GLOBAL GENETIC DIVERSITY OF *PLASMODIUM VIVAX* METACASPASE 2 AND 3 CATALYTIC REGIONS

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Introduction: Metacaspases (MCAs) are proteases absent in metazoans that have been proposed as potential drug targets for protozoan diseases due to their involvement in key cellular processes. Three MCAs are described in *P. vivax*, but only *Pv*MCA1 has been studied for genetic diversity. **Objectives**: To analyze the genetic diversity of the C14 predicted catalytic domain of *Pv*MCA2 and *Pv*MCA3, and the structural impact of nonsynonymous single-nucleotide polymorphism (nsSNPs). **Methods:** The C14 region was sequenced by Sanger from 53 *P. vivax* isolates collected in the Brazilian Amazon. Global sequences (n=516) were extracted from MalariaGEN. Diversity, neutrality, population differentiation, mismatch distribution, and species divergence, using *P. cynomolgi* and *P. knowlesi* as outgroups, were analyzed in DNASP. SSD and raggedness p-values were obtained via parametric bootstrap. Structural modeling was performed by AlphaFold3 and validated by MolProbity and QMEANDisCo, and the impact of amino acid change was predicted by SIFT, PolyPhen-2, MutPred2, and DDGun. nsSNPs were mapped on PyMOL. **Results:** Both domains showed low diversity (*Pv*MCA2: pi= 0.00028; *Pv*MCA3: pi=0.00013), negative Tajima's D, and neutrality index > 1, suggesting purifying selection. The sudden expansion model was rejected for both genes (SSD P<0.001), supporting selection rather than demographic expansion. Domains also showed contrasting fixation index (Fst): *Pv*MCA2, 0.244; *Pv*MCA3, 0.010. Only two and four nsSNPs were observed for *Pv*MCA2 and *Pv*MCA3, respectively, all geographically restricted and with no significant impact on the predicted domains. Haplotype networks displayed star-like topologies with contemporary Brazilian isolates monomorphic, belonging to the dominant haplotype. **Conclusion:** *Pv*MCAs catalytic regions are under purifying selection globally, consistent with essential functional constraint. Contrasting differentiation between domains suggests distinct evolutionary dynamics.