Complement component 3 mutations alter the longitudinal risk of pediatric malaria and severe malarial anemia

Abstract

Severe malarial anemia (SMA) is a leading cause of childhood morbidity and mortality in holoendemic *Plasmodium falciparum* transmission regions. To gain enhanced understanding of predisposing factors for SMA, we explored the relationship between complement component 3 (C3) missense mutations [rs2230199 (2307C>G, Arg>Gly^{102}) and rs11569534 (34420G>A, Gly>Asp^{1224})], malaria, and SMA in a cohort of children (n = 1617 children) over 36 months of follow-up. Variants were selected based on their ability to impart amino acid substitutions that can alter the structure and function of C3. The 2307C>G mutation results in a basic to a polar residue change (Arg to Gly) at position 102 (β-chain) in the macroglobulin-1 (MG1) domain, while 34420G>A elicits a polar to acidic residue change (Gly to Asp) at position 1224 (α-chain) in the thioester-containing domain. After adjusting for multiple comparisons, longitudinal analyses revealed that inheritance of the homozygous mutant (GG) at 2307 enhanced the risk of SMA (RR = 2.142, 95%CI: 1.229–3.735, $P = 0.007$). The haplotype containing both wild-type alleles (CG) decreased the incident risk ratio of both malaria (RR = 0.897, 95%CI: 0.828–0.972, $P = 0.008$) and SMA (RR = 0.617, 95%CI: 0.448–0.848, $P = 0.003$). Malaria incident risk ratio was also reduced in carriers of the GG (Gly^{102}Gly^{1224}) haplotype (RR = 0.941, 95%CI: 0.888–0.997, $P = 0.040$). Collectively, inheritance of the missense mutations in MG1 and thioester-containing domain influence the longitudinal risk of malaria and SMA in children exposed to intense *Plasmodium falciparum* transmission.

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