A Model-based Approach to Genetic Association Testing in Malaria Studies

Morine Akoth, John Odhiarnbo and Bernard Omolo
Institute of Mathematical Sciences, Strathmore University, Nairobi, Kenya.
University of South Carolina — Upstate, United States of America.

In human genetics, heterozygote advantage (heterosis) has been detected in studies that focused on specific genes, but not in genome-wide association studies (GWAS). For example, heterosis is believed to confer resistance to certain strains of malaria in patients heterozygous for the sickle-cell gene HbS. Yet the power of allele-based tests can be substantially diminished by heterosis. Since GWAS (and haplotype-associations) also utilize allele-based tests, it is unclear to what degree GWAS could underachieve because heterosis is ignored. In this study, we propose a two-step approach to genetic association testing in malaria studies in a GWAS setting that may enhance the power of the tests, by identifying the underlying genetic model first before applying the association tests. We fit generalized linear models for the dominant, recessive, additive and heterotic effects and perform tests of significance using the MAX and the allelic tests, noting the minimum p-values across all the models and the proportion of tests that a given genetic model was deemed the best, using simulated data. Case-control genotype data on malaria from Kenya and the Gambia are used for validation. Results show that the allelic test returned a number of false negatives under the heterosis model, suggesting reduced power in testing genetic association. Thus, GWAS and haplotype associations should be treated with caution, unless the underlying genetic model had been determined.

Keywords: Allelic test; case-control study; genome-wide association; malaria; maximum test.