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Advances in understanding the genetic basis of antimalarial drug resistance

Eric H Ekland[1] and David A Fidock[1,2]

The acquisition of drug resistance by *Plasmodium falciparum* has severely curtailed global efforts to control malaria. Our ability to define resistance has been greatly enhanced by recent advances in *Plasmodium* genetics and genomics. Sequencing and microarray studies have identified thousands of polymorphisms in the *P. falciparum* genome, and linkage disequilibrium analyses have exploited these to rapidly identify known and novel loci that influence parasite susceptibility to antimalarials such as chloroquine, quinine, and sulfadoxine-pyrimethamine. Genetic approaches have also been designed to predict determinants of *in vivo* resistance to more recent first-line antimalarials such as the artemisinins. Transfection methodologies have defined the role of determinants including *pfcrt*, *pfmdr1*, and *dhfr*. This knowledge can be leveraged to develop more efficient methods of surveillance and treatment.

Addresses
Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY 10461, USA

Corresponding author: Fidock, David A (df2260@columbia.edu)
[1] Present address: Departments of Microbiology and Medicine, College of Physicians and Surgeons at Columbia University, New York, NY 10032, USA.
[2] Present address: Department of Medicine, College of Physicians and Surgeons at Columbia University, New York, NY 10032, USA.

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Introduction

Malaria devastates the lives of millions of people each year. Eradication efforts based on the use of chloroquine (CQ) faltered in the 1960s, following the development of drug-resistant parasites [1]. Other antimalarial drug regimens, such as sulfadoxine-pyrimethamine (SP), have also selected for resistant parasites [2]. Recent genetic and genomic advances have paved the way for discoveries into the origins and spread of antimalarial drug resistance and the underlying molecular mechanisms. Researchers can now use data from genome sequencing projects to identify genetic regions linked to resistance phenotypes. The development of transfection and integration techniques permits researchers to test candidate genes for their contribution to resistance under controlled laboratory conditions. Genetic markers can also now be readily tracked in natural populations. These innovations can be used to predict drug efficacy in the field, with implications for public health policy. Here, we review how these new methodologies can expand and accelerate research into antimalarial drug resistance.

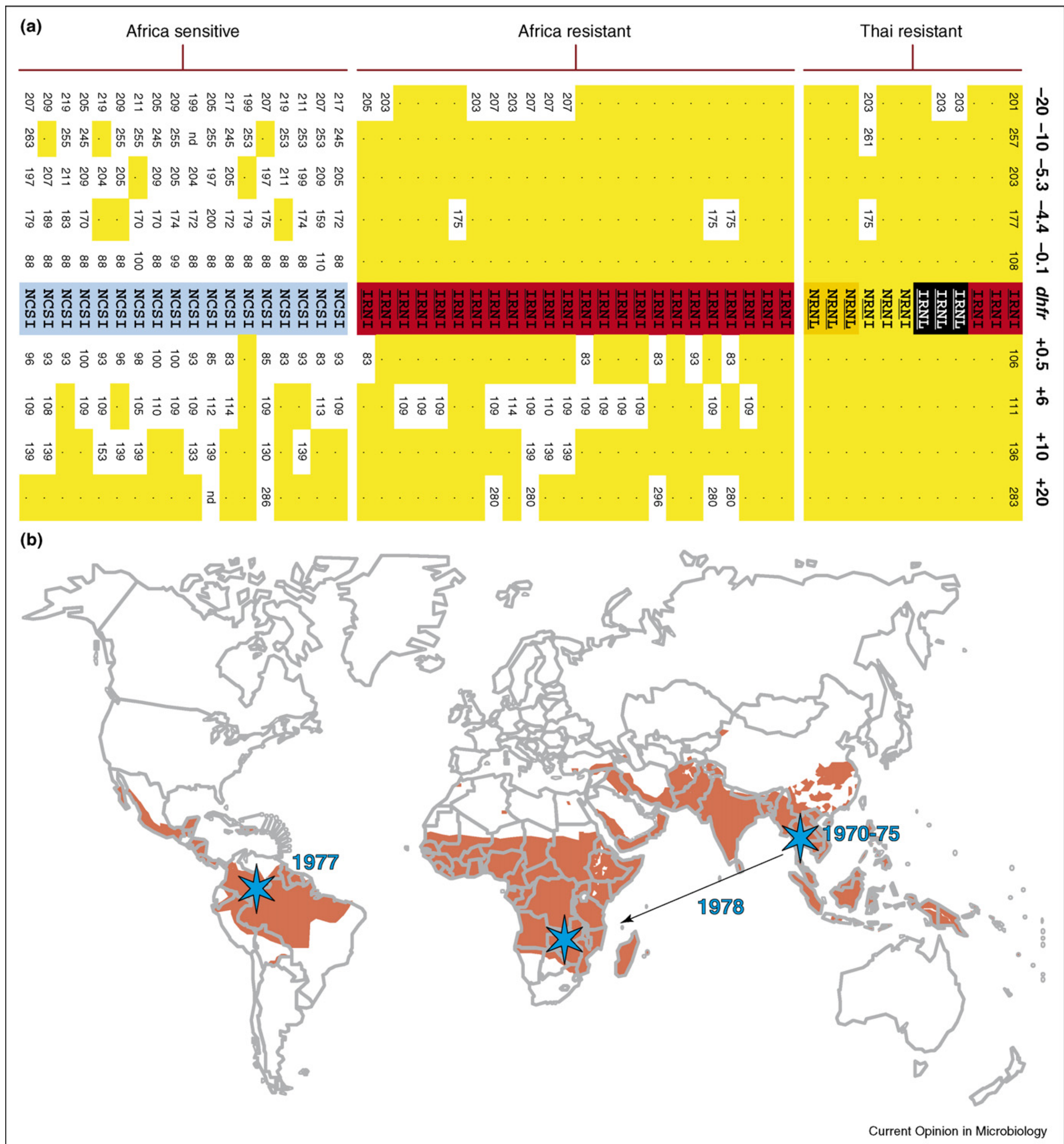
Genomic studies

Using polymorphisms to identify resistance loci

The sequencing and annotation of the 23 Mb *P. falciparum* genome in 2002 provided a superb resource for localizing and identifying gene candidates within a particular locus [3]. Linking a specific locus with a given phenotype such as drug resistance, however, requires the ability to compare the genotypes of resistant and sensitive parasites. Rather than sequencing the entire genome of each resistant or sensitive clone, recent advances have exploited the presence of conserved polymorphisms in the genome as surrogate markers for the resistance determinant(s). Polymorphisms can include microsatellites (consisting of repeats of a short nucleotide sequence), single nucleotide polymorphisms (SNPs), or small insertions or deletions (indels).

A trio of papers, published in *Nature Genetics* in early 2007, moved the field substantially closer to a comprehensive polymorphism map for the *P. falciparum* genome [4•,5•,6••]. These papers describe the sequencing of the entire genome, or of selected regions, from multiple *P. falciparum* strains. The authors estimate the number of SNPs in the *P. falciparum* genome as ranging from about 25 000 to 50 000, corresponding to one SNP every 400–800 base pairs. In *P. falciparum*, as in humans, these SNPs do not segregate randomly. Instead they tend to cluster in 'blocks', called haplotype blocks, delimited by recombination hotspots. Association studies thus need only to track a signature set of SNP tags that identify a particular haplotype block. Studies indicate that recombination rates vary substantially between different strains of *P. falciparum*, with ones in Africa demonstrating the highest rates [7•]. The number of polymorphisms varies for different gene classes and for different regions within chromosomes. This presumably reflects the influence of diversifying selection exerted on genes by factors such as host immunity and drug selection. [4•,5•,6••,7•,8]. High rates of recombination, such as those observed among African *P. falciparum* strains [7•], will tend to obscure the linkage between ancestral traits. The phenomenon of drug resistance, however, is a relatively recent evolutionary event. Consequently, the use of linkage disequili-

Figure 1



Identification of a selective sweep of mutant *dhfr* conferring pyrimethamine resistance from Asia to Africa. **(a)** Genotype data are shown for 12 Thai isolates with *dhfr* alleles that harbor 2–4 resistance mutations, 24 African isolates with triple-mutant alleles, and 18 African parasites with sensitive *dhfr* alleles. The four-letter codes designate amino acids present at positions 51, 59, 108, and 164 in the predicted DHFR protein. Amino acids conferring resistance are underlined, and *dhfr* alleles are shaded yellow, orange, red, and black in the order of increasing resistance. The sensitive allele is shaded blue. Fragment lengths are shown for eight microsatellites positioned at −0.1, −4.4, −5.3, −10, and −20 kb upstream and +0.5, +6, +10, and +20 kb downstream of *dhfr*. Dots and yellow shading indicate microsatellite sizes that are identical to the predominant resistant haplotype (shown on rightmost column). Figure reproduced from Roper *et al.* [9], reprinted with permission from AAAS. **(b)** Selective sweep of *dhfr* triple mutants. Resistance to pyrimethamine originated and spread in Southeast Asia in the early 1970s. Triple-mutant-resistant parasites arrived *circa* 1978 in Africa, by unknown routes, and spread in a selective sweep. Data from McCollum *et al.* [10] suggest an

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