ABSTRACT

Malaria is the main cause of paediatric morbidity and mortality in holoendemic areas. The populations in these areas have similar transmission intensity and infection rates of Plasmodium falciparum malaria but present different malaria outcomes. The cause of the different clinical outcomes is poorly understood. Pf. has exerted selective pressure on the human genome leading to genetic variability in the host's immune response genes mediating protection and susceptibility to Pf. malaria. Natural Cytotoxicity Triggering Receptor 3 directly interacts with ligands on parasitized Red Blood Cells activating natural killer cells to carry out cell-mediated cytotoxicity of Pf. pRBCs. However, the contribution of NCR3 promoter polymorphisms in conditioning malaria disease outcomes such as acquisition of parasitaemia, severe malaria anaemia (Hb<5.0 g/dL, any density parasitaemia) and high density parasitaemia (≥10000 parasites/μL) in paediatric population in a holoendemic area has not been elucidated. Therefore, the study determined the association between NCR3 (-412C/G and -172G/A) genotypes and haplotypes, and acquisition of parasitaemia, high density parasitaemia, and severe malaria anaemia in a paediatric population presenting at Siaya County Hospital. The study assayed archived blood spot samples (n = 612) of children (aged 3-36 months) presenting with severe malaria anemia and controls of similar age and gender. The samples were genotyped for NCR3 (-412C/G and -172G/A) polymorphisms using TaqMan real-time PCR technique. Haplotypes were constructed using HPlus Version 2.5. Logistic regression analyses controlling for the confounding effects of age, gender, HIV-1, sickle-cell anemia, G6PD and bacteremia, results showed that there was no association between NCR3 (-412C/G and -172G/A) genotypes/haplotypes with acquisition of parasitaemia. However, the NCR3 -412GG genotype was associated with HDP (GG, OR 0.469, 95% CI; 0.252-0.873, P = 0.017) while the NCR3 -412CG genotype was associated with increased risk to SMA (CG, OR 1.636, 95% CI; 1.018-2.631, P = 0.042). The carriage of CC (NCR3 -412C and -172C) haplotype was associated with a risk to HDP (OR 1.934, 95% CI; 1.104-3.389, P = 0.021) while the GC (NCR3 -412G and -172C) haplotype was associated with increased susceptibility to SMA (Hb<5.0 g/dL) (OR 1.635, 95% CI; 1.015-2.634, P = 0.043). Taken together, these results demonstrate that NCR3 (-412C/G and -172G/A) promoter variants condition malaria outcomes in paediatrics in a holoendemic area. Future studies should determine how other genetic factors work together with NCR3 promoter variants to condition malaria outcomes among paediatric population and this can provide an insight to the causal link as well as pharmaceutical interventions.