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Dihydrofolate Reductase I164L Mutation in Plasmodium falciparum, Madagascar

To the Editor: Malaria remains a major public health problem and a primary cause of illness in Madagascar (1). Since 2005, the National Malaria Control Program has revised its treatment policy and replaced chloroquine (CQ) with artesunate plus amodiaquine as first-line therapy for uncomplicated malaria and CQ with sulfadoxine-pyrimethamine (SP) for prevention of malaria during pregnancy. The latter choice was partially supported by high effectiveness of SP and absence of pyrimethamine resistance in Madagascar, in contrast to proximal African countries such as the Comoros Islands (2,3).

Analysis of the molecular basis of antimalarial drug resistance has demonstrated that mutations in the dihydrofolate reductase (dhfr) and dihydropterate synthase genes are associated with development of SP resistance. It has been assumed that pyrimethamine resistance conferred by multiple mutations arose through stepwise selection of the S108N single mutant (except for the A16V/ S108T allele). This single-point mutation decreases the sensitivity of dhfr to pyrimethamine in vitro by ≈10× (4). Subsequent mutations, such as N51I and C59R, cause additional decreases in the sensitivity of dhfr to pyrimethamine. Parasites with a triple-mutant allele (S119/R/S108N) are less sensitive to pyrimethamine in vitro, and patients infected with these parasites have a high probability of not responding to SP treatment (5).

Addition of I164L to 511/S9R/108N creates a quadruple-mutant allele and decreases the sensitivity of dhfr by ≈1,000× (4), eliminating the clinical effectiveness of SP, as observed in Southeast Asia and South America. However, the situation in Africa seems to be different because most studies conducted since the mid 1990s have shown the quadruple mutant to be rare, even in areas of intensive pyrimethamine use (6). Increasing SP resistance is principally a result of rapid selection for parasites that carry a triple-mutant allele that arose in Southeast Asia and has spread widely in Africa (7,8).

In 2006, blood samples were obtained from 114 children 6 months to 15 years of age enrolled in a clinical trial monitoring the efficacy of SP in treatment of uncomplicated Plasmodium falciparum malaria. The dhfr gene from pretreatment samples was sequenced at the Genomics Platform of the Pasteur Institute in Paris, France. Four (3%) samples contained the 108N single-mutant allele, 37 (32%) contained the 511/59R/108N triple-mutant allele, and 1 (<1%) contained the I164L single-mutant allele. This latter allele was obtained from the blood of a 15-year-old girl from Ejeda in southern Madagascar. At enrollment in the trial, she had an axillary temperature of 37.8°C and a P. falciparum asexual parasite count of 74,880/µL. She was treated with the standard SP regimen (25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine as a single dose on day 0). On the basis of the World Health Organization 2003 protocol (9), early treatment failure was noted on day 2, when the patient had signs of malaria with a temperature of 40°C and a parasite count of 770/µL. She was successfully retreated with a rescue regimen (quinine, 8 mg base/kg, 3 times a day for 7 days).

To confirm detection of the I164L allele, parasite DNA was extracted from blood spots obtained on days 0, 1, and 2 and sequenced. DNA templates were sent to a second independent laboratory (Department of Genome Sciences, University of Washington, Seattle, WA, USA) to rule out misiden-
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