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Computational analysis of polymorphisms of ubiquitin carboxyl–terminal esterase L1 (UCHL1) gene involved in Parkinson's disease

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ABSTRACT

Presence of genetic variations is a key player among many others which affect susceptibility and progression of the disease. Single nucleotide polymorphisms are the most frequent variations in human genome. Ubiquitin carboxyl-terminal esterase L1 (UCHL1) located on chromosome 4p14 is one of the potential candidate neuropathogenic protein involved in Parkinson's Disease. The aim of this study was to investigate the functional consequences of UCHL 1 single nucleotide polymorphisms (SNPs) to understand the biological basis of complex traits and diseases as the Genetics of human phenotypic variation could be understood by knowing the functions of SNPs derived from the data available in dbsSNP data base and different computer applications are used. Nonsynymous SNPs are relevant in many of the human inherited disease since they change the aminoacid sequence of the protein. Few common single –nucleotide polymorphisms (SNPs) of the UCHL1 genes were analyzed by using different bioinformatics tools based on evolutionary analysis- sequence homology based, structure based approach. Protein structural analysis was also performed by using I- Mutant. It was recognized that rs6063 and rs74315205 SNPs of UCHL1 gene were found to be more damaging in PD and is responsible for the alteration in the levels of expression. Conclusion: It has been concluded that among the entire SNPs of UCHL1 gene, the mutation in rs6063 and rs74315205 have the most significant effect on functional variation. The study suggested that G191R, G199 R, G88R and R231G variants of UCHL1 could directly or indirectly destabilize the amino acid interactions and hydrogen bond networks thus explaining the functional deviations of protein to some extent. These results may further form the basis of large- scale population based association studies.

KEY WORDS: PARKINSON'S DISEASE, SINGLE NUCLEOTIDE POLYMORHISMS, SNP, UCHL 1 GENE

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INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's affecting approximately 1–2% of the population over the age of 65 and reaching a prevalence of almost 4% in those aged above 85. Resting tremor, bradykinesia, rigidity, and postural instability are the main clinical symptoms of the disease often accompanied by nonmotor symptoms including autonomic insufficiency, cognitive impairment, and sleep disorders (Gómez *et al.* 2015).

There are two forms of the disease, the sporadic and familial forms. The patients with familial PD are distinguished from the ones who suffer from sporadic PD because of the early onset, greater consanguinity rate, and greater frequency of similar disease in their parents Familial PD cases are of 10% of the total no of cases and are based on the genetic component of the disease (Christine and Ana 2012). There is a life risk of 1.3% for women and 2% for men as per the study of Olmstead country. The disease is going to increase in the future to come due to the medical expenses and other reasons (Prasad *et al.* 2016).

UCHL1 /Park 5 gene is a compelling candidate gene for PD (Maraganore *et al.* 2004) on biological grounds because the protein it encodes plays a pivotal role in the ubiquitin proteasome system (UPS), displays neuron-specific expression and is found in Lewy bodies, the neuropathologic hallmark of PD .The ubiquitin proteasome system regulates the degradation of key regulatory proteins as well as misfolded and damaged proteins (Aaron & Yong 2014). Ubiquitin carboxy-terminal hydrolase L1 (UCHL1) is a 223-a.a. protein which is a component of the UPS, which cleaves the carboxy-terminal peptide bond of polyubiquitine chains, working as a deubiquitinating enzyme (Liu *et al.* 2002). It encodes for one of the most abundant proteins in the brain. Mutations in this target were found to be responsible for a genetic form of PD. It is thought a mutation at amino acid position 93 for methionine may decrease UCHL1 hydrolase activity, leading to accumulation of proteins that should have been degraded, and subsequently the progression of PD (Contu *et al.* 2014).

One of the important gene specific mutations described for the familial forms of PD, include autosomal dominant mutations of UCHL1 (PARK5). However, the pathogenic mechanisms underlying mitochondrial dysfunction in familial PD require further detailed investigation at the molecular level. The loss of dopaminergic neurons in PD is preceded by the formation of Lewy Bodies, insoluble proteinaceous inclusions enriched with ubiquitinated aggregates, as well as displaying extensive protein oxidative modification, (Hyo and Sun 2015).

The structure of UCH-L1 contains a central β-sheet that is flanked on either side by α-helices as shown in figure 1. In the crystal structure, UCH-L1 is an asymmetric dimer; however, equilibrium sedimentation analysis showed that the protein is monomeric in solution. The catalytic triad comprises Cys90, His161, and Asp176; in the crystal structure, the side chains of these residues are not close enough for catalytic activity, suggesting that in the absence of substrate, UCH-L1 is in an inactive form. In addition, the active site is covered by a loop (L8) that has been suggested to restrict the size of substrates that can access the active-site cleft (Bishop *et al.* 2016).

A single nucleotide polymorphism (SNP) is a source of variance in a genome. A SNP is a single base mutation in DNA. SNPs are the most simple form and most common source of individual genetic polymorphism in the human genome (90% of human DNA polymorphisms). A SNP in a coding region may have two different effects on the resulting protein: Synonymous, the substitution causes no amino acid change to the protein it produces; non synonymous, the substitution results in an alteration of the encoded amino acid. One half of all coding sequence SNPs result in non- synonymous codon changes (Smith 2002). A non- synonymous single nucleotide polymorphism (nsSNP) occurring in a coding gene may cause an amino acid substitution in the corresponding protein product, thus affecting the phenotype of the host organism .Non synonymous variants constitute more than 50% of the mutations known to be involved in human inherited diseases Single nucleotide polymorphisms (SNPs) (Kumar 2009). Computational methods are sufficiently fast and flexible to provide reliable predictions of functionally significant SNPs with a high accuracy of 80–85% when combined with sequence, structure, and phylogenetic relationships (Minyue *et al.*, 2014). Here we are trying to consider computationally a suitable protocol for missense mutation (point mutation/single amino acid polymorphism) analysis before wet lab experimentation and provided an optimal path for further clinical and experimental studies.

MATERIAL AND METHODS

The data on protein sequence and variants (single amino acid polymorphisms/missense mutations/point mutations) for UCHL1 gene were collected from NCBI database (http://www.ncbi.nlm.nih.gov/snp/)of SNP by applying appropriate limits like homo-sapiens, Chromosome 4, cited in Pubmed etc. to detect the detrimental point mutants.

Further deleterious SNP analysis were performed using the computational tools sorting intolerant from tolerant (SIFT) and Polyphen 2 for nsSNPs and FASTSNP and UTRscan for UTR SNPs.

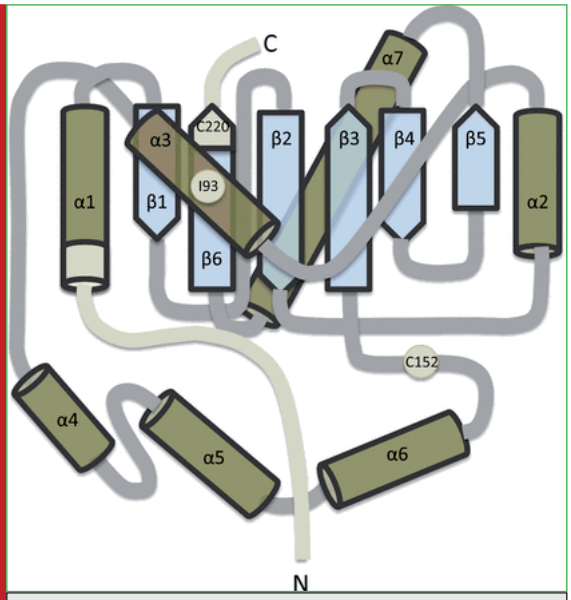

FIGURE 1. Schematic of UCH-L1 structure, Schematic illustrating the α-helical and β-strand structure of UCH-L1. The residues 1–11 at the N-terminus, 220–223 at the C-terminus and residues Ile^{93} and Cys^{152} are highlighted. It has been proposed that modification at these points can affect the hydrophobic core of β-strands that are otherwise protected from solution.

SEQUENCE HOMOLOGY BASED METHOD (SIFT)

We have used the program SIFT (http://sift.bii.a-star.edu.sg/index.html) to detect deleterious coding nonsynonymous SNPs. SIFT is a sequence homology-based tool to predict whether an amino acid substitution in a protein would be tolerated or damaging (Pauline *et al*., 2003). We performed SIFT by submitting the query in the form of SNP IDs or chromosome positions and alleles in nsSNVs tool. Variants at the position with tolerance index score #0.05 were considered as deleterious. A lower tolerance index indicates that the particular amino acid substitution likely has a more functional impact (Pauline *et al*., 2001).

STRUCTURE HOMOLOGY BASED METHOD (POLYPHEN)

Analyzing the damaged coding nonsynonymous SNPs at the structural level is considered to be very important to understand the functional activity of the protein of concern. We have used PolyPhen server (http://genetics.bwh.harvard.edu/pph2/) for this purpose. This is an automatic tool that predicts the possible impact of an amino acid substitution on a number of features, including the sequence, phylogenetic, and structural information. The query was submitted in the form of protein sequence with mutational position and substitution. The PolyPhen output comprises a score that ranges from 0 to 1, with zero indicating a neutral effect of amino acid substitutions on protein function. Conversely, a high score represents a variant that is more likely to be damaging (Ramensky *et al*., 2002).

FUNCTIONAL SIGNIFICANCE OF NONCODING SNPS IN REGULATORY UNTRANSLATED REGIONS

The Web server FastSNP (http://fastsnp.ibms.sinica.edu.tw) was used for predicting the functional significance of the 5' and 3' UTRs of the UCHL 1 gene (Hsiang *et al*., 2006). The FastSNP server follows the decision tree principle with external Web service access to TF Search, which predicts whether a noncoding SNP alters the transcription factor-binding site of a gene. The score was given by this server on the basis of levels of risk with a ranking of 0, 1, 2, 3, 4, or 5. This signifies the levels of no, very low, low, medium, high, and very high effect, respectively.

SCANNING OF UTR SNPS IN UTR SITE

The 5' and 3' UTRs are involved in various biological processes such as posttranscriptional regulatory pathways, stability, and translational efficiency. We used the program UTRscan (http://itbtools.ba.itb.cnr.it/utrscan) which allows one to search the user-submitted sequences for any of the patterns collected in the UTR site (Graziano and Sabino 1999). UTRsite is a collection of functional sequence patterns located in 5' or 3' UTR sequences. Briefly, two or three sequences of each UTR SNP that have a different nucleotide at an SNP position are analyzed by UTRscan, which looks for UTR functional elements by searching through user-submitted sequence data for the patterns defined in the UTRsite and UTR databases. If different sequences for each UTR SNP are found to have different functional patterns, this UTR SNP is predicted to have functional significance. The Internet resources for UTR analysis are UTRdb and UTRsite. UTRdb contains experimentally proven biological activity of functional patterns of UTR sequence from eukaryotic mRNAs (Graziano *et al*., 2002). The UTRsite has the data collected from UTRdb and also is continuously enriched with new functional patterns.

SUPPORT VECTOR MACHINE (I-MUTANT 3.0 AND FOLD- X)

The analyses were also conducted by using I-Mutant Suite is a suite of support vector machine (SVM)- based predictors of protein stability changes according to Gibbs free energy change, enthalpy change, heat capac-

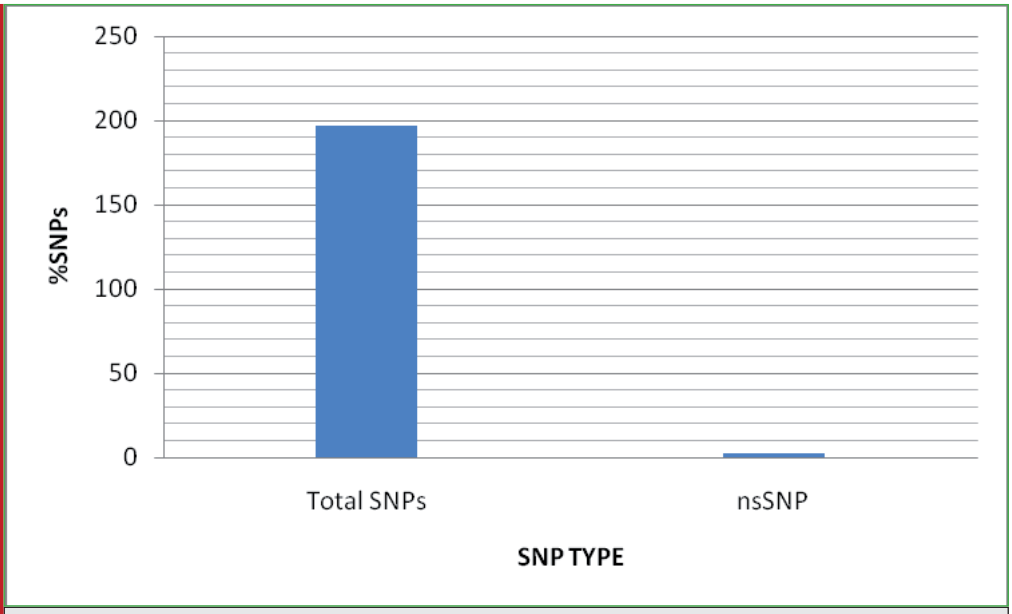

FIGURE 2. A graphical representation of distribution of nonsynonymous, SNPs for UCHL 1 (based on the dbSNP database).

ity change, and transition temperature (Capriotti *et al.*, 2005).The analysis was performed based on protein sequence combined with mutational position and correlated new residue. And the output result of the predicted free energy change (DDG) classifies the prediction into one of three classes: largely unstable (DDG, 20.5 kcal/mol), largely stable (DDG.0.5 kcal/mol), or neutral (-0.5# DDG#0.5 kcal/mol). IMutant Suite is available at (http://gpcr2.biocomp.unibo.it/cgi/predictors/I-Mutant3.0/I-Mutant3.0.cgi).

The FASTA sequence of protein retrieved from UniProt was used as an input to predict the mutational effect on protein stability. I-Mutant also provides the scores for free energy alterations, calculated with the FOLD-X energy based web server (Schymkowitz *et al.*, 2005). FOLD-X is a computer algorithm for quantitative estimation of interactions facilitating the stability of proteins. The FOLD-X tool was used to provide the comparison between wild type and mutant models in the form of van der Waals clashes, which greatly influence the energy decomposition.

RESULTS AND DISCUSSION

SINGLE AMINO ACID POLYMORPHISM DATASET FROM NCBI DBSNP DATABASE

The dbSNP database contains both validated and non-validated polymorphisms. In spite of this drawback, we opted to avail the dbSNP because the allelic frequency of most of nsSNPs of UCHL 1 has been recorded there and that is the most extensive SNP database. We selected 15 SNPs, out of which 2 were nsSNPs, as shown in Fig. 2.

DELETERIOUS SINGLE POINT MUTANTS IDENTIFIED BY THE SIFT PROGRAM

The conservation level of a particular position in a protein was determined by using a sequence homology-based tool, SIFT. The protein sequences of 64 variants were submitted independently to the SIFT program to determine the tolerance index. The higher the tolerance index, the less functional impact a particular amino acid substitution is likely to have, and vice versa. Among the 64variants, 24 were found to be deleterious, having a tolerance index score of ≤0.05. The results are shown in Table 2.

UTRSCAN ANALYSIS

Functional SNPs in UTR found by the UTRscan server Polymorphisms in the 3' UTR affect gene expression by

Table 1: SIFT classification

Ranking	Risk Division
0	No effect
1	Very low
2	Low
3	Medium
4	High
5	Very high

Table 2: SIFT analysis of SNPs, Variants with tolerance index ≤0.05 score are considered as deleterious while others are taken to be tolerant.

SNPs	Amino acid Change	Score	Prediction
rs6063	G191R	0.002	DELETERIOUS
	G191R	0.002	DELETERIOUS
	G199R	0.002	DELETERIOUS
	G199R	0.002	DELETERIOUS
	G88R	0.003	DELETERIOUS
	G88R	0.003	DELETERIOUS
rs1799895	R231G	0.017	DELETERIOUS
rs45454496	E3931K	0.037	DELETERIOUS
	E3898K	0.037	DELETERIOUS
	E941K	0.055	TOLERATED
	E22K	0.057	TOLERATED
	E1022K	0.147	DELETERIOUS
	E1837K	0.186	TOLERATED
	E1846K	0.188	TOLERATED
	E529K	0.233	TOLERATED
	E878K	0.368	TOLERATED
rs62625014	S389F	0.054	TOLERATED
	S320F	0.101	TOLERATED
	S320F	0.101	TOLERATED
	S320F	0.101	TOLERATED
	S320F	0.101	TOLERATED
rs63749888	E47Q	0.102	TOLERATED
	E37Q	0.248	TOLERATED
rs66785829	V3601D	0.011	DELETERIOUS
	V3634D	0.012	DELETERIOUS
	V644D	0.063	TOLERATED
	V201D	0.067	TOLERATED
	V725D	0.193	TOLERATED
	V550D	0.209	TOLERATED
	V1549D	0.28	TOLERATED
	V1540D	0.282	TOLERATED
rs74315205	E864K	0	DELETERIOUS
rs75353611	D25V	0.003	DELETERIOUS
	D25V	0.003	DELETERIOUS
	D27V	0.003	DELETERIOUS
	D25V	0.003	DELETERIOUS
	D25V	0.027	DELETERIOUS
rs112534524	G261A	0.27	TOLERATED
	G261A	0.274	TOLERATED
	G261A	0.277	TOLERATED
	G261D	0.114	TOLERATED
	G261D	0.119	TOLERATED
	G261D	0.126	TOLERATED
rs121912705	T754N	0.039	DELETERIOUS
	T3744N	0.053	TOLERATED
	T3711N	0.055	TOLERATED
	T311N	0.302	TOLERATED
	T660N	0.386	TOLERATED
	T835N	0.45	TOLERATED
	T1659N	0.535	TOLERATED
	T1650N	0.556	TOLERATED
rs121912706	R3873W	0.001	DELETERIOUS
	R3906W	0.001	DELETERIOUS
	R916W	0.002	DELETERIOUS
	R1821W	0.003	DELETERIOUS
	R997W	0.003	DELETERIOUS
	R1812W	0.004	DELETERIOUS
	R853W	0.049	DELETERIOUS
	R504W	0.06	TOLERATED
rs180843436	E137K	0.014	DELETERIOUS
	E486K	0.015	DELETERIOUS
	E3537K	0.021	DELETERIOUS
	E3570K	0.021	DELETERIOUS
	E580K	0.06	TOLERATED
	E661K	0.061	TOLERATED
	E1485K	0.062	TOLERATED
	E1476K	0.063	TOLERATED
rs199473343	L1622M	0.168	TOLERATED
	L1655M	0.169	TOLERATED
	T854N	0.105	TOLERATED
	T3844N	0.147	TOLERATED
	T3811N	0.148	TOLERATED
	T411N	0.267	TOLERATED
	T935N	0.356	TOLERATED
	T1759N	0.432	TOLERATED
	T1750N	0.434	TOLERATED
	T760N	0.476	TOLERATED
rs386833750	CC2D2A	0	DELETERIOUS
rs386833752	T1065M	0.001	DELETERIOUS
	T1114M	0.001	DELETERIOUS

affecting the ribosomal translation of mRNA or by influencing the RNA half-life. Table 3 shows the list of SNPs in the 3 that are predicted to be damaging because of the presence of regulatory elements and are of functional significance. We used the UTRscan server for this purpose. We analyzed the same 64 variants in UTRscan that were analyzed by the SIFT. The UTRscan server finds patterns of regulatory region motifs from the UTR data-

Table 3: UTRScan analysis of the SNPs where Uorf - Upstream open reading frame.IRES- Internal ribosome entry site, MBE-Mushashi Binding site

SL.No	SNPs	No of signal Matches	Regulatory Elements				
1	rs6063	4	uORF	MBE		GY-BOX	ARE2
2	rs6533526	4	uORF	MBE	IRES	K-BOX	
3	rs62625014	4	uORF	MBE	IRES	BRD-BOX	
4	rs35530544	1	uORF				
5	rs36210415	1	uORF				
6	rs45570339	2	uORF	MBE			
7	rs63749888	4	uORF	MBE	IRES	PAS	
8	rs66785829	4	uORF	MBE	IRES	SXL	
9	rs72544141	3	uORF	MBE		PAS	
10	rs72556370	2	uORF			PAS	
11	rs74315205	2	uORF		IRES		
12	rs74821926	4	uORF	MBE	IRES	PAS	
13	rs75353611	4	uORF	MBE	IRES	PAS	
14	rs77335374	3	uORF	MBE	IRES		
15	rs77408163	4	uORF	MBE	IRES	PAS	
16	rs77449454	4	uORF	MBE	IRES	GY-BOX	
17	rs79228041	5	uORF	MBE	ADH_DRE	SXL_BS	GY-BOX
18	rs112534524	2	uORF	MBE			
19	rs121912705	1	uORF				
20	rs121912706	2	uORF		IRES		
21	rs121913101	3	uORF		IRES	DMRT1_RE	
22	rs121913103	2	uORF			DMRT1_RE	
23	rs121913105	1	uORF				
24	rs121918124	1	uORF				
25	rs121918125	1	uORF				
26	rs121965070	1	uORF				
27	rs140126678	2	uORF	MBE		PAS	
28	rs143228029	4	uORF	MBE	IRES	SXL_BS	
29	rs148654834	3	uORF	MBE		PAS	
30	rs148654834	3	uORF	MBE		PAS	
31	rs199473643	1		MBE			
32	rs202247811	1			IRES		
33	rs386833750	1	uORF				
34	rs386833751	1			IRES		
35	rs386833752	1			IRES		
36	rs386833757	2	TOP		IRES		
37	rs386833760	2		MBE	IRES		
38	rs386833761	2		MBE	IRES		
39	rs587778769	1			IRES		
40	rs587778773	1			IRES		
41	rs587778775	2		TOP	IRES		
42	rs587778776	1			IRES		
43	rs587778801	1			IRES		
44	rs587778809	3	uORF		IRES	PAS	
45	rs587778811	1			IRES		
46	rs796051882	1	BRD-BOX				

Table 4: PolyPhen analysis

SNP	Mutation effect	Scoring
rs6063	Probably Damaging	1
rs1799895	Bengin	0.067

base and gives information about whether the matched pattern is damaged. Various studies have shown that the transcriptional regulation is biologically important and the alteration in the transcriptional compo-nents leads to disease.

DAMAGING SINGLE POINT MUTATIONS IDENTIFIED BY THE POLYPHEN SERVER

The structural levels of alteration were determined by applying the PolyPhen program.64 protein sequences of nsSNPs investigated in this work were submitted as input to the PolyPhen server and the results are shown in Table 4. A PSIC score difference of 0.5 and above was considered to be damaging. we could infer that the results obtained on the basis of sequence details (SIFT) were in good correlation with the results obtained for structural details (PolyPhen), as can be seen from Tables 2 and 4. Interestingly, some of the deleterious variants identified by SIFT also were seen to be less stable by the Polyphen server. It is predicted that the rs6063 mutation effect is the damaging one among the SNPs identified. Hence the mutations occurring with this nsSNP would be of prime importance in the identification of UCHL 1 induced Parkinson's disease according to SIFT and Poly-Phen results.

FUNCTIONAL SNPS IN UTR FOUND BY THE FASTSNP SERVER

By the use of Fast SNP server functionally significant variants were predicted as shown in table 5. According to this server, the functional information derived about rs6063 predicted it as damaging with a score of 0.741. Studies show that SNPs have functional effects on protein structure by a single change in the amino acid (Cargill *et al.*, 1999 & Sunyaev *et al.*, 2000) and on transcriptional regulation (Prokunina *et al.*, 2002 & Prokunina *et al.*, 2004).

STRUCTURAL ANALYSIS OF MUTANT STRUCTURES

Out of all the above methods the SNPs predicted to be deleterious i.e., rs6063 and rs74315205 were mapped to the native structure by I mutant 2.0 server to understand its structural stability.

PREDICTION OF PROTEIN STRUCTURAL STABILITY

I-Mutant is a neural network based routine tool used in the analysis of protein stability alterations by consider-

Table 5: Fast SNP analysis

Functional Category	Prediction Tool	Prediction Result	Prediction Detail
protein coding	PolyPhen	**probably damaging**	rs6063.html
	SIFT	**damaging**	rs6063.html
	SNPeffect	**deleterious**	rs6063.1.html
	LS-SNP	**deleterious**	destabilizing.html destabilizing.html
	SNPs3D	**deleterious**	SNPs3D.html
	Ensembl-NS	**nonsynonymous**	rs6063.html
splicing_regulation	ESEfinder	**changed**	rs6063.A.html rs6063.G.html
	ESRSearch	**changed**	rs6063.A.html

Table 6: Protein structural stability based on standard free energy change Where, "WT" is the amino acid in native protein, "New" is mutant amino acid and DDG is the stability (DDG b 0: decrease stability, DDG N 0: increase stability).

Mutation	Position	WT	New	PH	Temperature	Stability	DDG
G191R	191	G	R	7.0	25	Decrease	-0.25
G199R	199	G	R	7.0	25	Decrease	-0.83
G88R	88	G	R	7.0	25	Increase	0.38
R231 G	231	R	G	7.0	25	Increase	0.48

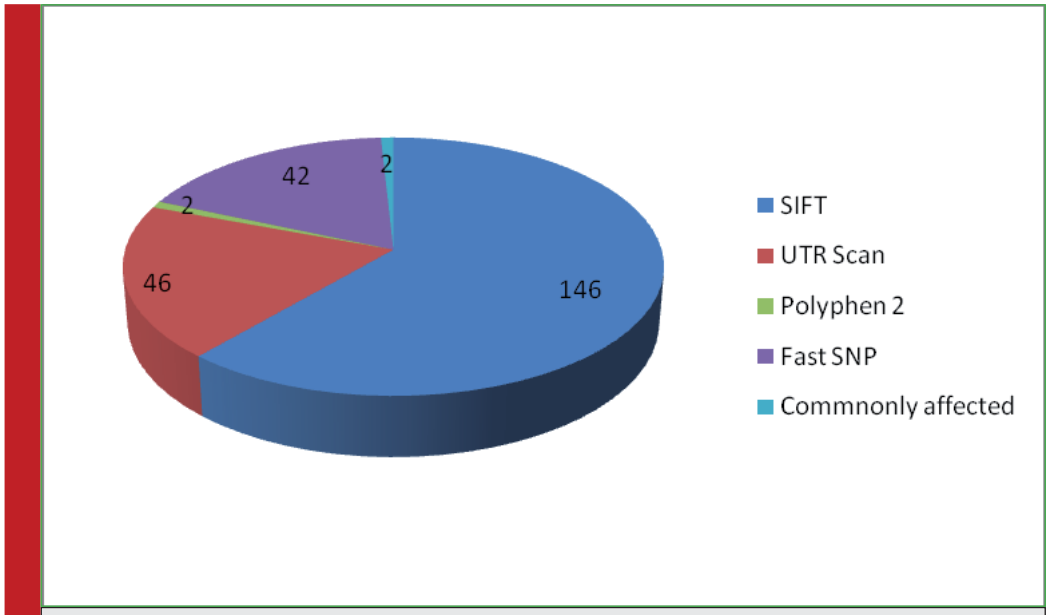

FIGURE 3. Status of SNPS derived through various algorithms

ing the single-site mutation. I-Mutant also provides the scores for free energy alterations, calculated with the FOLD-X energy based web server. By assimilating the FOLD-X estimations with those of I-Mutant, the 93% precision can achieved. The mutations of UCHL 1 gene have been selected on the basis of prediction scores of Poly Phen. These variants were given to I-Mutant web server to predict the DDG stability and reliability index (RI) upon mutation. Out of the 4 variants 2 were found to be less stable as shown in Table 6.

RATIONAL CONSIDERATION OF SIFT, UTR SCAN, POLYPHEN-2, FAST SNP AND I-MUTANT 3.0

We considered the 64 most potential hindering point changes for further course of examinations in light of the fact that they were generally discovered to be less steady, injurious, and harming by the I-Mutant 3.0, SIFT and Poly Phen-2 servers individually. The most commonly affected among the 6 computational tools has been taken for further studies i.e. 2 variants as shown in Figure 3.

CONCLUSION

Hence the combined approach using SIFT, UTRscan and Polyphen 2 predicts the mutation rs6063 and rs74315205 are most deleterious among the mutations for UCHL1 gene causing Parkinson's disease characterized. The recognition of these SNPs as deleterious ones provides insight into PD biology and presents as anti Parkinson's disease therapeutic targets and diagnostic markers .Since missense mutations are nucleotide substitutions that change an amino acid in a protein, the deleterious effects of these mutations are commonly attributed to their impact on primary amino acid sequence and protein structure. Structural analysis results showed that the amino acid residue substitutions which had the greatest impact on the stability of the UCHL 1 protein were mutations in rs6063 and rs74315205 and the variants like G191R, G199 R, G88R and R231G. Based on our results, we conclude that these SNPs should be considered important candidates in UCHL1 related P.D. Based on our results we conclude that these SNPs should be considered as important candidates in causing Parkinson's disease.

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DISCLOSURE STATEMENT

No competing financial interests exist.

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