Global genetic diversity of the *Plasmodium falciparum* malaria in pregnancy vaccine candidate VAR2CSA DBL2X

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Malaria infection during pregnancy (MIP) has adverse clinical consequences for both mothers and their unborn child, with no effective vaccine currently available. MIP is caused by *Plasmodium falciparum* infected erythrocytes sequestering to the placenta and massively accumulating. The binding tropism is mediated by VAR2CSA, a parasite-derived protein expressed on the infected erythrocyte surface, which binds to placental chondroitin sulfate A (CSA). Two vaccine candidates under development, PRIMVAC and PAMVAC, target overlapping constructs of the VAR2CSA CSA-binding region, ID1-DBL2X. Clinical data from Phase I trials suggest insufficient cross-reactivity of the candidates against heterologous VAR2CSA variants.

Little is known about the global genetic diversity of the ID1-DBL2X domain, which may impact vaccine efficacy. Here, we analysed >1,200 *P. falciparum* DBL2X sequences spanning 26 countries. 983 DBL2X haplotypes subdivided into four phylogenetic clades. Despite no geographic basis to this clustering, nucleotide diversity was greatest in African populations. The immensely polymorphic nature of DBL2X is principally driven by small insertions and deletions (indels), with increased indel density adjacent to the highly conserved CSA-binding residues. Ongoing work involves the identification of clade-specific consensus sequences to proactively support the development of a polyvalent VAR2CSA vaccine for broadly neutralising protection against MIP.