Bioinformatics Analysis of *Q0D1P0* Gene of Mangrove Endophytic Fungus *Aspergillus terreus*

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Abstract [**Objectives**] To analyze the gene structure of the protein that predicts 6-hydroxymellein synthase of *Aspergillus terreus* and predict the characteristics and functions of the protein structure encoded by the gene. [**Methods**] Various information analysis tools in NCBI, CBS and ExPASy websites were adopted. [**Results**] The *Q0D1P0* gene had a full length of 2 954 bp, with 952 amino acids in the coding area, and Q0D1P0 had the highest homology with the hypothetical protein ATETN484_0003008800. The molecular weight of Q0D1P0 protein was 105 040.56, the theoretical isoelectric point (pI) was 5.69 and the grand average of hydropathieity was -0.242. It was speculated that Q0D1P0 was an unstable and non-secretory hydrophilic protein located in cytoplasm without transmembrane domain or signal peptide. It could be predicted that the secondary structure of Q0D1P0 encoding protein consisted mainly of random coil, α-helix and a PKS-DH anhydrase domain. [**Conclusions**] The results will lay a theoretical foundation for cloning and expression of 6-hydroxymellein synthase and further understanding of its activity and function.

Key words *Aspergillus terreus*, 6-Hydroxymellein synthase, Bioinformatics

1 Introduction

Mangrove is a woody plant community that grows in the tropical and subtropical coasts and estuarine intertidal zone. It is a transitional ecosystem between land and sea, and is one of the four high-productivity marine ecosystems. Due to the edge effect, mangrove has high openness and a wide variety of species, and has unique ecological functions, such as wind and wave prevention, sediment promotion and shore protection, disaster prevention and reduction, sea water purification, air regulation and coast beautifying, *etc.* At present, it has become one of the key fronts for marine biodiversity protection and development, attracting the attention of all countries[1-2].

As a special plant community with both terrestrial and marine habitats, it is rich in endophytic fungi resources. Currently, more than 200 species of mangrove fungi have been isolated and identified[3-4], while *Aspergillus* fungi account for the majority[5-6], including bacteria that have the ability to degrade various pollutants, bacteria that have the ability to fix nitrogen and dissolve phosphorus efficiently, bacteria that are tolerant to salt and halophilic bacteria, and bacteria that can produce physiological active substances and secondary metabolites with anti-cancer and antibacterial effects[7-9]. On the basis of previous studies, it has been found that mangrove fungi can effectively produce isocoumarin with obvious antibacterial and anti-inflammatory activities, among which mellein and its derivatives are a major category[10].

Aspergillus terreus, belonging to *Aspergillus*, Trichocomaceae, Eurotiales, Eurotiomycetes, Ascomycota, is a type of fungus that exists widely in the sea and on land[11]. *A. terreus* is a pathogen that generally infects dogs and cattle, and it can cause nasosinusitis, osteomyelitis and even abortion. *A. terreus* usually causes superficial infections of people, such as ringworm and otomycosis. Known metabolites or toxins produced by *A. terreus* include natural herbicide aspterric acid, 6-hydroxymellein, terrein, terreic acid and lovastatin, *etc.*[12-13]. More and more secondary metabolites of *A. terreus* have been proved to have physiological activities such as bacteriostasis and cancer suppression[14]. *A. terreus* is a special carrier for the expression of biophysiological active substances. The information contained in *A. terreus* genome can be used to find the key to resist *A. terreus* toxin, which will help to improve the safety and quality of human health.

(*R*)-6-Hydroxymellein is an important natural product and an intermediate precursor of 6-methoxymellein, a plant antitoxin with antibacterial effect[15-16]. It is also an important precursor compound in the biosynthesis of terrein, a natural product with antibacterial, anti-proliferative and antioxidant effects[17]. The substance is mainly isolated from plants, insects (*Gromphadorina portentosa*), and microbial metabolites.

With common endophytic fungus *A. terreus* var. *terreus* in mangrove as the object, this paper explored the synthesis of 6-hydroxymellein synthase, one of the proteases with physiological active substances such as isocoumarin and terrein, and analyzed the gene structure information of its protein and the characteristics and functions of the protein structure encoded by the gene via various information analysis tools from NCBI, CBS and ExPASy websites, in order to provide a reference for cloning and expression of

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6-hydroxymellein synthase and further understanding of its activity and function.

2 Materials and methods

2.1 Materials 6-Hydroxymellein synthase of *A. terreus* was selected. The DNA, mRNA and protein sequence materials for bioinformation analysis were obtained from NCBI (www.ncbi.nlm.nih.gov) and UniProtKB of ExPASy database (www.expasy.org or www.uniprot.org/uniprot). The tools were the proteomic online analysis tools provided by the expert system for protein analysis of Swiss Institute of Bioinformatics (ExPASy, www.expasy.org). *ATEG* was the gene name of terrein synthase derived from NCBI (gene No.: 4354901; mRNA accession No.: XM_001210230.1; protein accession No.: XP_001210230.1).

2.2 Methods

2.2.1 Gene homology analysis Using the basic local alignment search tool (BLAST, www.ncbi.nlm.nih.gov/blast/) of National Center for Biotechnology Information (NCBI, www.ncbi.nlm.nih.gov), gene homology analysis was completed via Blastp.

2.2.2 Open reading frame coding area analysis. ORF finder (http://www.ncbi.nlm.nih.gov/gorforfig.cgi) was applied to find the open reading frame, and the coding protein sequence was deduced.

2.2.3 Physicochemical properties of protein. The basic physicochemical properties of Q0D1P0 protein, such as amino acid composition, relative molecular weight, isoelectric point (pI), *etc.*, were analyzed by protein physicochemical analysis forecasting tool Protparam program (https://web.expasy.org/protparam/).

2.2.4 Signal peptide and subcellular localization analysis. The signal peptide of Q0D1P0 protein was predicted using signal peptide cutting locus forecasting tool SignalP 3.0 program (http://www.cbs.dtu.dk/services/SignalP-3.0/). The location of Q0D1P0 protein in fungal cells was predicted using fungal protein subcellular localization prediction tool PSORT (https://wolfpsort.hgc.jp/).

2.2.5 Protein transmembrane structure and hydrophobicity analysis. The hydrophobicity and hydrophilicity of Q0D1P0 protein was analyzed using protein mass spectrometry calculation and expression tool Proscale program (https://web.expasy.org/protscale/). The transmembrane domain of Q0D1P0 was predicted using protein transmembrane helical prediction tool TMHMM program (http://www.cbs.dtu.dk/services/TMHMM-2.0/).

2.2.6 Prediction of protein modification sites and conserved domains. The phosphorylation site of Q0D1P0 was predicted using eukaryotic phosphorylation site prediction tool NetPhos (http://www.cbs.dtu.dk/services/NetPhos/). The conserved domain was predicted using conserved domain prediction tool (www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi). The structural domain was predicted using SMART (http://smart.embl-heidelberg.de/).

2.2.7 Protein structure analysis. The secondary structure of Q0D1P0 was analyzed using protein secondary structure prediction tool GOR (https://npsa-prabi.ibcp.fr/cgi-bin/npsa_automat.pl?page=npsa_gor4.html). Using structural homology modeling tool SWISS-MODEL (https://swissmodel.expasy.org/), the spatial conformation of protein was simulated through secondary structure alignment and folding.

3 Results and analysis

3.1 Homologous sequence alignment BLASTP analysis results showed that Q0D1P0 had the highest homology with the hypothetical protein ATETN484_000300880, with a consistency of 98% and a similarity of 91.98%. The NCBI accession No. of Q0D1P0 was XP_001210230.1, and that of the latter was GES58888.1.

3.2 Open reading frame coding area analysis According to NCBI's ORF Finder, the open reading frame encoding amino acid sequence of Q0D1P0 was obtained. The results showed that the gene had a full length cDNA of 2 954 bp, encoding 952 amino acids. The gene sequence contained 3 exons and 2 introns (1633 – 1680, 1803 – 1850), and the ORF length of this gene was 2 859 bp. The initiation codon was ATG and the termination one was TAA, and the gene did not encode a protein.

3.3 Physicochemical properties of protein The physicochemical properties of protein have important impacts on the function and application of proteins, especially enzymes. Protein pI is the pH of the solution when the charge carried by positive and negative ions in the solution is just "neutralized", which plays an important role in the separation and purification of proteins in electrophoresis. Protparam program showed that Q0D1P0 protein was composed of 952 amino acids, in which leucine content was the highest (11.6%) (Fig.1). The basic properties of Q0D1P0 protein were as follows: molecular formula: $C_{4651}H_{7399}N_{1273}O_{1427}S_{33}$; relative molecular weight: 105 040.56; total atoms: 14 783 (Fig.2); pI: 5.69; fat coefficient: 89.62. The total number of negatively charged residues (Asp + Glu) was 116, and that of positively charged residues (Arg + Lys) was 101. The instability coefficient in the solution was 45.85 > 40, indicating that it is an unstable protein. The grand average of hydropathieity was −0.242, predicting that it is a hydrophilic protein. Therefore, the overall prediction of Q0D1P0 is classified as an unstable hydrophilic protein.

When methionine was at the N terminal, it could be predicted that its half-life was 30 h in mammalian reticulocytes (*in vitro*), greater than 20 h in yeast (*in vivo*), and greater than 10 h in *Escherichia coli* (*in vivo*). When the protein concentration was 1 g/L and all of the cysteine residues formed cystine, the absorbance (ABS) was 0.949, and the molar extinction index at 280 nm in water was 99 655. When all cysteine residues did not form cysteine, the ABS was 0.940, and the molar extinction index at 280 nm in aqueous solution was 98 780.

Amino acid composition:

Ala (A)	65	6.8%
Arg (R)	51	5.4%
Asn (N)	36	3.8%
Asp (D)	58	6.1%
Cys (C)	15	1.6%
Gln (Q)	38	4.0%
Glu (E)	58	6.1%
Gly (G)	63	6.6%
His (H)	16	1.7%
Ile (I)	46	4.8%
Leu (L)	110	11.6%
Lys (K)	50	5.3%
Met (M)	18	1.9%
Phe (F)	34	3.6%
Pro (P)	52	5.5%
Ser (S)	89	9.3%
Thr (T)	57	6.0%
Trp (W)	12	1.3%
Tyr (Y)	22	2.3%
Val (V)	62	6.5%
Pyl (O)	0	0.0%
Sec (U)	0	0.0%
(B)	0	0.0%
(Z)	0	0.0%
(X)	0	0.0%

Fig. 1 Amino acid composition of Q0D1P0

Atomic composition:

Carbon	C	4651
Hydrogen	H	7399
Nitrogen	N	1273
Oxygen	O	1427
Sulfur	S	33

Formula: $C_{4651}H_{7399}N_{1273}O_{1427}S_{33}$
Total number of atoms: 14783

Fig. 2 Atomic composition of Q0D1P0

3.4 Signal peptide and subcellular localization analysis After the initiation codon, an RNA region encoding a sequence of hydrophobic amino acids is called the signal peptide sequence, which can guide the newly synthesized protein into secretion pathway or organelles of different membrane structures. It is generally located at the N terminal of the amino acid sequence, and determines the localization of the protein in the cell. Signal peptide analysis by SignalP 3.0 (Fig. 3) showed that the maximum original shear site fraction at the 38th amino acid was 0.046; the maximum integrated shear site fraction at the 19th amino acid was 0.034; and the maximum signal peptide fraction at the 5th amino acid was 0.235. The possibility values of signal peptide and signal anchor were 0, suggesting that Q0D1P0 had no signal peptide and was a non-secretory protein.

The localization of Q0D1P0 protein in cells was analyzed using PSORT online software (Fig. 4). Among the localization results, the Q0D1P0 protein located in cytoplasm had the highest average score (certainty = 0.450), followed by microbody (certainty = 0.300), mitochondrial matrix space (certainty = 0.100) and lysosome (certainty = 0.100). Therefore, it can be presumed that the protein is located in the cytoplasm.

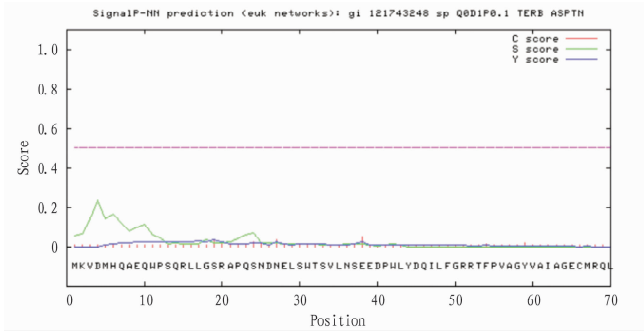

Fig. 3 Signal peptide analysis of Q0D1P0 protein by SignalP 3.0

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----- Final Results -----

                cytoplasm --- Certainty= 0.450(Affirmative) < succ>
      microbody (peroxisome) --- Certainty= 0.300(Affirmative) < succ>
mitochondrial matrix space --- Certainty= 0.100(Affirmative) < succ>
        lysosome (lumen) --- Certainty= 0.100(Affirmative) < succ>


----- The End -----
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Fig. 4 Subcellular localization analysis of Q0D1P0 protein by PSORT

3.5 Protein transmembrane structure and hydrophobicity The hydrophilicity and hydrophobicity of a protein are determined by the average performance of the hydrophilicity of all the amino acids, which is determined by the group they carry. According to the principle of like dissolves like, polar groups can be easily dissolved in water, while non-polar groups have lower affinity with water. The hydrophobicity of the amino acid sequence of Q0D1P0 was analyzed by Proscale tool (Fig. 5). The predicted results showed that the hydrophilicity was strongest at the 133rd amino acid residue in the polypeptide chain, with a score of −3.078 (Min), and the hydrophobicity was strongest at the 543rd and 544th amino acid residues, with a score of 2.322 (Max). Overall, 17 amino acid residues had scores close to or below −2, and 7 amino acid residues had scores close to or above 2, suggesting that Q0D1P0 is a hydrophilic protein, which is in agreement with the analysis of physicochemical properties.

Transmembrane domain is often represented by the effector region of transmembrane proteins, the transmembrane parts of which are β-folded or α-helical structures, playing an important role in protein transport and plasma membrane binding. It has a directional influence on understanding protein function by figuring out whether a protein has a transmembrane domain. TMHMM was used to analyze the transmembrane domain of Q0D1P0 protein (Fig. 6), and the results showed that all amino acids were located on the surface of the biofilm without transmembrane phenomenon. Therefore, it can be inferred that Q0D1P0 is a protein not involved in cell signal transduction.

3.6 Prediction of protein modification sites and conserved domains Phosphorylation is a way to regulate protein function and activity by modifying the addition of residues such as serine (S), tyrosine (Y) and threonine (T) or the removal of phosphate radicals in amino acid sequences. NetPhos was used to predict the phosphorylation site of Q0D1P0 (Fig. 7), and the results showed there were 29 serine residues, 13 threonine residues, and 8 tyrosine residues.

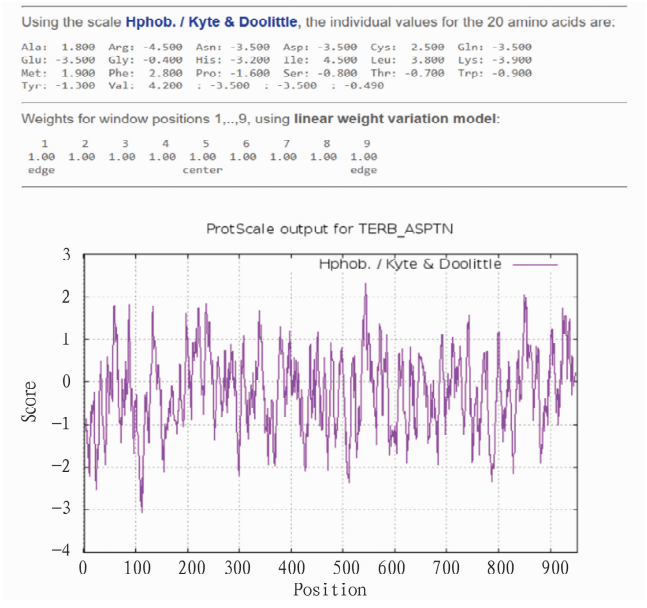


Fig. 5 Hydrophobicity analysis of Q0D1P0 protein by Proscale

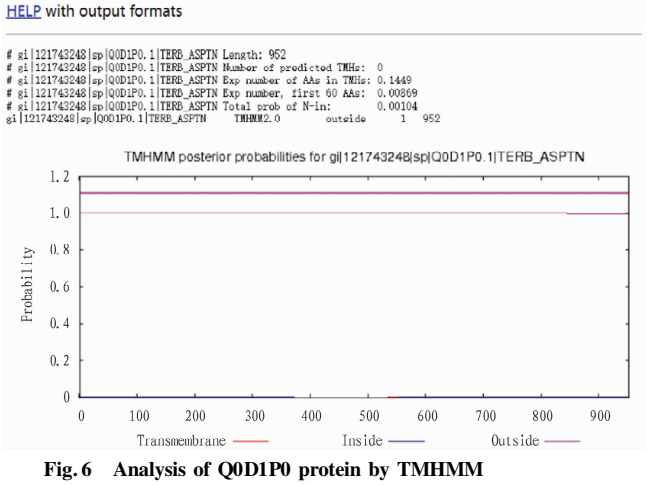


Fig. 6 Analysis of Q0D1P0 protein by TMHMM

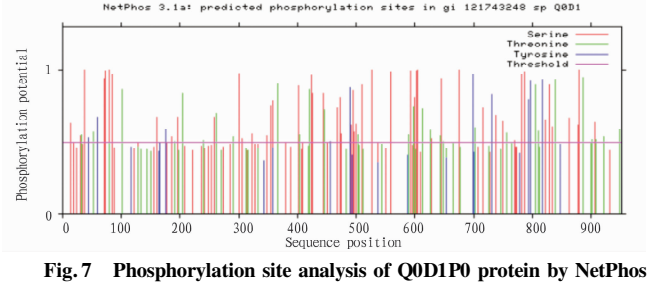


Fig. 7 Phosphorylation site analysis of Q0D1P0 protein by NetPhos

Conserved domain refers to the invariant or the same domain in biological evolution or a protein family, which can indicate the retained amino acid sequence that is most critical to the function of a protein during the evolution of a protein family. CCD tool was used to analyze the conserved domain of Q0D1P0 (Fig. 8). The results showed that Q0D1P0 had a PS-DH conserved domain between the 15th and 285th amino acids and NADB-Rossmann conserved domain between the 854th and 935th amino acids. The NADB domain is present in dehydrogenases of many metabolic pathways, predicting that Q0D1P0 protein is a member of the hot_dog superfamily with dehydrogenase effects.

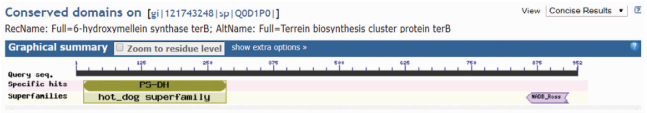


Fig. 8 Conserved domain prediction of Q0D1P0 protein by CCD

SMART tool analysis (Fig. 9) showed that Q0D1P0 protein might have a PGS-DH dehydrase domain found in polyketide synthase, located at the 14th – 182nd amino acids. There might be four regions of low complexity.

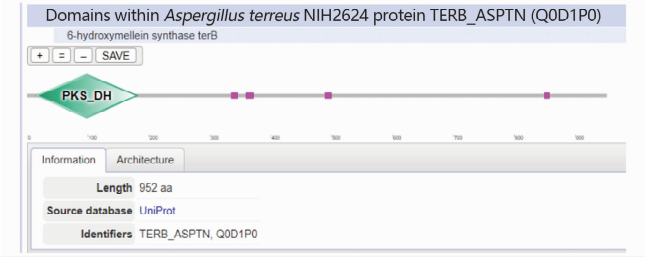
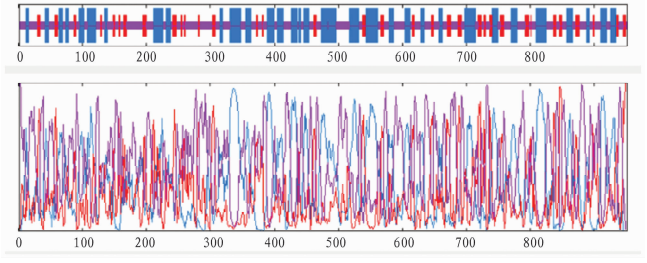


Fig. 9 Functional domain analysis of Q0D1P0 protein by SMART

3.7 Prediction of protein secondary and tertiary structure

Protein secondary structure refers to the specific conformation formed by the backbone atoms of the peptide main chain circling or folding along a certain axis, that is, the spatial arrangement of the backbone atoms of the peptide chain, which does not involve the side chain of amino acid residues. The secondary structure prediction tool GOR was used to predict Q0D1P0 encoding protein (Fig. 10). The results showed that the secondary structure of Q0D1P0 contained α-helix (H), extended chain (E) and random coil (L), accounting for 34.14%, 15.55% and 50.32%, respectively.



Note: Blue. α -helix; Red: Extended chain; Pink: Random coil.

Fig. 10 Analysis of secondary structure of Q0D1P0 protein by GOR

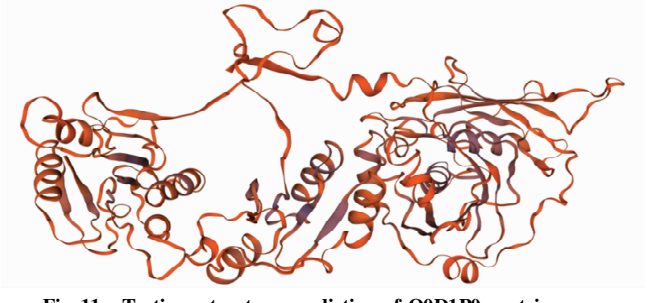


Fig. 11 Tertiary structure prediction of Q0D1P0 protein

Swiss-Model simulated the construction of a 3D model of Q0D1P0 to display the 3D structure of the protein (Fig. 11). The results showed that the sequence characteristic values of the 5 matching models were relatively low, with the highest value of 19.7%. It can be speculated that Q0D1P0 played the role of polyketone synthetase supplement module 3 – 4 in *A. terreus* as homodimer, and had the functions of monooxygenase/methyltransferase psoF and fatty acid synthetase. As shown in Fig. 11, Q0D1P0 contained a large number of random coil and α-helix, without β-folding, which was consistent with the predicted results of secondary structure.

4 Conclusions and discussion

As a filamentous fungus with important economic value, *A. terreus* has been used in large-scale industrial fermentation production of itaconic acid and lovastatin[18-19]. Previous studies have found that terrein, the secondary metabolite of *A. terreus*, has good cytotoxic activity and can inhibit the proliferation of various tumor cells such as breast cancer, ovarian cancer and liver cancer[20-21]. Recent studies have found that terrein has no significant antibacterial activity against *E. coli*, but its broad-spectrum cytotoxic activity is still of research value[22].

6-Hydroxymellein synthetase is a multifunctional enzyme with both methyltransferase and oxidoreductase activities, and can mediate the synthesis of terrein, playing an important role in the secondary metabolism of *A. terreus*. The test successfully predicted the biochemical and structural characteristics of *Q0D1P0* gene and its encoding protein. *Q0D1P0* gene has a full length of 2 954 bp and an open reading frame length of 2 859 bp, encoding 952 amino acids. The relative molecular weight of Q0D1P0 protein is predicted to be 105 040.56, and the theoretical pI is 5.69, which is predicted to be classified as an unstable hydrophilic protein. It may be confirmed that 6-hydroxymellein is a key intermediate in the biosynthesis of terrein[23-24]. It is predicted that Q0D1P0 is a non-secretory protein located in cytoplasm without transmembrane region and signal peptide; the proportions of α-helix (H), extended chain (E) and random coil (L) of Q0D1P0 coding protein are 26.90%, 20.71% and 52.38%, respectively, and the protein has a PSS-DH domain. Proteins that also possess the PKS-DH domain include erythromycin dehydratase and rifamycin polyketide synthase, *etc.* It is estimated that Q0D1P0 played the role of polyketone synthetase supplement module 3 – 4 in *A. terreus* as homodimer, which is consistent with the secondary structure and function analysis results of 6-hydroxymellein synthetase in ginseng cells[25]. In addition, it is also predicted that Q0D1P0 encoding protein has the NADB domain with dehydrogenase effect, and may also have the functions of monooxygenase/methyltransferase psoF and fatty acid synthetase. Considering that less is known about *A. terreus* protein ATETN484_0003008800, which has a high homology with Q0D1P0 coding protein, there are some deviations in the predicted results in the test. In this study, 6-hydroxymellein synthetase is roughly studied at the molecular level combined with bioinformatics analysis, and the physicochemical properties and physiological functions of 6-hydroxymellein synthetase are preliminarily understood, in order to lay a foundation for cloning and expression of 6-hydroxymellein synthetase in the next step.

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