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Comparative Genome Analysis of Phormidesmis priestleyi ULC007 and Some Representatives of Genus Phormidium (Cyanobacteria)

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Abstract. Cyanobacteria live in a wide range of habitats encompassing freshwater, marine, and terrestrial ecosystems. They are one of the most morphologically diverse groups. Techniques based on polyphasic taxonomy were introduced to cyanobacterial systematics in an attempt to overcome the shortcomings brought by the traditional emphasis on morphological features. Recent advances in genomics are greatly accelerating our understanding of cyanobacterial taxonomy. Genomes available in NCBI's GenBank were selected to comprehensively clarify the genetic similarities and differences of representatives of genus *Phormidium* and *Phormidesmis priestleyi* ULC007 (former *Phormidium priestleyi*). We performed a comparative genomic analysis, which includes analysis of genome characteristics and annotation of the subsystem, classification of functionally annotated common genes and automatic annotation of secondary metabolic gene clusters. Results showed that about 83% of the genes in the studied cyanobacterial genomes were identified as genes with unknown functions, and those with annotated functions were mainly involved in: (I) cofactors, vitamins, prosthetic groups, and pigments; (II) cell wall and capsule; (III) RNA metabolism; (IV) protein metabolism; (V) DNA metabolism, (VI) fatty acids, lipids, and isoprenoids; (VII) respiration; (VIII) stress response; (IX) amino acids and derivatives; and (X) carbohydrates We found that *Phormidesmis priestleyi* ULC007 possess seven genes involved in the chemotaxis. The *in silico* identification, annotation and analysis of the secondary metabolite biosynthesis gene clusters of the most promising targets within the studied cyanobacterial genomes showed presence of specific secondary metabolite genes, which need further detailed analyses.

Key words: Cyanobacteria, genome, genomics, *Phormidium*, *Phormidesmis*, secondary metabolites.

Introduction

The phylum Cyanobacteria includes oxygenic phototrophic bacteria, that are considered as the ancestors of the plant chloroplasts. They have thrived on our planet for at least 2.33–2.4 billion years ago (Bekker et al., 2004; Schirrmeister et al., 2015). Cyanobacteria are able to inhabit most of Earth's environments (oceans, lakes, soils, deserts and hot springs) because they evolved mechanisms to detect and rapidly adapt to environmental changes by using a complex of signaling molecules (including secondary metabolites) to regulate the

physiology or metabolism (Agostoni & Montgomery, 2014).

Morphologically, cyanobacteria are one of the most diverse groups of organisms distributed worldwide. Techniques based on polyphasic taxonomy were introduced to cyanobacterial systematics in an attempt to overcome the shortcomings caused by the traditional emphasis on morphological features (Hoffmann et al., 2005; Komárek et al., 2014; Vandamme et al., 1996). The sequence analysis of the 16S rRNA gene is commonly used for the revision of cyanobacterial genera, but it is unsuitable for a clear and undoubtful assessment of the subgeneric categories (Johansen & Casamatta, 2005).

Genomics is currently the most promising framework for correcting mistakes caused by the traditional taxonomics and clearing out the complicated evolutionary relationships of several polyphyletic taxa persisting in the cyanobacterial classification. Sequencing of genomes from cyanobacteria allows not only increasing the knowledge of the molecular genetics of this phylum, but also to understand the evolution and diversity related to the morphology, photosynthesis, secondary metabolism, and endosymbiosis (Dagan et al., 2013; Shih et al., 2012). Advances in the genome sequence technology have caused a deluge of genome sequences for cyanobacteria. Their genomes are different in size (from 1.44 to 12.07 Mb), ploidy (from two to more than 20 copies of the circular genome per cell) or GC content (30–60%), probably due to processes of gaining and losses of genes transferred by plasmids, insertion sequences (Cassier-Chauvat et al., 1997) and/or cyanophages (Hess, 2011; Shih et al., 2012). The number of cyanobacterial genomes is approximately 0.6% of all prokaryotic genomes available at this moment (Banack et al., 2012; Schirrmeister et al., 2015). More than 20 years after the publication of the first cyanobacterial genome (*Synechocystis sp.* PCC 6803), just a few over 400 cyanobacterial genomes are available in public databases, a number that pales in comparison to more than 30,000 complete genomes available for strains classified in 50 bacterial and 11 archaeal phyla (Land et al., 2015).

In 2009, another new genus (*Phormidesmis*, *Leptolyngbyaceae*) was separated from the genus *Phormidium* (*Oscillatoriaceae*) based on morphological, ultrastructural, and molecular analyses. *Leptolyngbyaceae* and *Oscillatoriaceae* belong to the most difficult cyanobacterial taxa for proper identification (Komárek et al., 2014). Recently, Raabová et al. have conducted revision of the genus *Phormidesmis* analyzing 26 *Phormidesmis* strains by using morphological, ultrastructural and phylogenetical features. Based on the results, they classified two new species (*Phormidesmis arctica* and *Phormidesmis communis*) and transferred *Leptolyngbya nigrescens* to *Phormidesmis nigrescens* (Raabová et al., 2019). Despite the revision, the ambiguities within genus *Phormidesmis* remained unresolved. These organisms are limited ecologically, and some species were found only in a specific ecological niche (Raabová et al., 2019). *Phormidesmis priestleyi* ULC007 is a freshwater cyanobacterium isolated from Antarctica. The strain *Phormidesmis priestleyi* ULC007 was originally isolated from Lake Bruehwiler, a shallow freshwater lake of 1 ha (Hodgson et al., 2004). *Phormidesmis molle*, which is a type species of the genus *Phormidesmis*, contains strains from tropical and subtropical swamps in Central America and was described from similar localities across tropical and subtropical regions (Turicchia et al., 2009).

Different cyanobacterial strains produce a variety of secondary metabolites, some of which are toxic (Dittmann et al., 2015; Pearson et al., 2016). On the other hand, many marine, terrestrial and freshwater cyanobacteria produce a wealth of natural

products with interesting biological activities (Jones et al., 2009; Jones et al., 2010; Welker & Von Döhren, 2006). The genetic origins of specialized metabolites and the mechanisms, which drive their evolution are poorly understood. About 5-6% of the cyanobacterial genomes are used for production of secondary metabolites (Calteau et al., 2014). The known cyanobacterial natural products includes more than 1100 secondary metabolites with complex and interesting chemical structures. They can be assigned as peptides, polyketides, isoprenoids, alkaloids, lipids, and terpenes (Jones et al., 2009; Welker & Von Döhren, 2006).

The aim of this study was to identify similarities and differences between *Phormidesmis priestleyi* ULC007 (former *Phormidium priestleyi*) and other representatives of genus *Phormidium* by using a comparative genomics analysis, which includes genome feature analysis and subsystem annotation, classification of functionally annotated common genes and automatic annotation of secondary metabolite gene clusters.

Material and Methods

Available genomes of representatives of the genus *Phormidium* (*Phormidium ambiguum* IAM M-71, *Phormidium pseudopriestleyi* FRX01, *Phormidium tenue* FACHB-1052, and *Phormidium willei* BDU 130791) along with *Phormidesmis priestleyi* ULC007 were retrieved from the GenBank and the Joint Genome Institute's Integrated Microbial Genomes database (JGI-IMG). The RAST-Server (Rapid Annotation using Subsystems Technology) and the SEED viewer were used for the automatic annotation of genes and functional classification in subsystems (Aziz et al., 2008; Overbeek et al., 2014). For genome-wide identification, annotation and analysis of secondary metabolite biosynthesis gene clusters in cyanobacterial genomes was used the antiSMASH Server (Blin et al., 2019).

Results and Discussion

Nowadays, many cyanobacterial genomes have been sequenced and annotated. This information can be used to identify biological pathways presented in all cyanobacteria as the proteins involved in such processes are encoded by a so called core-genome. The complete genome sequences for four *Phormidium* species (*Ph. ambiguum* IAM M-71, *Ph. pseudopriestleyi* FRX01, *Ph. tenue* FACHB-1052, and *Ph. willei* BDU 130791) were compared with the complete genome sequence of a representative of the genus *Phormidesmis* (*Phormidesmis priestleyi* ULC007). General genome features (genomic statistics and subsystem statistics-SEED) for all complete genomes used in this study are shown in Table 1.

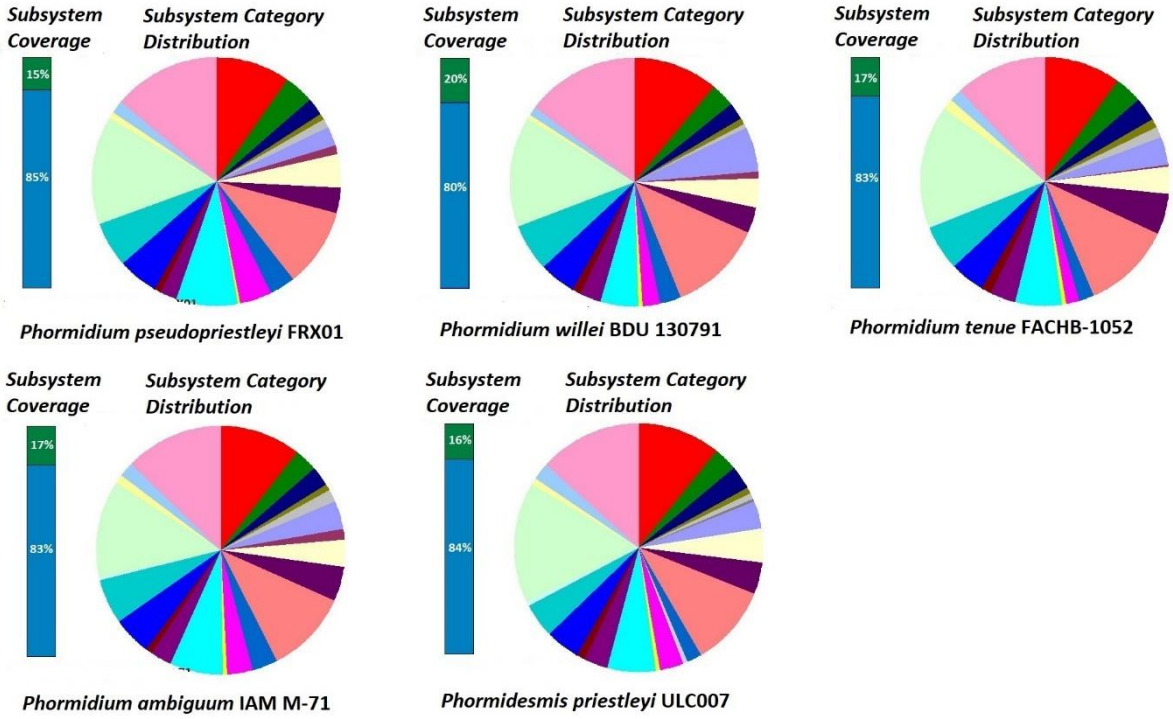
Genomes ranged in size from 4.60 Mb (*Phormidium willei* BDU 130791) to 7.41 Mb (*Phormidium ambiguum* IAM M-71). The genome of *Phormidesmis priestleyi* ULC007 (5.71 Mb with an overall GC content of 48.6 %) is similar in size to genomes of the representatives of *Phormidium*. *Phormidium tenue* FACHB-1052, and *Phormidium willei* BDU 130791 are characterized by a higher GC content (56.0% and 53.4%, respectively). *Phormidium ambiguum* IAM M-71 has the lowest GC content (39.5%). Results showed that there are large differences in the number of contigs and the N50 value between the different cyanobacterial strains. Contigs ranged from 39 (*Phormidium tenue* FACHB-1052) to 678 (*Phormidium pseudopriestleyi* FRX01). *Phormidesmis priestleyi* ULC007 has 167 contigs. *Phormidium pseudopriestleyi* FRX01, and *Phormidium willei* BDU 130791 are characterized by a lower N50 value (10908 and 34265, respectively) (Table 1). The number of subsystems (243-290), coding sequences in subsystems (15-20%) and coding sequences not in subsystems (80-85%) are similar between all genomes (Table 1). Selection pressures may cause changes in genetic factors such as genome size, G-C percentage, gene number, and evolutionary rates. While cyanobacteria may develop individual strategies for interacting with the environment, several of their systems are globally conserved (Simm et al., 2015).

Table 1. Comparison of the genomic features and subsystem annotation of the studied strains.

Statistics	ULC007	BDU 130791	FACHB-1052	FRX01	IAM M-71
Genomic statistics					
N of contigs	167	171	36	678	90
Total size (Mb)	5714281	4600567	5821333	5965908	7410502
Proteins	5196	3929	5051	4719	6262
Genes	5455	4077	5200	5101	6474
Pseudogenes	211	103	100	317	141
GC content (%)	48.6	53.4	56.0	47.4	39.5
N50	106941	34265	248526	10908	196225
Number of RNAs	42	42	43	59	65
Subsystem statistics – SEED					
N of subsystems	278	243	278	264	290
N of coding sequences	6075	4424	5687	6794	6842
Coding sequences in	950	853	955	968	1158
subsystems/%	16%	20%	17%	15%	17%
Coding sequences not in	5125	3571	4732	5826	5684
subsystems/%	84%	80%	83%	85%	83%

The gene composition and putatively identified functional differences between the cyanobacterial species were assessed by using Rapid Annotation and Subsystems Technology (RAST-Server) (Fig. 1.). The RAST server automatically produces two classes of asserted gene functions: subsystem-based assertions are based on recognition of functional variants of subsystems, while nonsubsystem-based assertions are filled in using more common approaches based on integration of evidence from a number of tools. The results of the RAST Server and SEED viewer subsystem annotation showed that analyzed cyanobacterial genomes are considerably similar (Fig. 1). An average of 83% of genes in the studied genomes were identified as genes with unknown functions, and those with annotated functions were mainly involved in: (I) cofactors, vitamins, prosthetic groups, and pigments; (II) cell wall and capsule; (III) RNA metabolism; (IV) protein metabolism; (V) DNA metabolism, (VI) fatty acids, lipids, and isoprenoids; (VII) respiration; (VIII) stress response; (IX) amino acids and derivatives; and (X) carbohydrates. The most prominent difference was observed for motility and the chemotaxis. Not all of the genes involved in the motility and chemotaxis were presented in all studied cyanobacterial strains. Most of them were detected only in *Phormidesmis priestleyi* ULC007 (Fig. 1). In the cyanobacterial chemotaxis, these genes encode proteins defined as: positive regulator of CheA protein activity (CheW), chemotaxis protein CheV (EC 2.7.3.-), chemotaxis response regulator protein-glutamate methylesterase CheB (EC 3.1.1.61), multdomain signal transduction protein including CheB-like methylesterase, maltose/maltodextrin ABC transporter, substrate binding periplasmic protein MalE, methyl-accepting chemotaxis protein I (serine chemoreceptor protein), chemotaxis protein methyltransferase CheR (EC 2.1.1.80).

Cyanobacteria are subject of scientific investigation in regard to their production of toxic and non-toxic secondary metabolites. The presence of secondary metabolite biosynthesis gene clusters (BGCs) was tested using the antiSMASH platform (Blin et al., 2019). The genome of *Phormidesmis priestleyi* ULC007 contains 8 regions encoding BGCs (terpene; type II polyketide synthase (T2PKS); NRPS-like fragment; non-ribosomal peptide synthetase (NRPS) and type I polyketide synthase (T1PKS)).



Subsystem Feature Counts	ULC007	BDU 130791	FACHB -1052	FRX01	IAM M-71
Cofactors, Vitamins, Prosthetic Groups, Pigments	139	125	132	123	164
Cell Wall and Capsule	38	33	44	52	46
Virulence, Disease and Defense	37	25	40	25	39
Potassium metabolism	12	9	14	13	12
Photosynthesis	0	0	0	0	0
Miscellaneous	9	6	18	12	26
Phages, Prophages, Transposable elements, Plasmids	4	2	1	3	1
Membrane Transport	44	64	47	32	56
Iron acquisition and metabolism	2	7	4	15	21
RNA Metabolism	57	43	46	56	55
Nucleosides and Nucleotides	51	37	68	40	70
Protein Metabolism	132	136	152	132	167
Cell Division and Cell Cycle	26	31	22	42	48
Motility and Chemotaxis	7	0	0	0	0
Regulation and Cell signaling	38	24	24	50	51
Secondary Metabolism	5	4	5	5	10
DNA Metabolism	83	56	80	103	105
Fatty Acids, Lipids, and Isoprenoids	35	30	44	26	45
Nitrogen Metabolism	14	14	18	12	12
Dormancy and Sporulation	1	1	1	2	1
Respiration	59	52	55	66	75
Stress Response	54	65	77	75	90
Metabolism of Aromatic Compounds	7	3	4	3	5
Amino Acids and Derivatives	199	161	204	178	197
Sulfur Metabolism	9	6	15	9	16
Phosphorus Metabolism	27	13	24	22	28
Carbohydrates	164	153	149	165	194

Fig. 1. Classification of functionally annotated common genes between cyanobacterial strains ULC007, BDU 130791, FACHB-1052, FRX01, and IAM M-71. Between eighty percent and eighty-five percent of genes in these "core" genomes are hypothetical and are not represented in the figure.

Results showed a large number of regions encoding BGCs in the genome of *Phormidium ambiguum* IAM M-71 (11 regions encoding BGCs - lanthipeptide-class-V; non-ribosomal peptide synthetase (NRPS); siderophore; terpene; phenazine; lassopeptide; linear azol(in)e-containing peptides (LAP) and lanthipeptide class-II) (Table 2). The number of regions encoding BGCs in the other representatives of genus *Phormidium* is between 4 and 8. The different types of secondary metabolite clusters are included here (arylpolyene; terpene; siderophore; RiPP-like; phenazine; thioamitides, thiopeptide; resorcinol; NRPS; T1PKS and NRPS-like). The terpene is specific for all studied cyanobacterial species; non-ribosomal peptide synthetase (NRPS) is specific for all strains without *Phormidium pseudopriestleyi* FRX01; *Phormidesmis priestleyi* ULC007 and *Phormidium willei* BDU 130791 encode NRPS-like and T1PKS; *Phormidium pseudopriestleyi* FRX01 and *Phormidium tenue* FACHB-1052 encode arylpolyene; siderophore is specific for *Phormidium pseudopriestleyi* FRX01 and *Phormidium ambiguum* IAM M-71; some secondary metabolites are species-specific - T2PKS (*Phormidesmis priestleyi* ULC007), RiPP-like (*Phormidium pseudopriestleyi* FRX01), thioamitides, thiopeptide and resorcinol (*Phormidium tenue* FACHB-1052), lanthipeptide-class-V, lassopeptide, LAP and lanthipeptide-class-II (*Phormidium ambiguum* IAM M-71) (Table 2). Genomic content can be changed by neutral processes or due to adaptation of the organism to different environmental conditions (Barrick et al., 2009; Koonin, 2009; Tenaillon et al., 2016). Taking in account that 83% of the identified genes have an unknown function, it is very difficult at this stage to conclude from the encoded secondary metabolites that there is a significant difference between the two genera *Phormidesmis* and *Phormidium*. In addition to the morphology and molecular phylogeny, the isolation and identification of specific gene clusters or metabolites (or groups of metabolites) would give a more complete and realistic picture of the justification for separating the representatives of these two genera into different taxonomic categories.

Table 2. Secondary metabolites produced by studied cyanobacterial species.

Region	Type	From	To	Most similar known cluster	Similarity
***Phormidesmis priestleyi* ULC007**					
Region 11.1	Terpene	49,266	70,072	-	-
Region 22.1	Terpene	25,098	45,913	-	-
Region 45.1	T2PKS, NRPS-like	63,729	160,746	Cichopeptin, NRP	15%
Region 46.1	NRPS, terpene	37,585	75,615	-	-
Region 51.1	NRPS, T1PKS, NRPS-like	1	59,806	Puwainaphycin F, Minutissamide A, B, C, D NRP	76%
Region 78.1	Terpene	1	15,726	-	-
Region 79.1	NRPS	1	29,783	-	-
Region 132.1	NRPS	24,888	73,841	Nostopeptolide A2, Polyketide + NRP:Cyclic depsipeptide	-
***Phormidium pseudopriestleyi* FRX01**					
Region 26.1	Arylpolyene	1	7,941	-	-

Region 138.1	Terpene	10,796	31,616	-	-
Region 373.1	Siderophore	1	11,575	-	-
Region 552.1	RiPP-like	1	3,072	-	-
Phormidium tenue FACHB-1052					
Region 2.1	Phenazine	130,964	151,422	-	-
Region 4.1	Arylpolyene	43,773	84,786	-	-
Region 7.1	Thioamitides, thiopeptide	6,918	32,005	-	-
Region 19.1	Resorcinol	33,576	58,279	-	-
Region 20.1	NRPS	22,721	52,507	Cyanopeptin, NRP	75%
Region 23.1	Terpene	7,855	39,848	Hopene, Terpene	15%
Region 34.1	Terpene	42,905	63,831	-	-
Region 36.1	Terpene	16,019	37,248	-	-
Phormidium willei BDU 130791					
Region 28.1	Terpene	16,008	36,898	-	-
Region 36.1	T1PKS, NRPS	1	36,780	Nostopeptolide A2, Polyketide + NRP: Cyclic depsipeptide	25%
Region 47.1	NRPS-like	1	33,117	-	-
Region 77.1	Terpene	5,548	22,637	-	-
Region 82.1	NRPS-like	1	20,129	-	-
Region 95.1	Terpene	1	17,535	-	-
Phormidium ambiguum IAM M-71					
Region 1.1	Lanthipeptide-class-V	132,930	175,212	-	-
Region 2.1	NRPS	14,197	63,330	Nostocyclopeptide A2, NRP	28%
Region 2.2	Siderophore	109,211	126,128	-	-
Region 14.1	Terpene	25,551	46,480	Trichamide, RiPP: Cyanobactin	18%
Region 31.1	Phenazine	1	16,230	Kedarcidin, Polyketide:Iterative type I + Polyketide:Enediyne type I	1%
Region 36.1	Lassopeptide	15,654	37,959	-	-
Region 39.1	LAP	6,892	30,538	-	-
Region 57.1	Terpene	1	32,508	Malleobactin A, B, C, D, NRP: NRP siderophore	7%
Region 64.1	Lanthipeptide-class-II	1	13,657	-	-
Region 67.1	Lanthipeptide-class-II	226,317	249,727	-	-
Region 89.1	Terpene	201,922	224,279	Geosmin, Terpene	100%

Conclusions

A comparative genomics analysis was conducted (including a genome feature analysis and subsystem annotation, the classification of functionally annotated common genes and the automatic

annotation of secondary metabolite gene clusters) to identify similarities and differences between *Phormidesmis priestleyi* ULC007 (previously classified as *Phormidium priestleyi*) and other representatives of genus *Phormidium*.

Using a comparative genomic approach, we found that *Phormidesmis priestleyi* ULC007 possess more genes involved in the motility and chemotaxis compared to the *Phormidium* species. The comparative genome analysis of studied cyanobacterial species allowed us to establish that some of the cyanobacterial species have specific secondary metabolite biosynthesis gene clusters, but this is not enough to support the recent taxonomic separation of these species. Many of the secondary metabolites are common to most cyanobacterial strains.

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