Integrated OMICS platforms identify LAIR1 genetic variants as novel predictors of cross-sectional and longitudinal susceptibility to severe malaria and all-cause mortality in Kenyan children

Abstract

Background

Severe malarial anaemia (SMA) is a leading cause of childhood mortality in holoendemic *Plasmodium falciparum* regions.

Methods

To gain an improved understanding of SMA pathogenesis, whole genome and transcriptome profiling was performed in Kenyan children (n = 144, 3–36 months) with discrete non-SMA and SMA phenotypes. Leukocyte associated immunoglobulin like receptor 1 (LAIR1) emerged as a predictor of susceptibility to SMA ($P < 1 \times 10^{-2}$, OR: 0.44–1.37), and was suppressed in severe disease (−1.69-fold, P = 0.004). To extend these findings, the relationship between *LAIR1* polymorphisms [rs6509867 (16231C>A); rs2287827 (18835G>A)] and clinical outcomes were investigated in individuals (n = 1512, <5 years) at enrolment and during a 36-month longitudinal follow-up.

Findings

Inheritance of the 16,231 recessive genotype (AA) increased susceptibility to SMA at enrolment (OR = 1.903, 95%CI: 1.252–2.891, P = 0.003), and longitudinally (RR = 1.527, 95%CI: 1.119–2.083, P = 0.008). Carriage of the 18,835 GA genotype protected against SMA cross-sectionally (OR = 0.672, 95%CI: 0.480–0.9439, P = 0.020). Haplotype carriage (C16231A/G18835A) also altered cross-sectional susceptibility to SMA: CG (OR = 0.717, 95%CI: 0.527–0.9675, P = 0.034), CA (OR = 0.745, 95%CI: 0.536–1.036, P = 0.080), and AG (OR = 1.641, 95%CI: 1.160–2.321, P = 0.005). Longitudinally, CA carriage was protective against SMA (RR = 0.715, 95%CI: 0.554–0.923, P = 0.010), while AG carriage had an additive effect on enhanced SMA risk (RR = 1.283, 95%CI: 1.057–1.557, P = 0.011). Variants that protected against SMA had elevated *LAIR1* transcripts, while those with enhanced risk had lower expression ($P < 0.05$). Inheritance of 18,835 GA reduced all-cause mortality by 44.8% (HR = 0.552, 95%CI: 0.329–0.925, P = 0.024), while AG haplotype carriage increased susceptibility by 68% (HR = 1.680, 95%CI: 1.020–2.770, P = 0.040).

Interpretation

These findings suggest *LAIR1* is important for modulating susceptibility to SMA and all-cause childhood mortality.

Keywords: Leukocyte associated immunoglobulin like receptor 1, *Plasmodium falciparum* malaria, Severe malarial anaemia, All-cause mortality

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