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Pharmacogenetics research in different disease models: Our experience in Brazilian population

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In humans, the enzyme N-acetyltransferase2 (NAT2), coded by NAT2 gene, is the main metabolizer of isoniazid, dapsone and hydralazine, used for the treatment of tuberculosis, leprosy and resistant hypertension, diseases highly incidents in Brazil. We studied NAT2 in different Brazilians populations for these three disease models. In the first study, we showed the predominance of NAT2 slow acetylation alleles in Rio and Goias states. However, population from Rio showed a higher heterogeneity in NAT2 allele distribution and significant higher frequency of intermediate phenotype. Six new SNPs were identified (29T>C, 152G>T, 203G>A, 228C>T, 458C>T e 600A>G) and seven new alleles were characterized. Further, we performed an in silico molecular modeling and structural protein analyses of NAT2. The new SNP (152G>T-Gly51Val) is directly involved in substrate recognition, SNP (203G>A-Cys68Tyr) modifies the catalytic site by the loss of a functional group and SNPs (458C>T, 578C>T, 683C>T and 838G>A) facilitate enzyme degradation; all of them alter the acetylation activity to slow acetylation. In a subsequent study to evaluate the influence of CYP2E1, GSTT1, GSTM1 and NAT2 genotypes on isoniazid-induced hepatitis in TB patients and found that only NAT2 slow acetylation phenotype represented a risk factor for the occurrence of this outcome during TB treatment. In a more recent study, the influence of the acetylation phenotypes in anti-hypertensive effect of hydralazine in patients with RH was evaluated. Again, the predominance of slow acetylation phenotype was observed and only slow acetylators had significant blood pressure reductions after hydralazine use, however, with a high incidence of ADRs.

Biography

Adalberto Rezende Santos has completed PhD in Cellular and Molecular Biology from Oswaldo Cruz Foundation (Fiocruz), Rio de Janeiro, Brazil. He is a Senior Investigator and Substitute Head of the Laboratory of Molecular Biology Applied to Mycobacteria of Oswaldo Cruz Institute, Supervisor at the post-graduation programs of Cellular, Molecular Biology, and Clinical Medicine from Fiocruz and Federal University of Rio de Janeiro respectively. He is ad hoc consultant of the Executive Secretariat of Science Technology and Environment and of the Ministry of Health, Brazil. He is the of the *Journal of Infectious Diseases and Pharmacogenomics*.

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