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In Silico Investigation of PAH Gene Mutations in Iran: Identification and Docking Simulation of Potential Pathogenic Variants

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Abstract

Background: Phenylketonuria (PKU) is the most prevalent inherited metabolic disorder resulting from a malfunction in the phenylalanine hydroxylase (PAH) enzyme. The diverse and consanguineous nature of the Iranian population offers a valuable opportunity to investigate autosomal recessive disorders.

Methods: We investigated 159 mutations in the PAH gene reported in Iran using various computational approaches. Pathogenicity and stability of genetic variants were assessed using tools like ACMG, Fathmm, CADD, SIFT, PolyPhen-2, Mutation Taster, MUpro, and I-Mutant 2.0. Amino acid conservation was analyzed with Clustal Omega and Consurf web servers. Secondary and tertiary modeling of wild-type and mutant PAH enzymes was performed using PSIPRED and I-TASSER, respectively, and 3D structures were visualized with PyMOL. Protein-protein interactions were explored using the STRING database, and potential pathogenic variants were identified through the Iranome Genomic Database. Additionally, we conducted protein-ligand docking simulations with Molegro Virtual Docker (MVD) to evaluate the structural and functional consequences of the putative pathogenic mutation (c.688G>A).

Results: Our analysis revealed that 80.8% of mutations occur in conserved regions, especially within the catalytic domain, with nearly half being missense mutations. The c.688G>A variant was identified

as a putative pathogenic mutation according to the Iranome Genomic Database. The cohort had a consanguinity rate of 31.67%. Docking studies indicated that this variant results in a significant loss of a catalytic site residue in the catalytic domain. PCR sequencing was the most common genetic testing method, accounting for 71.5% of cases.

Conclusion: This study provides insights for future functional research, genetic counseling, and the development of diagnostic tools, including a strip assay kit

Key words: PAH Gene, Phenylketonuria, Iran, Spectrum of Mutation.

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