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Structural modeling identifies *Plasmodium vivax* 4-diphosphocytidyl-2C-methyl-D-erythritol kinase (IspE) as a plausible new antimalarial drug target

Kavita Kadian[a], Sonam Vijay[a], Yash Gupta[a], Ritu Rawal[a], Jagbir Singh[a], Anup Anvikar[b], Veena Pande[c], Arun Sharma[a,*]

[a] Protein Biochemistry and Structural Biology Laboratory, National Institute of Malaria Research (ICMR), Sector-8, Dwarka, New Delhi, India
[b] Epidemiology and Clinical Research, National Institute of Malaria Research (ICMR), Sector-8, Dwarka, New Delhi, India
[c] Department of Biotechnology, Kumaun University, Nainital, Uttarakhand, India

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ABSTRACT

Malaria parasites utilize Methylerythritol phosphate (MEP) pathway for synthesis of isoprenoid precursors which are essential for maturation and survival of parasites during erythrocytic and gametocytic stages. The absence of MEP pathway in the human host establishes MEP pathway enzymes as a repertoire of essential drug targets. The fourth enzyme, 4-diphosphocytidyl-2C-methyl-D-erythritol kinase (IspE) has been proved essential in pathogenic bacteria, however; it has not yet been studied in any *Plasmodium* species. This study was undertaken to investigate genetic polymorphism and concomitant structural implications of the *Plasmodium vivax* IspE (*Pv*IspE) by employing sequencing, modeling and bioinformatics approach. We report that *Pv*IspE gene displayed six non-synonymous mutations which were restricted to non-conserved regions within the gene from seven topographically distinct malaria-endemic regions of India. Phylogenetic studies reflected that *Pv*IspE occupies unique status within *Plasmodia* genus and reflects that *Plasmodium vivax* IspE gene has a distant and non-conserved relation with human ortholog Mevalonate Kinase (MAVK). Structural modeling analysis revealed that all *Pv*IspE Indian isolates have critically conserved canonical galacto-homoserine-mevalonate-phosphomevalonate kinase (GHMP) domain within the active site lying in a deep cleft sandwiched between ATP and CDPME-binding domains. The active core region was highly conserved among all clinical isolates, may be due to > 60% β-pleated rigid architecture. The mapped structural analysis revealed the critically conserved active site of *Pv*IspE, both sequence, and spacially among all Indian isolates; showing no significant changes in the active site. Our study strengthens the candidature of *Plasmodium vivax* IspE enzyme as a future target for novel antimalarials.

1. Introduction

In the pursuit of development of novel drugs to tackle resistance in malaria species, a search for new antimalarial compounds has been intensified. Isoprenoid biosynthesis pathway has emerged as an essential metabolic pathway and its enzymes as prominent target candidates for drug intervention studies in bacteria and parasites [1,2]. Isoprenoids are the largest and a diverse family of natural cellular molecules that comprises many essential primary and secondary metabolites which are indispensable for metabolic functions such as protein prenylation and electron transport chain [3]. Ubiquitous synthesis of isoprenoids by all known organisms further emphasizes the essentiality of isoprenoids in normal growth and development [4]. In malaria parasite, isoprenoid precursors are crucial for development in liver stages, parasite multiplications and gametocytogenesis [5–7].

The biosynthesis of isoprenoids requires two universal precursors, isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP). In mammalian host, IPP and DMAPP are synthesized via a mevalonate (MVA) pathway while *Plasmodium* parasites utilize the Methylerythritol phosphate (MEP) pathway for the synthesis of isoprenoid precursors [8]. Both the pathways are chemically and enzymatically different [4]. Recent studies have exploited MEP pathway for inhibitor development in the erythrocytic stages of the parasite. IspC, the first enzyme in the unbranched MEP pathway has been successfully inhibited in malaria parasite using fosmidomycin [9,10]. Another compound MMV008138 against IspD has been recently identified [10,11]. These studies manifest the crucial role of MEP pathway in various biochemical functions of the parasite and their potential as a promising drug target. A functional IspD homolog has been reported in human host [12] and all the active candidates against parasite IspD need to be screened against Human IspD for specificity [13].The absence of IspE homolog from human host further supports IspE as a

* Corresponding author at: Protein Biochemistry and Structural Biology Laboratory, National Institute of Malaria Research (ICMR), Sector-8, Dwarka, New Delhi, India.
E-mail addresses: arushar@gmail.com, sharmaa@icmr.org.in (A. Sharma).

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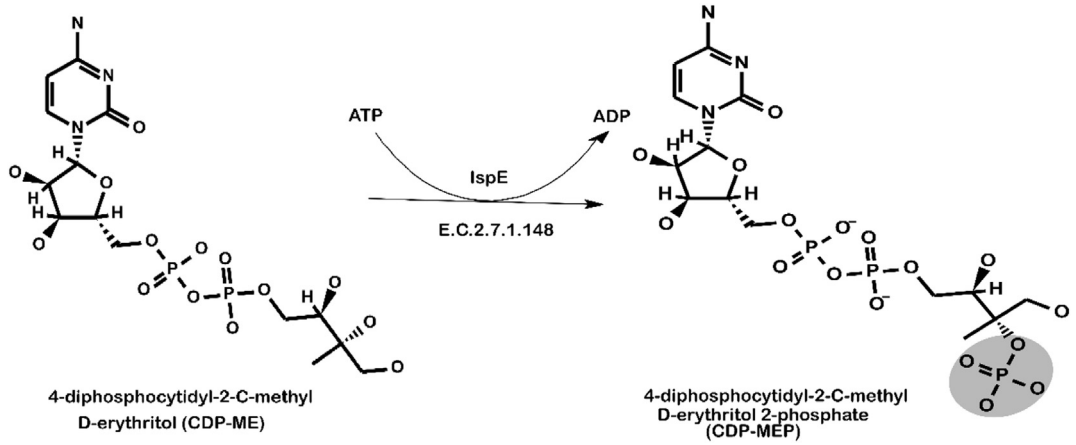

Fig. 1. The fourth step in the MEP pathway. The ATP-dependent phosphorylation reaction catalyzed by 4-diphosphocytidyl-2C-methyl-D-erythritol kinase (IspE).

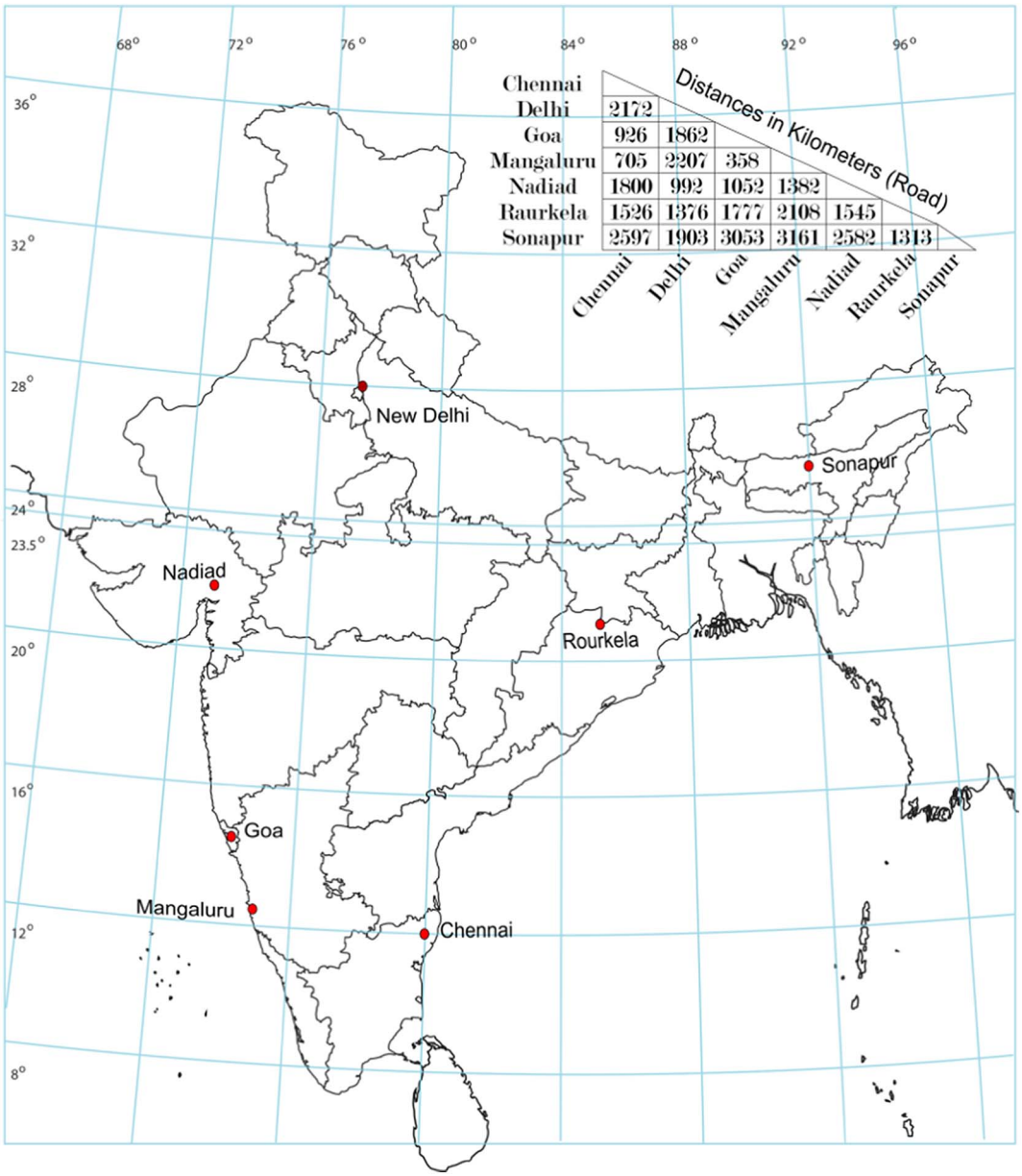

Fig. 2. Map of India showing *Plasmodium vivax* sample collection sites.