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ICAM-1 Kilifi variant is not associated with cerebral and severe malaria pathogenesis in Beninese children

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Abstract

Background: Cytoadhesion and sequestration of *Plasmodium falciparum* infected red blood cells (iRBC) in the micro-vasculature of vital organs are a major cause of malaria pathology. Several studies have provided evidence on the implication of the human host intercellular adhesion molecule-1 (ICAM-1) as a major receptor for iRBCs binding to *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) in the development of severe and cerebral malaria. The genetic polymorphism K29M in the immunoglobulin-like domain of ICAM-1, known as ICAM-1 Kilifi, has been associated with either increased or decreased risk of developing cerebral malaria.

Methods: To provide more conclusive results, the genetic polymorphism of ICAM-1 Kilifi was assessed by PCR and sequencing in blood samples from 215 Beninese children who presented with either mild or severe malaria including cerebral malaria.

Results and conclusions: The results showed that in this cohort of Beninese children, the ICAM-1 kilifi variant is present at the frequencies of 0.27, similar to the frequency observed in other African countries. This ICAM-1 kilifi variant was not associated with disease severity in agreement with other findings from the Gambia, Tanzania, Malawi, Gabon, and Thailand, suggesting no evidence of a direct link between this polymorphism and the pathogenesis of severe and cerebral malaria.

Keywords: *Plasmodium falciparum*, Malaria, cerebral malaria, Polymorphism, ICAM-1, ICAM-1 kilifi

Background

Malaria presents a heavy burden on people living in endemic areas, with an increase in global mortality to 627,000 in 2020 compared to 405,000 registered in 2019 attributed to the Covid-19 pandemic consequences. Fifteen to 25% of case fatality rate occur among African children with cerebral malaria [1–4]. *Plasmodium falciparum*, the deadliest species, causes several clinical manifestations ranging from asymptomatic and mild infections to life threatening severe malaria, including cerebral malaria. The disease severity has been associated with sequestration of infected red blood cells (iRBCs) within the brain micro-vessels, leading to inflammation, reduction of the blood–brain barrier (BBB) integrity and brain swelling increasing intracranial pressure [3, 5–7]. Furthermore, the accumulation of iRBCs results in microvascular clogging, hypoxia, and activation of inflammatory cytokines, which in turn increase the expression of endothelial cell adherence molecules

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(eCAM) and accelerate the accumulation of iRBCs capillary beds [8].

Several receptors, including: thrombospondin, cluster of differentiation 36 (CD36), intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), platelet endothelial cell adhesion molecule/cluster of differentiation 31 (PECAM/CD31), neural cell adhesion molecule (NCAM), P and E-selectin, integrin $\alpha v\beta 3$, globular C1q receptor (gC1qR), chondroitin sulfate A (CSA), and haemagglutinin (HA), have been shown to be implicated in iRBC cytoadhesion [9–16].

ICAM-1 was found to be up-regulated in endothelial cells and co-localized with iRBCs in brain tissue of children who died from cerebral malaria [17, 18]. *In vitro* static and flow cytoadhesion experiments showed that ICAM-1 mediates attachment of *P. falciparum* iRBCs to cell membrane [19]. Compared to controls, the plasma concentration of soluble form of ICAM-1 is increased in malaria-infected patients [20–23]. ICAM-1 is also expressed constitutively on monocytes, which are often present with the parasites at sites of cerebral microhaemorrhages in cerebral malaria [24].

ICAM-1 remains a receptor of major interest, and several authors have investigated its role in the pathogenesis of severe malaria [25–31]. Specific ICAM-1 binding to brain microvessels is mediated by the β variant of Duffy-binding like domain (DBLβ) of type A *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) [32]. Recently, parasite strains able to bind both ICAM-1 and Endothelial Protein C Receptor (EPCR) have been isolated and characterized, strengthening the potential role of these two receptors in cerebral malaria [27, 33, 34].

Other studies have focused on the genetic polymorphism of ICAM-1, but these studies have led to contradictory conclusions. A single nucleotide polymorphism (SNP) corresponding to a mutation at locus 56 of the coding sequence, corresponding to position 29 on the mature protein, has been observed at a high frequency in Africa. This non-synonymous coding polymorphism (A/T) leads to a lysine to methionine change (K29M) in the N-terminal domain of ICAM-1. This mutation, known as the ICAM-1^{Kilifi} genotype, was found to predispose children to cerebral malaria in Kenya and Nigeria [35, 36]. However, in other studies conducted in Gambia, Malawi, and Kenya, this mutation was not associated with severe malaria, but was rather associated with protection from severe malaria in a study performed in Gabon [37–40]. Consequently, ICAM-1^{Kilifi} mutation has generated more interest for its potential implications in the mechanisms of pathogenesis of severe and cerebral malaria and has been extensively investigated in cytoadhesion functional studies [41, 42]. Besides, it has also been reported a marginal association of another mutation on exon 6 (rs5498) of ICAM-1with the susceptibility to severe malaria in a case–control study performed in Nigeria [36]. This mutation and the ICAM-1^{Kilifi} have not been found to be associated with susceptibility to severe malaria in whole genome associated study [43]. In the light of these contradictory findings in earlier studies, the frequency of ICAM-1^{Kilifi} was investigated in Beninese children with distinct clinical conditions of malaria, including uncomplicated malaria (UM), severe non cerebral malaria (SNCM) and cerebral malaria (CM), to assess the potential association of ICAM-1^{Kilifi} polymorphism with malaria severity.

Methods

Patients

This study was conducted in Cotonou, southern Benin during malaria transmission periods from June to September 2012 and from May to July, 2013. South of Benin is characterized by a subtropical climate, with 2 rainy seasons where *P. falciparum* malaria is endemic with approximately 33 infective bites per person annually [27]. Children less than six years of age presenting at Centre Hopitalier Universitaire Mère-enfant de la Lagune (CHUMEL), Centre National Hospitalier Universitaire Hubert Koutoucou Mega (CNHU-HKM), or to Hôpital Suru-Léré were screened by rapid diagnostic test for malaria (DiaQuick Malaria *P. falciparum* Cassette, Dialab®; Hondastrasse, Austria) and were admitted in the study if they meet the criteria defined by the World Health Organization (WHO) [28]. All malaria cases had microscopically-confirmed *P. falciparum* infection. Three clinical groups were formed including, (1) Cerebral Malaria group (CM) which consisted in children with severe malaria and coma as defined by Blantyre coma score ≤ 2, with the exclusion of any other causes of coma, (2) Severe non-cerebral malaria group (SNCM) which includes children presenting with one or more of the following symptoms; pulmonary edema, acute respiratory distress syndrome, acute kidney failure, abnormal liver function, hemoglobinuria, or severe anemia with absence of coma BCS > 2, (3) Uncomplicated Malaria group (UM): defined as *P. falciparum* parasitaemia with fever, headache, or myalgia without signs of severe malaria and/or evidence of vital organ dysfunction.

After obtaining informed and written consent from children parents or guardians, 2 to 7 ml of venous blood samples were collected into tubes containing citrate phosphate dextrose adenine and 20 µl of each sample were spotted and dried on Whatman (3MM) filter paper. All participants were treated according to the guidelines established by the Beninese Ministry of Health.

DNA extraction and PCR

DNA was extracted using Chelex® beads [44]. Briefly, a 2 mm diameter disc was cut from Whatman filter paper and incubated at 4 °C overnight in 0.5 mL of phosphate-buffered saline (PBS) containing 0.5% saponin. The filter paper was washed twice in saponin-free PBS, placed in 100 µl of distilled water containing 10% Chelex® (Biorad, Marnes-la-Coquette, France), then incubated at 100 °C for 20 min to elute DNA. Tubes were centrifuged at 12000x*g*, and the supernatant transferred to a new tube. One microlitre of this suspension was used to perform PCR for immunoglobulin (Ig)-like domain of *icam-1* gene using the primers and PCR conditions described by Fernandez-Reyes et al. [35]. The 263-bp amplified fragment spanning codon 29 was sequenced from the 5′- and 3′-ends using an automated DNA sequencer (ABI Prism; Perkin Elmer Corp, Eurofins, Paris, France).

Statistical analysis

The statistical analysis was performed on Prism v7 software (GraphPad Software, Inc., San Diego, CA, USA). Quantitative variables were compared between the three groups using the non-parametric Kruskall-Wallis test. Association between the ICAM-1^{Kilifi} genotype and clinical groups was performed using a chi-square test to compare genotypes as well as allele frequencies. P-value from the global chi-square assessing if there is at least one difference between the three groups are reported. The level of statistical significance was set at 0.05.

Results

Clinical and biological characteristics of patients

The base line characteristics, the clinical and the biological parameters of the children enrolled in the study are summarized in (Table 1). Briefly, we included 74 children with cerebral malaria (CM), 71 with severe non cerebral malaria (SNCM) and 70 with uncomplicated malaria (UM). There was no significant difference in age, male to female ratio, temperature, and parasitaemia. However, haemoglobin level was significantly different between clinical groups with a P-value of P < 0.0001. As expected, the deaths occurred among children in the group of CM and SNCM with a high mortality rate of 43% in children with CM compared to 17% in children with SNCM, P = 0.014.

Allelic frequency at ICAM- 29 position of enrolled children

Fragments of the N-terminal immunoglobulin-like domain of ICAM-1, were successfully amplified and sequenced in 215 individuals after genomic DNA extraction from blood samples. Hardy Weinberg Equilibrium test performed in UM sample to detect potential population stratification or problems in genotyping showed no deviance from the expected frequencies of genotypes (P = 0.78). The allelic frequencies of the mutant were 0.22 in CM group and 0.3 in both SNCM and UM groups. Even if we observe a higher frequency of wild type K29/K29 genotype in cerebral malaria group, the comparison of allelic and genotypic frequencies between the clinical groups showed no significant difference (respectively P = 0.18 And P = 0.19 global chi2 test) in the proportions of wild-type and mutant alleles or genotypes. The allelic and genotypic frequencies are presented in (Table 2).

Discussion

The biological mechanisms driving towards severe malaria pathology involve parasite virulence, host immunological backgrounds and host genetic factors. Among these factors parasite proteins expressed on the surface of erythrocytes such as PfEMP1 and host endothelial receptors play a major role. The results of the present study which aimed to investigate the possible association

Table 1 Clinical and biological characteristics of *P. falciparum*-infected children enrolled in the study

Characteristics	Clinical groups		
	Cerebral malaria	**Severe non-cerebral malaria**	**Uncomplicated malaria**
Number of patients	74	71	70
Age, median (range), months	36 (5–72)	30 (9–60)	36 (5–60)
Sex ratio (male/female)	1.46 (44/30)	0.86 (33/38)	1.12 (37/33)
Geometric mean parasitaemia (95% CI; [range]) asexual parasites/µl	44,400 (15,100–34,900) [2,720–864,000]	21,800 (32,700–83,900) [156–650,000]	22,300 (16,000–42,900) [75–247,000]
Body temperature, median (range) °C	38.5 (35.5–40.9)	38.0 (36.0–41.0)	38.5 (36.0–40.7)
Haemoglobin, median (range) g/dl*	6.0 (0.8–12.9)	8.6 (3.1–11.5)	8.6 (5.0–13.6)
Blantyre score, median (range)	2 (0–2)	3.5 (3–5)	5 (–)
Number of deaths (%)*	32 (43.2)	12 (16.9)	0

[*] The difference between different groups was statistically significant for haemoglobin (*P* < 0.0001) and the number of deaths (*P* = 0.014). 95% CI, 95% confidence interval

Table 2 Genotypes and allelic frequency at ICAM-1- 29 loci

Clinical group	Genotype (n, %)			Frequency	
	K29/K29	K29/M29	M29/M29	K29	M29
Cerebral malaria (n = 74)	49 (66.2)	17 (23.0)	8 (10.8)	0.78	0.22
Severe non-cerebral malaria (n = 71)	40 (56.3)	18 (25.4)	13 (18.3)	0.69	0.31
Uncomplicated malaria (n = 70)	36 (51.4)	26 (37.1)	8 (11.4)	0.70	0.30
Total (n = 215)	125 (58.1)	61 (28.4)	29 (11.4)	0.72	0.27

K29/K29 are wild-type homozygous patients; K29/M29 are heterozygous individuals; M29/M29 indicate homozygous patients with the ICAM-1^{Kilifi} mutation. n, number of patients or samples

between the ICAM-1^{Kilifi} genotype and the predisposition to cerebral or severe malaria in African children from Benin show a high frequency of this mutation which reached (0.27%) consistent with earlier finding in other African countries. However, no association between the ICAM-1^{Kilifi} variant and the occurrence of cerebral or severe malaria has been found. These results are in agreement with those found in studies obtained on 2685 Gambian children, 200 Gabonese and 477 Thai individuals, but in contradiction to those of the initial study carried out on 547 Kenyan children [35, 37–39]. The importance of ICAM-1 receptor in the pathogenicity of severe malaria and the unequal distribution of the ICAM-1^{Kilifi} which reached frequencies between 20 to 30% in high malaria transmission region of Africa, around 5% in lower transmission area of East-Asia, and at only 0.4 to 1.1% in non-endemic area suggest a selective pressure exerted by malaria at this locus [38].

Functional studies showed that the iRBCs binding site is part of the two first domains of ICAM-1, overlaps but is distinct from that of Lymphocyte functional associated Antigens (LFA), Macrophage receptor 1 (Mac-1) and human rhinovirus [45, 46]. Indeed, another study showed that the conformational changes produced by the 'Kilifi polymorphism' occur at the L43 loop of domain 1 ICAM-1 and the monoclonal antibody 15.2 that maps to this region blocks the binding of iRBCs to both ICAM-1^{ref} and ICAM-1^{Kilifi} forms. Furthermore, both static and dynamic cytoadhesion experiments showed that phenotypic differences in the binding characteristics between these two ICAM-1 variants may depend on *P. falciparum* strains used in experimental assays. Thus, *P. falciparum* ITG iRBCs binds equally to ICAM-1^{Ref} and ICAM-1^{Kilifi}, however *P. falciparum* A4 iRBCs strain binds weakly to ICAM-1^{Kilifi} [41]. The difference in binding was more important in the dynamic assays, suggesting that ICAM-1^{Kilifi} may select high-affinity binding parasites at sequestration sites within the brain microvessels [47]. These observations were confirmed later using three different parasite lines (ItG, JDP8, A4) with different binding ability to wild type ICAM-1^{ref} to evaluate their adherence-capacities to a panel of mutant ICAM-1 proteins (ICAM-1$^{K29M(Kilifi)}$, ICAM-1$^{S22/A}$, ICAM-1$^{L42/A}$ and ICAM-1$^{L44/A}$) both under flow and static conditions. The results showed that iRBCs binding to some ICAM-1 mutants was reduced to 80% or completely abolished for some isolates, while the iRBCs binding to ICAM-1^{Kilifi} was reduced in only 50% of isolates, emphasizing the importance of parasite PfEMP1 variants used in the interaction with ICAM-1 [48].

More recently, the ICAM-1^{Kilifi} mutation was shown to be significantly associated with child hospitalisation in Tanzania supporting the link between this mutation with malaria severity, but independent from the cytoadherence pattern of iRBCs on ICAM-1, which can also depend on binding of these isolates to other receptors rather than ICAM-1 in these [49].

These findings may explain the contradictory results on the association of this variant with cerebral malaria [37, 39, 40] which, seems to also depend on PfEMP-1 and non PfEMP1 variants expressed at the surface of iRBCs and support the frequency-dependent model of selection explanation proposed by Fry et al. [38]. a mechanism which have been proposed among others to underlie host-parasite evolutionary dynamic. This model is based on an established equilibrium between polymorphism frequency in human and that of parasite strains due to competition between strains preferring binding on either ICAM-1^{Kilifi} or ICAM-1^{ref}, the change in host in allele frequency will favor the expansion of the corresponding high binding parasite strains which will select in return against the most frequent allele in host bringing the system to equilibrium at which all individuals will have the same risk of developing severe or cerebral malaria irrespective of their ICAM-1 genotype [38]. The ICAM-1^{Kilifi} mutation was also linked to the protection from highly prevalent non-malarial febrile illness in sub-Saharan Africa such as sepsis, suggesting that this polymorphism play a role in the modulation of inflammatory response to pathogens by ICAM-1 and may subsequently explain the high frequency of this polymorphism within African populations [49, 50].

Conclusion

The results of the present study indicate that ICAM-1^{Kilifi} polymorphism is not directly associated to severe or cerebral malaria development. However, a role in the pathogenesis, depending on the parasite variants implicated in the interaction with ICAM-1 ^{Kilifi} cannot be completely excluded.

Abbreviations

CM: Cerebral malaria; EPCR: Endothelial Protein C Receptor; ICAM-1: Intercellular adhesion molecule-1; iRBCs: Infected red blood cells; PfEMP1: *Plasmodium falciparum* Erythrocyte membrane protein 1; SNP: Single nucleotide polymorphism; SNCM: Severe non cerebral malaria; UM: Uncomplicated malaria.

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Author contributions

RT, LKB, PD designed the study and wrote the protocol. NTN, coordinated field and clinical activities. SA, MJA, AA, GNA organized and supervised patient inclusion and collected patient data and blood samples. SB, DSD, NT performed PCR. RT, YA, JM analysed the data and interpreted the results and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Sequencing data generated and analysed in this study are available in this manuscript. Other data can be obtained from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the institutional ethics committee of the Research Institute of Applied Biomedical Sciences, Cotonou, Benin (authorization no. 006/CER/ISBA/12). Prior to blood collection, all parents and guardians of children included in the study signed an informed consent form to participate.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. WHO. World malaria report. Geneva: World Health Organization; 2019.
2. Dondorp AM, Fanello CI, Hendriksen IC, Gomes E, Seni A, Chhaganlal KD, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet. 2010;376:1647–57.
3. Seydel KB, Kampondeni SD, Valim C, Potchen MJ, Milner DA, Muwalo FW, et al. Brain swelling and death in children with cerebral malaria. N Engl J Med. 2015;372:1126–37.
4. WHO. World malaria report 2021. Geneva: World Health Organization; 2021.
5. Molyneux ME. Cerebral malaria in children: clinical implications of cytoadherence. Am J Trop Med Hyg. 1990;43:38–41.
6. Greiner J, Dorovini-Zis K, Taylor TE, Molyneux ME, Beare NA, Kamiza S, et al. Correlation of hemorrhage, axonal damage, and blood-tissue barrier disruption in brain and retina of Malawian children with fatal cerebral malaria. Front Cell Infect Microbiol. 2015;5:18.
7. Sahu PK, Duffy FJ, Dankwa S, Vishnyakova M, Majhi M, Pirpamer L, et al. Determinants of brain swelling in pediatric and adult cerebral malaria. JCI Insight. 2021;6:e145823.
8. van der Heyde HC, Nolan J, Combes V, Gramaglia I, Grau GE. A unified hypothesis for the genesis of cerebral malaria: sequestration, inflammation and hemostasis leading to microcirculatory dysfunction. Trends Parasitol. 2006;22:503–8.
9. Barnwell JW, Asch AS, Nachman RL, Yamaya M, Aikawa M, Ingravallo P. A human 88-kD membrane glycoprotein (CD36) functions in vitro as a receptor for a cytoadherence ligand on *Plasmodium falciparum*-infected erythrocytes. J Clin Invest. 1989;84:765–72.
10. Cooke BM, Berendt AR, Craig AG, MacGregor J, Newbold CI, Nash GB. Rolling and stationary cytoadhesion of red blood cells parasitized by *Plasmodium falciparum*: separate roles for ICAM-1, CD36 and thrombospondin. Br J Haematol. 1994;87:162–70.
11. Ockenhouse CF, Tegoshi T, Maeno Y, Benjamin C, Ho M, Kan KE, et al. Human vascular endothelial cell adhesion receptors for *Plasmodium falciparum*-infected erythrocytes: roles for endothelial leukocyte adhesion molecule 1 and vascular cell adhesion molecule 1. J Exp Med. 1992;176:1183–9.
12. Treutiger CJ, Heddini A, Fernandez V, Muller WA, Wahlgren M. PECAM-1/CD31, an endothelial receptor for binding *Plasmodium falciparum*-infected erythrocytes. Nat Med. 1997;3:1405–8.
13. Pouvelle B, Matarazzo V, Jurzynski C, Nemeth J, Ramharter M, Rougon G, et al. Neural cell adhesion molecule, a new cytoadhesion receptor for *Plasmodium falciparum*-infected erythrocytes capable of aggregation. Infect Immun. 2007;75:3516–22.
14. Siano JP, Grady KK, Millet P, Wick TM. *Plasmodium falciparum*: cytoadherence to alpha(v)beta3 on human microvascular endothelial cells. Am J Trop Med Hyg. 1998;59:77–9.
15. Biswas AK, Hafiz A, Banerjee B, Kim KS, Datta K, Chitnis CE. *Plasmodium falciparum* uses gC1qR/HABP1/p32 as a receptor to bind to vascular endothelium and for platelet-mediated clumping. PLoS Pathog. 2007;3:1271–80.
16. Fried M, Duffy PE. Adherence of *Plasmodium falciparum* to chondroitin sulfate A in the human placenta. Science. 1996;272:1502–4.
17. Turner GD, Morrison H, Jones M, Davis TM, Looareesuwan S, Buley ID, et al. An immunohistochemical study of the pathology of fatal malaria. Evidence for widespread endothelial activation and a potential role for intercellular adhesion molecule-1 in cerebral sequestration. Am J Pathol. 1994;145:1057–69.
18. Turner GD, Ly VC, Nguyen TH, Tran TH, Nguyen HP, Bethell D, et al. Systemic endothelial activation occurs in both mild and severe malaria. Correlating dermal microvascular endothelial cell phenotype and soluble cell adhesion molecules with disease severity. Am J Pathol. 1998;152:1477–87.
19. Gray C, McCormick C, Turner G, Craig A. ICAM-1 can play a major role in mediating *P. falciparum* adhesion to endothelium under flow. Mol Biochem Parasitol. 2003;128:187–93.

20. Jakobsen PH, Morris-Jones S, Ronn A, Hviid L, Theander TG, Elhassan IM, et al. Increased plasma concentrations of sICAM-1, sVCAM-1 and sELAM-1 in patients with *Plasmodium falciparum* or *P. vivax* malaria and association with disease severity. Immunology. 1994;83:665–9.
21. Kawai S, Matsumoto J, Aikawa M, Matsuda H. Increased plasma levels of soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell molecule-1 (sVCAM-1) associated with disease severity in a primate model for severe human malaria: *Plasmodium coatneyi*-infected Japanese macaques (*Macaca fuscata*). J Vet Med Sci. 2003;65:629–31.
22. Wenisch C, Varijanonta S, Looareesuwan S, Graninger W, Pichler R, Wernsdorfer W. Soluble intercellular adhesion molecule-1 (ICAM-1), endothelial leukocyte adhesion molecule-1 (ELAM-1), and tumor necrosis factor receptor (55 kDa TNF-R) in patients with acute *Plasmodium falciparum* malaria. Clin Immunol Immunopathol. 1994;71:344–8.
23. Wenisch C, Looareesuwan S, Parschalk B, Graninger W. Soluble vascular cell adhesion molecule 1 is elevated in patients with *Plasmodium falciparum* malaria. J Infect Dis. 1994;169:710–1.
24. Clark IA, Awburn MM, Harper CG, Liomba NG, Molyneux ME. Induction of HO-1 in tissue macrophages and monocytes in fatal falciparum malaria and sepsis. Malar J. 2003;2:41.
25. Avril M, Tripathi AK, Brazier AJ, Andisi C, Janes JH, Soma VL, et al. A restricted subset of var genes mediates adherence of *Plasmodium falciparum*-infected erythrocytes to brain endothelial cells. Proc Natl Acad Sci USA. 2012;109:E1782–90.
26. Bengtsson A, Joergensen L, Barbati ZR, Craig A, Hviid L, Jensen AT. Transfected HEK293 cells expressing functional recombinant intercellular adhesion molecule 1 (ICAM-1)–a receptor associated with severe *Plasmodium falciparum* malaria. PLoS ONE. 2013;8:e69999.
27. Avril M, Bernabeu M, Benjamin M, Brazier AJ, Smith JD. Interaction between Endothelial Protein C receptor and Intercellular Adhesion Molecule 1 to mediate binding of *Plasmodium falciparum*-infected erythrocytes to endothelial cells. Bio. 2016;7:e00615.
28. Lennartz F, Bengtsson A, Olsen RW, Joergensen L, Brown A, Remy L, et al. Mapping the binding site of a cross-reactive *Plasmodium falciparum* PfEMP1 monoclonal antibody inhibitory of ICAM-1 binding. J Immunol. 2015;195:3273–83.
29. Carrington E, Otto TD, Szestak T, Lennartz F, Higgins MK, Newbold CI, et al. In silico guided reconstruction and analysis of ICAM-1-binding var genes from *Plasmodium falciparum*. Sci Rep. 2018;8:3282.
30. Olsen RW, Ecklu-Mensah G, Bengtsson A, Ofori MF, Kusi KA, Koram KA, et al. Acquisition of IgG to ICAM-1-binding DBLbeta domains in the *Plasmodium falciparum* Erythrocyte Membrane Protein 1 antigen family varies between groups A, B, and C. Infect Immun. 2019;87:e00224-e319.
31. Badaut C, Visitdesotrakul P, Chabry A, Bigey P, Tornyigah B, Roman J, et al. IgG acquisition against PfEMP1 PF11_0521 domain cassette DC13, DBLbeta3_D4 domain, and peptides located within these constructs in children with cerebral malaria. Sci Rep. 2021;11:3680.
32. Smith JD, Craig AG, Kriek N, Hudson-Taylor D, Kyes S, Fagan T, et al. Identification of a *Plasmodium falciparum* intercellular adhesion molecule-1 binding domain: a parasite adhesion trait implicated in cerebral malaria. Proc Natl Acad Sci USA. 2000;97:1766–71.
33. Lennartz F, Adams Y, Bengtsson A, Olsen RW, Turner L, Ndam NT, et al. Structure-guided identification of a family of dual receptor-binding PfEMP1 that is associated with cerebral malaria. Cell Host Microbe. 2017;21:403–14.
34. Tuikue Ndam N, Moussiliou A, Lavstsen T, Kamaliddin C, Jensen ATR, Mama A, et al. Parasites causing cerebral falciparum malaria bind multiple endothelial receptors and express EPCR and ICAM-1-binding PfEMP1. J Infect Dis. 2017;215:1918–25.
35. Fernandez-Reyes D, Craig AG, Kyes SA, Peshu N, Snow RW, Berendt AR, et al. A high frequency African coding polymorphism in the N-terminal domain of ICAM-1 predisposing to cerebral malaria in Kenya. Hum Mol Genet. 1997;6:1357–60.
36. Amodu OK, Gbadegesin RA, Ralph SA, Adeyemo AA, Brenchley PE, Ayoola OO, et al. *Plasmodium falciparum* malaria in south-west Nigerian children: is the polymorphism of ICAM-1 and E-selectin genes contributing to the clinical severity of malaria? Acta Trop. 2005;95:248–55.
37. Bellamy R, Kwiatkowski D, Hill AV. Absence of an association between intercellular adhesion molecule 1, complement receptor 1 and interleukin 1 receptor antagonist gene polymorphisms and severe malaria in a West African population. Trans R Soc Trop Med Hyg. 1998;92:312–6.
38. Fry AE, Auburn S, Diakite M, Green A, Richardson A, Wilson J, et al. Variation in the ICAM1 gene is not associated with severe malaria phenotypes. Genes Immun. 2008;9:462–9.
39. Ohashi J, Naka I, Patarapotikul J, Hananantachai H, Looareesuwan S, Tokunaga K. Absence of association between the allele coding methionine at position 29 in the N-terminal domain of ICAM-1 (ICAM-1(Kilifi)) and severe malaria in the northwest of Thailand. Jpn J Infect Dis. 2001;54:114–6.
40. Kun JF, Klabunde J, Lell B, Luckner D, Alpers M, May J, et al. Association of the ICAM-1 Kilifi mutation with protection against severe malaria in Lambarene. Gabon Am J Trop Med Hyg. 1999;61:776–9.
41. Craig A, Fernandez-Reyes D, Mesri M, McDowall A, Altieri DC, Hogg N, et al. A functional analysis of a natural variant of intercellular adhesion molecule-1 (ICAM-1 Kilifi). Hum Mol Genet. 2000;9:525–30.
42. Tse MT, Chakrabarti K, Gray C, Chitnis CE, Craig A. Divergent binding sites on intercellular adhesion molecule-1 (ICAM-1) for variant *Plasmodium falciparum* isolates. Mol Microbiol. 2004;51:1039–49.
43. Damena D, Denis A, Golassa L, Chimusa ER. Genome-wide association studies of severe *P falciparum* malaria susceptibility: progress, pitfalls and prospects. BMC Med Genomics. 2019;12:120.
44. Plowe CV, Djimde A, Bouare M, Doumbo O, Wellems TE. Pyrimethamine and proguanil resistance-conferring mutations in *Plasmodium falciparum* dihydrofolate reductase: polymerase chain reaction methods for surveillance in Africa. Am J Trop Med Hyg. 1995;52:565–8.
45. Berendt AR, McDowall A, Craig AG, Bates PA, Sternberg MJ, Marsh K, et al. The binding site on ICAM-1 for *Plasmodium falciparum*-infected erythrocytes overlaps, but is distinct from, the LFA-1-binding site. Cell. 1992;68:71–81.
46. Ockenhouse CF, Betageri R, Springer TA, Staunton DE. *Plasmodium falciparum*-infected erythrocytes bind ICAM-1 at a site distinct from LFA-1, Mac-1, and human rhinovirus. Cell. 1992;68:63–9.
47. Adams S, Turner GD, Nash GB, Micklem K, Newbold CI, Craig AG. Differential binding of clonal variants of *Plasmodium falciparum* to allelic forms of intracellular adhesion molecule 1 determined by flow adhesion assay. Infect Immun. 2000;68:264–9.
48. Madkhali AM, Alkurbi MO, Szestak T, Bengtsson A, Patil PR, Wu Y, et al. An analysis of the binding characteristics of a panel of recently selected ICAM-1 binding *Plasmodium falciparum* patient isolates. PLoS ONE. 2014;9:e111518.
49. Mwanziva C, Mpina M, Balthazary S, Mkali H, Mbugi E, Mosha F, et al. Child hospitalization due to severe malaria is associated with the ICAM-1Kilifi allele but not adherence patterns of *Plasmodium falciparum* infected red blood cells to ICAM-1. Acta Trop. 2010;116:45–50.
50. Jenkins NE, Mwangi TW, Kortok M, Marsh K, Craig AG, Williams TN. A polymorphism of intercellular adhesion molecule-1 is associated with a reduced incidence of nonmalarial febrile illness in Kenyan children. Clin Infect Dis. 2005;41:1817–9.

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