

Multidrug resistant genetic factors in malaria parasites

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Malaria, an infectious disease, is caused by a parasite which is spread by mosquitoes. When the mosquito bites a person, the parasites are introduced from the mosquito's saliva into a person's blood. The parasites then travel to the liver where they mature and reproduce. Credit: National University of Singapore

NUS scientists in collaboration with researchers from Novartis have

discovered two genetic markers in *Plasmodium falciparum*, the deadliest malaria parasite that can cause it to develop resistance against a new antimalarial drug.

The growing resistance to anti-infective drugs has become a global problem, threatening to derail infection control efforts. Malaria [drug resistance](#) is no exception. Reports of resistance against artemisinin [combination therapy](#) (ACT), the current gold standard for [malaria](#) treatment, have become increasingly prevalent. This raises concerns on current malaria treatment and control efforts. Apart from an increasing need to develop new antimalarial drugs, it is also important to identify countermeasures to delay and/ or minimise the development of resistance against these new drugs.

The research team involving Prof Paul C. HO and his former Ph.D. student Dr. Michelle LIM from the Department of Pharmacy, NUS and Prof Pablo BIFANI from the Novartis Institute for Tropical Diseases has identified two previously unreported genes in *Plasmodium falciparum*, and the putative mechanism which can cause it to develop resistance towards a new antimalarial drug. *Plasmodium falciparum* currently affects hundreds of millions of people worldwide.

Prof Ho said, "The discovery of these genetic markers and an early understanding of the drug resistance mechanisms will allow for better combination therapy while monitoring the effectiveness of new antimalarial drugs and minimising the development of drug resistance during clinical application."

An imidazolopiperazine (IPZ) class of drug compounds (saturated cyclic amines) with activity in both liver- and blood-stage parasites has been developed as a new type of antimalarial drug for use in prophylaxis, treatment and prevention of malaria disease transmission. Although IPZs have recently been shown to be highly effective against the [malaria](#)

[parasite](#), there is a strong tendency for the parasite to develop resistance to the drug. The research team has developed a selection method that enables them to isolate malaria parasite mutants which have evolved drug-resistant properties against this new antimalarial drug. By performing whole-genome sequencing of these drug-resistant *Plasmodium falciparum* clones, they found two previously unreported genes associated with drug resistance, an acetyl-CoA transporter (pfact) and a UDP-galactose transporter (pfugt).

Prof Bifani said, "The identified mechanisms causing this drug [resistance](#) are members of a family of membrane transporter proteins (major facilitator superfamily or MFS) responsible for the translocation of small molecules across the cellular membranes which was not previously associated with [drug resistance](#) in parasites. Knowledge of this association will help in future efforts in drug discovery, diagnostics and combination therapy."

More information: Michelle Yi-Xiu Lim et al. UDP-galactose and acetyl-CoA transporters as *Plasmodium* multidrug resistance genes, *Nature Microbiology* (2016). [DOI: 10.1038/NMICROBIOL.2016.166](https://doi.org/10.1038/NMICROBIOL.2016.166)

Provided by National University of Singapore

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