



Interethnic variation of the *MMP-9* microsatellite in Amerindian and Mexican Mestizo populations: considerations for genetic association studies

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ABSTRACT. We studied the interethnic variation of the *MMP-9* microsatellite in the Mestizo and Amerindian populations using

blood samples collected from 435 healthy unrelated individuals from the Central Valley of Mexico. DNA samples were genotyped using the -90 (CA)₁₂₋₂₇ repeat near the *MMP* transcriptional start site using capillary electrophoresis. Our data were compared with those from African, Asian, and European populations (N = 729). Both Mestizo and Amerindian populations were in Hardy-Weinberg equilibrium ($P \geq 0.05$). However, strong genetic heterogeneity was found within the Mestizo population (94%, $P \leq 0.0001$), which exhibited the highest frequency of Amerindian, African, and European alleles. Likewise, Amerindians showed 6.7% variation among populations ($P \leq 0.0001$), suggesting a genetic substructure potentially associated with linguistic affiliations. These findings were corroborated with principal component and population differentiation analyses, which showed relative proximity among the Mestizos and their historical parental populations: Asian ($F_{ST} \geq 0.05$), European ($F_{ST} \geq 0.09$), and African ($F_{ST} \geq 0.02$). Nevertheless, important differences were found between Mestizo and Nahuas ($P \leq 0.0001$), and between Mestizo and Me'Phaas ($P \leq 0.0001$). These findings highlight the importance of determining local-specific patterns to establish the population variability of *MMP-9* and other polymorphic markers. Validation of candidate markers is critical to identifying risk factors; however, this depends on knowledge of population genetic variation, which increases the possibility of finding true causative variants. We also show that dissimilar ethnic backgrounds might lead to spurious associations. Our study provides useful considerations for greater accuracy and robustness in future genetic association studies.

Key words: MMP-9; Polymorphisms; Population genetics; Ethnicity; Mexican Mestizo population; Amerindian