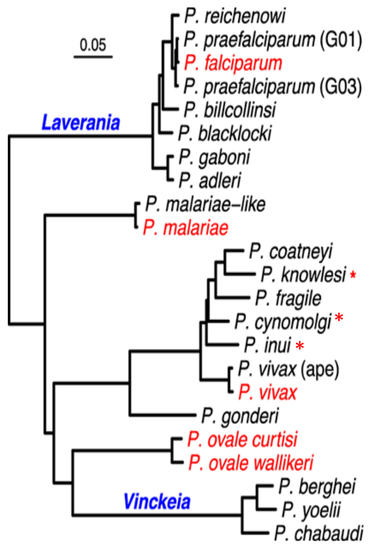
The Origin and Evolution of *Plasmodium falciparum*

Martha Kivecu[1], Brian Omondi[2], Reuben Nowell[1] , Paul Sharp[1]

Institute of Ecology and Evolution, University of Edinburgh[1]

Institute of Immunology and Infection Research, University of Edinburgh[2]

Background



- Malaria is caused by protozoan parasites belonging to the *Plasmodium* genus
- *P. falciparum* is the most prevalent species and causes the most severe form of malaria
- *Plasmodium falciparum* evolved from the zoonotic transmission of a gorilla parasite (*Plasmodium praefalciparum)* (Liu *et al.* 2010)
  - The two species are very closely related
  - *P. falciparum* exhibits much lower genetic diversity than *P. praefalciparum*

Fig 1: Evolutionary relationships of mammalian *Plasmodium* parasites. Human parasites are shown in red, and the zoonotic parasites are indicated by asterisks. (Sharp *et al*. 2020)

The timing of, and the nature of the event at, the origin of *P. falciparum* remain the subject of debate:

- For both humans (Harpending 2000) and the bacterium *Helicobacter pylori* (Linz *et al.* 2007), there is a negative correlation between levels of genetic diversity and distance from East Africa suggesting that the bacterium co-migrated with humans (~70,000 years ago)
- The pattern of decreasing diversity with distance has been suggested to be a result of the "founder effect". Each migration creates a bottleneck leading to a novel population with decreased diversity
- Tanabe *et al*. (2010), found that within-population nucleotide diversity of *P. falciparum* negatively correlated with distance from Central Africa (using two housekeeping genes, 519 samples, 7 sites) (Fig. 2)

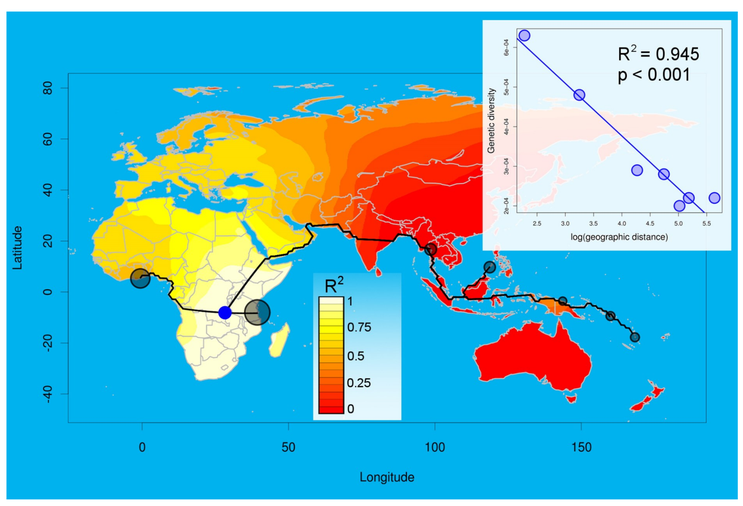


Fig 2: Spatial correlation of *P. falciparum* genetic diversity. (Tanabe *et al.* 2010)

- Tanabe *et al.* (2010) speculated that humans were infected before they migrated from Africa and carried the parasite along (~70,000 years ago)
- Otto *et al.* (2018) estimated that *P. falciparum* originated ~50,000 years ago, via a protracted speciation process, involving introgression
- However, transmission dynamics of *P. falciparum* are thought to be too weak for the parasite to have been maintained in human hunter-gatherer populations (Carter & Mendis 2002)
- Sharp *et al.* (2020) have suggested a single origin event, with an extreme genetic bottleneck, on a much more recent timescale, around 5,000-10,000 years ago:
  - Levels of diversity within *P. falciparum* can be explained within this timescale by short-term molecular clock estimates (Sundararaman *et al*. 2016)
  - Human mutations that confer resistance to *P. falciparum* are estimated to have arisen within the last 6,000 years (Tishkoff *et al*. 2001; Hedrick 2011)
  - Consistent with the period of adoption of agriculture in West Africa

General Objective:

To utilise the *Pf7* MalariaGEN dataset to evaluate the genomic origin and evolution of *Plasmodium falciparum*

Specific Objectives:

1. To determine the geographical distribution of genome-wide genetic diversity and its implications for the origin of *P. falciparum*
2. To evaluate how *P. falciparum* genetic diversity fits with the time of origin of the parasite
3. To evaluate what could be causing certain genes to have unusual patterns of genetic diversity

Methods

MalariaGen Data (Pf7.0)
n = 20,864, 97 sites, 33 countries

↓ Pass FastQC

n = 16,203, 95 sites, 33 countries

↓ Fws >= 0.95

n = 10,348, 95 sites, 33 countries

↓ >= 5 samples per site

n = 10,333, 88 sites, 33 countries

- Over 20,000 sequences were downloaded from the MalariaGEN Pf7 dataset
- FastQC was used to check the quality of raw sequencing data
- Fws characterizes the genetic diversity within an individual sample compared to that of the local population
  - Fws = 1− (Hw/Hs)

Results

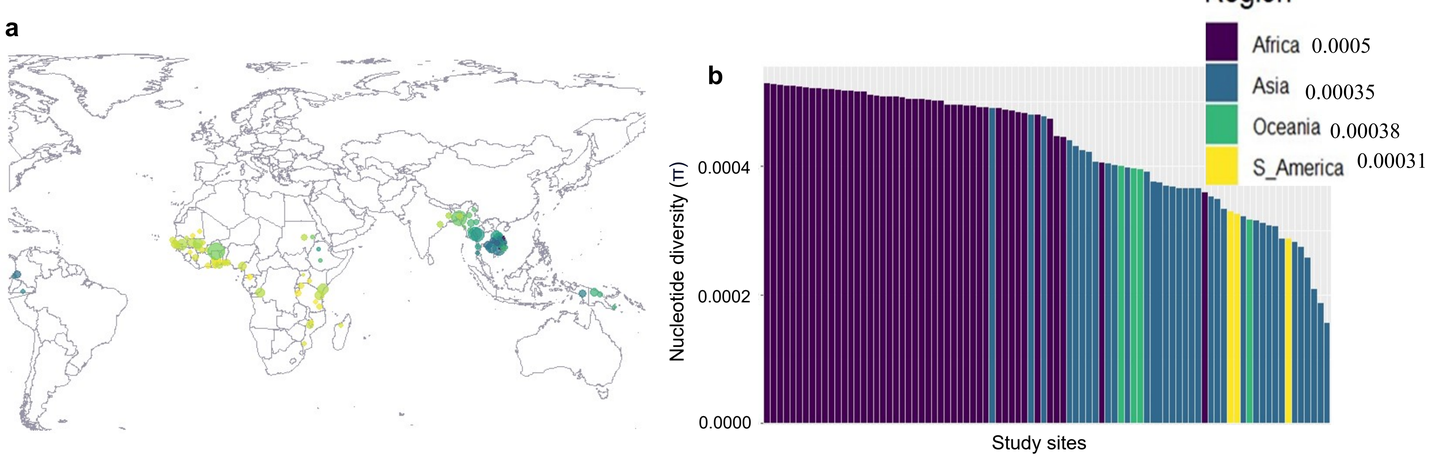


Fig 3 (a) Geographical distribution of the study sites and the genome-wide nucleotide diversity. The lighter colour represents high genetic diversity. **(b)** A bar chart of nucleotide diversity from all 88 study sites.

- The average nucleotide diversity was found to be higher at African sites compared to other regions (Fig 3a & 3b)
- African sites had nucleotide diversity of at least 0.0004, except for two sites in Ethiopia (Fig 3b)

Origin analysis

- 1052 potential origins were systematically sampled based on a grid of 2000
- Least-cost geographical distances were calculated from each potential origin in Africa to all the study sites (gDistance package in R). Movement over land was assigned conductance (inversely proportional to resistance of movement) twice that of the coastline
- Correlation analysis was performed between genome-wide genetic diversity and the distance
  - The highest negative correlation was found in the western part of central Africa (Fig 4).
    - This is close to the region where Gorillas harbouring *P. falciparum* were found (Fig 5)

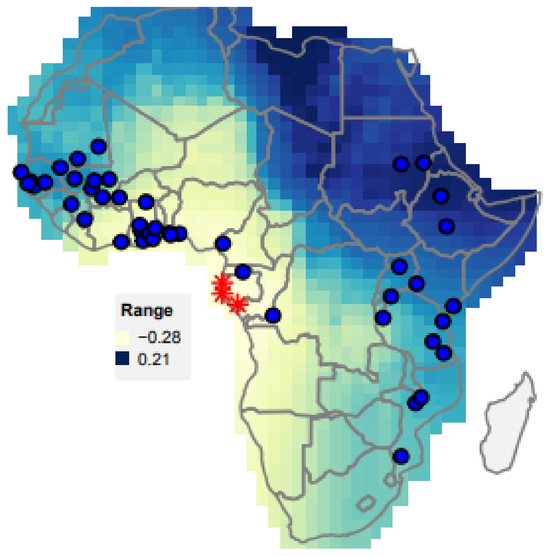


Fig 4: The pattern of correlation of genetic diversity with geographical distance from potential origins in Africa. The colour scale represents the strength of correlation. The blue circles indicate sampling sites; the red asterisks indicate locations with the highest negative correlation

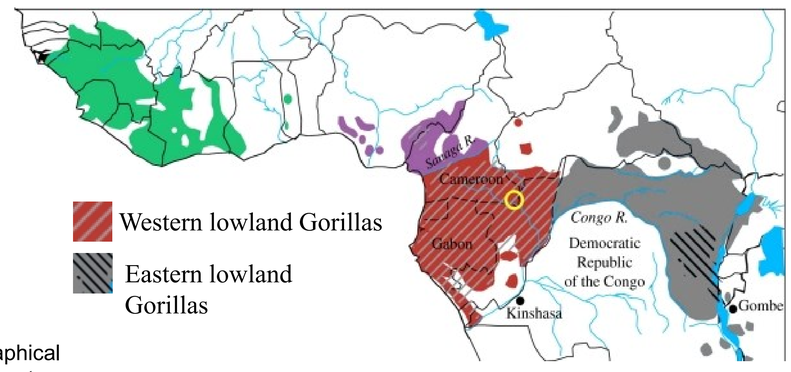
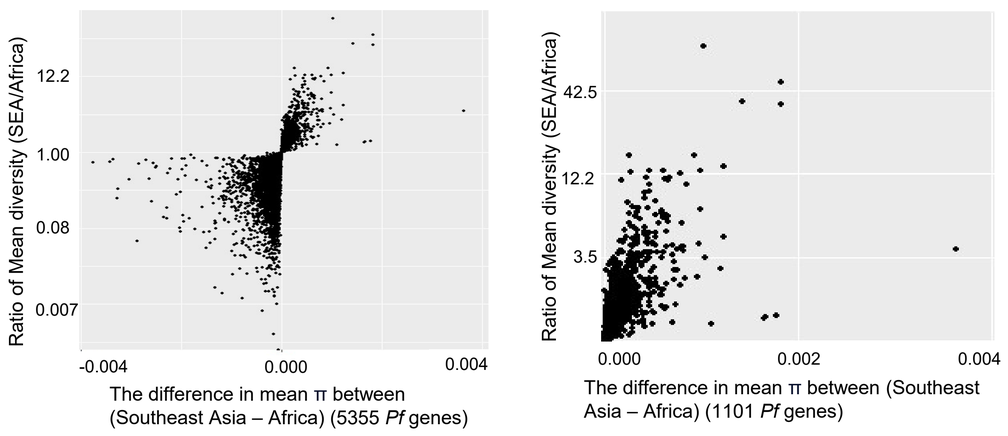


Fig 5: Geographical distribution of great ape populations across Africa

Discussion and Conclusions

- This study shows that the genetic diversity of *P. falciparum* declines with distance from the region where western gorillas are found
- This correlation is expected to be disrupted over time by demographic factors. For example, *Plasmodium vivax* originated in Africa but exhibits the highest genetic diversity in SE Asia.
- *P. vivax* is thought to have infected humans for (at least) 30,000 years
- This origin of *P. falciparum* is deduced to be much more recent

Next: Evaluate genes with unusual diversity patterns



- Nucleotide diversity of 5,355 *P. falciparum* genes was analysed
- Evaluate which genes have statistically significant higher diversity in SE Asia than in Africa

Acknowledgement: The financial support of the British Society of Parasitology in the form of a travel award and The Darwin Trust of Edinburgh