**C. elegans** as a Genetic Model System to Identify Parkinson's Disease-Associated Therapeutic Targets

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**Abstract:** Parkinson’s disease (PD) is a neurodegenerative disorder characterized by motor and non-motor symptoms and the selective loss of dopaminergic neurons. The etiology of idiopathic PD is likely a combination of genetic and environmental factors. Despite findings from mammalian studies that have provided significant insight into the disorder, the molecular mechanisms underlying its pathophysiology are still poorly understood. The nematode *Caenorhabditis elegans* (*C. elegans*) is a powerful system for genetic analysis. Considering *C. elegans* short lifespan, high genetic and neurobiochemical conservation with humans, as well as the availability of facile genetic tools, the nematode represents a highly efficient and effective model system to explore the molecular basis of PD. In this review we describe the utility of *C. elegans* for PD research, and the opportunity the model system presents to identify therapeutic targets.

**Keywords:** Nematode, dopamine, Parkinson’s disease, neurodegeneration, neuroprotection.

**1. INTRODUCTION**

**1.1. Parkinson’s Disease**

Parkinson’s disease (PD) is the second most common age-related neurodegenerative disorder affecting approximately 1-2% of the population over the age of 50 [1-3]. PD has a peak age of onset at approximately 60 years of age, and the prevalence increases approximately two-fold at age 75 years [4-6]. PD is characterized by rhythmic shaking and involuntary movement (tremor-at-rest), slowness of movement (bradykinesia), increased muscle tone (rigidity), and loss of postural reflexes [4, 7]. While the motor symptoms largely dominate the clinical picture of PD, patients also develop a range of non-motor dysfunctions. These symptoms include orthostatic hypotension, dementia, depression, and sleeping disorders [8]. These non-motor features arising from extranigral neuronal losses can be an additional source of considerable consternation and disability [9].

A molecular hallmark of PD is the loss of dopaminergic (DAergic) neurons in the substantia nigra pars compacta (SNpc) [1, 3, 10, 11]. In idiopathic PD the symptoms become apparent when more than 70% of the striatal and 50% of the nigral DAergic neurons are lost [12]. Neurodegeneration also occurs in other areas of the brain including the dorsal motor nucleus of the vagus, locus ceruleus (LC), and olfactory nuclei. The neuropathology is often accompanied by the presence of fibrillary cytoplasmic inclusions called Lewy bodies (LBs) and Lewy neuritis (LNs) [13]. LBs and LNs contain the presynaptic protein α-synuclein and ubiquitin protein deposits, which occur in dead or dying dopamine-producing neurons in the SNpc as well as the LC and other regions of the nervous system, including the cortex, limbic areas, and central and peripheral divisions of the autonomic nervous system [3, 4, 8, 12, 14]. Pathological confirmation upon autopsy has been the standard criterion for PD diagnosis with the observation of LBs in association with neuronal loss in the SN. However, LBs are also detected in brains of individuals with a range of other non-Parkinsonian clinical syndromes, including dementia with LBs, Alzheimer’s disease, and Gaucher disease [13]. Furthermore, a mutation in the protein parkin, a component of the multiprotein E3 ubiquitin ligase complex that can cause recessive juvenile PD, and one of the more prevalent PD-associated mutations, is not generally associated with development of LBs, limiting the utility of LBs as a diagnostic tool.

Etiological and pathological evidence suggest that there are both genetic and environmental components that contribute to the development of PD [2, 4, 10]. The vast majority of PD cases are sporadic, however approximately 15-20% of patients have a known family history of the disease [11]. PD is more common in rural areas, and increased rates of the disorder are associated with the use of pesticides and herbicides [15, 16]. Rare familial forms of PD provide insight into the pathobiologic mechanisms of the disorder. Current studies indicate that there are at least 16 loci and 11 genes associated with the development of PD [17]. Genetic studies suggest that oxidative stress, mitochondrial dysfunction, protein aggregation and proteasome dysregulation play integral roles in PD-associated cell death [18].

In the early stages of PD the symptoms generally respond well to therapeutics that enhance the levels of dopamine...
(DA) in the caudate nucleus and putamen [1, 4]. L-dihydroxyphenylalanine (L-DOPA), a precursor of DA, is the most efficacious compound in this class. Unlike DA, L-DOPA traverses the blood-brain barrier and boosts DA synthesis in the cells that remain alive in the SN [1]. However this treatment does not alter the progression of the disease, nor does it inhibit the neuropathology or motoric symptoms. Furthermore, the therapeutic efficaciousness declines over time that may eventually lead to premature death [17]. Currently there are no proven neuroprotective or neurorestorative therapies for PD, and treatment options largely focus on providing symptomatic relief. In this review, we briefly describe the strengths of C. elegans as a genetic model, and discuss its utility in identifying and characterizing PD-associated genes and therapeutic targets.

1.2. C. elegans as a Genetic Model

Caenorhabditis elegans (C. elegans) was first introduced as a model system by Sydney Brenner in the early 1960s to explore the genetics of developmental biology, physiology, and behavior, and since then has been utilized to identify and characterize the molecular components involved in pathophysiology and disease [19-21]. The power of this system lies in its small size and short life span, relative ease of genetic manipulation, well-characterized cell biology, and high molecular conservation with vertebrates [21].

The nematode is an anatomically simple organism that contains approximately 1000 cells of which about one-third are neurons, and their transparency allows for visualization of organs and neurons in vivo [19]. Adult animals grow to approximately 1 mm in 3 days, are able to live 2.5 weeks or longer, and each hermaphrodite can produce over 300 progeny within several days of reaching adulthood [19]. The animals are easily maintained in the laboratory, as tens of thousands can grow on bacteria on agar in a single 90 mm petri dish. C. elegans can also grow in liquid medium, allowing for high throughput analysis of toxicants or therapeutic lead compounds in 96 or 384 well petri dishes [22, 23]. Primary cell cultures can be generated quickly from nematode embryos to examine specific cell function or morphology [24]. The animals can also be stored almost indefinitely in liquid nitrogen or at -80°C, reducing the necessity for maintaining actively growing strains [25].

The abundance of genetic tools to elucidate the role genes play in a particular phenotype underscores the power of the model system. The C. elegans genome has been fully sequenced, and the number of genes in the nematode is virtually identical to the number in humans (~20,000) [26, 27]. Mutant genes can easily be propagated from one generation to the next by hermaphrodite self-fertilization, or transferred to another strain though male fertilization [19, 21, 28]. Over 8000 mutant animals are available at the National Institute of Health Caenorhabditis Genetics Center (http://www.cgc.cbs.umn.edu/) for nominal costs. Transgenic animals containing green fluorescent protein (GFP) transcriptional or translation reporter constructs that allow for cellular and intracellular protein localization analysis can be generated in as little as 3 days [29]. Furthermore, recent breakthroughs in facilitating homologous recombination in the worm now allows for site directed insertion of genetic constructs and functional deletions [30].

Forward and reverse genetics also allows for the facile identification or functional characterization of genes involved in cellular processes. In forward genetics, a chemical or physical mutagen is utilized to identify genes involved in a behavioral or cellular phenotype; this approach requires no a priori knowledge of the gene’s function [19]. Specific mutations can be mapped in as little as week [31]. Reverse genetic approaches can incorporate mutagens to generate genetic nulls, or RNA interference (RNAi) can be implemented to decrease protein expression [19, 32]. RNAi screens that introduce gene specific double stranded RNA (dsRNA) into C. elegans by soaking in an aqueous solution containing dsRNA or through feeding bacteria expressing dsRNA can be utilized for high throughput approaches to identify genes involved in particular cellular processes [4, 32]. RNAi bacteria feeding libraries that virtually cover the entire genome allow for the completion of a whole genome screen in as little as a month [32].

Although C. elegans is a relatively simple and powerful genetic tool, it is the high conservation of the genome and molecular pathways with humans that provide significant opportunities to identify and characterize novel genes and modifiers involved in disease. The nematode’s nervous system contains almost all of the known signaling and neurotransmitter systems found in vertebrate systems, including serotonin, acetylcholine, glutamate, octopamine, gamma amino butyric acid (GABA), and DA [21, 33]. Of the 302 neurons in the hermaphrodite, 8 are DAergic, while the male contains an additional 3 pairs of DA neurons in the tail that are involved in mating [21]. The DAergic system is also particularly well-conserved as genes and molecular pathways involved in the processing, packaging, and transport of DA in humans are all found in the nematode [21, 34]. C. elegans is sensitive to a large number of human neuroreactive compounds that also appear to interact with human orthologous targets in the worm, suggesting that compounds that inhibit DA neuronal death in the nematode will likely be relevant therapeutic leads for PD [21, 35].

2. PD-ASSOCIATED GENES AND C. ELEGANS

2.1. α-Synuclein

α-Synuclein (SNCA) was the first gene identified that is associated with the development of familial PD [36]. The presence of multiple copies of the α-synuclein gene has also been correlated with the development of idiopathic PD [2, 4, 36-38]. α-synuclein is a 140 amino acid cytosolic and lipid-binding phosphoprotein that is expressed in numerous areas of the brain including the substantia nigra, hypothalamus and olfactory neurons, and is found in high abundance in the pre-synaptic terminals [2, 7, 9]. Although the physiological functions of α-synuclein are not well defined, the protein appears to be involved in the regulation of neural plasticity, cellular differentiation, and DA release and transport [39, 40]. α-synuclein has also been shown to interact with tubulin and histones [41, 42].

α-Synuclein is a major component of the protein aggregates LBs and LNs that are a molecular hallmark of PD. α-synuclein is a highly abundant protein in the brain that
may account for up to 1% of the cytosolic fraction \[43\]. The protein is highly flexible and has limited defined secondary or tertiary structure in solution \[44\]. Mutations within α-synuclein (A53T or A30P) or increased expression due to multiple copies of the gene increase the probability that α-synuclein will polymerize into fibrillar structures or misfolded aggregates that may contribute to the development of PD \[2, 45\]. Although it is not clear how α-synuclein may contribute to DA neuron pathology, α-synuclein oligomers may alter plasma membrane Ca$^{2+}$ permeabilization, cause the accumulation of docked vesicles at the plasma membrane disrupting synaptic transmission, and/or accumulate at the mitochondrial membranes leading to cytotoxicity and cell death \[3, 38\].

*C. elegans* does not contain an apparent homologue to the human protein, and thus provides an opportunity to explore the role that human α-synuclein may have on worm DA neuron vulnerability \[20\]. We previously generated the first *C. elegans* models for PD by expressing GFP behind the dopamine transporter (DAT) promoter and either exposing the animals to the PD-associated neurotoxicant 6-hydroxydopamine (6-OHDA) or co-expressing WT or A53T mutant α-synuclein behind a pan-neuronal or the DAT promoter \[46, 47\]. Exposure to the PD-associated toxicant or overexpression of α-synuclein caused significant DA neuronal death \[46, 47\]. Overexpression of α-synuclein also confers motor deficits and results in α-synuclein-containing aggregates in some DA neurons \[46, 47\]. Furthermore, overexpression of human α-synuclein also increases *C. elegans* lifespan, consistent with vertebrate studies that the protein may also protect against pro-apoptotic stimuli \[48\]. Overall these studies indicate that human α-synuclein-induced DA neuropathology in the nematode recapitulates significant attributes of α-synuclein toxicity in vertebrates and suggests that the model may be useful in identifying therapeutic targets or leads found in the human disease.

Exploitation of the *C. elegans* α-synuclein model has been used to identify potential PD-associated therapeutic targets \[35\]. A relatively facile approach has been to identify modulators of α-synuclein aggregation through reverse genetic screens. Nollen and colleagues incorporated a whole-genome RNAi screen to identify genes for which a decrease in expression results in a greater number of α-synuclein inclusions \[49\]. The age-associated genes sir-2.1/SIRT1 and lagr-1/LASS2 were among the genes identified in the screen, suggesting that therapeutics that target these molecular pathways may modulate PD-associated pathologies.

Candidate gene approaches using RNAi have also been incorporated to identify modulators of α-synuclein toxicity in *C. elegans*. Hamamchi and colleagues evaluated 900 genes based on vertebrate studies and functional predictions and identified 20 for which a decrease in expression enhanced misfolding of α-synuclein \[50\]. The list of genes included orthologs of previously known PD-associated genes including djr-1.1, pink-1, and hrdl-1 (E3 ubiquitin ligase). Overexpression of a number of these genes was later shown to protect DA neurons from α-synuclein-induced degeneration \[50, 51\]. Potential druggable targets also include an acetylcholine receptor subunit (acr-22) and a serine-threonine kinase (T07F12.4) \[50\]. Similarly, Kuwahara and coworkers performed an RNAi screen of 1673 genes, and identified 10 genes for which a decrease in expression in nematodes pan-neuronally expressing α-synuclein resulted in decreased growth and motor dysfunction \[52\]. Four genes were identified that are part of the endocytic pathway, supporting the role of α-synuclein in vesicular trafficking. All of the screen hits have human homologs and half of the genes may represent potential drug targets as they function as a kinase or GTPase.

Microarray analysis has recently been utilized to identify genes that may be involved in α-synuclein toxicity. Vartiainen and colleagues found 433 genes up- and 67 genes down-regulated in *C. elegans* overexpressing human α-synuclein \[53\]. Significant changes were observed in the expression of genes associated with mitochondrial function, the proteasome, cellular development, and a number of histones, consistent with the roles of α-synuclein in vertebrate studies \[3, 38, 42, 53\]. Significant changes in miRNAs were also identified including miR-64 and miR-65, which appear to regulate the genes mdl-1 (a transcription factor) and ptc-1 (homologous to human PTCH) \[54\]. Whether miRNA mimics or anti-miRNAs can be developed as a therapeutic for neurodegenerative diseases remains to be further explored \[55\]. Current efforts are particularly focused in oncology and will likely be informative to the feasibility for therapeutic intervention in neurodegeneration \[56\]. Overall these results indicate that the *C. elegans* α-synuclein model recapitulates key aspects of vertebrate systems, and suggests that novel molecular modulators identified in *C. elegans* genetic screens or microarray studies may likely provide relevant therapeutic targets for PD.

### 2.2. Parkin

The parkin gene is associated with autosomal recessive juvenile parkinsonism (AR-JP), accounting for nearly 50% of autosomal recessive familial early-onset cases of PD \[4, 57, 58\]. Mutations in parkin also result in a loss of DA neurons in the SN and LS and unlike many mutant proteins associated with the development of PD, are not generally associated with LB formation \[2, 58\]. Common clinical features include an early age of onset, slow progression of the disease, lower limb dystonias, diurnal fluctuations and hyper-reflexia \[2\]. Mutations in parkin associated with PD include deletions, duplications and triplications of exons, and frameshift and point mutations \[4, 59\]. Mutations in parkin are currently considered to be the main contributor associated with familial PD \[11\].

The parkin (PARK2/PRKN) gene is one of the largest genes in the human genome (NCBI: 1,380,383 bases) and appears to have one of the highest ratios of non-coding to coding DNA lengths \[11\]. Parkin is expressed in pre- and postsynaptic processes and cell bodies of neuronal somata \[57, 60\]. The parkin gene encodes a 465 amino acid protein that contains a ubiquitin-like domain (UBL) in its amino-terminus, a linker region (LINKER), two RING finger domains in its carboxy-terminus and a cysteine rich in-between RING finger domain (IBR) \[2, 4, 57, 61\]. The majority of clinically relevant mutations discovered to date are localized within the RING-IBR-RING domain suggesting that this region is essential to protein function \[11, 61\]. Parkin functions as a ubiquitin ligase and is associated with the ubiquitin-proteasome system (UPS) that
plays an important role in maintaining intracellular homeostasis through the clearance of unwanted proteins [11].

The C. elegans gene pdr-1 shares significant homology with human parkin gene [20]. pdr-1 encodes a 386 amino acid protein, PDR-1, which interacts with enzymes of the ubiquitin/proteasome pathway and mediates E3 activity. Similar to human parkin, PDR-1 interacts with E2 and E4 enzymes involved in cytosolic protein stress response and the endoplasmic reticulum-associated protein degradation (ERAD) pathway [57]. PDR-1 is expressed in many tissues, with muscles and neurons having particularly high expression [57].

Mutations in PDR-1 can inhibit C. elegans larval development, confer hypersensitivity to ER stress, and cause significant cellular aggregation that can be similar to parkin point mutations in PD [10, 57]. A loss-of-function mutation (lof) in pdr-1 results in an overall decrease in ubiquitination and enhanced vulnerability to mitochondrial complex I inhibitors including rotenone, fenperoximate, pyridaben, and stigmatellin [62]. A lof in pdr-1 also results in greater DA neuron sensitivity to PD-associated toxicant 6-OHDA [35]. These results are consistent with vertebrate studies and suggest that therapeutics that target the ubiquitination pathway or reduce ROS levels may inhibit parkin-induced neuropathology.

2.3. DJ-1

DJ-1 mutations are associated with autosomal recessive PD, and DJ-1 mutations occur at a frequency of 1-2% in early-onset cases [63]. DJ-1 belongs to the Thü/PpPl superfamily of proteins (Pfam01965) [64]. The protein is ubiquitous in the brain, and is localized in the cytosol and the mitochondria [17, 64]. The precise role of DJ-1 remains largely unknown, although it appears to be involved in a wide range of cellular processes including cell cycle regulation, sperm maturation, fertilization, control of gene transcription, and regulation of mRNA stability [64]. DJ-1 also may regulate oxidation-reduction-dependent signaling pathways and antioxidant gene expression [65]. DJ-1 gene deletion studies indicate that the protein plays a role in inhibiting the degeneration of midbrain dopaminergic neurons, and is associated with perturbed mitochondrial dynamics, apoptosis and autophagic dysregulation, linking it with functions mediated by the PD-associated proteins parkin and PINK1 [17, 66]. DJ-1 also has been shown to inhibit α-synuclein aggregation [66].

C. elegans contains two orthologs to human DJ-1, DJR-1.1 and DJR-1.2. DJR-1.1 and DJR-1.2 encode approximately 186 amino acid proteins and share 44-53 percent identity with the human protein sequence. C. elegans djr-1.1 may share functional coupling with α-synuclein and pdr-1 [62]. As with pdr-1, Ved and coworkers found that transgenic animals expressing α-synuclein, lacking functional djr-1.1 were more vulnerable than wild type animals to mitochondrial complex I inhibitors, rotenone, fenperoximate, pyridaben, or stigmatellalin [62]. The nematodes can be partially rescued by the antioxidant probucol, the mitochondrial complex II activator D-beta-hydroxybutyrate, or the anti-apoptotic bile acid taouroursodeoxycholic acid [62]. These results are consistent with vertebrate studies, and suggest that PD-associated toxicants that target C. elegans mitochondrial proteins may provide further insight into the molecular pathways involved in neurodegeneration and elucidate novel molecular targets to limit the pathology.

2.4. LRRK2

LRRK2 is associated with an autosomal-dominant familial PD and a late-onset sporadic form of the disease [14]. LRRK2 mutations account for approximately 5% of patients with familial and 2% of sporadic PD, and as high as 40% in particular ethnic populations [9, 67]. LRRK2 is a 2527 amino acid leucine-rich repeat kinase 2 protein, also known as dardarin [14, 68]. It is a member of ROCO family and is comprised of several independent, highly conserved domains, including a Roc (Ras of complex protein) domain, an N-terminal leucine-rich repeat (LRR) domain, a mitogen-activated protein kinase kinase kinase (MAPKKK) domain, a C-terminal WD40 repeat domain and ankyrin repeats (ANK) [10, 60, 67, 69-72]. PD-associated mutations are concentrated in the central catalytic regions of the GTPase (R1441C/G) and kinase (G2019S) domains that largely increase kinase activity [17]. In vitro studies suggest that perturbed kinase activity may underlie the pathogenic properties of LRRK2 mutations, inclusion body formation and cytotoxicity, most likely through a gain-of-function mechanism [72].

LRRK2 is believed to play a role in neuronal outgrowth, phosphorylation of the translation inhibitor eukaryotic initiation factor 4E (eIF4E), and in cytoskeletal dynamics by phosphorylation of moesin, which anchors the cytoskeleton to the plasma membrane [17]. In mammals LRRK2 is highly expressed in brain regions associated with PD including the cerebral cortex, caudate-putamen and SN [67, 70, 72]. The kinase has been localized in the cytoplasm, as well as associated with lipid rafts, mitochondria, Golgi transport vesicles, lysosomes and endosomes [70, 72]. The LRRK2 protein is also found in LBs and LNs of sporadic PD [70, 71].

The LRRK2 gene is conserved across species from invertebrates to human [73]. lrk-1 is the C. elegans orthologue of human LRRK2, and shares 25% identity and 44% overall similarity to the human protein [74]. The LRK-1 protein is a 2393 amino acid protein that is ubiquitously expressed in most of the body regions of the worm including the head and tail neurons, the pharynx, the distal tip cells, and the canal-associated neurons (CAN) [75]. LRK-1 has been shown to be required for organization of synaptic vesicle proteins within axons and dendrites [76].

Overexpression of human wild-type LRRK2 in C. elegans decreases rotenone-induced DA neuron degeneration, while an apparent functional mutation in the endogenous gene lrk-1 increases the pathology [74, 76]. These results suggest that LRRK2 may have a neuroprotective function. However, in the absence of exogenous stressors, age-dependent loss of DA neurons is observed in strains overexpressing either WT or mutant LRRK2 [74, 77]. The degeneration though can be attenuated by a reduction in overall levels of LRRK2 as worms overexpressing LRRK2 but mutant for lrk-1 show...
significantly less DA neuron degeneration suggesting that LRK-1 gene dosage may play an integral role DA neuron vulnerability [77]. Yao and colleagues also found that the DA neuron toxicity associated with overexpression of tyrosine hydroxylase, the enzymatic precursor for DA, is reduced in a lrk-1 mutant, suggesting that LRK-1 may be involved in DA signaling [77].

2.5. PINK1

The PTEN-induced putative kinase 1 (PINK1) gene shows a high degree of homology to the serine/threonine kinases of the calcium/calmodulin family [4, 78]. In vertebrates, PINK1 is expressed in cells throughout the body, with particularly high expression in the SN [65]. PINK1 is expressed in the mitochondria and the cytoplasm, and the kinase activity in the latter likely contributes to reducing oxidative stress in the mitochondria and cytotoxicity [79].

Mutations within PINK1 have been implicated in conferring abnormal mitophagy, disrupting the mitochondrial fission-fusion balance, increasing mitochondrial calcium levels and interfering with electron transport, consistent with mitochondrial dysfunction contributing to the development of PD [17, 65, 80, 81]. PINK1 also functions to reduce oxidative stress and prevent the release of cytochrome c via phosphorylation of one of its endogenous substrates [82].

PINK-1 is the C. elegans ortholog of human PINK1. The nematode kinase is approximately 36% identical and 54% similar to the mammalian protein [75]. PINK-1 is expressed in neurons, musculature and vulval tissues, and localizes to the cytoplasm and the mitochondria. A PINK-1 loss of function results in a reduction in brood size, and defects in neurite outgrowth and mitochondria [75]. The mutation also results in greater sensitivity to paraquat, suggesting that the function of pink-1 may be to limit damage from ROS and play a role in mitochondrial homeostasis [75]. Interestingly, mutations within lrk-1 suppress the pink-1 phenotypes suggesting a functional linkage between the PD-associated proteins [75] (Table 1).

3. DISCUSSION

In this review we have described how C. elegans has been utilized to explore the genetic and molecular bases of PD-associated cellular dysfunction, and the potential to utilize the system to identify molecular modulators and potential therapeutic targets. PD-associated proteins have been shown to play roles in lipid and vesicle dynamism (α-synuclein), protein degradation (parkin), cytoskeletal dynamics and kinase activity (LRRK2), and oxidative stress and mitochondrial homeostasis (DJ-1, PINK1, parkin).

Table 1. PD-Associated Genes and C. elegans Orthologs

<table>
<thead>
<tr>
<th>Location</th>
<th>PD Gene</th>
<th>Inheritance</th>
<th>C. elegans Ortholog</th>
<th>% Similarity (E-Value)</th>
<th>C. elegans Mutants</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>PARK1/4 4q21</td>
<td>SNCA/α-synuclein</td>
<td>autosomal dominant</td>
<td>nh</td>
<td>—</td>
<td>BY273 (Pdat::GFP, Pα-synuclein)</td>
<td>[2, 4, 10, 17, 37, 38, 47, 48, 60, 62, 89]</td>
</tr>
<tr>
<td>PARK2 6q25.2-27</td>
<td>PRKN/Parkin</td>
<td>autosomal recessive</td>
<td>pdr-1</td>
<td>42.0 (5.0E-49)</td>
<td>VC1024 pdr-1(gk448)</td>
<td>[2, 4, 11, 57, 59, 60, 62, 90-93]</td>
</tr>
<tr>
<td>PARK5 4p14</td>
<td>UCH-L1</td>
<td>autosomal dominant</td>
<td>ubh-1 ubh-2 ubh-3 ubh-4</td>
<td>57.0 (3.0E-40) 58.0 (8.0E-34) 57.0 (4.0E-33) 47.0 (3.0E-13)</td>
<td>ubh-1(tm526) ubh-2(tm2287) ubh-3(tm2250) ubh-4(tm2310)</td>
<td>[2, 4, 10, 12, 17, 60]</td>
</tr>
<tr>
<td>PARK6 1p35-36</td>
<td>PINK1</td>
<td>autosomal recessive</td>
<td>pink-1</td>
<td>50.0 (1.0E-60)</td>
<td>RB2547 pink-1(ok3538)</td>
<td>[4, 7, 10, 62, 75, 78, 90, 93, 94]</td>
</tr>
<tr>
<td>PARK7 1p36</td>
<td>DJ-1</td>
<td>autosomal recessive</td>
<td>djr-1.1 djr-1.2</td>
<td>68.0 (2.0E-57) 62.0 (5.0E-42)</td>
<td>djr-1.1(tm918) djr-1.2(tm1346)</td>
<td>[4, 62, 63, 66, 90, 93-96]</td>
</tr>
<tr>
<td>PARK8 12q12</td>
<td>LRRK2</td>
<td>autosomal dominant</td>
<td>lrk-1</td>
<td>46.0 (1.0E-45)</td>
<td>lrk-1(tm1898)</td>
<td>[4, 10, 67, 69, 72, 73, 75, 97]</td>
</tr>
<tr>
<td>PARK9 1p36</td>
<td>ATP13A2</td>
<td>autosomal recessive</td>
<td>catp-5 catp-6 catp-7</td>
<td>54.0 (c = 0) 54.0 (3.0E-148) 56.0 (c = 0)</td>
<td>catp-5(ok4481) catp-6(ok3478) catp-7(tm4438)</td>
<td>[4, 7, 10, 17]</td>
</tr>
<tr>
<td>PARK11 2q36-37</td>
<td>GIGYF2</td>
<td>autosomal dominant</td>
<td>nh</td>
<td>—</td>
<td>—</td>
<td>[4, 7, 10, 17]</td>
</tr>
<tr>
<td>PARK13 2p13</td>
<td>HTRA2</td>
<td>autosomal dominant</td>
<td>nh</td>
<td>—</td>
<td>—</td>
<td>[4, 10, 17]</td>
</tr>
<tr>
<td>PARK14 22q13</td>
<td>PLA2G6</td>
<td>autosomal recessive</td>
<td>D1037.5</td>
<td>51.0 (1.0E-42)</td>
<td>none</td>
<td>[17, 98]</td>
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<tr>
<td>PARK15 22q11</td>
<td>FBXO7</td>
<td>autosomal recessive</td>
<td>nh</td>
<td>—</td>
<td>—</td>
<td>[17]</td>
</tr>
</tbody>
</table>

Similarity was determined using NCBI BLASTP.

nh - no apparent homologue.
Considering the relatively small number of genes in which mutations are directly associated with the development of familial PD, there are likely interconnected molecular pathways that lead to the DA neuronal pathology in both the familial and idiopathic disorders.

Vertebrate studies, as well the C. elegans studies summarized here, suggest that a number of the PD-associated proteins physically or functionally interact with each other. The array of genetic tools provided by the nematode, including the utility of knocking down multiple gene expression, incorporating forward and reverse genetic screens, and observing cellular and organelle morphological changes in vivo, provide a remarkable opportunity to evaluate the interrelationships between PD gene orthologues [20, 23]. Genetic screens to identify modulators of DA neuronal death also provide opportunities to identify novel therapeutic targets and leads that can inhibit the DA neuronal death [20, 23, 35].

The etiology of idiopathic PD is likely multifactorial and includes both genetic and environmental components. Recent vertebrate studies have associated abnormal expression of metal transporters (DMT1) and stress-responsive transcription factors (Nrf2) to play a role in the development of PD [83-86]. Recent studies in C. elegans indicate that the orthologous proteins, SMF-1 and SKN-1, respectively, are expressed in the nematode DA neurons and affect the vulnerability of the neurons to environmental insult [87, 88]. The interactions of familial PD-associated proteins with proteins that respond directly to environmental stress are not well understood. The genetic tools available for C. elegans provide a significant opportunity to directly explore the potential molecular interactions between these PD-associated proteins as well as to identify novel modulators of the pathogenesis that may yield new neurotherapeutic targets.

ABBREVIATIONS

DA = Dopamine  
LB = Lewy body  
LC = Locus ceruleus  
LN = Lewy neuritis  
lol = Loss of function  
PD = Parkinson’s disease  
RNAi = RNA interference  
SN = Substantia nigra

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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