The African origin of plasmodium vivax

LETTER TO THE EDITOR

The African origin of *Plasmodium vivax*

Paul M. Sharp[1,*], Lindsey J. Plenderleith[1], Richard Culleton[2] and Beatrice H. Hahn[3]

[1]Institute of Evolutionary Biology and Centre for Immunity, Infection and Evolution, University of Edinburgh, Edinburgh EH9 3FL, UK, [2]Division of Molecular Parasitology, Ehime University, Ehime 791-0295, Japan and [3]Departments of Medicine and Microbiology, University of Pennsylvania, Philadelphia, PA 19104, USA

* Corresponding author: Institute of Evolutionary Biology and Centre for Immunity, Infection and Evolution, University of Edinburgh, Edinburgh EH9 3FL, UK.
E-mail: paul.sharp@ed.ac.uk

Rougeron and colleagues recently reviewed the origin of the two major human malaria parasites, *Plasmodium falciparum* and *Plasmodium vivax* (Rougeron *et al.* 2021). They supported their arguments with an evolutionary tree intended to depict the relationships among mammal-infecting *Plasmodium* species. However, the phylogeny they represented is based on outdated analyses, and some (erroneous) guesswork. More recent analyses of larger datasets have yielded different results, which are key for correctly interpreting the origins of *P. vivax*.

The phylogeny shown by Rougeron *et al*. (2021) in Fig. 1, with relevant aspects repeated in Fig. 3, is described as "mostly based on the results of Galen *et al.* (2018)". Galen *et al.* (2018) were interested in the higher order relationships among *Plasmodium* and other genera of Haemosporidian parasites and used a dataset of 21 proteins conserved across this broad range of species. More recent analyses by several groups have focused on *Plasmodium* species infecting mammals, using 30 protein sequences encoded by the apicoplast genome (Arisue et al. 2019), or more than 1,000 protein sequences encoded by the nuclear genome (Rutledge et al. 2017; Sharp et al. 2020); these studies have yielded results that differ from the phylogeny shown in Fig. 1 of Rougeron *et al.* (2021) in important ways.

First, in Fig. 1 *P. fragile*, from macaques, is shown as the basal lineage of the clade including *P. gonderi*, *P. vivax* and various species infecting Southeast Asian primates. This is curious, since the phylogeny in Galen *et al*. (2018) as well as many analyses by others (e.g., Arisue *et al*. 2019; Sharp *et al*. 2020) have consistently identified *P. gonderi* (from African monkeys) as clearly the basal lineage of this clade. Moreover, all of these phylogenies place *P. fragile* with *P. knowlesi* and *P. coatneyi*, within the radiation of other species infecting Southeast Asian primates.

Second, in Fig. 1 the *P. vivax* group, i.e., *P. vivax* together with closely related "*P. vivax*-like" (from apes) and *P. simium* (a recent transmission from humans to South American monkeys), is shown as lying within the radiation of species infecting Southeast Asian primates. This relationship was previously inferred from small numbers of

mitochondrial sequences (Mu *et al*. 2005; Hayakawa *et al*. 2008), but is clearly outdated. More recent analyses place *P. vivax* basal to the clade of Southeast Asian parasites (Arisue *et al*. 2019; Sharp *et al*. 2020).

Finally, in Fig. 1 *P. carteri* is shown, tentatively, as clustering outside a clade containing the *P. vivax* group plus *P. simiovale*, *P. fieldi* and *P. cynomolgi*. Again, this is inconsistent with the literature, since all published phylogenies where the position of *P. carteri* has strong support depict this species as the closest relative of the *P. vivax* group (Loy *et al.* 2017, 2018).

These discrepancies have important implications for the origin of *P. vivax* in humans. In early studies of limited sequence data, *P. vivax* appeared to emerge from within the radiation of numerous species infecting primates in Southeast Asia, leading to a widespread belief that the human parasite originated via an ancient transmission from monkeys in that part of the world (Escalante et al. 2005; Mu et al. 2005; Hayakawa et al. 2008). However, this did not explain why people across central Africa have an extremely high frequency of the Duffy-negative mutation, which largely prevents infection by *P. vivax*. The discovery in Africa of very closely-related *P. vivax*-like parasites in apes (Liu *et al*. 2010; Prugnolle *et al.* 2013; Liu et al. 2014), and of another closely-related species, *P. carteri*, were clearly inconsistent with the Asian hypothesis. Instead, these findings indicated that the common ancestor of *P. carteri* and the *P. vivax* group existed in Africa. Indeed, given that (i) all five major lineages within the mammalian *Plasmodium* radiation appear to have originated in Africa (Sharp *et al.* 2020), (ii) the earliest divergence on the lineage leading to *P. vivax* involves two parasites (*P. gonderi* and *Plasmodium* sp. DAJ-2004) that are only found in African monkeys, and (iii) a later split separates the African *P. vivax*-related clade (including *P. carteri*) from the clade of parasite species infecting Southeast Asian primates, the only tenable interpretation is that the ancestor of the parasites infecting primates in Asia migrated out-of-Africa only *after* the divergence of the ancestor of the *P. vivax*-related clade. Since *P.vivax*-like can infect humans (Prugnolle *et al.* 2013), it is also evident that these parasites most likely circulated among all ape species in sub-Saharan Africa, including humans; then,

after the spread of the Duffy-negative mutation in humans across Africa, the only *P. vivax* remaining in humans resulted from a lineage that had escaped out-of-Africa (Sharp *et al*. 2020).

Rougeron et al. concluded that the origin of *P. vivax* “remains unclear”, suggesting that there is still a debate between the out-of-Africa and out-of-Asia scenarios. However, current phylogenetic evidence is inconsistent with the out-of-Asia hypothesis. The other compelling evidence comes from genetic diversity. Daron *et al*. (2021) found that levels of genetic diversity among human *P. vivax* strains decline with the distance from Southeast Asia, and Rougeron et al. have taken this finding as support for the out-of-Asia scenario. However, this claim ignores the fact that *P. vivax*-like strains in African apes exhibit 8 times more genetic diversity than human *P. vivax* (Gilabert *et al*. 2018; Loy *et al*. 2018). Scenarios whereby an ancestor of *P. vivax* was transmitted from monkeys to humans in Southeast Asia, spread across Asia to reach apes in sub-Saharan Africa, and then underwent a bottleneck in humans are far-fetched (Prugnolle *et al*. 2013), and fail to explain the origin of *P. carteri*.

In conclusion, current phylogenetic evidence indicates that the lineage leading to *P. vivax* never left Africa, until it migrated out-of-Africa recently with humans (Sharp *et al.* 2020). The phylogenetic relationships presented by Rougeron *et al.* (2021) are erroneous, and as a consequence they obfuscate the progress made by the field in elucidating the origins of human malaria parasites.

REFERENCES

Arisue N, Hashimoto T, Kawai S *et al.* Apicoplast phylogeny reveals the position of *Plasmodium vivax* basal to the Asian primate malaria parasite clade. *Sci Rep* 2019;**9**:7274.

Daron J, Boissiere A, Boundenga L *et al*. Population genomic evidence of *Plasmodium vivax* Southeast Asian origin. *Sci Adv* 2021;**7**:eabc3713.

Escalante AA, Cornejo OE, Freeland DE et al. A monkey's tale: The origin of *Plasmodium vivax* as a human parasite. *Proc Natl Acad Sci* 2005;**102**:1980-5.

Galen SC, Borner J, Martinsen ES *et al.* The polyphyly of *Plasmodium*: comprehensive analyses of the malaria parasites (order Haemosporida) reveal widespread taxonomic conflict. *R Soc Open Sci* 2018;**5**:171780.

Gilabert A, Otto TD, Rutledge GG *et al. Plasmodium vivax*-like genome sequences shed new insights into *Plasmodium vivax* biology and evolution. *PLoS Biol* 2018;**16**:e2006035.

Hayakawa T, Culleton R, Otani H *et al.* Big bang in the evolution of extant malaria parasites. *Molec Biol Evol* 2008;**25**:2233-9.

Liu W, Li Y, Learn GH *et al*. Origin of the human malaria parasite *Plasmodium falciparum* in gorillas. *Nature* 2010;**467**:420-5.

Liu W, Li Y, Shaw KS *et al.* African origin of the malaria parasite *Plasmodium vivax. Nat Commun* 2014;**5**:3346.

Loy DE, Liu W, Li Y *et al.* Out of Africa: origins and evolution of the human malaria parasites *Plasmodium falciparum* and *Plasmodium vivax. Int J Parasitol* 2017;**47**:87-97.

Loy DE, Plenderleith LJ, Sundararaman SA *et al*. Evolutionary history of human *Plasmodium vivax* revealed by genome-wide analysis of related ape parasites. *Proc Natl Acad Sci* 2018;**115**:E8450-9.

Mu J, Joy DA, Duan J *et al*. Host switch leads to emergence of *Plasmodium vivax* malaria in humans. *Molec Biol Evol* 2005;**22**:1686-93.

Prugnolle F, Rougeron V, Becquart P *et al*. Diversity, host switching and evolution of *Plasmodium vivax* infecting African great apes. *Proc Natl Acad Sci* 2013;**110**:8123-8.

Rougeron V, Boudenga L, Arnathau C *et al*. A population genetic perspective on the origin, spread and adaptation of the human malaria agents *Plasmodium falciparum* and *Plasmodium vivax. FEMS Microbiol Rev* 2021;fuab047:1-24.

Rutledge GG, Bohme U, Sanders M *et al*. *Plasmodium malariae* and *P. ovale* genomes provide insights into malaria parasite evolution. *Nature* 2017;**542**:101-4.

Sharp PM, Plenderleith LJ, Hahn BH. Ape origins of human malaria. *Ann Rev Microbiol* 2020;**74**:39-63.