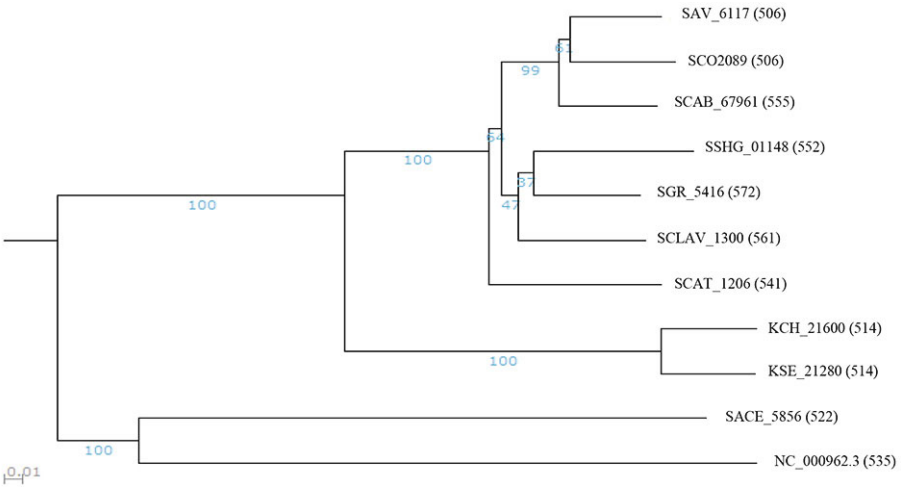

Fig. 2. Phylogenic comparison of actinomycetes MurE proteins (UDP-*N*-acetylmuramyl-L-alanyl-D-glutamate: DAP ligase; UMT synthase) by average distance tree. Prefixes of actinomycetes MurE proteins are as follows: SACE, *Saccharopolyspora erythraea* NRRL 2338; NC, *Mycobacterium tuberculosis* H37Rv; KCH, *Kitasatospora cheerisanensis* KCTC 2395; KSE, *Kitasatospora setae* KM-6054; SGR, *Streptomyces griseus* subsp. *griseus* NBRC 13350; SCLAV, *Streptomyces clavuligerus* ATCC 27064, SAV, *Streptomyces avermitilis* MA-4680; SCO, *Streptomyces coelicolor* A3(2); SCAB, *Streptomyces scabiei* 87.22; SSHG, *Streptomyces albus* J1074; SCAT, *Streptomyces cattleya* NRRL 8057. The number in parenthesis is the number of amino acids in MurE proteins.

component. The phylogenic comparison of the main MurEs clearly demonstrates this difference of cell wall composition. Deducing from the cell wall composition, the MurE of *Saccharopolyspora erythraea* (SACE_5856) and *M. tuberculosis* (NC_000962.3) can incorporate *meso*-DAP, but *Streptomyces* MurEs (SCO2089, SAV_6117, SCAT_1206, SGR_5416, and SCAB_67961) might ligate LL-DAP on UAG. In the average distance tree, MurE proteins of *Kitasatospora* (KCH_21600 and KSE_21280) are placed in a separate clade between MurE proteins of *Streptomyces* species and those of *Saccharopolyspora erythraea* or *Mycobacterium tuberculosis* (Fig. 2). It implies that *Kitasatospora* MurEs might exhibit the substrate specificity both on LL-DAP and *meso*-DAP as the third amino acid during peptidoglycan biosynthesis. However, the further studies should be done in order to clarify this suggestion.

Several gene clusters for the biosynthesis of secondary metabolites were found in the draft genome including type I polyketide synthase (PKS) gene clusters (KCH_04080~KCH_04120, and KCH_45030~KCH_45040), type II PKS gene cluster (KCH_73510~KCH_73550), nonribosomal peptide synthetase (NRPS) gene clusters (KCH_06280~KCH_06390, KCH_45400~KCH_45410, KCH_61460~KCH_61470, and KCH_70790~KCH_70800), and PKS/NRPS hybrid gene clusters (KCH_67350~KCH_67370, and KCH_74020~KCH_74040). The number of gene clusters for the secondary metabolites was less than *K. setae* (Ichikawa *et al*., 2010).

Among them, the gene cluster for bafilomycin biosynthesis was assigned on the first type I PKS gene cluster (KCH_04080~KCH_04120). This gene cluster in *K. cheerisanensis* is located at left subtelomeric region, differently from the genome of *K. setae* having it at right subtelomeric region (Fig. 1). Further the architecture of this gene cluster is inverted in this draft genome, which implies that the bafilomycin biosynthetic gene cluster could be horizontally transferred to both strains.

The organization of bafilomycin biosynthetic gene cluster was the same as that of *S. lohii* and *S. griseus* (Hwang *et al*., 2013; Zhang *et al*., 2013). The 57.6 kb of PKS region con-

Table 5. The organization of bafilomycin biosynthetic gene cluster of *K. cheerisanensis* KCTC 2395

Gene accession number	Number of amino acid	Deduced function	The closest protein (GenBank number)	Gene strain	Homology (%)
KCH_03990	359	hypothetical protein	WP_014140404.1	*K. setae* KM-6054	93
KCH_04000	320	malonyl transferase	EYU71412.1	*Streptomyces* sp. PCS3-D2	91
KCH_04010	213	hypothetical protein	WP_018568166.1	*Streptomyces* sp. PsTaAH-124	84
KCH_04020	639	AfsR family transcriptional regulator	WP_018487292.1	*Streptomyces* sp. CcalMP-8W	83
KCH_04030	220	SAM-dependent methyltransferase	WP_018568169.1	*Streptomyces* sp. PsTaAH-124	93
KCH_04040	366	FkbH	WP_018961924.1	*Streptomyces* sp. CNB091	92
KCH_04050	371	acyl-CoA dehydrogenases	WP_019761696.1	*Streptomyces* sp. Wigar10	91
KCH_04060	89	methoxymalonate biosynthesis protein	WP_014140396.1	*K. setae* KM-6054	88
KCH_04070	289	3-hydroxyacyl-CoA dehydrogenase	WP_014140395.1	*K. setae* KM-6054	91
KCH_04080	2097	modular polyketide synthase V	KDQ71156.1	*Streptomyces* sp. NTK 937	86
KCH_04090	3392	modular polyketide synthase IV	KDQ71155.1	*Streptomyces* sp. NTK 937	87
KCH_04100	3915	modular polyketide synthase III	KDQ71154.1	*Streptomyces* sp. NTK 937	88
KCH_04110	4988	modular polyketidesynthase II	ADC79617.1	*S. lohii* ATCC BAA-1276	86
KCH_04120	4759	modular polyketide synthase I	KDQ71153.1	*Streptomyces* sp. NTK 937	85
KCH_04130	410	5-aminolevulinate synthase	WP_014140389.1	*K. setae* KM-6054	92
KCH_04140	514	amide synthetase	ADC79614.1	*S. lohii* ATCC BAA-1276	89
KCH_04150	518	AMP-dependent synthetase	WP_014140387.1	*K. setae* KM-6054	91

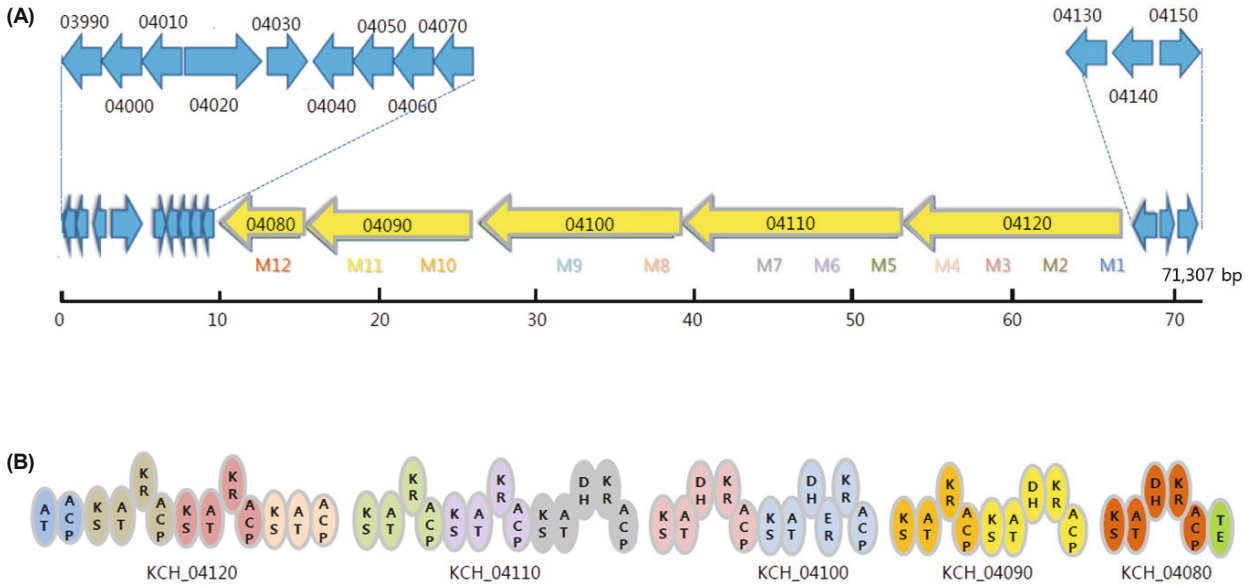

Fig. 3. The bafilomycin biosynthetic gene cluster found in the genome draft of *K. cheerisanensis* KCTC 2395. (A) In the gene cluster having 71,307 bp in length, 17 ORFs including 5 modular polyketide synthase (PKS) genes were found, as described in Table 5. The gene accession numbers under the prefix "KCH_" are described near the arrow representing the gene direction. (B) Domain analysis of 5 modular PKS genes by MAPSI (Management and Analysis for Polyketide Synthase type I) tool (Tae *et al.*, 2009).

sisted of 12 PKS modules in 5 different PKS genes, was assumed to be responsible for the biosynthesis of plecomacrolide backbone including 16-membered macrocyclic lactone (Fig. 3). All the modules showed high similarities with typical type I PKS genes. In downstream of PKS region, the genes for methoxymalonate biosynthesis were located, among which a gene for FkbH-like protein was assumed to play an important role in the production of methoxymalonyl-CoA from glyceryl-CoA. Further the genes encoding flavensomycinyl-ACP biosynthesis for the post-PKS tailoring were also found in the upstream of PKS region (Table 5).

The resistance genes to β-lactam antibiotics including AmpC β-lactamase (KCH_10470; KCH_10480) and metallo-β-lactamase (KCH_19220; KCH_36670) were identified. The other putative resistance genes to aminoglycoside antibiotics (KCH_00980; KCH_00990) and to chloramphenicol (KCH_72240; KCH_73860) were also found in this draft genome.

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