

## STRUCTURAL ANALYSIS OF R426H AND R426C MUTATIONS IN 21 - HYDROXYLASE ENZYME FOR TESTING A NEW HUMAN P450C21 MODEL

Maturana, V. G.<sup>1</sup>, Soardi, F. C.<sup>1</sup>, Vicentini, R.<sup>1</sup>, Quaresma, A. J. C.<sup>2</sup>, Kobarg, J.<sup>2</sup>, De Mello, M. P.<sup>1</sup>

<sup>1</sup>Centro de Biologia Molecular e Engenharia Genética (CBMEG)-UNICAMP, Campinas, SP, <sup>2</sup>Centro de Biologia Molecular e Estrutural (CEBIME)-LNLS, Campinas, SP.

Deficiency of steroid 21-hydroxylase (CYP21) is the most common cause of congenital adrenal hyperplasia (CAH). Mutations in the *CYP21A2* gene are responsible for the disease. Frequently, patients carry deletion of the *CYP21A2* or pseudogene-derived point mutations, whereas new mutations are constantly described. The rare mutation R426C was identified for the first time in a Brazilian patient. In order to test structural variations of *CYP21A2* missense mutations - R426C and R426H - and validate a new human P450c21 model, the structural consequences of both mutations were compared by Sting Millenium free software (EMBRAPA). A previous biochemical *in vitro* analysis for both mutations revealed an almost absent CYP21 activity. Structural analysis suggested that R426 residue is very important for 21-hydroxylase normal functions as it is one of four residues needed for heme propionate coordination. The aminoacid change R426C abolished of all interactions between residues observed in the wild-type protein as predicted before by PDB-1DT6 model. In contrast, the R426H variation maintained the original interaction with R91 and created new interactions with different residues. Those are structural modifications within an important region for substrate ligation. Therefore, for both variations PDB-1SUO-based model used in this study confirmed the drastic effects upon the enzyme activity.

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