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Genome announcement

Complete genome sequence of *Streptomyces venezuelae* ATCC 15439, a promising cell factory for production of secondary metabolites

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ABSTRACT

Streptomyces venezuelae ATCC 15439, which produces 12- and 14-membered ring macrolide antibiotics, is a platform strain for heterologous expression of secondary metabolites. Its 9.05-Mb genome sequence revealed an abundance of genes involved in the biosynthesis of secondary metabolites and their precursors, which should be useful for the production of bioactive compounds.

The genus *Streptomyces* is a Gram-positive bacterium belonging to the actinomycetes, which is mainly isolated from soil (Hopwood, 2006). Most strains of *Streptomyces* are recognized as industrial bacteria producing an array of antibiotics and other bioactive natural compounds through secondary metabolism. Among them, *Streptomyces venezuelae* ATCC 15439 is a versatile producer synthesizing various macrolide antibiotics. They include the 12-membered ring macrolides YC-17, methymycin, neomethymycin, and novamethymycin (Zhang and Sherman, 2001) as well as the 14-membered ring macrolides narbomycin, pikromycin, neopikromycin, and novapikromycin (Lee et al., 2006), which are biosynthesized by enzymes encoded in the pikromycin-biosynthetic gene cluster (Xue et al., 1998). The strain has been used as a platform strain for secondary metabolite biosynthesis because the strain has advantageous features for heterologous expression such as fast growth, relative ease of genetic engineering, and an abundant supply of precursors for secondary metabolites (Kim et al., 2015b). We analyzed the genome sequence of *S. venezuelae* ATCC 15439 to investigate its genomic features and to explore genetic elements related to secondary metabolism.

To determine the genome sequence of strain ATCC 15439, sequencing was performed using the Applied Biosystems 3730xl DNA Analyzer and the Ion Torrent PGM™ sequencer by GenoTech Corporation (Daejeon, South Korea). Three genomic libraries (~200 bp, ~2 kb and ~35 kb) were constructed and nucleotide sequences with 100-fold coverage of the ATCC 15439 genome were generated. A hybrid genome assembly was accomplished by the Phred/Phrap/Consed software package (http://www.phrap.org) and CLC Genomics Workbench (CLC bio, Inc.). Sequence gaps between contigs were filled using PCR amplification followed by Sanger sequencing. Genome annotation was performed using an in-house pipeline (Archer et al., 2011; Song et al., 2010). RNAmmer and tRNAscan-SE were respectively used to detect rRNA and tRNA genes. Protein coding genes were predicted by Glimmer and GeneMark.hmm and Prodigal. AutoFACT was used for automatic functional assignment of the coding sequences with the public databases, GenBank, COG, UniRef90 and KEGG. Manual curation of the predicted results was performed using Artemis.

The complete genome of ATCC 15439 is composed of a linear chromosome of 9,054,831 bp with 71.74% G+C content. The

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Table 1
Genomic features of *Streptomyces venezuelae* ATCC 15439.

Feature	Chromosome
Total genome size (bp)	9,054,831
G + C content (%)	71.74
Number of protein-coding genes	8080
Number of ribosomal RNA operons	7
Number of transfer RNA genes	72

genome contains 8080 protein-coding genes, 72 tRNA genes, and 7 rRNA operons (Table 1). Genes involved in secondary metabolite biosynthesis were detected in the ATCC 15439 genome, encoding putative antibiotics, siderophores, and signal molecules. They were distributed as more than 30 gene clusters in the genome. In addition to the *pik* gene cluster for macrolide production (Xue et al., 1998), gene clusters encoding type I, II, and III polyketide biosynthetic enzymes were also found in the genome. The genome analysis also demonstrated that the strain possesses various gene clusters for peptide secondary metabolites, encoding proteins for producing nonribosomal peptides, lantipeptides, a bacteriocin, and a cyclic dipeptide. Other secondary metabolites were expected to be made and excreted by ATCC 15439. They include hopanoid, 2-methylisoborneol, geosmin, ectoine, melanin, indolocarbazole, pyrrolnitrin, and desferrioxamine.

Genomic studies of *Streptomyces* spp. have been crucial to establish a genetic basis for elucidating and utilizing beneficial natural products (Kim et al., 2015c; Medema and Fischbach, 2015; Song et al., 2010, 2012). The genome analysis of *S. venezuelae* ATCC 15439 will provide valuable information to understand the secondary metabolism, to produce target molecules en masse, and to develop it as a heterologous host of choice (Hwang et al., 2014; Kim et al., 2015a).

Nucleotide sequence accession number

Complete genome sequences of *S. venezuelae* ATCC 15439 has been deposited in the GenBank database under the accession number CP013129.

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