CHARACTERIZATION OF UGT FAMILY GENES IN AMAZON INDIGENOUS POPULATIONS

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Introduction: Anthracycline-based chemotherapy, commonly used in the treatment of breast and hematologic cancers, is effective but may lead to acute cardiac toxicity (ACT), particularly in individuals with impaired drug clearance due to genetic variants. Glucuronidation, a major detoxification and drug elimination pathway, is catalyzed by the UDP-glucuronosyltransferase (UGT) enzyme family. As these enzymes play a central role in hepatic biotransformation, the presence of genetic variants may reduce enzymatic activity, resulting in the accumulation of toxic metabolites. Indigenous populations are known to experience severe toxicities when treated with various chemotherapeutic agents, including doxorubicin, an anthracycline widely used in cancer therapy. However, there is a notable lack of pharmacogenomic studies investigating the presence and clinical implications of these genetic variants in Indigenous peoples, who, due to their unique genetic ancestry, may exhibit distinct drug response profiles. **Objectives:** To evaluate the epidemiological-molecular profile of UGT family genes in Indigenous populations from the northern Amazon region of Brazil, in order to contribute to the understanding of the genetic role in unfavorable responses to cancer treatment in these underrepresented populations. **Methods:** A total of 64 Indigenous individuals from the Brazilian Amazon region, representing 12 different ethnic groups and with no familial relationships among them (INDG group), were selected for this study [CONEP 1062/2006 and 123/98]. DNA was extracted using the phenol-chloroform method, and exome libraries were prepared with the Nextera Rapid Capture Exome (Illumina) and SureSelect Human All Exon V6 (Agilent) kits. Allelic variants in genes from the UGT family were annotated using the ViVa software (Viewer of Variants). Allele frequencies in the INDG group were determined by allele counting and compared using Fisher's exact test with five continental populations from phase 3 of the 1000 Genomes Project (AFR, EUR, AMR, EAS, and SAS). **Results:** The analysis of the genes, after quality control, identified a total of 48 variants in two genes of the UGT family: *UGT1A1* and *UGT1A6*. The most commonly observed mutations were synonymous variants, single nucleotide variants (SNVs), variants located in intronic regions, and those predicted in silico to have a modifier functional impact. Our main finding was the identification of two variants that, to date, have been found exclusively in the Indigenous study population: one in the *UGT1A1* gene with a low predicted functional impact, and another in *UGT1A6* with a modifier impact. Fisher's exact test revealed that, among the 48 variants found in the Indigenous population, 11 showed statistically significant differences in allele frequency in at least three of the five continental populations analyzed. **Conclusion:** The identification of novel UGT1A variants in Indigenous Amazonian populations highlights genetic differences that may affect drug metabolism, particularly the risk of anthracycline-induced cardiotoxicity. Given the key role of UGT1A6 in detoxification, variants may impair drug clearance and increase toxicity. These findings underscore the importance of including underrepresented populations in pharmacogenomic research to advance more equitable and effective personalized therapies.

Keywords: Anthracyclines; amazonian indigenous; phamacogenomics.