CYP21 MODELLING FOR STRUCTURAL ANALYSES OF NORMAL AND DISEASE-RELATED PROTEIN VARIANTS

Soardi, F.C.[1], Maturana, V.G.[1], Vicentini, R[1], Quaresma, A.J.C.[2], Kobarg, J.[2], De Mello, M.P.[1]

[1]Centro de Biologia Molecular e Engenharia Genética (CBMEG)-UNICAMP, Campinas, SP. [2]Centro de Biologia Molecular e Estrutural (CEBIME)-LNLS, Campinas, SP.

Steroid 21-hydroxylase deficiency is a common autossomal recessive disorder. *CYP21* pseudogene-derived mutations, gene deletion and conversion are responsible for 95% of the cases. New and rare mutations are observed in the remaining mutated alleles. Clinical manifestations depend directly on the structure-function relationship of mutant proteins. Several bioinformatic techniques have been used to analyze both normal and mutant variants, in order to improve understanding of this relationship. In the present study, one normal (K102R) and three disease-related (G56R, H62L and R408C) CYP21 variants were analysed. Structural analyses were performed using rabbit CYP2C5 (PDB-1DT6) and CYP2B4 (PDB-1SUO) structures as models. Each enzyme variant was evaluated by comparing changes in polarity, distances to heme group and steroid binding site, and heme surface accessibility. The conservation of each aminoacid residue was compared by alignment to human, murine, canine, ovine, porcine, and bovine CYP21 sequence. The K102R variant is not a conserved residue therefore the aminoacid change do not cause important structural alterations. In contrast, both G56R and R408C disease-related mutations are very conserved and resulted in drastic enzyme conformation changes. In addition, H62L mutation, although it is not very conserved among mammalian, it caused relevant structural changes as L62 looses the interaction with D67 residue which is important for β-sheet stability.

Key words: CYP21; CAH; Structural model.

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