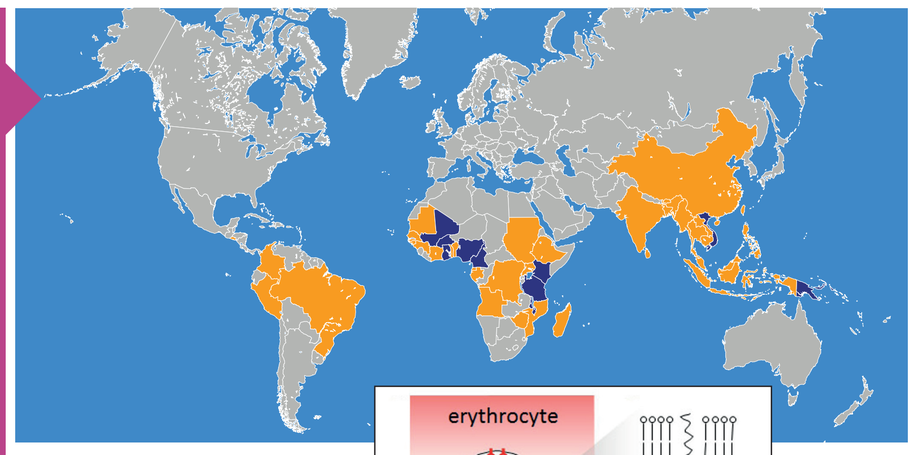
The Wellcome Trust Centre for
Human Genetics

UNIVERSITY OF OXFORD

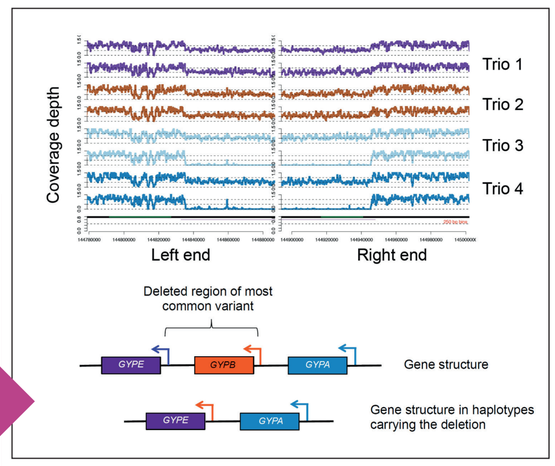
A global network for genomic epidemiology of malaria

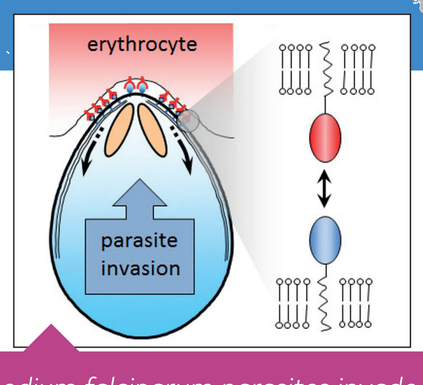
There were over 500,000 deaths from malaria in 2013, mostly African children

The Malaria Genomic Epidemiology Network (MalariaGEN) is an international community of researchers working to understand how genetic variation in humans, Plasmodium parasites, and Anopheles mosquitoes affects the biology and epidemiology of malaria in more than 40 countries (orange). The panels below illustrate key findings from a severe malaria GWAS involving partners in 8 countries (purple)



The genomic region around the glycophorin genes has signatures of ancient balancing selection going back millions of years. Deep sequencing of different African population allows us to map the complex patterns of variation that have evolved and to pinpoint specific structural variants that drive GWAS signals of resistance to severe malaria





Plasmodium falciparum parasites invade human erythrocytes. Our recent GWAS reveals a malaria resistance locus at a cluster of genes encoding erythrocyte membrane proteins known as glycophorins (red) that are binding receptors for parasite invasion ligands such as EBA175 (blue)

WHAT WAS KNOWN

- Malaria is an ongoing evolutionary arms race between *Plasmodium* parasites, *Anopheles* mosquitoes and humans
- The parasites and mosquitoes have developed resistance to all major antimalarial drugs and insecticides, while humans can resist malaria with genes such as sickle haemoglobin
- The scientific field was fragmented into multiple small studies that often disagreed with each other

WHAT WE DID

- Establish a global data sharing network with capacity building in data analysis for researchers in malaria-endemic countries.
- Work with partners in 40 countries to collect over 100,000 samples for genetic analysis of parasite, mosquito and human populations.
- Build the largest clinical dataset on severe malaria to enable definitive genome-wide association studies of disease susceptibility.
- Develop methods for large-scale genome sequencing of parasites and mosquitoes collected in resource-poor settings.
- Bring together consortia of international experts to establish gold standards for population genomic analysis of malaria parasites and their mosquito vectors

WHAT THIS ADDS

- Discovery of novel malaria resistance loci in the human genome, including a cluster of genes that encode erythrocyte surface proteins which the parasite uses as receptors for host cell invasion
- Knowledge of the genetic architecture of artemisinin-resistant *P. falciparum* as it emerges across Southeast Asia, including markers of the genetic background on which new resistance mutations tend to emerge
- A high resolution map of the genomic diversity of *An. gambiae*, the major vector of malaria in Africa, revealing new insights into the genetic processes involved in insecticide resistance and incipient speciation
- Open access data on over 1 million *P. falciparum* polymorphisms and 50 million *An. gambiae* polymorphisms with an interactive web application to explore complex patterns of variation in different locations
- A new generation of multi-centre studies of parasite diversity and antimalarial drug resistance in Africa, led by African scientists who have been nurtured by MalariaGEN's capacity building programme

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