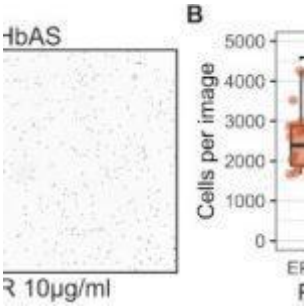
How Sickle-trait hemoglobin protects against severe Plasmodium falciparum malaria



Sickle-cell trait hemoglobin mutations (HbAS) are known to protect against *Plasmodium falciparum* malaria. In a recent clinical trial Jens E. V. Petersen et al, investigated the mechanism behind this.

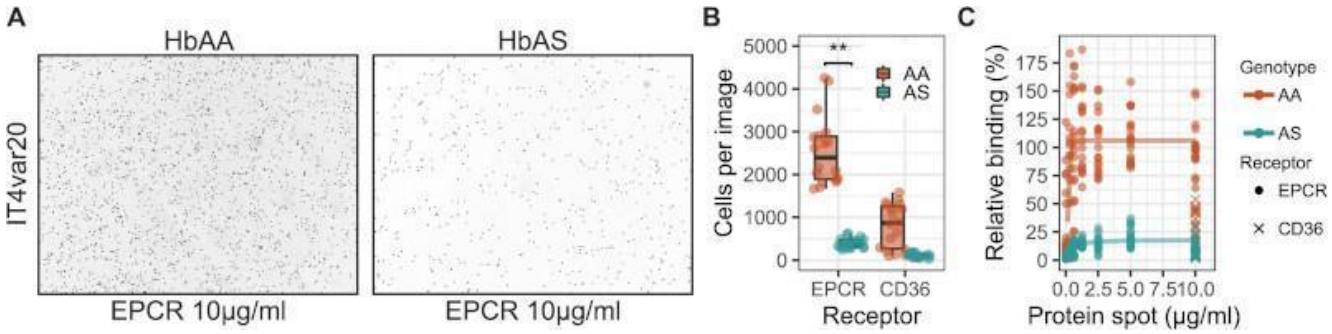
“Severe malaria is governed in part by the expression of the *Plasmodium falciparum* Erythrocyte Membrane Protein 1 (PfEMP1) that are encoded by *var* genes, specifically those variants that bind Endothelial Protein C Receptor (EPCR).”

The researchers investigated the effect of the sickle-cell trait on *var* gene expression and function in Malian children *in vitro* and in field-collected parasites, including the *var* genes that illicit severe malaria by mediating infected erythrocyte adhesion to host EPCR.

Parasite RNA was compared in sickle-cell trait and non-sickle-cell trait children and the data showed that HbAS does not affect overall *var* transcription or the type of *var* genes expressed but does reduce “parasites ability to adhere to both CD36 and EPCR *in vitro*, by attenuating the expression of parasite proteins (PfEMP1) on the erythrocyte surface”.

“In adhesion assays using recombinant host receptors, sickle-trait reduced adhesion by 73–86% to CD36 and 83% to EPCR.”

The researchers concluded that sickle-cell trait does not have a direct effect on *var* gene transcription but does reduce the surface expression and function of PfEMP1. This study may provide a direct mechanism that explains how the sickle-cell hemoglobin trait protects against severe malaria.



Sickle-trait hemoglobin effects on erythrocyte adhesion to EPCR.
A) Erythrocytes infected with IT4 parasite-strain expressing IT4var20 adhering to spots of recombinant EPCR on a petri-dish. B) Quantification of IT4var20-infected normal (HbAA) erythrocytes and sickle-cell trait (HbAS) erythrocytes adhesion to 10 µg/ml EPCR and CD36 spots. Each condition was done as 2 protein spots on separate petri-dishes, each imaged 3 times. The assay was done 3 independent times (n = 3). Wilcoxon's signed rank test was used to evaluate statistical significance (** p-value = 0.0002). C) Relative adhesion across protein spots at different concentrations normalized to the mean adhesion to EPCR at 10 µg/ml. Four parameter logistic curve was fitted to the normalized data for HbAA and HbAS. (Source: Petersen et al, 2021)

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Journal Article: Petersen et al. 2021. Sickle-trait hemoglobin reduces adhesion to both CD36 and EPCR by Plasmodium falciparum-infected erythrocytes. PLOS Pathogens.

Summary by Bonamy Holtak