Molecular Modeling Analysis of the Functional Impact of Single Nucleotide Polymorphisms in Human N-acetyltransferase 2 Gene

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Arylamine N-acetyltransferase 2 (*NAT2*) gene plays a crucial role in xenobiotics metabolism of many drugs and exogenous chemicals. Genetic factors have been described as risk factors, such as the acetylation polymorphism in *NAT2* gene, exposing patients to an increased risk of adverse drug reaction or lack of therapeutic efficacy. A clear bimodal distribution is observed that segregates the rapid acetylator phenotype, associated with a normal acetylation capability, from the slow acetylator one, as a result of reduced enzyme activity. The frequency of these two main phenotypes varies remarkably with ethnic origin. The aim of the study reported here was to predict from the structure of the NAT2 enzyme the possible functional effects of the single nucleotide polymorphisms (SNPs) found in the *NAT2* genes of individuals from Rio de Janeiro and Goiás States, Brazil. We utilized the NAT2 crystal structure (PDB 2PFR) as a template to model the SNPs resulting in amino acid substitutions I10T, L24I, G51V, C68Y, L135V, T153I, I158L, T193M, E203D, Y208H, P228L, K256E and V208M. From the analysis of the new interatomic contacts made by each mutated amino acid we concluded that the substitutions G51V, C68Y, T193M and P228L are likely to affect NAT activity. Noteworthy, C68Y belongs to the Cys^{68}-His^{107}-Asp^{122} catalytic triad characteristic of NATs. The structural features of these amino acid substitutions provide insights into how minor changes in the NAT2 protein sequence can implicate substantial effects on the enzyme structure and function. Molecular dynamics simulations are underway to further characterize the effect of these mutations on the stability, substrate specificity and catalysis by the human NAT2 enzyme.

Keywords: *Human N-acetyltransferase 2 (NAT2), single nucleotide polymorphism (SNP), molecular modeling, structure/function*

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