Population-based validation of dihydrofolate reductase gene mutations for the prediction of sulfadoxine-pyrimethamine resistance in Uganda.

A.O. Talisuna, P. Langi, T.K. Mutabingwa, W. Watkins, E. Van arck, T.G. Egwang, U. D'Alessandro

Transactions of The Royal Society of Tropical Medicine and Hygiene, Volume 97, Issue 3, May-June 2003, Pages 338–342, https://doi.org/10.1016/S0035-9203(03)90163-5

Received: 21 July 2002
Revision received: 18 November 2002
Accepted: 18 November 2002
Published: 01 June 2003

Abstract

Mutations in the dihydrofolate reductase gene (*dhfr*) of *Plasmodium falciparum* have been proposed as molecular markers for the surveillance of sulfadoxine-pyrimethamine (SP)-resistant malaria, but such proposals have not been validated. At 7 Ugandan sites in 1999, we determined the population-based prevalence of infections with mutations and the mutant allele frequency of *dhfr* codons 108, 51, and 59 using a random sample of infected individuals aged 1–45 years. Sulfadoxine-pyrimethamine treatment failure was independently estimated by *In vivo* in 327 children aged 6–59 months with clinical malaria. The prevalence of infections with the single point mutations and the *dhfr* codons 108 and 51 mutant allele frequency were not correlated to SP treatment failure. However, the *dhfr* codon 59 mutant allele frequency was positively correlated to SP treatment failure (r= 0.72, P= 0.06). The ratio of the infections with the mutant to wild genotype (M/W) and that of the mutant to wild allele (MA/WA) had the same values. Both *dhfr* codon 59 M/W and MA/WA ratio were significantly and positively correlated to SP treatment failure (*r= 0.73, P= 0.05*). Moreover, the prevalence of infections with only 2 mutations (Asn-108 plus Ile-51) was significantly and inversely correlated to the prevalence of infections with 3 mutations (Asn-108 plus Ile-51 plus Arg-59) (*r = 0.92, P = 0.004*), suggesting the stepwise accumulation of the *dhfr* mutations is Asn-108 Ile-51 Arg-59 and further supporting the idea of using the *dhfr* codon 59 M/W ratio as a molecular index for the prediction of SP treatment failure. At the population level, the *dhfr* codon 59 M/W ratio is a simple and stable index for the estimation of SP treatment failure.

Keyword: malaria, *Plasmodium falciparum*, chemotherapy, drug resistance, sulfadoxine-pyrimethamine, *dhfr* gene mutations, Uganda