Higher African Ancestry Proportion is Associated with Greater Vivax Malaria Incidence in Young Amazonians: A Population-based Cohort Study

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ABSTRACT

Background. *Plasmodium vivax* originated from African ape–infecting lineages, where malaria-protective variants (e.g., *ACKR1*/Duffy) were selected in humans over 5,000–10,000 years. Five centuries after its introduction into the Americas, *P. vivax* infects local populations with admixture from American native (AMR), African (AFR), and European (EUR) ancestral sources. How genetic ancestry influences malaria risk remains little explored in admixed New World populations.

Methods. We studied a household-based cohort of 1,454 Amazonians aged <1-104 years (mean, 29.1 years), who contributed 6,578.4 person-years of follow-up (2014-2018). The outcome is laboratory-confirmed *P. vivax* infection. Participants were genotyped with the Axiom Precision Medicine Diversity Research Array 2.0. We used PCA of 211,428 genotyped variants to estimate global genetic ancestry across the genome. Mixed-effects negative binomial regression models assessed associations between ancestry and malaria incidence, adjusting for sex, age, socioeconomic status, and *ACKR1* genotype, including an interaction term between age and AFR ancestry.

Results. Average global ancestry proportions were 0.226 AFR (95% CI, 0.223-0.229), 0.280 AMR (95% CI, 0.274-0.286), 0.494 EUR (95% CI, 0.488-0.500). Participants experienced 1,717 infections with *P. vivax*, with an average incidence rate of 26.1 (95% CI, 24.9-27.4) cases/100 person-years at risk. Higher AFR ancestry (>20%), but not AMR ancestry, was associated with twice the risk of vivax malaria in those aged <16 years, but this effect was attenuated among older participants. We hypothesize that those with higher AFR ancestry are repeatedly infected throughout childhood and acquire clinical immunity earlier than their low-risk counterparts.

Conclusion. These results point to genetic ancestry as a major contributor to vivax malaria risk in Amazonians and highlight the value of including admixed populations in studies of genetic determinants of malaria susceptibility.