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Special Issue: Computational drug designing and molecular docking analyses

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Computational drug designing: A new paradigm for the treatment of Parkinson's disease

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Abstract

Parkinson's disease is the second age related neurodegenerative disorder, affects almost 10 million people worldwide. Sporadic cases of PD resulted from aging and environmental factors while familial cases resulted from mutations in LRRK2, SNCA, PRKN, GBA, UCHL1, DJ-1, and PINK1. However, some genes mutations are not inherited (sporadic). Computational approaches played a major role in the development of drug used in clinical practice. These computational methods have evolved with the experimental methods that underpin the development of novel compounds against disease. In this review article we elaborate mechanisms of gene variants involves in Parkinson's disease, to epitomize computationally derived inhibitors against these variants, utilizing *in silico* approaches to find the molecules and explain the effect of particular molecule binds with target molecules.

Introduction

Parkinson Disease (PD) was expressed by James Parkinson about 2 centuries ago in 1817 having irregular muscular power. From 100,000 people worldwide, almost 35 new cases expressed every year [1, 2]. PD is an escalating neurodegenerative disease caused by characteristic motor symptoms of rhythmic shaking in hands, arms, head legs, and improper postural balance [3]. The symptoms of PD include cortico-balance degeneration (CBD), multiple system atrophy (MSA) and synucleinopathies (tauopathies). The accumulation of top ranked proteins having deteriorating neuron and glia lessen the PD [4]. There are peculiar neuropathological changes in brain in PD. The irregular proteinaceous spherical bodies called Lewy bodies are formed [5]. In substantianigra Lewy bodies (which contain α-synucline) and loss of dopaminergic neuron facilitate the reduction of voluntary movement which is a significant neuropathological finding [6]. The causes of PD include genetic cause, environmental factors, aging and the genetic causes may include mutation in single gene (**Fig. 1**).

Numerous genes are involved while VPS35, SNCA and LRRK2 are autosomal dominant and DJ1, parkin and PINK are recessive [7]. The dysregulation in DJ1,PRKN, PINK1, LRRK2, SNCA, VPS35 and GBA genes lead to PD [8]. The environmental factors include oxidative stress, passive smoking, strenuous exercise, plasma urate and traumatic brain injury [9].

The dopaminergic neurons damage in the pars compact (portion of SN which is medial to pars reticulate) of substantianigra (structure in midbrain that involve in movement) involve in motor symptoms and olfactory impairment include in non-motor symptoms [10, 11]. There are six neuropathological disease changes in PD. The first two pre-symptomatic stages of PD are the inclusion bodies pinched to medulla oblongata and olfactory bulb. In third and fourth stages, the substantianigra and other nuclei of the midbrain and forebrain become ostentatious with the continuation of the disease. At this stage, the patients begin to show clinical symptoms of PD. In last two stages, neocortex show various symptoms [12].

Although, the degeneration of dopaminergic nigrostriatal neurons with Lewy bodies is significant correlate of motor dysregulation in PD, however the damage in cytoskeleton of other nerve cells tryptaminergic, adrenergic, cholinergic glutamatergic, GABA-ergic, and noradrenergic nerve also observed in PD [13]. Many FDA approved are available for the treatment of typical Parkinson's disease (**Fig. 2**).

Computer aided drug design use in rational drug design aims at to reduce the time to analyze and develop drugs and to determine target for novel drug candidates. It is useful for proximate design of prodrugs. The first step of drug design is to identify the appropriate target molecule linked with a disease (**Fig. 3**) [14]. The computational approaches used in disclosure of therapeutic compounds [15]. By using a broad area of computational approaches computer aided drug designing linked with medicinal chemistry and drug discovery, which surpasses both practical applications and novel methodologies [16]. Although, the conventional approaches has expensive trial procedures [17].

Various computational approaches utilized for drug designing including structure-based drug designing. This approach necessitate recognition of an appropriate protein target [18, 19]. A typical structure based drug designing is begin with the identifications and corroboration of the structure [20]. X-ray crystallography and Nuclear Magnetic Resonance (NMR) are employed for 3D structural prediction through experimental analyses. Homology modeling is an infallible method to determine the computational 3D structure predictions. Virtual screening has been to scrutinize different compounds by screening large chemical libraries [19, 21, 22]. Different databases such as ZINC and ChEMBL are used for virtual screening [23, 24]. Usually, structure based virtual screening is performed on the 3D structure experimentally solved through X-ray crystallography and NMR while ligand based virtual screening is employed for computationally predicted structures [25, 26]. *De novo* design is used to design the novel compounds [27].

Ligand based drug designing is utilized to develop therapeutically active compounds in order to observe such molecule that are interrelate with target [28].The function of a protein depends on its structure and Quantitative structure-activity relationship (QSAR) utilized to study the association between the structure and function [29]. Comparative molecular field analysis (CoMFA), an approach of 3D QSAR is widely used [30]. Pharmacophore represents a conceptual model to describe the structure binding affinity relationship [31]. Computational drug designing includes to identify the active binding site, screening of chemical libraries to identify potent hit molecule, to optimize

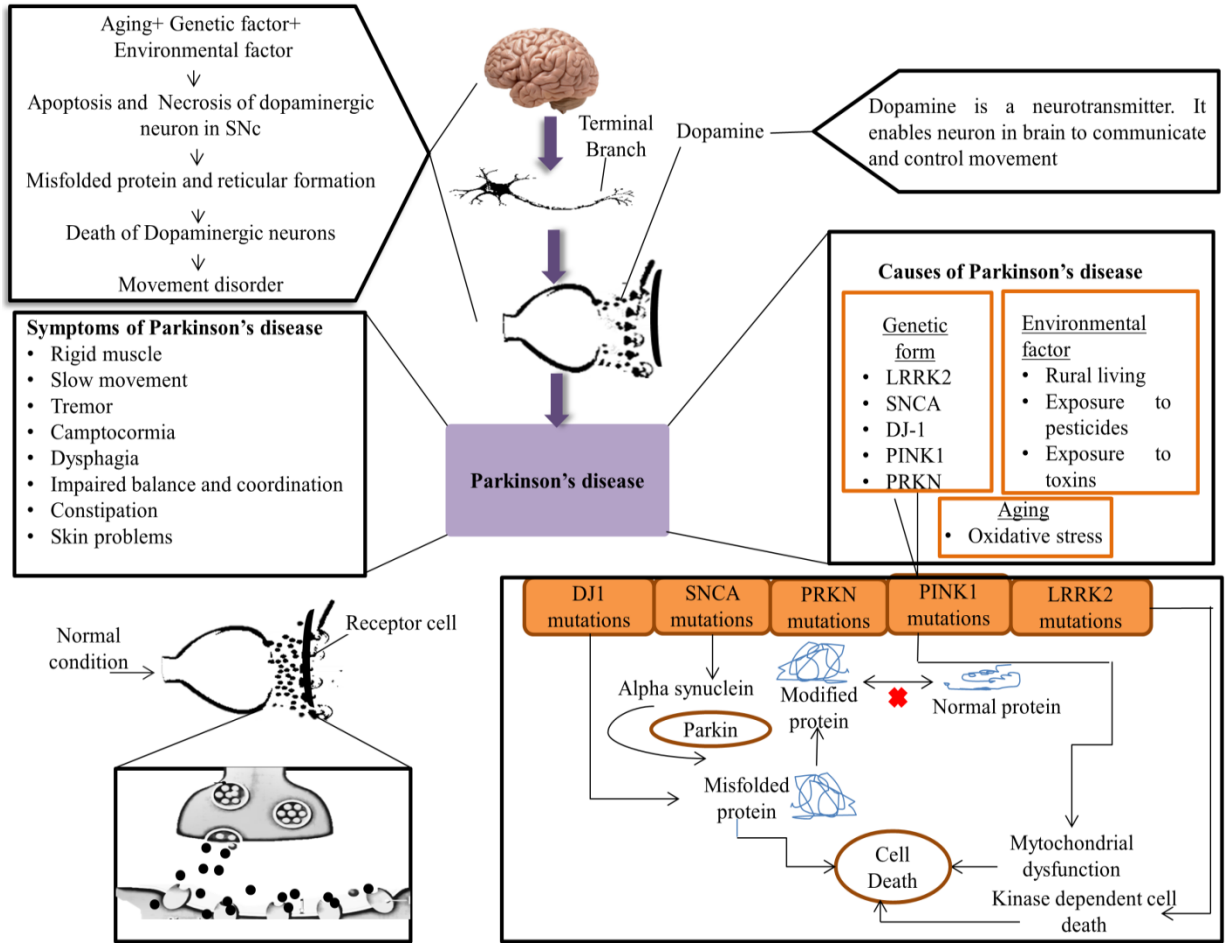

Fig. 1: Genetic mutation, environmental factor and oxidative stress induce dopaminergic cell death which causes movement disorder.

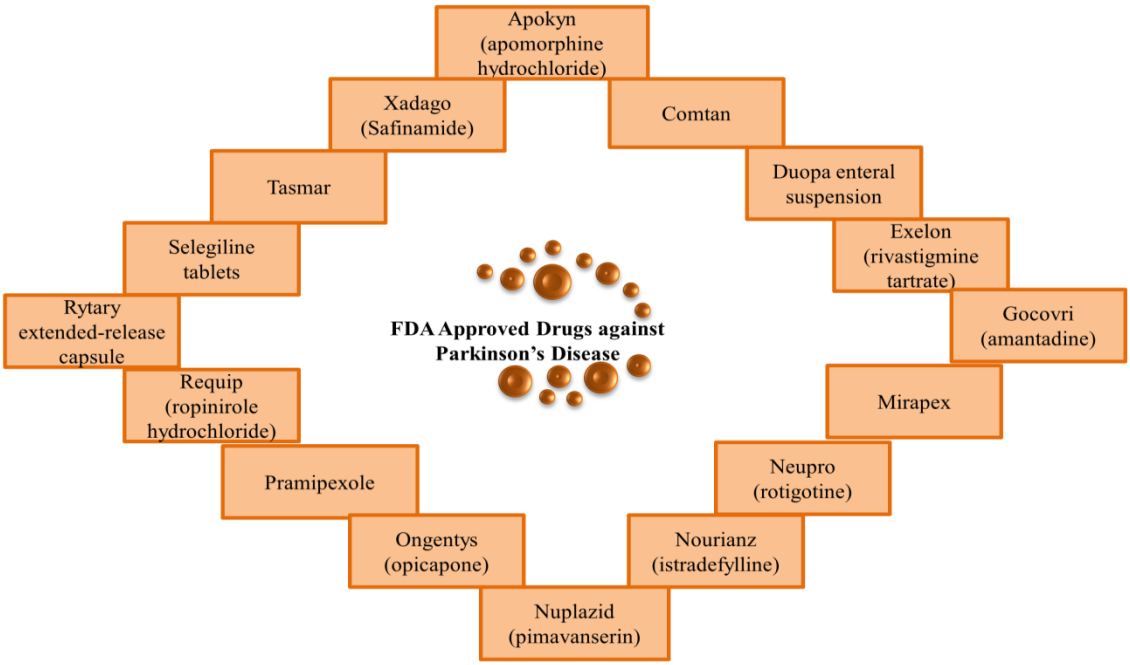

Fig. 2: FDA approved drugs for the treatment of Parkinson's disease

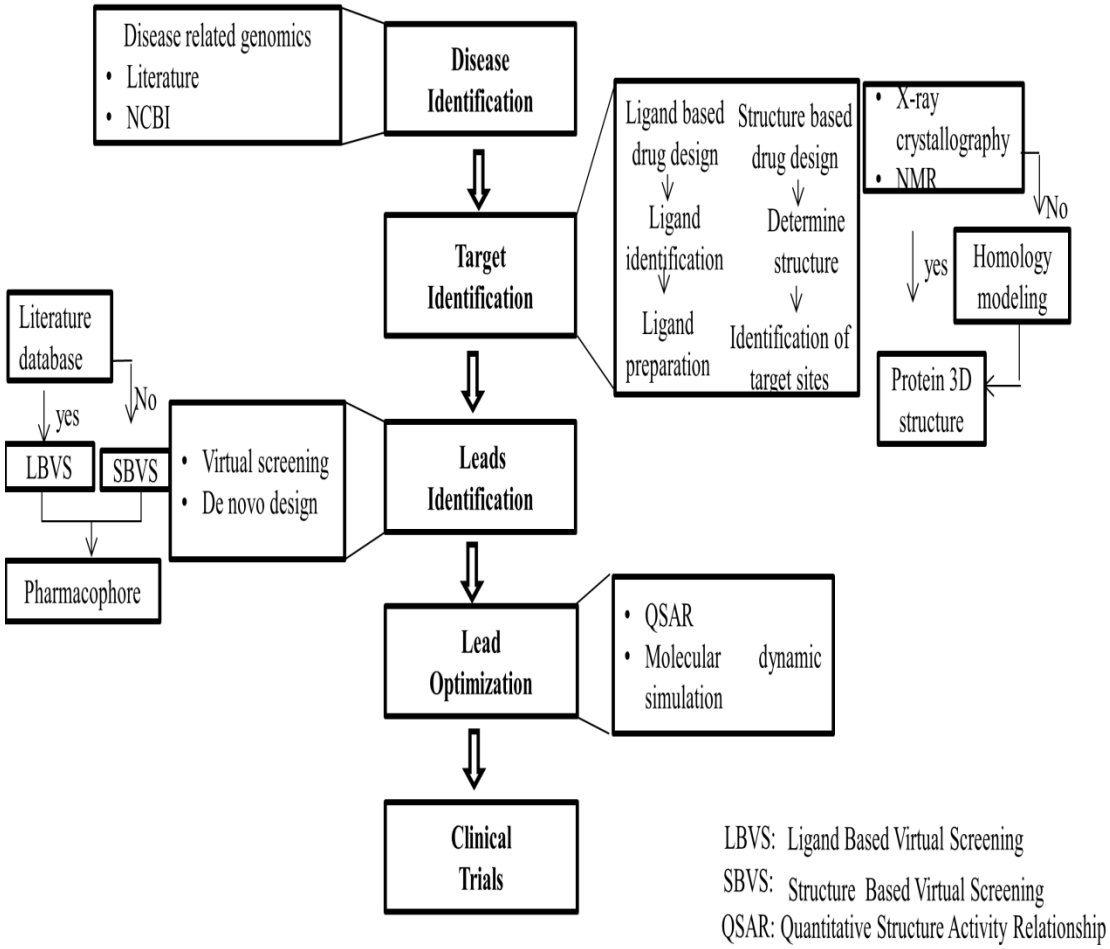

Fig. 3: Schematic representation of drug discovery process.

Genetics of Parkinson's disease and computational drug designing

It has been reported that mutations in the, PINK1, PLA2G6, DJ1, PRKN, ATP13A2, FBXO7, SYNJ1, DNAJC6, VPS13C, C19orf12, RAB39B, LRRK2, SNCA, VPS35 and UCHL1 are involved in PD [33]. GBA is considered as a risk gene of PD [34]. VPS35 mutations are rarely cause PD [35]. There has been limited literature available for PINK1, DJ1, PRKN [36]. *SNCA*, *PINK1*, LRRK2, *PRKN* and *DJ1 (Table 1) are most common causative genes involved in PD [37]*. In this review article, 9 genes (PRKN, PINK1, DJ1, ATP13A2, LRRK2, SNCA, VPS35, GBA and UCHL1) will be discussed. However, computational work on UCHL1, GBA, VPS35 and PRKN is a challenge in computational drug designing.

The mutation in Leucine-Rich Repeat Kinase 2 (*LRRK2*) have significant involvement in the cause of PD [66]. ROCO protein family has multi-domain serine-threonine repeat kinase [67]. LRRK2 encoded the dardarin protein. The leucine-rich region of dardarin has large number of amino acids. These regions are interacting with other proteins through signal transduction. The interaction of phosphate groups in proteins known as phosphorylation that helps the brain for cell manufacturing processes leads to the enzymatic function of dardarin as kinase activity. The large amount of protein formation leads to the autophagy of the cells through phosphorylations [66]. *LRRK2* encodes a protein of 2527 amino acids [68]. Several cellular and signaling pathways including mitochondrial function, retromer complex modulation and autophagy regulation are associated to LRRK2 [67]. LRRK2 is responsible for PD which inherit in autosomal dominant pattern [69]. In both inherited and non-inherited PD cases, missense mutations are present in case of LRRK2. The decrease

in LRRK2 kinase activity can be determined by using systematic computational approaches. The drug resistance can be identified by using 3D structures of LRRK2 functional domains. In both wild and mutant conformations, the binding efficiency of L-dopa is analyzed followed by virtual screening to determine small molecules. The binding efficiency of recently identified inhibitors can be analyzed through Molecular Dynamics (MD) simulations [70].

Table 1: Summarized PD related genes and computationally derived drugs against variants.

Gene name	***LRRK2***	***SNCA***	***PINK1***	***PRKN***	***DJ1***
Cytogenetic location	12q12	4q21	1p35-p36	6q26	1p36.23
Locus	PARK8	PARK1 and PARK4	PARK6	PARK2	PARK7
Protein	Leucine-rich repeat protein kinase 2	Alpha-synuclein	PTEN-induced putative kinase 1	Parkin	Parkinson's disease protein
Inheritance pattern	Account for ~7% familial worldwide and Sporadic autosomal dominant (AD) PD	Account for familial and closely resemblance with sporadic Autosomal dominant (AD) PD	Cause autosomal recessive (AR) early-onset PD and account for familial and 1-4% sporadic PD	Account for about 50% of familial and 18% of sporadic autosomal recessive (AR) early onset in Europeans.	Cause familial more than sporadic PD and account for about 0.4% early onset autosomal recessive (AR) PD
Functions	Scaffolding protein, Contribute toward the neuronal cell death	Regulate glucose level, dopamine synthesis. chaperone activity.	Maintain mitochondrial integrity and functions	Function in respiratory chain, mitophagy and mitochondrial dynamics	Transcriptional regulation, antioxidant response, and chaperone functions
Mutations	G2019S 12020T mutations	A30P, E46K, H50Q, G51Dand A53T	Non-sense, missense and frameshift mutations are common	Rearrangements, deletions or insertions, although point mutations have been also reported	Leu166Pro, Ala104, Glu163, Met26, Glu64 and Asp149
Computationally derived drugs	LRRK2 inhibitors	Mitoquinonemesy-late and Ubiquinone-10	L-DOPA	-----	Bacoside-A and L-DOPA
References	[36, 38-47]	[39, 47-54]	[33, 39, 47, 55-59]	[33, 39, 47, 55, 60]	[33, 47, 56, 61-65]

The selective and brain-permeable LRRK2 inhibitors can be designed with vast efforts which could be a good treatment option for PD [71]. A guanosine triphosphate hydrolase (GTPase) domain (Ras of complex – ROC) and an adenosine triphosphate (ATP)-utilizing kinase are two distinct but functionally related enzymatic domains of ROCO protein family (**Fig. 4**). Among the 50 reported mutations of *LRRK2*, G2019S point mutation is the most common pathogenic mutation. The pathogenic mutations has been classified as gain-of-function mutations because it enhance the LRRK2 kinase activity [72]. The degeneration and death of brain cells could stop by removal of phosphorylations which binds with ribosomal s15 and protein production can be blocked by regulating low dose of anisomycin. The study of structural, functional and mutational analyses of LRRK2 could be helpful in drug designing. A series of 2,4_diaminopyrimidine inhibitors developed by using homology modeling aim to develop brain permeable highly effective and selective LRRK2 inhibitors [43]. 2-anilino-4-methylamino-5-chloropyrimidine and HG-10-102-01 are considered as the effective inhibitors of wild-type LRRK2 and G2019S mutant [44]. An application of 160 cell permeable and ATP competitive kinase inhibitor for LRRK2 de-phosphorylation at serine cluster such as Ser910/935/955/973 shows positive results [36]. *In silico* modeling used to generate mino-pyrimidine GNE-7915 and has been accounted as effective, brain-penetrant and non-toxic inhibitor of LRRK2 [46].

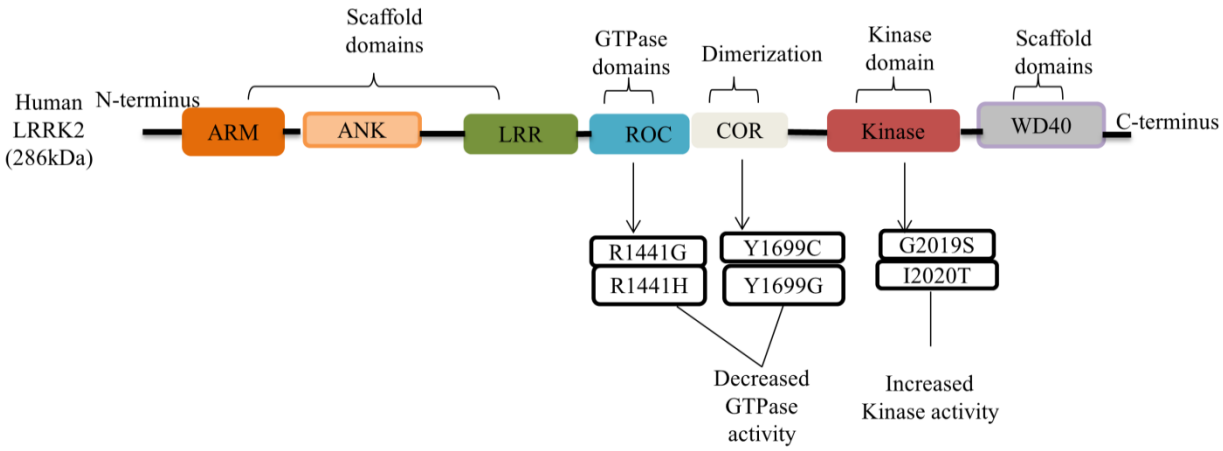

Fig. 4: LRRK2 domain structure and PD linked mutations

SNCA was first reported gene involved in PD (alpha-synuclein) having missense mutation. The encoded protein, alpha-synuclein forms toxic oligomers and accumulate in the neurons that eventually visible as Lewy bodies, which perform a significant role in the molecular origination and development of PD [73]. It is mainly found in the presynaptic terminals of neuron cells, made up of 140 different amino acids that attaches the protein to membrane[54]. Alpha-synuclein is capable of adopting different structural conformations formed by low pH, heat, organic solvent and metal ions. It is an unstructured and unfolded protein and the product of chameleon proteins. Structurally, alpha-synuclein has three regions. C-terminus balances the aggregation of alpha-synuclein, the central NAC region which is highly hydrophobic and the N-terminal region is concerned with lipid binding [74].

A18T, A29S, A30P, E46K, H50Q, G51D, A53E, A53T are the eight different mutations involved to cause PD. The most common 5 missense mutation are A30P, E46K, H50Q, G51D and A53T (**Fig. 5**), promotes α-Synuclein aggregation. The oligomerization enhanced by A30P mutation whereas aggregation process is reduced by G51D and A53E mutations. Alpha-synuclein gene cause familial PD in rare cases however sporadic Parkinsonism is mainly caused by the aggregation of synuclein [74]. *SNCA* duplication accounts for 1-2% of PD cases [75]. The alpha-synuclein protein investigated at the mutated level to elucidate the novel molecules. The modeling of the mutated structures followed by structure-based pharmacophore prediction reported antioxidants compounds such as Mitoquinonemesylate and Ubiquinone-10. Hydrogen bond donor/acceptor, hydrophobic, aromatic features were also determined. Virtual screening was done to scrutinize the best hits from the Drug bank database [54].

The activation of parkin occurs through the phosphorylation of *PINK1* (PTEN-Induced Kinase1). The mitochondrial degradation by mitophagy occurs through signals provided by ubiquitylation of substrates chains of parkin at outer mitochondrial membrane (OMM) [76]. It provides protection to neurons against damaged mitochondria [77]. PINK1 kinase activity is significant as PINK1 mutations are mostly present in kinase domain [76]. During mitochondrial internal control, PINK1 and parkin functionally cooperate to identify, label and remove the damaged organelles [78]. By various molecular methods, missense mutation in PINK1 can interfere with mitochondrial internal control [79]. The loss of function occurs due to instability of transcript in PINK1 p.Q456X at protein level [80]. Almost like PINK1 wild-type, mutant p.G411S on damage forms dimer at OMM [81]. The novel p.1368N mutation is described by complete inspection of PINK1 regulation and designing of drug using clinical approaches. On mitochondrial stress, the stability of p.1368N is seriously damaged. The polish family having p.1368N mutation, the blood and skin specimens were retrieved and observed the parkinsonian traits on dominant side [59].

PRKN encoded the parkin RBR E3 ubiquitin protein ligase having 465 amino acids. The loss of function causes mitochondrial dysfunction, impaired mitophagy and accumulation of proteins [82, 83]. RING0, RING1, In-Between-RING (IBR) and RING2 are four zinc coordinating domains in parkin linked to N-terminal Ub-like domain and form a core (RORBR). PINK1 activates parkin and depolarization damaged the mitochondria and phosphorylates adjacent Ub. The attachment of parkin to phospho-Ub

helps in PINK1 phosphorylation of parkin Ubl (Ub-likedomain) and activates parkin [84]. In PD patients, about 16.4% and 17.2% mutations are reported in the RING and REP domains of parkin having 10.2% and 11% are disease-causing. Parkin performs several cellular functions including mitophagy, vesicle trafficking and cell cycle [83]. Parkin saves the degeneration of dopamine (DA) neurons [85]. Parkin is restricted particularly to cytosol, however endogenous parkin is present relatively in a small proportion within the mitochondria and also outside the mitochondria. Parkin played a regulatory role in mitochondria by promoting the removal of damage mitochondria through mitophagy [86].

In 2003, a genic form of PD were first identified in Deglycase (*DJ1*) or PARK7 (Parkinsonism Associated Deglycase), 189 amino acid. *DJ1* located at chromosome 1(1p36.23), and 20kDa [65, 87, 88]. DJ1 contributes to the oxidative stress response [89]. The autosomal recessive PD caused by *DJ1* due to Leu166Pro (L166P) mutation (**Fig. 6**) that weakens the dimer resulting in low protein level by promoting DJ1 degradation [87]. The sporadic type of PD is due to the mutated *DJ1* which demonstrates reduced nuclear localization and translocation to mitochondria. DJ-1 isoforms were determined through homology modeling [90].

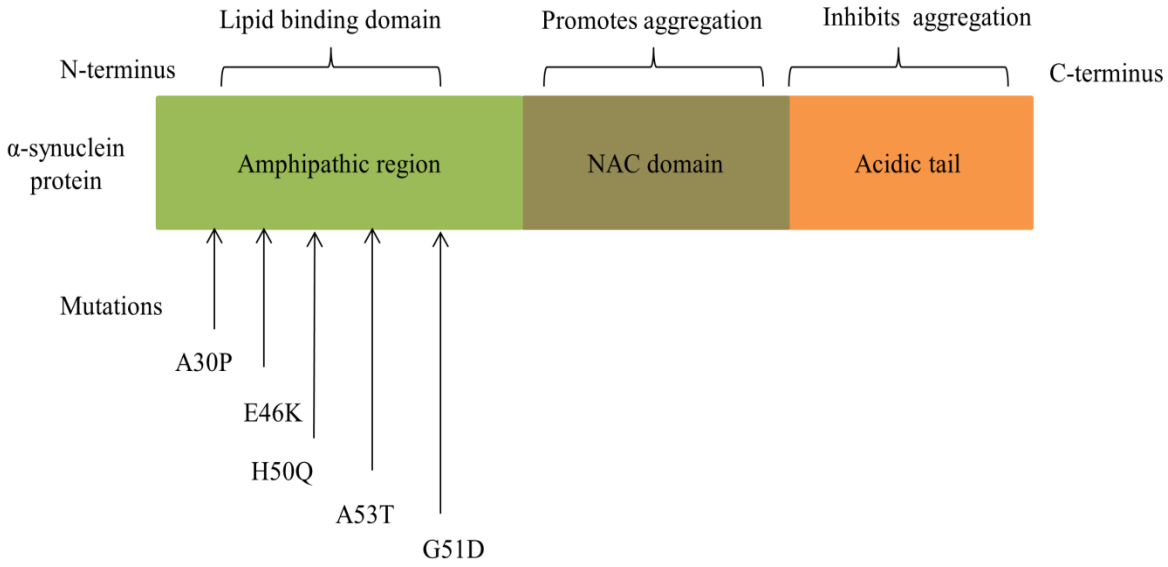

Fig. 5: Genomic structure of alpha synuclein protein and PD linked mutations

DJ1 is a significant target for developing new therapeutic agents due to its characteristic of oxidative sensor. In rat PD models, the dopaminergic neurons protected by using the recombinant wild-type DJ1. The treatment of L-DOPA is normally given to PD patients having signs as tremors, rigidity, abnormal thinking, perceptions and cognitive decline [65]. By using various computational methods, the interactions between DJ1 and ligands, Bacoside-A and L-DOPA were studied. The molecular docking studies revealed that Bacoside-A interacted at the reported binding site and binding atomic coordination were evaluated with the template complex coordination. The analyses of active binding sites against DJ-1 and molecular docking analyses of Bacoside-A with active binding site showed potential target site. The treatment of neurodegenerative disorders can be done by using *in silico* method for identifying ligands by means of practical software and online tools [64].

GBA encodes G case, 497 amino acids encode for glucocerebrocidase (G case) located at chromosome 1(1q21), is a risk factor for sporadic PD. G case concerned with the metamorphosis of glycosylceramide and involves in the endo-lysosomal pathway. The mutations in *GBA* inclined to fold incorrectly leads to nonfunctional G case [91-93].

The homozygous mutation in *GBA* has been linked with Gaucher disease, considered as associated with PD [92, 94]. A single heterozygous mutation in *GBA* regarded as linked with PD [34].Improper G case activity causes accumulation of alpha-synuclein [94]. GBA are not performed its function appropriately in the endoplasmic reticulum due to mutations and creates amass of protein in cellular cavity causes cell death [95]. K198T, E326K, T369M, R496H, V394L,

D409H, L444P, and N370S are the variants of *GBA* (**Fig. 7**). However, N370S and L444P are common [96].MD simulations showed that NN-DNJ is suitable against protein with N370S mutation.

Ambroxol has shown significance performance against N370S and L444P mutations [91]. Through, high throughput screening lead compounds NCGC758 and NCGC607 showed potential for therapeutic development [97].

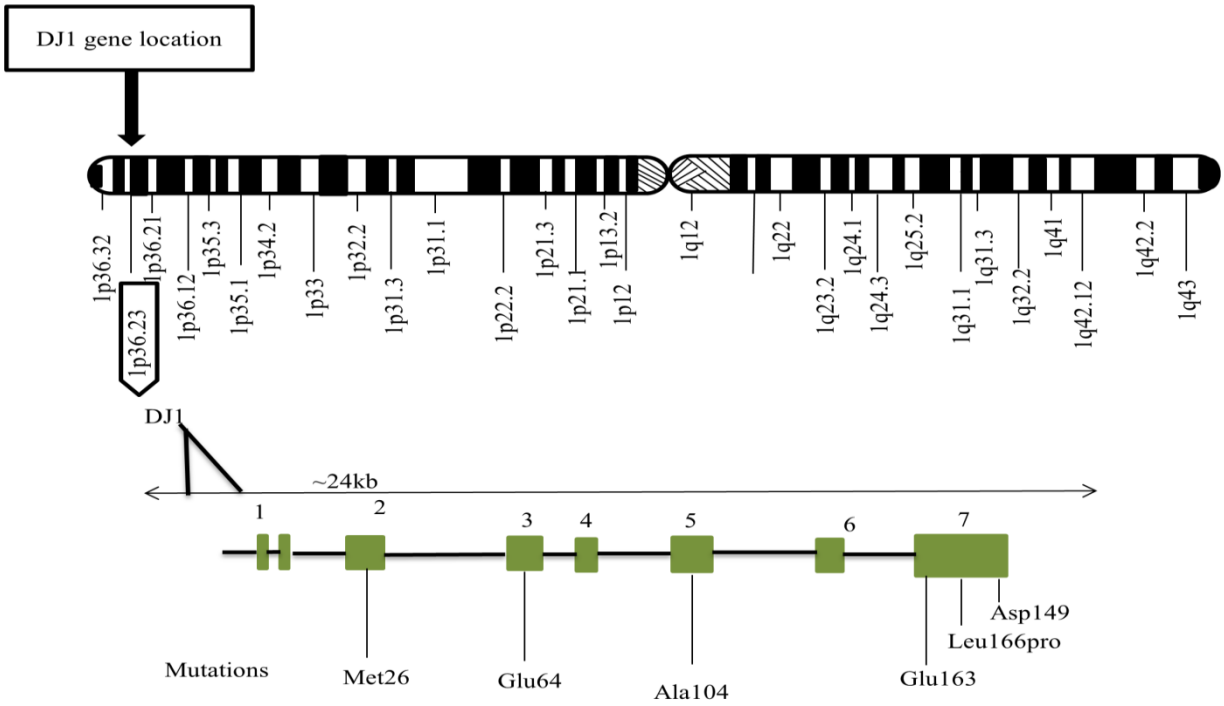

Fig. 6: Schematic representation of DJ1 showing the location of mutations identified in PD

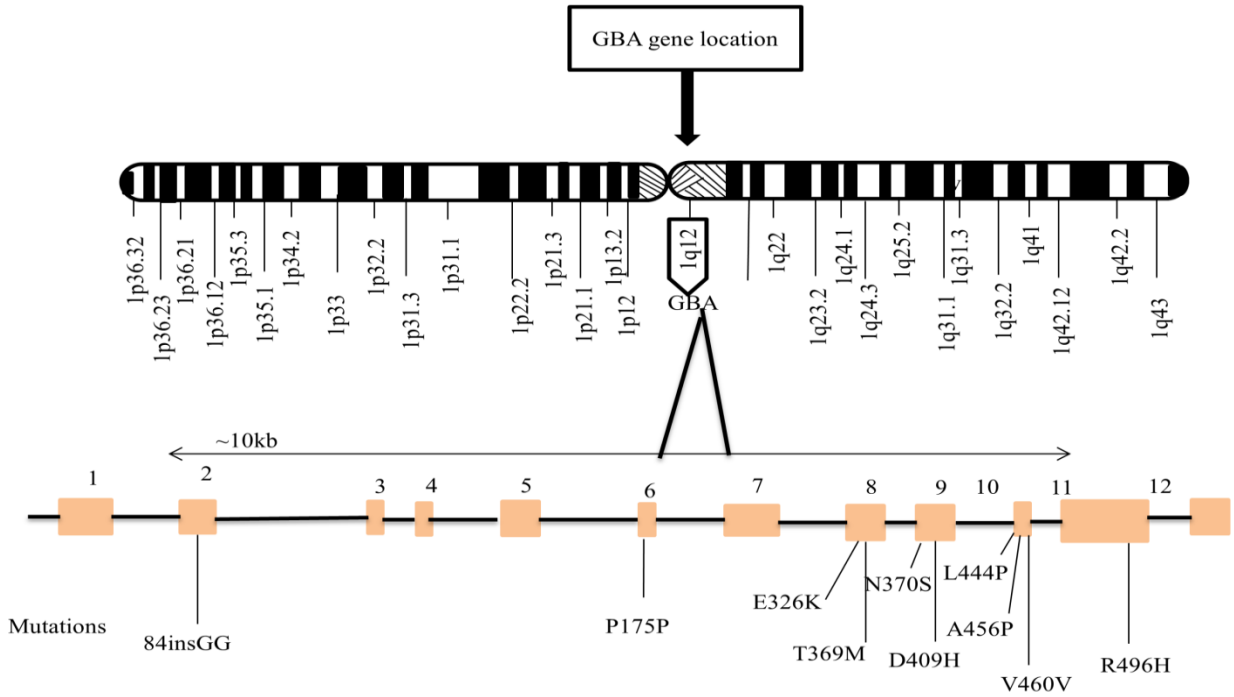

Fig. 7: Schematic representation of GBA showing the location of mutations identified in PD

Vacuolar Protein Sorting-associated protein35 (*VPS35*), a causative genes linked with familial and sporadic autosomal dominant PD encodes for a 796 amino acid subunit of membrane recycling retromer complex with a relative molecular mass of 92kDa [35, 47, 98]. Retromer present throughout the neuron involves in recycling of transmembrane protein [99], endosomal sorting and protein trafficking. It also involves in the transportation of protein in mitochondria during autopahgosome formation [100]. The mutation in *VPS35* leads to abnormal trafficking cause PD and also causes disturbance in the function of mitochondria and dopaminergic cell loss [101]. The mutations in *VPS35* occur due to improper binding of WASH (WASP and Scar homologue) complex. D620 (VPS35 mutation) decreases the capability of VPS35 to cohere with WASH complex and disruption of endosomal sorting and endosomal recruitment of WASH complex. Improper WASH binding reduced the autophagosome formation. The overexpression of D620N VPS35 disrupts the trafficking of GluR1 that changed the synaptic transmission. VPS35 mutation disrupts the mitochondrial dynamics and functions. D620N, P316S, R524W, L774M, R32S, I560T, H599R, M607V, 551S are the variants of *VPS35* linked to PD. D620N occurs in high frequency [99]. VPS35 variants responded well to L-dopa [102].

UCHL1 encodes 223 amino acids enzyme called Ubiquitin C-terminal hydrolase L1 [103, 104]. A copious protein in the brain with cytogenetic location at 4p14. The mutation in *UCHL1* causes reduction in the catalytic activity of enzyme called hydrolase, which disturb Ubiquitin proteasome system, involves in protein catabolism and contribute to the late-onset form of PD [93, 105, 106]. *UCHL1* harbor 193M and S18Y PD [107]. The whole exome sequencing identified two new *UCHL1* variants called Arg178Gln and Ala216Asp [106]. α-synuclein protein degraded and cause the formation of Lewy bodies due to variations in ubiquitin proteasomal system [108].

In 2006 in Chilean family, a PD associated gene recognized named *ATP13A2*. It comprises 1180 amino acids, responsible for the production of lysosomal p-type ATPase, come out with revelation of Kufor-Rakeb syndrome (KRS). ATP13A2 mutation confer to neuronal ceroid lipofuscinoses (NCLs) [109, 110] and highly expressed in substantianigra. The key function of *ATP13A2* is to regulate the cation homeostasis [111]. Mutations in ATP13A2 contribute to the Juvenile and early-onset form of PD which disturbs the lysosomal function, leads to mitochondrial dysfunction. p.I441F and p.A1069T are the variants of ATP13A2 [47, 112]. ATP13A2 prevents the alpha-synuclein assemblage, so mutation promotes the overexpression of alpha-synuclein resulting in cell death [113]. The abnormal accumulation of cations like manganese, zinc, iron ad cadmium can cause neurodegeneration because ATP13A2 involves in trans membrane transport of these cations [114].

Bioinformatics and drug designing

This is an era of Big Data with scientists producing a vast amount of data using bioinformatics. Computational methods used in computational drug designing for target identification, lead identification and optimization utilized bioinformatics tools and databases. Bioinformatics employing computational, mathematical and statistical ways is a very recent emerging interdisciplinary science that finds the solution of biological problems. The methods of designing new drugs using bioinformatics tools have opened up a new field of research [115, 116] . The growing demand for additional drug design in the short term with minimal risk is leading to greater interest in bioinformatics. Bioinformatics tools can provide knowledge about possible nucleotide and protein sequence information, types of protein expression data, disease relatives, variations, homology, map information and structure information which helps in designing novel inhibitors against neurological disorders [117, 118].

Conclusion

Parkinson's disease is a challenging disease as it affects the neuron, which is the building block of human nervous system. Computational drug designing techniques focused to identify new drug candidates utilizing *in silico* techniques to identify new compounds as therapeutic agents. Emergence of computational drug designing offer more opportunities to understand Parkinson's disease.

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Conflict of interest

The authors declare no conflict of interests.

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