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Investigating a Novel Bi-allelic Mutation in HPD-Like Protein: Docking Simulation Insights and Literature Overview

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Abstract

Background: Hereditary Spastic Paraplegia (HSP) is a rare neurodegenerative disorder characterized by progressive weakness and spasticity in the lower limbs. Mutations in the HPDL gene are associated with Spastic Paraplegia 83 (SPG83), an autosomal recessive form of HSP. Although HPDL mutations are known to contribute to SPG83, the molecular mechanisms underlying their role remain poorly understood, primarily due to the rarity of the condition. This study aims to investigate the genetic basis of HSP in two consanguineous families from Iran.

Methods: Whole-exome sequencing (WES) was utilized to identify genetic variants in the probands. To assess the pathogenic potential of the identified variants in the HPDL gene, various computational tools such as SIFT, CADD, Mutation Taster, Polyphen-2, and PANTHER were employed. Conservation analysis of the HPDL protein sequence was conducted using Clustal Omega and ConSurf tools, while the 3D structure of HPDL variants was predicted using the I-TASSER server. Protein-protein interactions involving HPDL were explored through the STRING database. Additionally, the DynaMut web server was used to evaluate the impact of the identified mutations on protein dynamics and stability. The effects of the variants on protein stability were further assessed using the I-Mutant and MUpro web servers. Finally, protein-ligand docking simulations were performed using Molegro Virtual Docker (MVD), a state-of-the-art integrated platform.

Results: WES identified two biallelic missense mutations: c.3G>C (p.Met1Ile) and c.128G>A (p.Arg43Pro) in the HPDL gene. The c.128G>A mutation is novel and is reported here for the first time in a patient with SPG83. Trio-based co-segregation analysis confirmed the inheritance of these variants. A thorough literature review indicated a significant consanguinity rate (49.55%) among families with HPDL mutations. Additionally, based on ΔΔG predictions and protein flexibility analysis, it was found that the p.Arg43Pro variant led to a reduction in molecular flexibility.
Conclusion: This study reinforces the association between HPDL mutations and HSP, specifically SPG83. Moreover, our bioinformatics findings represent an initial step toward validating the identified variant as a pathogenic mutation, paving the way for future functional studies.
Key Words: Hereditary spastic paraplegia, Spastic paraplegia 83, HPDL gene, Whole Exome Sequencing, Iran

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