

Haplotypes of IL12B promoter polymorphisms condition susceptibility to severe malaria and functional changes in cytokine levels in Thai adults.

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Source

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Abstract

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. IL12Bpro (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-gamma (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 IL12Bpro1.1 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 IL12Bpro2.2 genotype (wild type). Individuals with the IL12Bpro1.1 genotype also had the lowest IL-12p40 (p = 0.002) and the highest IFN-gamma (p = 0.004) levels. Construction of haplotypes revealed that carriage of the IL12Bpro-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-gamma (p = 0.06). Thus, genotypic and haplotypic variation at IL12Bpro and IL12B 3' UTR in this population influences susceptibility to severe malaria and functional changes in circulating IL-12p40 and IFN-gamma 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-gamma levels.