

ABSTRACT

Locally varying selection on pathogens may be due to differences in drug pressure, host immunity, transmission opportunities between hosts, or the intensity of between-genotype competition within hosts. Highly recombining populations of the human malaria parasite *Plasmodium falciparum* throughout West Africa are closely related, as gene flow is relatively unrestricted in this endemic region, but markedly varying ecology and transmission intensity should cause distinct local selective pressures. Genome-wide analysis of sequence variation was undertaken on a sample of 100 *P. falciparum* clinical isolates from a highly endemic region of the Republic of Guinea where transmission occurs for most of each year and compared with data from 52 clinical isolates from a previously sampled population from The Gambia, where there is relatively limited seasonal malaria transmission. Paired-end short-read sequences were mapped against the 3D7 *P. falciparum* reference genome sequence, and data on 136,144 single nucleotide polymorphisms (SNPs) were obtained. Within-population analyses identifying loci showing evidence of recent positive directional selection and balancing selection confirm that antimalarial drugs and host immunity have been major selective agents. Many of the signatures of recent directional selection reflected by standardized integrated haplotype scores were population specific, including differences at drug resistance loci due to historically different antimalarial use between the countries. In contrast, both populations showed a similar set of loci likely to be under balancing selection as indicated by very high Tajima's *D* values, including a significant overrepresentation of genes expressed at the merozoite stage that invades erythrocytes and several previously validated targets of acquired immunity. Between-population *F_{ST}* analysis identified exceptional differentiation of allele frequencies at a small number of loci, most markedly for five SNPs covering a 15-kb region within and flanking the *gdv1* gene that regulates the early stages of gametocyte development, which is likely related to the extreme differences in mosquito vector abundance and seasonality that determine the transmission opportunities for the sexual stage of the parasite