Genetic variation in interleukin-7 is associated with a reduced erythropoietic response in Kenyan children infected with *Plasmodium falciparum*

Abstract

Background

Severe malarial anemia (SMA) is a leading cause of malaria-related morbidity and mortality in children. The genetic factors that influence development of SMA and inefficient erythropoiesis, a central pathogenic feature of SMA, are only partially understood.

Methods

We performed a pilot Genome-wide Association Study (GWAS) on children with *Plasmodium falciparum*. The GWAS was performed using the Illumina® Infinium® HD Super Assay in conjunction with Illumina's® Human Omni2.5-8v1 BeadChip (with > 2.45 M markers). Data were analyzed using single SNP logistic regression analysis with an additive model of inheritance controlling for covariates. Results from our pilot global genomics study identified that variation in interleukin (IL)-7 was associated with enhanced risk of SMA. To validate this finding, we investigated the relationship between genotypes and/or haplotypes of two single nucleotide polymorphisms (SNPs) in *IL7* [72194 T/C and – 2440 A/G] and susceptibility to both SMA and inefficient erythropoiesis [i.e., reticulocyte production index (RPI) < 2.0 in anemic children (Hb < 11.0 g/dL). Children presenting with *P. falciparum* malaria (< 3 years, $n = 883$) were stratified into two groups: Uncomplicated malaria (UM, $n = 718$) and SMA ($n = 165$).

Results

Regression modeling, controlling for anemia-related confounders, revealed that carriage of the TC genotype at position 72194 T/C was associated with enhanced susceptibility to inefficient erythropoiesis (OR = 1.90; 95% CI 1.09–3.30; $P = 0.02$) as was homozygous CC (OR 5.14; 95% CI = 1.20–21.99; $P = 0.03$). Consistent with this finding, individuals with the CA (72194C/−2440A) haplotype had an increased risk of inefficient erythropoiesis (OR = 1.90; 95% CI = 1.10–3.30; $P = 0.02$), whereas TA haplotype carriers had marginal protection against inefficient erythropoiesis (OR = 0.24; 95% CI = 0.06–1.21; $P = 0.05$). These observations were supported by Cochran-Armitage trend test for inefficient erythropoiesis (CA > TA > CG; $P < 0.01$). Although none of the genotype and/or haplotypic

variants were significantly associated with SMA, the direction of the risk profiles were consistent with the erythropoiesis results.

Conclusion

Taken together, variation in *IL7* is associated with erythropoietic responses in children with falciparum malaria, a central physiological feature contributing to development of SMA.

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