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# *In silico* prediction of *UCLH1* disease-causing SNPs and its effects on protein stability

Isaac Cherian[a,b], Thejaswini Venkatesh[b,**], Prisho Mariam Paul[a,*]

[a] Department of Botany and Biotechnology, CMS College, Kottayam 686001, India
[b] Department of Biochemistry and Molecular Biology, Central University of Kerala, Kasargod 671316, India

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ABSTRACT

UCHL1 (Ubiquitin Carboxy-terminal hydrolase L1) is a deubiquitinating enzyme that is selectively expressed in neurons and repairs the neurons after injury by removing abnormal proteins through autophagy and UPP (ubiquitin proteasome pathway). It co-localizes with α-synuclein in Nigral Lewy bodies causing sporadic Parkinson's disease (PD) and *UCHL1* S18Y variant has been identified as a risk factor. Additionally, p.E7A, p.R178Q and p.A216D are associated with early onset progressive neuro-degeneration. A total of 3518 SNPs (Single Nucleotide Polymorphisms) within *UCHL1* are documented in NCBI and no comprehensive studies have addressed the effects of these SNPs. We analysed thirty non-synonymous (ns) SNPs using Ensembl Variant Effect Predictor (VEP) and iSTABLE prediction tools and eleven nsSNPs were found to be deleterious, possibly/probably damaging and alter protein stability. ConSurf analysis revealed that 8/11 nsSNPs were conserved and these SNPs were subjected to 3D molecular dynamic studies. Furthermore, PolymiRTS database 2.0 analysis indicated that 4/24, 3′-UTR SNPs affected the conserved miRNA target site or created a new target site for other miRNAs. Also, GeneMANIA predicted that UCHL1 forms interactome with several neuronal and ubiquitin pathway genes. To conclude, SNP analysis of *UCHL1* has predicted eight ns-SNPs and four 3′- UTR SNPs that show divergence from its normal activity and may affect the function of other gene components within its interacting network.

## 1. Introduction

Ubiquitin proteasomal pathway (UPP) is a major pathway of protein degradation. It consists of ubiquitin, a highly conserved 76 amino acid protein that can be conjugated to lysine residues, either singly or as polyubiquitinated chains on target proteins for its degradation (Kravtsova-Ivantsiv and Ciechanover, 2012). Ubiquitination also regulates protein membrane trafficking, endocytosis and DNA repair (Grabbe et al., 2011). Deubiquitinases (DUBs) remove ubiquitin from substrate proteins and human genome contains nearly 90 DUBs. Ub C-terminal hydrolase (UCH) forms a subgroup of DUBs and consists of four members namely UCHL1 (ubiquitin C-terminal hydrolase L1), UCHL3 (ubiquitin C-terminal hydrolase L3), UCHL5 (ubiquitin C-terminal hydrolase L5) and BAP1 (BRCA1 associated protein 1; UCHL2) (Bishop et al., 2016). *UCHL1* is located on chromosome 4, contains 9 exons and codes for 223 amino acids. UCHL1 protein is globular with a conserved peptidase C12 superfamily catalytic domain and short N- and C- terminal extensions (Das et al., 2006). The C12 polypeptide backbone forms a 'Gordian knot' which consists of two lobes of α-helices surrounding a tightly packed conserved hydrophobic core of β-strands and prevents its own unintentional proteasomal degradation (Virnau et al., 2006). UCHL1 exists in inactive conformation and requires protein-protein interaction for the activation of catalytic triad within the active site (Bishop et al., 2016). It is predominantly expressed in brain and makes upto 5% of the total neuronal protein. It is weakly expressed in gonads and fibroblasts at healing sites (Honoré et al., 1991). Its major fraction in sensory and motor neurons localizes to cytoplasm and in the absence of lipid binding domain, it is predicted to be membrane associated through macromolecular complexes (Bishop et al., 2014). It has high affinity for C-terminal end of ubiquitin and cleaves short disordered peptides and increases monomeric ubiquitin levels (Osaka et al., 2003). It also aids full folding of nascent ubiquitin polypeptide post-translationally and it has also been suggested to be an ubiquitin ligase (Larsen et al., 1998; Bilguvara et al., 2013).

Being an abundant brain protein, variants of *UCHL1* are associated with neuro-degeneration. A point mutation at E7A was identified as the

*Abbreviations:* AD, Alzheimer's Disease; CCDC, Coiled-coil Domain Containing; DUB, Deubiquitinating Enzyme(s); miRNA, MicroRNA(s); PD, Parkinson's Disease

* Correspondence to: Prisho M Paul, Department of Botany and Biotechnology, CMS College, Kottayam 686001, Kerala, India.
** Correspondence to: Thejaswini Venkatesh, Department of Biochemistry and Molecular Biology, Central University of Kerala, Kasargod 671316, Kerala, India.
*E-mail addresses:* thejaswinivenkatesh@cukerala.ac.in (T. Venkatesh), pmprisho@gmail.com (P.M. Paul).

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