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Hypervariability in a leading *P. vivax* malaria vaccine candidate, C-terminal merozoite surface protein 1

It is widely accepted that the C-terminal 42 kDa (p42) and 19 kDa (p19) processing fragments of *Plasmodium* Merozoite Surface Protein-1 (MSP-1) are targets of immune protection. To begin to assess the degree for polymorphism in these MSP-1 vaccine candidates, we have investigated the sequence diversity in the *P. Vivax* MSP-1 p42 processing fragment, in 19 natural isolates, from *P.vivax* infected patients in Kataragama. Sequence analysis of PvMSP-1 p42 in the 19 PCR positive isolates revealed 11 sequences of Belem origin and 8 sequences of Salvador-1 (Sal-1) origin, Among the isolates, these two strains are 98-100% homologous across this region, with one notable exception. This corresponds to a highly polymorphic block of 38 amino acids (24% amino acid homology among isolates) However, this polymorphism appears to be derived largely by re-assorting a dimorphism at each variable position. This type of restricted variability suggests that in spite of its diversity, there may nevertheless be a defined structure for this region of the molecule and that the diversity may be functionally important. Alternatively, it may be specifically designed for maximal effect in immune evasion, as a highly exposed immunogenic loop structure.

In striking contrast, a single nucleotide substitution was detected in the cysteine rich C-terminal 19 kDa region, resulting in a lysine to glutamate substitution. This was detected in only one isolate among the 19 isolates investigated for sequence diversity.

Since the PvMSP-1 p42 C-terminal antigen is clearly hypervariable in the context of natural infections, a vaccine based on a single version of this antigen, might not induce an effective immunity against the multiple forms. In contrast, the PvMSP-1 p19 domain appears to be well conserved and thus appears to be a considerably more promising vaccine candidate.