Computational Identification and Analysis of Deleterious Non-synonymous Single Nucleotide Polymorphisms (nsSNPs) in the Human *POR* gene: A Structural and Functional impact

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Abstract

Cytochrome P450 oxidoreductase (POR) protein is essential for steroidogenesis, and POR gene mutations are frequently associated with P450 Oxidoreductase Deficiency (PORD), a disorder of hormone production. To our knowledge, no previous attempt has been made to identify and analyze the deleterious/pathogenic non-synonymous single nucleotide polymorphisms (nsSNPs) in the human POR gene through an extensive computational approach. Computational algorithms and tools were employed to identify, characterize, and validate the pathogenic SNPs associated with certain diseases. To begin with, all the high-confidence SNPs were collected, and their structural and functional impacts on the protein structures were explored. The results of various in silico analyses affirm that the A287P and R457H variants of POR could destabilize the interactions between the amino acids and the hydrogen bond networks, resulting in functional deviations of POR. The literature study further confirms that the pathogenic mutations (A287P and R457H) are associated with the onset of PORD. Molecular dynamics simulations (MDS) and essential dynamics (ED) studies characterized the structural consequences of prioritized deleterious mutations, representing the structural destabilization that might disrupt POR biological function. The identified deleterious mutations at the cofactor's binding domains might interfere with the essential interactions between the protein and cofactors, thus inhibiting POR catalytic activity. The consolidated insights from the computational analyses can be used to predict potential deleterious mutants and understand the disease's pathological basis and the molecular mechanism of drug metabolism for the application of personalized medication.

Keywords: POR; Mutations; Molecular dynamics simulation; Principal component analysis; Free energy landscape mapping