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In silico FUNCTION- AND STRUCTURE-CHARACTERIZATION OF A HYPOTHETICAL PROTEIN FROM *Plasmodium vivax Sal-1*

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ABSTRACT

Malaria is a mosquito-borne infectious disease of humans caused by eukaryotic protists of genus *Plasmodium*. *Plasmodium falciparum* is mainly responsible for severe form of malaria while malaria caused by *P. vivax, P. ovale* and *P. malariae* is characteristically milder disease and seldom fatal. The present study was undertaken to characterize the function and structure of a hypothetical protein from *Plasmodium vivax sal-1* (Accession No XP-001615924.1) retrieved from NCBI. Different tools and databases were used to predict the function and structure of this hypothetical protein. The results showed the presence of Fasciclin 1 domain in the hypothetical protein. Fasciclin 1domain represents an ancient adhesion domain common in plants and animals. It is an insect neural cell adhesion molecule involved in axonal guidance that is attached to the membrane by a GPI-anchored protein. Results from various *in silico* studies predicted the role of hypothetical protein in cell adhesion.

Key words: Cell adhesion, Fasciclin, hypothetical protein, malaria

INTRODUCTION

Malaria is a mosquito-borne infectious disease of humans caused by eukaryotic protists of genus *Plasmodium*. Malaria is common in tropical and subtropical regions, especially in Sub-Saharan Africa, Asia and America, where they get considerable amounts of rainfall and constant hot temperature. The steady warm temperature and moisture offer mosquitoes a conducive environment for breeding. The malarial disease is caused by a protozoan, discovered in 1880 by Charles Louis Alphonse Laveran who first observed it in a blood smear taken from a patient who died of malaria(Nye and Edwin, 2002). Symptoms of malaria are fever, shivering, arthralgia (joint pain), vomiting, anemia (caused by hemolysis), retinal damage and in extreme cases leads to coma and death (Morris, 1843).

Four species of malarial parasite include *Plasmodium falciparum* causing severe infection and *P. vivax, P. ovale* and *P. malariae* causing milder form of infection (Sternberg, 1883). Malaria spread can be reduced by controlling the mosquito bites by use of inexpensive mosquito nets (pore size 1.2 mm), insect repellents, spraying insecticides inside houses and preventing stagnation of water. The prophylactic and therapeutic measures against malarial parasite have not been much effective in combating the disease completely. Mosquirix (RTS, S) is a licensed recombinant protein-based malarial vaccine (Walsh, 2015), yet the production of a readily available vaccine that gives high level protection for longer period is a major challenge. Presently, atovaquone-proguanil (Malarone) and Doxycycline are the two medicines recommended for traveler (Wellems, 2002), as

the parasite has developed resistance against the most widely used first line antimalarial drug chloroquine (Francis,1997; D'Acremont, 2010).

P. falciparum is the most virulent form while *P. vivax* is the most common cause of frequent and recurrent malaria (Lindsay, Hutchinson, 2006). Also, it is the most prevalent parasite in Asian continent. *P. vivax* accounts for 65% of malaria cases in Asia and South America (Vogel, 2013). This present study was aimed to functionally characterize the hypothetical protein obtained from NCBI database and evaluate its role in the disease caused by the *P. vivax*.

MATERIALS AND METHODS

The hypothetical protein (Accession No. XP_001615924.1) was retrieved from NCBI. The BLASTP was performed on this hypothetical protein with non-redundant database using protein BLAST tool in NCBI (*https://blast.ncbi.nlm.nih.gov/Blast.cgi?PAGE=Proteins*). The conserved domains in proteins were determined by using conserved domain database in NCBI (*https://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi*).

The location of proteins in cell was determined by using pSORT web server (*www.psort.org*). The protein family was searched by using Pfam database (*pfam.xfam.org*) while InterPro was used to perform protein signature (*https://www.ebi.ac.uk/interpro*). KEGG was performed to find out the involvement of hypothetical protein in the pathway of human disease (*www.genome.jp/kegg*). The secondary structure of proteins was predicted by using the PS^2 tool (*ps2v2.life.nctu.edu.tw*).

RESULTS AND DISCUSSION

BLASTP results against non-redundant database showed that the hypothetical protein of *Plasmodium vivax SaI-1* (sequence length, 261 amino acid) was similar to the heme detoxification protein of *Plasmodium falciparum 3D7* (Fig. 1). The heme detoxification protein of *P. falciparum 3D7* was selected because the other 2 proteins with higher level of similarity were both hypothetical.

The conserved domain database (CDD) is a database of well-annotated multiple sequence alignment models and derived database search models for ancient domains and full-length proteins. CDD defines conserved domains as recurring units in molecular evolution, the extent of which can be determined by sequence and structure analysis. The CDD results showed matches with three domains, Fascilin, FAS 1, Fascilin superfamily. Above results revealed that the hypothetical protein had Fascilin conserved domain (Fig. 2).

Fig. 1: BlastP results showing similarity of hypothetical protein of *Plasmodium vivax Sal-1* with heme detoxification protein of *Plasmodium falciparum 3D7*

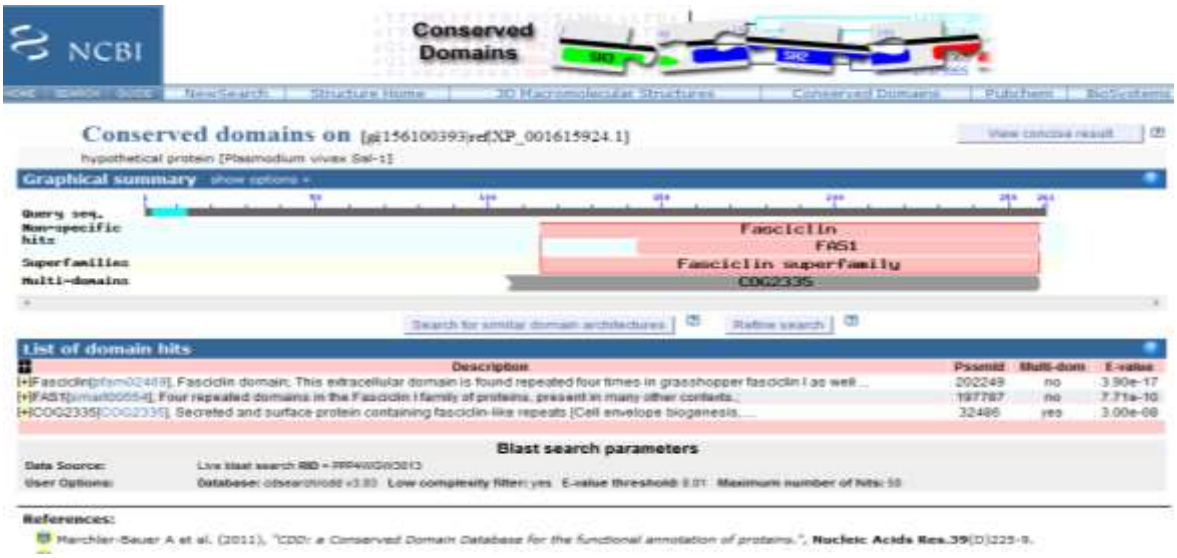

Fig. 2: CDD showing the hypothetical protein of *Plasmodium vivax sal-1* has Fasciclin domain

Pfam-A is manually curated portion of database that contains over 10,000 entries. It contains information about protein domains and families. The Pfam results further corroborated the presence of Fascilin domain in hypothetical protein sequence from 114 to 260 amino acids (Fig. 3). The Fascilin domain is an extracellular domain of about 140 amino acid residues. It has been suggested that the Fascilin domain represents an ancient cell adhesion domain common to plants and animals; related to Fascilin domains are also found in bacteria (Clout, 2003).

InterPro is a database of protein families, domains and functional sites wherein identifiable features of known proteins can be applied to new protein sequences so as to functionally characterize them. InterPro results showed the presence of Fasciclin domain in hypothetical protein (Fig. 4).

As seen in KEGG DISEASE pathway of human disease malaria, there is a protein involved in cell adhesion (Fig. 5). The present study revealed that the hypothetical protein has a Fasciclin domain and it is concluded that the protein has a function of cell adhesion and is involved in malarial pathway.

(PS)^2 server was used for predicting the secondary structure of hypothetical protein. The method uses effective consensus strategy by combining PSI-BLAST, IMPALA and T-Coffee in both template selection and target-template alignment. The final three-dimensional structures are

Fig. 3: Pfam showing one significant match of Fasciclin family

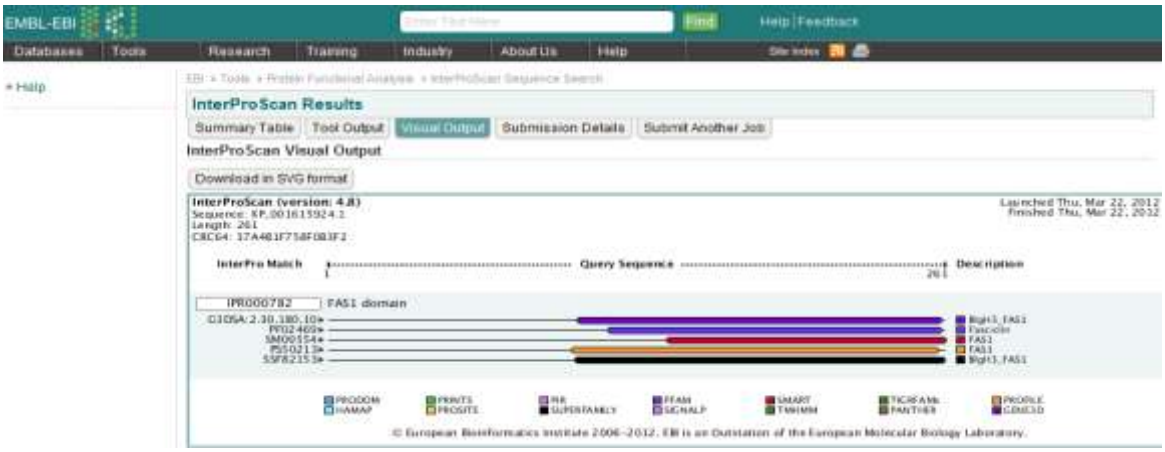

Fig. 4: InterPro showing hypothetical protein of *Plasmodium vivax Sal-1* revealing the presence of Fasciclin from Pfam, FAS1 domain from SMART & PROFILE and BlgH3_FAS1 from CATH & SUPERFAMILY

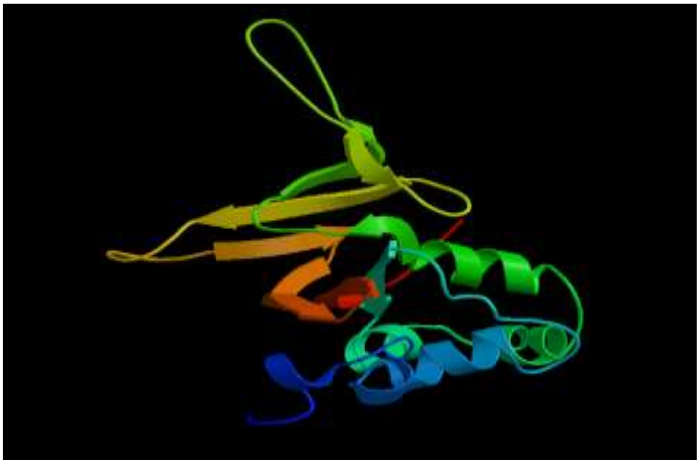

Fig. 5: $(PS)^2$ showing the predicted secondary structure of the hypothetical protein of *Plasmodium vivax Sal-1*

built using the modeling package MODELLER. The predicted secondary structure consisted of α-helices and anti-parallel β-sheets (Fig. 5). The study was undertaken to predict the function and structure of hypothetical protein from *P. vivax Sal-1* (accession No. XP_00161592 4). Various *in silico* tools were used for its characterization. The information on protein was retrieved from NCBI. Then BLASTP was performed to find proteins similar to the query protein. The results showed a number of significant hits corresponding to the query protein. The hit with accession No. XP_001348620.1, which belonged to heme detoxification protein (HDP) of *Plasmodium falciparum 3D7* with query coverage of 71% and bit score 333, was selected for all further studies. CDD showed that the hypothetical protein of *P. vivax Sal-1* (accession No. XP_001615924) had Fasciclin domain and belonged to Fasciclin superfamily. It was found that HDP of *P. falciparum 3D7* had same domain i.e. Fasciclin domain as shown by CDD. HDP plays critical role in adhesion of parasites to the host cells. Pfam and InterPro results corroborated these findings by showing that the hypothetical protein had FAS1 domain. As seen in KEGG pathway, there is a protein involved in cell adhesion in malarial parasite. Hence, it is concluded that the putative role of hypothetical protein of *P. vivax Sal-1* could be in cell adhesion in malaria pathway.

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