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Doxycycline Resistance in Plasmodium falciparum Linked to Single Nucleotide Polymorphisms in the Plasmodium falciparum apicoplast Small Subunit Ribosomal RNA (pfSSrRNA) gene

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Plasmodium falciparum, a protozoan parasite known as malaria, widely impacts human health; thus antimalarial drug investigations are critical. Doxycycline is a commonly used antimalarial prophylactic, but its mechanism of action is unclear. In prokaryotes, doxycycline works as an antibacterial by disrupting protein translation via the small subunit ribosome. Interestingly, *P. falciparum* has a small subunit ribosome of prokaryotic origins in the apicoplast, a plastid-like organelle. Therefore, we hypothesized that doxycycline works in *P. falciparum* by inhibiting protein synthesis via the small subunit ribosomal RNA and that mutations in the gene encoding the *P. falciparum* apicoplast small subunit ribosomal RNA (*pfSSrRNA*) are associated with doxycycline resistance. We generated nine doxycycline-resistant parasite lines with continuous incremental drug pressure over approximately twelve months. Resistant lines had doxycycline IC_{50} values of ~2.4 μM while the drug-free control had an IC_{50} of 587 nM, resulting in a ~4 fold decrease in doxycycline susceptibility as measured by 96-hour growth inhibition assays. Sequencing of the *pfssrRNA* gene in a resistant line revealed a g439a single nucleotide polymorphism (SNP). We suspect this mutation reduces parasite susceptibility to doxycycline by altering the molecular structure of the apicoplast SSrRNA, so that doxycycline can no longer inhibit protein synthesis. Future studies involve cloning the resistant lines, sequencing *pfssrRNA* for all resistant lines, and characterizing the drug phenotypes of the resistant lines to doxycycline and a panel of standard antimalarial drugs. Understanding how doxycycline works will help health care professionals better combat doxycycline resistance in the field.