Polymorphic variability in immune response genes, such as *IL12B*, encoding the IL-12p40 subunit is associated with susceptibility to severe malaria in African populations. Since the role of genetic variation in conditioning severe malaria in Thai adults is largely unexplored, the functional association between *IL12B* polymorphisms [i.e., *IL12B*pro (rs17860508), and *IL12B* 3' UTR T/G (rs3212227)], severe malaria, and cytokine production was examined in patients with *Plasmodium falciparum* infections (n=355) recruited from malaria endemic areas along the Thai-Myanmar border in northwest Thailand. Circulating IL-12p40 ($p$=0.049) and IFN-γ ($p$=0.051) were elevated in patients with severe malaria, while only IL-12p40 was significantly higher in severe malaria patients with hyperparasitaemia ($p$=0.046). Carriage of the *IL12B*pro1.1 genotype was associated with enhanced severity of malaria (OR, 2.34; 95% CI, 0.94–5.81; $p$=0.066) and hyperparasitaemia (OR, 3.42; 95% CI, 1.17–9.87; $p$=0.025) relative to the *IL12B*pro2.2 genotype (wild type). Individuals with the *IL12B*pro1.1 genotype also had the lowest IL-12p40 ($p$=0.002) and the highest IFN-γ ($p$=0.004) levels. Construction of haplotypes revealed that carriage of the *IL12B*pro-2/3' UTR-T haplotype was associated with protection against severe malaria (OR, 0.51; 95% CI, 0.29–0.90; $p$=0.020) and reduced circulating IFN-γ ($p$=0.06). Thus, genotypic and haplotypic variation at *IL12B*pro and *IL12B* 3' UTR in this population influences susceptibility to severe malaria and functional changes in circulating IL-12p40 and IFN-γ levels. Results presented here suggest that protection against severe malaria in Thai adults is associated with genotypic variants that condition enhanced IL-12p40 and reduced IFN-γ levels.

**Keywords:** *IL12B, P. falciparum,* severe malaria, single nucleotide polymorphism, haplotype