Pharmacogenetic variability of tuberculosis biomarkers in native and mestizo Peruvian populations

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Abstract

In Peru, 29,292 people were diagnosed with tuberculosis in 2022. Although tuberculosis treatments are effective, 3.4-13% are associated with significant adverse drug reactions, with drug-induced liver injury (DILI) considered the most predominant. Among the first-line antituberculosis drugs, isoniazid (INH) is the main drug responsible for the appearance of DILI. In liver, INH is metabolized by N-acetyltransferase-2 (*NAT2*) and cytochrome P450 2E1 (*CYP2E1*). Limited information exists on genetic risk factors associated with the presence of drug-induced liver injury (DILI) to anti-tuberculosis drugs in Latin America, and even less is known about these factors in the native and mestizo Peruvian population. The aim of this study was to determine the prevalence of *NAT2* and *CYP2E1* genotypes in native and mestizo population. An analytical cross-sectional analysis was performed using genetic data from mestizo population in Lima and native participants in south of Peru from the EPIGEN - Brazil project. *NAT2* acetylator genotype was determined as fast, intermediate and slow, and *CYP2E1* genotypes were classified as c1/c1, c1/c2 and c2/c2, from molecular tests and bioinformatic analyses. Of the 472 participants, 36 haplotypes were identified in the mestizo population and 6 haplotypes in native population paired with *NAT2*. In mestizo population, the most frequent *NAT2**5B and *NAT2**7B haplotypes were associated with DILI risk; while in natives, *NAT2**5G and *NAT2**13A haplotypes were the most frequent and associated with decreased risk of DILI. For *CYP2E1*, c1/c1 and c1/c2 genotypes are the most frequent in native and mestizo populations, respectively. The linkage disequilibrium of *NAT2* and CYP2E1 SNPs was estimated using the solid spine method, detecting a block between all SNPs native population. In addition, a block between rs1801280 and rs1799929 for *NAT2* was detected in the mestizo population. Despite the limitations of a secondary study, it was possible to report associations between *NAT2* and *CYP2E* alleles with Peruvian native and mestizo population by prevalence ratios. The results of this study will help the development of new therapeutic strategies for a Tuberculosis efficient control between populations.

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