An alternative dogma on reduced artemisinin susceptibility: A new shadow from east to west

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In PNAS, Demas et al. (1) show, by long-term in vitro selection using culture-adapted *Plasmodium falciparum* isolates from Senegal, that the gene encoding the actin-binding protein *P. falciparum* coronin (*pfcoronin*) and its genetic variants (G50E, R100K, and E107V) can reduce the susceptibility of the parasite to the active metabolite of the fast-acting antimalarial drug artemisinin, dihydroartemisinin (DHA). Resistance to artemisinins is a global threat in malaria control and elimination efforts (2).

Artemisinin resistance, first reported in Southeast Asia and still extremely rare, was associated with the *P. falciparum* *Pf*Kelch13-propeller domain (*kelch13* mutations: Y493H, R539T, I543T, and C580Y) (3). *Pf*Coronin, which is structurally similar to Kelch13, is believed to interact with F-actin via its N-terminal propeller domain and to mediate actin organization and motility in merozoites and sporozoites (4, 5). The worldwide map of the occurrence of *kelch13*, however, indicates absence of the Asian artemisinin-resistance alleles in Africa (6–8). So far, it is not clear whether the *pfcoronin* variants G50E, R100K, and E107V occur in natural *P. falciparum* populations—in particular, in clinical isolates from Africa.

We looked at a total of 353 *P. falciparum* patient isolates that were earlier characterized for the absence of *kelch13* gene mutations (7–10) from 4 African countries to verify whether these isolates carry the *pfcoronin* mutations G50E, R100K, and E107V, which were described by Demas et al. (1) to be associated with reduced susceptibility to DHA. A total of 297 samples were successfully genotyped by direct Sanger sequencing. Details of the study groups from Gabon ($n = 102$), Congo ($n = 48$), Ghana ($n = 57$), and Kenya ($n = 90$) are described elsewhere (7–10). The *pfcoronin* mutations G50E, R100K, and E107V were not observed at all among the isolates. However, 14 distinct mutations, including several nonsynonymous substitutions, were identified in the *pfcoronin* exon-3 (Table 1). None of the isolates carried the Asian *kelch13* resistance alleles M476I, Y493H, R539T, I543T, and C580Y. The mutation P76S (DNA position C562T) was observed to be most frequent (>10%) among isolates from central and west Africa. There was no indication of artemisinin or artemisinin-based combination therapy resistance in these patients. The functional role of the observed *pfcoronin* P76S needs to be elucidated among central and west African *P. falciparum* isolates.

Much effort has been made in recent years to determine the genetic basis of artemisinin resistance, which still remains unclear to a large extent. There is an obvious difference in occurrence of *pfkelch13* and *pfcoronin* alleles between Asia and Africa, which may also cause differences in parasite clearance rates during treatment with artemisinin-containing antimalarial combinations. However, we should bear in mind that parasite clearance rate or failure of an artemisinin-containing antimalarial is also, and even most often, determined by the activity of the partner drug, such as lumefantrine, amodiaquine, piperaquine, and pyronaridine.

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Table 1. *pfcoronin* mutations observed in 4 African countries

Amino acid change	SNP position	Gabon, *n* (%) (*n* = 102)	Ghana, *n* (%) (*n* = 57)	Kenya, *n* (%) (*n* = 90)	Congo, *n* (%) (*n* = 48)	Total, *n* (%) (*N* = 297)
I53I	C495T	0	1 (2)	0	0	1 (0.3)
V62M	G520A	1 (1)	1 (2)	0	0	2 (0.7)
K69K/I/R	A542A/T/G	0	3 (5)	0	11 (23)	14 (5)
P76S	C562T	11 (11)	9 (16)	4 (4)	8 (17)	32 (11)
N110N/Y/D	A664A/T/G	0	1 (2)	0	5 (10)	6 (2)
N112N/Y/D	A670A/T/G	0	0	0	1 (2)	1 (0.3)
K115K/stop/E	A679A/T/G	0	0	0	1 (2)	1 (0.3)
L121L/F/L	A699A/T/G	0	0	0	1 (2)	1 (0.3)
K127K/stop/E	A715A/T/G	0	0	0	1 (2)	1 (0.3)
K127K/I/R	A716A/T/G	0	0	0	5 (10)	5 (2)
V128V	A720A/T/G	0	0	0	1 (2)	1 (0.3)
N134N/Y/D	A736A/T/G	0	0	0	4 (8)	4 (1)
N137N/Y/D	A745A/T/G	0	0	0	10	10 (3)
N137N/I/S	A746A/T/G	0	0	0	2 (4)	2 (0.7)

SNP, single nucleotide polymorphism.

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