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Comparative insight into nucleotide excision repair components of *Plasmodium falciparum*

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ABSTRACT

Nucleotide excision repair (NER) is one of the DNA repair pathways crucial for maintenance of genome integrity and deals with repair of DNA damages arising due to exogenous and endogenous factors. The multi-protein transcription initiation factor TFIIH plays a critical role in NER and transcription and is highly conserved throughout evolution. The malaria parasite *Plasmodium falciparum* has been a challenge for the researchers for a long time because of emergence of drug resistance. The availability of its genome sequence has opened new avenues for research. Antimalarial drugs like chloroquine and mefloquine have been reported to inhibit NER pathway mediated repair reactions and thus promote mutagenesis. Previous studies have validated existence and implied possible association of defective or altered DNA repair pathways with development of drug resistant phenotype in certain *P. falciparum* strains. We conjecture that a compromised NER pathway in combination with other DNA repair pathways might be conducive for the emergence and sustenance of drug resistance in *P. falciparum*. Therefore we decided to unravel the components of NER pathway in *P. falciparum* and using bioinformatics based approaches here we report a genome wide in silico analysis of NER components from *P. falciparum* and their comparison with the human host. Our results reveal that *P. falciparum* genome contains almost all the components of NER but we were unable to find clear homologue for p62 and XPC in its genome. The structure modeling of all the components further suggests that their structures are significantly conserved. Furthermore this study lays a foundation to perform similar comparative studies between drug resistant and drug sensitive strains of parasite in order to understand DNA repair-related mechanisms of drug resistance.

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1. Introduction

Genome integrity is continuously challenged by DNA lesions and an individual cell can undergo up to one million DNA changes per day [1]. Both prokaryotic and eukaryotic organisms have evolved a rigorous system of checks and balances through the DNA repair machinery to maintain this genome integrity. DNA repair processes including nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR), homologous recombination (HR) and non-homologous end-joining (NHEJ) exist in both prokaryotic and eukaryotic organisms, and many of the proteins involved are highly conserved throughout evolution [2]. NER is more complex in eukaryotes as compared to prokaryotes but the general principle is same. During NER, the proteins assemble to recognize, incise, and excise the damaged strand from the genomic DNA [2]. Generally NER removes bulky and cross linked DNA adducts that result in distortion of the double helix structure of DNA, caused by both exogenous factors (such as chemicals and UV) and endogenous factors (oxidizing reactive species). NER pathway can be divided into two related subpathways – global genome repair (GG-NER), which removes lesions from all regions of the genome and transcription-coupled repair (TC-NER), which repairs the damage from the transcribed strands of active genes [3].

The multifunctional cellular transcription initiation factor IIH (TFIIH) is involved in NER as well as transcription [4–6]. The mammalian TFIIH includes a core, containing the seven subunits XPB, XPD, p62, p52, p44, p34, and p8/TTD-A coupled to the cdk-activating kinase module (CAK) composed of the three subunits Cdk7, cyclin H, and MAT1 [4,7–10]. The XPD (RAD3) helicase plays the role of bridging between the core and CAK complex [4]. Various studies have shown that mutations in NER components result in rare disorders. Mutations in Xeroderma pigmentosum group B (XPB), Xeroderma pigmentosum group D (XPD), ERCC1-XPF, XPG and p8 (also known as TF2H5 and TTDA) subunits cause autosomal recessive disorders, such as trichothiodystrophy (TTD), Xeroderma pigmentosum (XP), Cockayne's syndrome (CS), Fanconi

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anemia and phenotypically heterogeneous forms of inherited disorder [7,11,12].

Malaria still has huge impact on human health and it is the world's second biggest killer after tuberculosis [13]. For more than a century, scientists have tried to eradicate or control malaria, but still about 627,000 human deaths worldwide annually with an estimated infection rate of 207 million cases per year have been reported [14]. Among five *Plasmodium* species that cause human malaria, *Plasmodium falciparum* is the most deadly species which has developed resistance to antimalarial drugs such as chloroquine, sulfadoxine-pyrimethamine and even artemisinin [14–16]. The emergence of resistance in *P. falciparum* depends on multiple factors for instance the mutation rate of the parasite and the fitness costs associated with the resistance mutations. An increased mutation rate is certainly advantageous for adapting to adverse environments caused by introduction of drug [16,17].

In human tumor cells, bacteria and some other organisms DNA repair pathways including NER, BER, MMR, HR and NHEJ have been linked to increased mutation rates and drug resistance [18–20]. Some reports which have shown that BER, MMR and DNA double-strand break repair (DSBR) pathways are somehow linked to drug resistance in *P. falciparum* and some of the proteins involved in these pathways can be the new anti-malarial drug targets [21–24]. Several non-synonymous single nucleotide polymorphisms (SNPs) in the MMR genes of artemisnin drug resistant strains in *P. falciparum* have been reported [15]. Previous studies have shown that antimalarial drugs including chloroquine, mefloquine, quinine and halofantrine inhibit the repair of UV light-induced DNA damage. So it has been proposed that altered DNA repair, either through defective repair mechanisms or drug-mediated inhibition, may be considered as the accelerator of drug resistance in the parasite [25].

TFIIH has role in transcription via interaction with RNA polymerase II. It has been reported that the inhibition of enzymatic activities of human XPB lead to the inhibition of RNA polymerase II-mediated transcription and likely NER [26]. Therefore the clinical symptoms observed in patients are most likely due to DNA repair defects and transcription deficiencies [7]. There are reports which suggest that transcriptional regulations are important in the control of gene expression in various life cycle stages of *P. falciparum* [27,28]. Any disturbance in the activity of components of TFIIH complex will most likely affect the development and growth of the parasite.

The present study was undertaken in order to find the homologues of NER components in *P. falciparum*. We have also done a comparative analysis of these components with the human host (*Homo sapiens*) and yeast (*Saccharomyces cerevisiae*). Overall here we have reported the bioinformatics based in silico analysis of all the components of NER from *P. falciparum*. Using these approaches we were unable to identify the homologues of two proteins (p62 and XPC) in *P. falciparum*. This report has set the foundation for further comparative analysis of NER components from drug resistant and susceptible parasite strains to understand the mechanism of drug resistance. In addition it will be worthwhile to biochemically characterize all the components in order to investigate their function in the malaria parasite.

2. Materials and methods

For this study, gene information was obtained from NCBI (http://www.ncbi.nlm.nih.gov) and Plasmodb (http://plasmodb.org/plasmo/). We have used different softwares and online servers for bioinformatics analysis, which are listed (Table S1). We used three species for bioinformatics based comparison and the PlasmoDB numbers and PDB numbers of templates are provided (Table 1). The downloaded sequences were used as query to match with the human homologue using BLAST search (www.ncbi.nlm.nih.gov). The corresponding human sequence was retrieved and various domains were manually assigned. Similarly the domains were also assigned manually in *P. falciparum* sequence and the data are presented in figures. The domain analysis was done using Scan Prosite at (http://expasy.org). Likewise the structural modeling was done using the swissmodel or phyre2 server. The molecular graphic images were produced using the UCSF Chimera package/PyMOL molecular graphic system. The comparative analysis of genome of three species was done through multiple sequence alignment using http://www.ebi.ac.uk/Tools/msa/clustalw2/. The protein–protein interaction analysis of different subunits of NER components of *P. falciparum* was done through http://string-db.org/ and the human homologues of the interacting

Table 1
PlasmoDB numbers and PDB accession numbers.

S. no.	Protein	Plasmodium gene ID	Molecular weight (kDa)	PDB ID of template (chain)	Percentage identity ~	Modeled residue range	Figure no.
1	XPB	PF3D7_1037600	102.87	4ernA	49	576–806	1
2	XPD	PF3D7_0934100	122.83	2VSF (A)	27	20–1021	2
3	p62	None	None	None	None	None	None
4	p52	PF3D7_1244200	111.87	3domC	19.178	841–907	3
5	p44	PF3D7_1314900	45.98	1z60 (A)	36	341–397	4 & S1
				2X5N (A)	19	90–260	
6	p34	PF3D7_1353500	38.32	4PN7 (A)	23	20–221	S2
7	p8	PF3D7_1441900	7.8	2jnj (B)	32	1–58	S3
8	Cyclin H	PF3D7_1463700	39.23	1JKW	18	13–294	S4
9	CDK7	PF3D7_1014400	37.98	1V0 (B)	42	7–309	S5
10	MAT1	PF3D7_0512300	31.30	1G25 (A)	28	1–65	S6
11	Centrin-2	PF3D7_0107000	19.6	3kf9 (A)	83	21–168	W1
12	ERCC1/Rad10	PF3D7_0203300	28.2	2a1i (A)	34	46–174	W2
13	XPF	PF3D7_1368800	204.53	2jpd	36	48–165	W3
14	XPG	PF3D7_0206000	178.7	1rxw (A)	23 and 25	5–130 and 1207–1424	W4
15	FBL3/Rad7	PF3D7_1123200	93.3	4kt1 (A)	18	476–773	W5
16	LIG1	PF3D7_1304100	104.5	2hiv (A)	28	175–896	W6
17	RAD23	PF3D7_1011700	44.3	1oqy (A)	22	1–387	W7
18	RPA1	PF3D7_0409600	70	1jmc	35	683–919	W8
19	RPA2	PF3D7_0904800	36	1jmc	30	10–189	W9
20	RPA3	PF3D7_1442100	44	4gnx	25	1–109	W10
21	XPA	PF3D7_0710400	43.8	1xpa	26	211–319	W11
22	XPC	None	None	None	None	None	None

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