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A novel functional variant in the stem cell growth factor promoter protects against severe malarial anemia.

Ouma C, Keller CC, Davenport GC, Were T, Konah S, Otieno MF, Hittner JB, Vulule JM, Martinson J, Ong'echa JM, Ferrell RE, Perkins DJ.

Source

University of New Mexico/KEMRI Laboratories of Parasitic and Viral Diseases, Centre for Global Health Research, Kenya Medical Research Institute, Kisumu, Kenya.

Abstract

Plasmodium falciparum malaria is a leading global cause of infectious disease burden. In areas in which P. falciparum transmission is holoendemic, such as western Kenya, severe malarial anemia (SMA) results in high rates of pediatric morbidity and mortality. Although the pathophysiological basis of SMA is multifactorial, we recently discovered that suppression of unexplored hematopoietic growth factors that promote erythroid and myeloid colony development, such as stem cell growth factor (SCGF) (C-type lectin domain family member 11A [CLEC11A]), was associated with enhanced development of SMA and reduced erythropoietic responses. To extend these investigations, the relationships between a novel SCGF promoter variant (-539C/T, rs7246355), SMA (hemoglobin [Hb] < 6.0 g/dl), and reduced erythropoietic responses (reticulocyte production index [RPI], <2.0) were investigated with Kenyan children (n = 486) with falciparum malaria from western Kenya. Circulating SCGF was positively correlated with hemoglobin levels (r = 0.251; P = 0.022) and the reticulocyte production index (RPI) (r = 0.268; P = 0.025). Children with SMA also had lower SCGF levels than those in the non-SMA group (P = 0.005). Multivariate logistic regression analyses controlling for covariates demonstrated that individuals with the homologous T allele were protected against SMA (odds ratio, 0.57; 95% confidence interval [95% CI] 0.34 to 0.94; P = 0.027) relative to CC (wild-type) carriers. Carriers of the TT genotype also had higher SCGF levels in circulation (P = 0.018) and in peripheral blood mononuclear cell culture supernatants (P = 0.041), as well as an elevated RPI (P = 0.005) relative to individuals with the CC genotype. The results presented here demonstrate that homozygous T at -539 in the SCGF promoter is associated with elevated SCGF production, enhanced erythropoiesis, and protection against the development of SMA in children with falciparum malaria.