Development of protective immunity against Plasmodium falciparum is partially mediated through binding of malaria-specific IgG to Fc gamma (γ) receptors. Variations in human FcγRIIA-H/R-131 and FcγRIIIB-NA1/NA2 affect differential binding of IgG sub-classes. Since variability in FcγR may play an important role in severe malarial anemia (SMA) pathogenesis by mediating phagocytosis of red blood cells and triggering cytokine production, the relationship between FcγRIIA-H/R131 and FcγRIIIB-NA1/NA2 haplotypes and susceptibility to SMA (Hb < 6.0 g/dL) was investigated in Kenyan children (n = 528) with acute malaria residing in a holoendemic P. falciparum transmission region. In addition, the association between carriage of the haplotypes and repeated episodes of SMA and all-cause mortality were investigated over a 3-year follow-up period. Since variability in FcγR can alter interferon (IFN)-γ production, a mediator of innate and adaptive immune responses, functional associations between the haplotypes and IFN-γ were also explored. During acute malaria, children with SMA had elevated peripheral IFN-γ levels (P = 0.006). Although multivariate logistic regression analyses (controlling for covariates) revealed no associations between the FcγR haplotypes and susceptibility to SMA during acute infection, the FcγRIIA-131H/FcγRIIIB-NA1 haplotype was associated with decreased peripheral IFN-γ (P = 0.046). Longitudinal analyses showed that carriage of the FcγRIIA-131H/FcγRIIIB-NA1 haplotype was associated with reduced risk of SMA (RR 0.65, 95% CI 0.46-0.90; P = 0.012) and all-cause mortality (P = 0.002). In contrast, carriers of the FcγRIIA-131H/FcγRIIIB-NA2 haplotype had increased susceptibility to SMA (RR 1.47, 95% CI 1.06-2.04; P = 0.020). Results here demonstrate that variation in the FcγR gene alters susceptibility to repeated episodes of SMA and mortality, as well as functional changes in IFN-γ production.