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Review

Strategies for Optimizing Genetic Mouse Models to Enhance the Understanding of Parkinson's Disease

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Abstract

Background: Parkinson's disease (PD) has become the fastest-growing neurodegenerative disorder worldwide. A valuable approach for unraveling the disease's mechanisms and new therapeutic targets involves investigating the PD-causing genes identified in families exhibiting the Mendelian inheritance of Parkinsonism. **Methods**: In this article, we review how genetically modified mouse models can be employed to decipher the genetic architecture of PD. **Results**: We first discuss how well the human motor and non-motor symptoms of PD are currently evaluated in these PD mouse models, highlighting limitations. The pathogenic roles of five inherited PARK genes in PD are then extensively examined through their respective genetic mouse models in terms of phenotypic and cellular impacts. Furthermore, we discuss the strengths and weaknesses of existing transgenic mouse models and highlight significant accomplishments and advancements in this field from 2018 to the present. **Conclusions**: Building upon the newfound understanding of PD, we propose potential directions for enhancing genetic mouse models to further unveil the underlying mechanisms of PD and advance therapeutic research.

Keywords: Parkinson's disease; mouse models; genetic models; gene-environment interactions; non-motor symptoms

1. Introduction

Parkinson's disease (PD) [1] is a slowly progressive, devastating neurodegenerative disorder with two hallmark neuropathological features: intracellular protein α-synuclein aggregation, called Lewy pathology, in several different brain regions, and prominent progressive death of dopaminergic neurons in the substantia nigra pars compacta (SNpc) [2–4]. According to human clinical autopsy data, Braak concluded that the propagation of α-synuclein (Lewy pathology) commences in the vagal nerve and lower brainstem, including the anterior olfactory nucleus, and peripheral and central medullary autonomic neurons; before progressing through the midbrain to eventually reach the neocortex [5,6]. This hypothesis has been successfully replicated in mouse models, where targeted α-synuclein seeding in the gut or olfactory bulb induces progressive pathology in line with Braak staging [7]. Notably, neuronal degeneration in PD is most pronounced in the ventrolateral tier of the SNpc, particularly in early disease stages [8,9]. Evidence suggests that degeneration of dopaminergic neurons begins at the dopaminergic terminals and gradually regresses toward the soma [10]. Postmortem tissue analysis and in vivo studies further support the spatial and temporal relationship between α-synuclein pathology and neurodegeneration [11–13].

The clinical hallmarks of PD are broadly categorized into motor symptoms and non-motor symptoms. Dopamine deficiency is the primary driver of the core motor and non-motor manifestations in PD patients [8,14]. The onset of motor symptoms is preceded by a prodromal phase, lasting many years, characterized by non-motor symptoms, including idiopathic rapid eye movement sleep disorder, depression, excessive daytime somnolence, fatigue, hyposmia, anxiety, constipation, hypotension, urinary dysfunction, and autonomic dysfunction [4,8,14–19]. During the

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pre-motor period, neuronal loss in the SN is relatively limited [11]. Many additional non-motor symptoms experienced by PD patients are non-specific and thus supportive but not diagnostic. Some of these include, gait disturbance, dystonia, gastrointestinal (GI) dysfunction, depression, anxiety, and cognitive changes. Nonetheless, these symptoms offer valuable indicators for PD modelling in animals [2,3,8,14,20–26]. The presence of parkinsonism remains a prerequisite for PD diagnosis. However, motor symptoms only emerge after a critical threshold of dopaminergic neuron loss is reached [10,11]. The onset of motor symptoms, such as bradykinesia, resting tremor, rigidity, akinesia, axial deformities, dysphagia, postural instability, and gait disorder, serves as the first indicator for clinical diagnosis [2,3,20–23,27]. The progressive nature of PD highlights the importance of understanding the spatiotemporal dynamics of neurodegeneration and α-synuclein pathology. Such diverse manifestations result from multifactorial mechanisms associated with PD at the cellular level, including apoptosis, mitochondrial dysfunction, oxidative stress, synaptic dysfunction, deficiency in the lysosome and proteasome system, axonal transport dysfunction, calcium homeostasis disorder and neuroinflammation [3,4].

Animal models, including drosophila, zebrafish, primates, and rodents, have been employed to investigate various aspects of PD for research purposes [28–31]. Rodents, such as mice, are particularly advantageous due to their ease of breeding, short life cycles, and ability to be genetically modified. Moreover, the developmental processes of the rodent brain closely resemble those of humans, making rodents an excellent model for studying genes related to PD [32]. Rodent models accounted for 85% of all research articles on animal studies of PD from 1990 to 2018 [29,33]. Many transgenic mouse models have been developed attempting to reproduce specific pathological features and motor symptoms of PD observed in humans.

However, it should be noted that mice do not naturally develop PD. While mice can be induced to exhibit certain Parkinsonian symptoms, the way these symptoms manifest may vary between species [1]. Developing genetic mouse models that fully replicate PD is challenging due to the inherent differences between mice and humans and the complex clinical presentation of the disease. Most transgenic mouse models focus on a limited number of well-established genes linked to inherited PD. A comprehensive review conducted by Breger and Fuzzati-Armentero [34] provided an extensive overview of transgenic mouse models of PD up until mid-2018. These authors emphasize the need to broaden the characterization of these models beyond the assessment of neurodegeneration and motor impairments. Most current models cannot reproduce the chronic progressive nature of human PD. The models do not adequately reflect the prodromal phase or slow evolution seen in patients. Furthermore, complete recapitulation of selective vulnerability, particularly the tier-specific loss in the SNpc, and the complex interaction between α-synuclein pathology, neuroinflammation, and systemic factors are often lacking. Inconsistent expression levels, promoter effects, and variability in protocols also contribute to differences in outcomes across studies. There is a need to improve and standardize experimental approaches in order to achieve a better evaluation of existing models, generate more replicable data, and uncover subtle features.

Since 2018, over 600 primary publications have explored transgenic mouse models of PD, offering additional insights into their utility for deciphering the genetic foundations of the human condition.

In this review, we aim to:

1. Systematically review, categorize, and analyze recent literature on transgenic PD mouse models, with a focus on novel phenotypic discoveries and model-specific characteristics;
2. Explore the significant interactions between environmental factors and gene mutations; and
3. Summarize and update the design of behavioral tests tailored to PD symptoms, proposing standardized criteria for classifying results to facilitate meaningful comparisons across different models.

Furthermore, this review aims to critically evaluate how transgenic mouse studies can be further refined to enhance their translational relevance, ultimately advancing our understanding of the genetic contributions to PD pathogenesis.

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2. Methods

We conducted an extensive literature search on PubMed, using the following search keywords: (gene name) AND (mouse model) AND (Parkinson's disease). To date, transgenic mouse models have been developed for 13 PARK genes (summarized in Tables 1 and 2). This review focuses on the five most extensively studied genes in the family of *PARK* loci, namely, *SNCA*, *PARKIN*, *LRRK2*, *PINK1*, and *DJ-1*, each of which has established genetic mouse models and well-characterized pathogenetic roles in PD. *SNCA* and *LRRK2*-linked PD are autosomal dominant, while *PRKN*, *PINK1* and *DJ-1*-linked PD are autosomal recessive. The following sections provide a detailed overview of their genetic architecture, molecular mechanisms, applications in mouse models, and latest research developments, offering a comprehensive view on the genetic contributions to PD. An introduction to the main genes, their pathogenic mutations and mutation effects are summarized (Table 1).

Table 1. Summary of common pathogenic mutations in the five most studied familial PD genes.

Gene	Protein and Related Pathway	Mutation	Mutation Effects
SNCA	*SNCA*-encoded α-synuclein n is a presynaptic neuronal protein involved in synaptic vesicle trafficking and neurotransmitter release. In PD, misfolded α-synuclein aggregates to form Lewy bodies, a pathological hallmark of PD.	A30P	Promote the insoluble aggregation of α-synuclein [36]
		E46K	Promote the insoluble aggregation of α-synuclein [37,38]
		H50Q	Promote the insoluble aggregation of α-synuclein [39]
		G51D	Increase the toxicity of aggregated fibrils [40]
		A53T/E	Promote the insoluble aggregation of α-synuclein [36,41]
		Duplication/Triplication	Promote the increased expression of α-synuclein [42,43]
LRRK2	*LRRK2*-encoded Leucine-Rich Repeat Kinase 2 (LRRK2) is a multifunctional kinase involved in intracellular signaling, vesicle trafficking, autophagy, and cytoskeletal dynamics. Malfunctional LRRK2 leads to neuronal toxicity through abnormal phosphorylation of downstream targets, causing impaired autophagy, mitochondrial dysfunction, and increased α-synuclein accumulation.	N1437H	Decrease GTPase activity [44]
		R1441C/G/H	Decrease GTPase activity [45,46]
		Y1699C	Decrease GTPase activity [47]
		G2019S	Increase central kinase domain activity [48]
		I2020T	Increase central kinase domain and GTPase domain activity [49]
PRKN	*PRKN*-encoded Parkin acts as an E3 ubiquitin-protein ligase that tags damaged proteins and mitochondria for degradation via the ubiquitin-proteasome system and mitophagy. Malfunctional Parkin results in mitochondrial dysfunction, impaired mitophagy, oxidative stress.	R42P	Decrease protein structure stability [50,51]
		K48A	Decrease protein-protein interactions [50,51]
		T240R	Nonsense mutation in exon 6, loss of function [52,53]
		R275W	Decrease protein structure stability [54]
		Q311TERM	Missense mutation in exon 8, loss of function [52,53]
PINK1	*PINK1*-encoded PTEN-Induced Putative Kinase 1 (Pink1) is a	G309D	Decrease kinase activity and dysregulate mitophagy [55–58]

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	mitochondrial kinase that detects mitochondrial damage and recruits Parkin to initiate mitophagy. Malfunctional Pink1 lead to defective mitophagy, mitochondrial depolarization, increased oxidative damage, resulting in accumulation of damaged mitochondria and neuronal stress in PD.	T313M	Inhibit phosphorylation [59]
		L347P	Decrease protein stability [60] and increase degradation [61]
		G411S	Decrease kinase activity [62]
		W437X	Lack the C-terminus and part of the kinase domain, loss the regulation of mitophagy [57]
		Q456X	Decrease protein expression level and kinase activity [62]
DJ-1	*DJ-1*-encoded protein deglycase DJ-1 functions as an oxidative stress sensor and antioxidant, protecting cells from oxidative stress and regulating mitochondrial function. Malfunctional DJ-1 impairs antioxidant defense, increasing oxidative damage, particularly in dopaminergic neurons.	L10P	Decrease protein stability [63]
		M26I	Decreases protein expression levels [64,65]
		Q45TERM	Nonsense mutation in exon 8, loss of function [66]
		A104T	Decrease protein stability [64] and increased degradation [67]
		P158DEL	Decrease protein stability [63]
		L166P	Decrease protein stability, increase protein degradation [64,67–69]

Although less frequently studied, transgenic mouse models targeting the other eight *PARK* genes (*PARK* 5, 9, 11, 13, 14, 17, 19, and 20) have also been recognized as pivotal tools for unraveling the pathogenesis of PD. Sixteen transgenic mouse models based on these eight genes are summarized in Table 2, selected according to the following criteria: (1) direct impact on viability and development, (2) evidence of PD-related neurodegeneration and synucleinopathy, (3) manifestation of motor and/or non-motor PD-like deficits, and (4) utility in mechanistic exploration of PD pathogenesis.

Table 2. Summary of transgenic mouse models of PD associated with *PARK* genes with less frequent PD-associated mutations.

Gene	Genetic Model	Mutation Effects	PD-Like Pathologies and Phenotypes
PARK5	*UCH-L1*^{I93M}	Reduction of hydrolase activity [70]	Dopaminergic neurodegeneration [71] Promote tubulin polymerization [72]
	NT-UCH-L1	N terminal cutting, induce aggregation	Tendency to be monoubiquitinated and readily aggregated [73]
PARK9	*ATP13A2*$^{-/-}$ *(AAV-Cre)*	Knockout, loss of function	Dopaminergic neurodegeneration [74] No PD-like neuropathology [75,76]
	ATP13A2$^{-/-}$		No motor deficit but decreased spontaneous movement [75] Gliosis in brain, lipofuscinosis, and endolysosomal abnormalities [75]
PARK11	*GIGYF2*$^{-/-}$	Knockout, loss of function	Die within the first 2 post-natal days [77]
	GIGYF2$^{+/-}$		Motor dysfunction [77]
PARK13	*MND2 (HTRA2*$^{-/-}$*)*	Knockout, loss of function	Brief lifespan (40 days) with organ hypoplasia and muscle wasting [78–81] Neurodegeneration and oligomeric α-synuclein aggregation [79,80,82]

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			Abnormal neural electrical activity and neuroinflammation [83,84]
PARK14	*PLA2G6*$^{-/-}$	Knockout, loss of function	Shorter lifespan [85] Dopaminergic and axonal neurodegeneration and striatal α-synuclein accumulation [86–88] Motor deficits [86,87]
	PLA2G6^{D331Y}	Decrease phospholipase activity [89]	Dopaminergic neurodegeneration [90] Mitochondrial dysfunction, ER stress, and mitophagy impairment [90]
	PLA2G6^{G373R}	No glycerophospholipid catalyzing enzyme [91]	Dopaminergic neurodegeneration [88] Motor deficit [88]
PARK17	*VPS35*$^{-/-}$	Knockout, loss of function	Early embryonic lethality [92] Rod cell death [93]
	VPS35$^{+/-}$	N/A	Corneal dystrophy [94]
	VPS35 ^{D620N}	Inhibit autophagy [95]	Dopaminergic neurodegeneration and α-synuclein aggregation [96] Motor deficit [96] Mitochondrial dysfunction and hippocampal neurogenesis impairment [96,97]
PARK19	*DNAJC6*$^{-/-}$	Knockout, loss of function	Impaired pre-synaptic plasticity in the primary visual cortex [98]
PARK20	*SYNJ1*$^{-/-}$	Knockout, loss of function	Brief lifespan [99]
	SYNJ$^{+/-}$	Impaired 5′-phosphatase activity	Reduction of dopaminergic terminals [99] Hyperactivity and motor deficit [99]
	SYNJ^{R258Q}	Impaired Sac1 domain phosphatase activity [100]	60% survival rate [101] No dopaminergic neurodegeneration but morphological abnormality [101]

3. Results and Discussion

Monogenic forms of PD follow Mendelian inheritance patterns and are classified as either autosomal dominant or autosomal recessive. Accordingly, transgenic mouse models of PD are broadly categorized into knockout and overexpression systems, each tailored to dissect distinct genetic mechanisms. Knockout models, designed to mimic autosomal recessive PD, eliminate or impair gene function to investigate proteostatic failure in dopaminergic neurons. Conversely, overexpression models replicate dominant gain-of-function pathologies, enabling studies of α-synuclein aggregation dynamics and neurotoxicity. These genetic models are further classified into germline and conditional modifications. Germline models involve global gene alterations affecting all cells in the animal, whereas conditional models use tissue-specific promoters or inducible systems to restrict gene expression changes to particular regions or time points. This flexibility allows researchers to explore the gene's effects in specific biological contexts, providing more targeted insights into the underlying mechanism.

There has been significant progress in genetic research related to PD. Various potential PD-related genes with numerous pathogenic mutations have been identified across diverse populations and lineages. An overview of PD-related genetic pathways and associated animal models has been comprehensively summarized elsewhere [35]. Based on this foundation, the present review aims to use monogenic forms of PD as examples to illustrate how genetic mouse models have advanced our understanding of this highly complex neurodegenerative disorder.

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3.1. SNCA (PARK1/4)

3.1.1. Physiological Functions of α-Synuclein

The human SNCA gene (Gene ID: 6622, National library of Medicine), located on chromosome 4q22.1, encodes the α-synuclein protein composed of 140 amino acids [102]. In healthy brains, α-synuclein is predominantly expressed in presynaptic terminals in a monomeric, unstructured form [103–107]. It acts as a non-classical chaperone protein that binds to SNARE (soluble N-ethylmaleimide sensitive factor attachment proteins receptor) protein synaptobrevin-2 and contributes to the assembly of SNARE-complex to facilitate synaptic vesicle trafficking and neurotransmitter release at presynaptic nerve terminals [108]. Mice lacking α-synuclein are viable and fertile but not exhibit any noticeable pathological abnormalities or motor deficits [109,110]. Furthermore, while individual knockouts of α-synuclein or β-synuclein do not impact dopamine levels, double knockout leads to a decrease in dopamine levels, suggesting functional redundancy between the two synucleins, likely due to their molecular similarity [111]. While the knockout models provide valuable insights into the physiological function of α-synuclein, it is important to note that all pathogenic *SNCA* mutations identified in familial PD are gain-of-function, emphasizing the importance of overexpression or knock-in models for accurately studying disease mechanisms [112].

3.1.2. SNCA Mono-Transgenic Mouse Models

Under pathological conditions, toxic oligomers and fibrillar aggregates of α-synuclein induce selective and progressive neuronal death by disrupting mitochondrial function, impairing lysosomal activity, and altering calcium homeostasis [113]. Accordingly, transgenic mice overexpressing wild-type (WT) α-synuclein or carrying knock-in SNCA mutations (e.g., $SNCA^{A53T}$, $SNCA^{E46K}$, $SNCA^{A30P}$, see Table 1) have been widely employed to replicate PD symptoms, including olfactory and autonomic dysfunction, cognitive deficits, circadian rhythm disturbances, and early motor deficits, along with the progressive formation of α-synuclein-positive inclusions [34,112,114–117].

Despite all the advances achieved through these α-synuclein models, a persistent challenge remains: the inconsistent and often limited nigrostriatal neurodegeneration observed across models. As highlighted in previous reviews, most mouse *SNCA* transgenic models do not exhibit dopaminergic neurodegeneration in the nigrostriatal area [116,118,119]. However, there are noteworthy transgenic models with stable nigrostriatal neuron loss. For example, Chesselet and colleagues characterized a model in which full-length, wild-type human α-synuclein was overexpressed under the Thy-1 promoter in C57BL6/DBA2 mice [120]. This model displayed 40% loss of striatal dopamine at 14 months of age, along with olfactory deficits, colonic deficits and progressive motor impairments (as assessed by beam walk and pole tests) [120]. Wakamatsu and colleagues generated a novel mouse model expressing truncated human α-synuclein (residues 1 to 130) on the C57BL6J/B6C3F1 background [121]. Immunoblot analysis revealed approximately 45% dopaminergic neurodegeneration in the SN at two months of age, but no further progressive degeneration was observed up to thirteen months [121]. Similarly, these models highlight the ongoing need for long-term screening, optimization of mouse strains, and refinement of transgenic vectors to more faithfully model the progressive neurodegeneration observed in human PD.

3.1.3. New Developments in α-Synuclein Transgenic Models

The long-term screening and optimization of mouse strains and transgenic vectors are required to refine, improve these *SNCA* transgenic mouse models. Recent studies using the Jackson Laboratory human *SNCA* overexpression mouse strain (Stock No. 023837) revealed progressive dopaminergic neurodegeneration, with ~50% loss of tyrosine hydroxylase (TH) positive neurons in the SN and striatum between 4 and 14 months [122]. In addition to brain pathology, aggregation of α-synuclein was observed in peripheral tissues. For example, α-synuclein was found aggregating in retina, particularly in the outer plexiform layer, leading to the degeneration of synaptic ribbons, and TH-

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positive retinal neurons by 18 months of age [123]. In addition, Lewy body-like aggregates were also observed in the colon at 4, 8, and 14-month-old [122], while enteric/vagus nerve α-synuclein deposition developed in SNCA^{G51D} mice at 12-month-old and progressed with age [124].

In addition to replicating key neuropathological features of PD, a range of non-motor symptoms were successfully discovered in *SNCA* transgenic mouse models, such as gastrointestinal dysfunction, olfactory deficits, and sleep disorders, as well as associated cellular-level pathologies. For example, colonic motility deficits have been observed in double-PAC-transgenic SNCA^{A53T} mice using bead expulsion test and whole-gut transit time test [125]. Taguchi and colleagues reported a progressive sleep disorder phenotype in BAC-SNCA^{A53T} transgenic mice, characterized by increased EMG variance between 5 and 13 months of age [126]. Notably, pre-motor olfactory deficits in SNCAA53T mice emerged by 6 months, closely resembling the prodromal phase of human PD [127]. In BAC-SNCAWT overexpression mice at thirteen months, compromised blood-brain barrier and degeneration of striatal blood vessels were observed [128]. Compared with the WT mice, SNCA^{A53T} carriers exhibited a significantly increased proportion of abnormal red blood cells [129]. The same mutation also induced the lymphadenectasis, enlargement of the lymph sinus, and upregulation of inflammatory cytokines (such as IL-1β, IL-6 and TNF-α) [130]. Supporting these findings, post-mortem examination of PD patients' brains show increased string vessel formation, consistent with microvascular degeneration in PD [131]. Collectively, these findings underscore the multifaceted role of α-synuclein in both central and peripheral pathologies in PD, emphasizing the relevance of *SNCA* transgenic mouse models for capturing these broader aspects of the disease.

3.1.4. Mechanistic Insights and Therapeutic Implications

SNCA transgenic models, while imperfect, have provided valuable insights into the mechanistic links between α-synuclein pathology, microglia activation and PD progression. Microglial activation through pathways involving NLRP3 inflammasomes, interleukin-1 receptor, and fractalkine signaling exacerbates neurodegeneration in PD models [132–135]. Another highlight is the interaction between α-synuclein and mitochondrial dysfunction and oxidative stress [136]. Disruption of mitochondrial transmembrane potential caused by α-synuclein-induced complex I inhibition leads to increased oxidative stress and mitophagy [105]. In turn, increased levels of oxidative stress can further accelerate the aggregation of α-synuclein, creating a self-reinforcing pathogenic loop [137].

The recognition of α-synuclein's pivotal role in PD pathogenesis has driven substantial progress in therapeutic innovation. Recent efforts to enhance translational validity in preclinical studies include the use of refined animal models that better replicate the spatiotemporal progression of human PD. These models are increasingly used to evaluate compounds that inhibit α-synuclein aggregation, block its cell-to-cell transmission, or promote its clearance through immunotherapy or autophagy enhancement (Table 3).

Table 3. Examples of PD treatment developments targeting α-synuclein.

Treatments	Involved Mechanism	Pathway/Function
1. Exosome-mediated antisense oligonucleotide 4	Expression	1. Blocks the expression of *SNCA* specifically in vivo and vitro [140]
2. Indatraline-conjugated antisense oligonucleotide		2. Attenuates the production of α-synuclein and related dopamine dysfunction [141,142]
3. Posiphen		3. Recognises *SNCA* mRNA and inhibits the expression of α-synuclein [125]
4. Nano-MgO micelle composite- α-synuclein-mRNA		4. Crosses the BBB to target the neurons and attenuates the expression of α-synuclein [143]

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1. Syn9048 (pan-α-synuclein antibody)	Transmission	1. Decreases the α-synuclein pathology in several brain regions by selectively binding to pathogenic α-synuclein, inhibiting its cell-to-cell transmission and promoting its clearance [144].
2. BIIB054 (human-derived α-syn antibody)		2. Binds with α-synuclein via high affinity to rescue the dopamine transporter loss and motor deficits [145].
3. Toll-like receptor 2		3. Blocks the transmission of α-synuclein between neuron-neuron and neuron-astrocyte [146].
1. Eicosanoyl-5-hydroxytryptamide	Aggregation	1. Activates the dephosphorylation of α-synuclein to reduce the protein fibrillation [147].
1. Felodipine	Degradation	1. Enhances autophagy to degrade α-synuclein aggregates [148]
2. Tat-βsyn-degron		2. A peptide that can cross the BBB and plasm membrane to knockdown α-synuclein [149]

As shown in Table 3, posiphen (inhibits α-synuclein expression) and BIIB054 (high affinity scavenger of α-synuclein) have currently entered the clinical trial phase. According to database ClinicalTrials.gov, a human PD related phase III clinical trial of posiphen, an inhibitor of acetylcholinesterase, has recently been conducted in over 450 subjects [138]. However, the development of BIIB054 was terminated during the Phase II clinical trial [138]. The trial results showed that patients treated with BIIB054 did not differ from those receiving placebo in MDS-UPDRS subscale scores or DaT-SPECT scans over a 52-week period [139]. These advancements underscore the therapeutic potential of targeting α-synuclein-driven mechanisms and highlight the continued importance of *SNCA* transgenic models in the preclinical evaluation of PD interventions.

3.2. LRRK2 (PARK8)

3.2.1. The Role of LRRK2 in PD

The human LRRK2 gene (NLM, gene ID 120892), located on chromosome 12q12 and comprising 53 exons, encodes a protein of 2527 amino acids called leucine-rich repeat kinase 2 (LRRK2). This multidomain protein functions as a kinase and directly phosphorylate threonine/serine residues of several Rab GTPase proteins, such as Rab 1, 5, 7, 8, 10, 12, and 39 [150,151]. Rab GTPases play diverse roles in coordinating intracellular membrane trafficking in cells [152], implicating LRRK2 in various pathogenic pathways associated with PD. The $LRRK2^{G2019S}$ mutation has been found in approximately 4% of all hereditary PD cases and 1% of sporadic PD cases worldwide, while $LRRK2^{R1441C}$ has been reported to exhibit over 90% penetrance by age 75 [153,154]. Postmortem studies reveal heterogeneity in LRRK2-linked PD, with some patients exhibiting both nigrostriatal neurodegeneration and Lewy pathology, while others showing selective SN degeneration without central Lewy bodies [155–157]. Importantly, heterozygous LRRK2 loss-of-function carriers do not develop PD [158], whereas gain-of-function mutations are associated with elevated PD risk [159]. This dichotomy underpins therapeutic strategies targeting LRRK2 inhibitors to counteract its pathogenic overactivity [160–162].

3.2.2. Challenges in Developing LRRK2 Mouse Models

Despite extensive efforts, developing robust LRRK2 transgenic mouse models that replicate PD pathology has proven difficult. Overexpression of wild-type or mutant human or mouse LRRK2, regardless of the promoter used, fails to produce consistent neurological or pathological symptoms [163–169]. Specifically, C57BL/6-based mouse models have not reliably recapitulated any PD

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pathological hallmarks [163,164,166,170–174]. For example, CMV-driven LRRK2^{G2019S} expression in C57BL/6J mice induced significant but modest neurodegeneration (14%) after 19 months, and LRRK2^{R1441C} expression in the same background failed to cause significant neurodegeneration in the SN area [175].

The FVB/N mouse strain, widely used due to its high transgenic efficiency, serves as one potential choice for developing LRRK2 transgenic mouse models. However, it similarly exhibits inconsistent outcomes with respect to the development of a neurodegenerative phenotype. While some studies reported significant loss of TH+ cells in the SN of LRRK2^{R1441C} FVB/N mice at 16 months [168], others observed no such effect [176]. LRRK2^{R1441G} mice only exhibited TH+ dendrites degenerating in SN pars reticulate without dopaminergic neurodegeneration in SNpc and ventral tegmental area at 10 months [177]. Additionally, FVB/N mice display chaotic circadian rhythm patterns and optical dysopia, which may contribute to the inconsistent behavioral test results [178]. These factors, along with the inconsistent reproducibility of dopaminergic neurodegeneration undermine the reliability of FVB/N strain in terms of a useful PD model.

3.2.3. Reproduction of Neuropathological, Functional and Molecular Features

Although LRRK2 mutations lead to minimal neurodegeneration in the substantia nigra, they still influence the function and morphology of neurons in C57BL/6 mice [179–181]. For example, both LRRK2^{R1441C} and LRRK2^{G2019S} contribute to the loss of primary cilia in choline acetyltransferase (ChAT) interneurons of the dorsal striatum [182,183]. Moreover, LRRK2^{G2019S} increases NADPH levels, resulting in metabolic changes in neurons [184]. Besides functional changes, LRRK2 causal variants also promote α-synuclein aggregation. For instance, recent exploration in LRRK2 transgenic mouse models revealed that the LRRK2^{R1441G} variant increased the levels of α-synuclein oligomers in the cortex (30.7%) and striatum (53.2%) by 18 months of age in C57BL/6 mice [185]. These findings suggest that LRRK2 mutations impact both neuronal function and α-synuclein pathology, confirming its involvement in PD pathogenesis.

These functional changes in neurons and α-synuclein aggregation are further reflected in motor deficits and non-motor manifestations. The expression of LRRK2^{R1441C} in the C57BL/6J strain caused the progressive impairment of locomotor activity [175]. Similar motor deficits were detected in LRRK2^{G2019S} mouse strain (created with both the BAC and PDGFB transgenic vectors) at 65 weeks old [186,187]. Additionally, LRRK2^{G2019S} contributes to skeletal muscle EMG spontaneous potential impairment and reduction of muscle strength and mass [188]. Non-motor phenotypes, such as sleep pattern disorders, depression-like behavior, and alterations in gut microbiota communities, have also been characterized in LRRK2G2019S mice [189–191]. The newly discovered variant, LRRK2^{R1628P} was reported to induce intestinal dysfunction in C57BL/6 mice [192], further expanding the phenotypic spectrum.

On the molecular level, LRRK2 mutations are implicated in PD-related molecular pathways involving inflammation, mitochondrial dysfunction, neurotransmitter transmission and ER stress. For example, LRRK2^{G2019S} increases pro-inflammatory cytokines in the skeletal muscles [188], and exacerbates mitochondrial DNA damage in the ventral midbrain [193]. Altered transcription resulting from LRRK2^{G2019S} leads to microglia sensitization and increased inflammation levels [194–198]. In addition, LRRK2^{G2019S} has been found to affect glutamatergic synaptic transmission, thereby influencing striatal synaptic plasticity and cognitive learning under stress [199–202]. The expression of LRRK2^{R1441G} decreases synaptogyrin-3 expression, which may impair dopamine reuptake [203]. Furthermore, LRRK2^{G2019S} leads to the accumulation of misfolded proteins in neurons and induces ER stress by promoting the expression of thrombospondin-1/transforming growth factor beta1 [204].

Proteomics analyses in mice have revealed that LRRK2 mutation leads to alterations in lysosomal proteases, cytoskeletal proteins, and protein translational machinery [205]. The increased LRRK2 kinase activity caused by LRRK2^{G2019S} can mistakenly recruit and activate the motor adaptor JNK-interacting protein 4 (JIP4), leading to deficits in autophagosome transport [206]. Additionally, LRRK2G2019S impairs glutamate clearance by affecting excitatory amino acid transporter 2 (EAAT2),

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potentially leading to glutamate overload and subsequent neurodegeneration [207]. These insights into proteomic and cellular dysfunction highlight the multifaceted contributions of LRRK2 mutations to PD pathogenesis, underscore the relevance of LRRK2 as a potential therapeutic target and supports the contention that LRRK2 transgenic mouse models have been useful tools in the study of PD more generally.

3.3. PRKN (PARK2)

3.3.1. The Role of Parkin in PD

The human PRKN gene (PARK2) (NLM, gene ID 5071), located on chromosome 6q26 and comprising 13 exons, encodes a protein of 465 amino acids called parkin, which acts as an E3 ubiquitin-protein ligase [208]. In the ubiquitin system, ubiquitin-protein ligase mediates the transfer of ubiquitin from the ubiquitin-conjugating enzyme to the substrate protein. The ubiquitin-tagged protein is then targeted for intracellular degradation [209]. When mitochondrial depolarization occurs, PINK1-dependent phosphorylation of parkin Ser 65 is essential for the formation of parkin ubiquitin-ester intermediates [210]. This phosphorylation enables conformational changes in the RING0 domain, exposing parkin's catalytic core only after ubiquitin itself is also phosphorylated at Ser65 [211]. Phosphorylated polyubiquitin chains on the mitochondrial outer membrane (MOM), generated by PINK1, then serve as a signal for parkin translocation [212,213]. Once recruited, activated parkin mediates the ubiquitylation of several proteins on the MOM, including TOMM70A, HK1 and MFN1 for mitophagy [212–216]. In addition to its role in mitochondrial quality control, parkin is also involved in the cell rescue signaling pathway and mitochondrial biogenesis via peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) [217]. Therefore, parkin plays an essential role in eliminating dysfunctional mitochondria [218–220].

3.3.2. Neurological Deficits in PRKN-Based PD Mouse Models

Over 200 PD-associated PRKN loss-of-function mutations have been identified. The loss of the PRKN leads to the accumulation of glutamate kainate receptors, contributing to neurodegeneration in the mouse SN at 6 months of age [221]. Synaptotagmin-11, a physiological substrate of parkin, has also been implicated to play an essential role in parkin deficiency-induced neurotoxicity [222]. In PRKN-KO mice, synaptotagmin-11 accumulates and its overexpression induces the loss of TH-positive neurons in the SNpc along with abnormal behaviors in methamphetamine-induced rotational test and gait analysis [222]. The loss of the PRKN leads to the accumulation of glutamate kainate receptors, contributing to neurodegeneration in the mouse SN at 6 months of age [221].

Beyond neuron death, deficiency affects key neuronal processes. In PRKN knockout models, the over-acetylation of the microtubule system in nigrostriatal neurons appears to contribute to mitochondrial damage via disorientating the transport of mitochondria and subsequent axonal degeneration [223]. Compared with control cells, the lack of PRKN leads to lower complexity of neurons including shorter neurite length, less terminal number and fewer branch points [224]. In a recent study, Regoni and colleagues used high magnification fluorescent microscopy (100x) to observe significantly more cytoplasmic vacuolization and disruptions in mitochondrial ultrastructure in the SN dopaminergic neurons of PRKN^{R275W} mice at just one month of age, confirming the essential role of parkin in early neuronal development and mitochondrial maintenance [225]. Apart from reproducing the dopaminergic neurodegeneration, newer PRKN mutations, such as PRKN^{S65A} and PRKN^{R275W}, have been reported to cause marked motor deficits and balance impairment in C57BL/6J mice by 12 months of age [225,226].

3.3.3. The Strain-Dependent Phenotypic Differences

However, traditional *PRKN* knockout models targeting exons 2, 3, or 7 have failed to recapitulate key phenotypic changes related to human PD [227–231]. In contrast, BAC-PRKNQ311TERM FVB mice, which carry a nonsense mutation in exon 8 (PRKNQ311TERM) [52], exhibit significant

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dopaminergic neurodegeneration in the substantia nigra and striatum with motor deficits at 16 months of age [232]. These mice also exhibited progressive accumulation of α-synuclein in the SN (at 16 months) [232] and significant neuroinflammation (at 12 months) and motor deficits (> 6 months) [233]. These findings suggest that the impact of *PRKN* mutations is highly strain-dependent and models based on the C57BL/6 background may have limited capacity to faithfully reproduce key PD pathology and phenotypes.

3.4. PINK1 (PARK6)

3.4.1. The Role of PINK1 in Mitochondrial Function and PD

The human PINK1 or PARK6 gene (NLM, gene ID 65018), located on chromosome 1p36.12, encodes a 581-amino acid serine/threonine kinase called PTEN-induced kinase 1 (PINK1) [55]. PINK1 plays a key role in mitochondrial quality control through its involvement in the ubiquitin-proteasome system. The N-terminal of the PINK1 precursor protein contains mitochondrial targeting sequences [234], allowing its import into mitochondria, where it anchors via interactions with proteins SYNJ2a and SYNJ2 Binding Protein [235]. Under normal conditions, mitochondrial proteases such as presenilin-associated rhomboid-like protease and mitochondrial processing peptidase mediate the import, processing, and degradation of the PINK1 precursor [236–238]. When mitochondrial depolarization occurs, PINK1 accumulates on the MOM and phosphorylates ubiquitin and Parkin to initiate mitophagy [210,211,213,236,237]. Furthermore, it has been shown that PINK1 binds to the pro-autophagic protein Beclin1 to enhance autophagy [57]. Loss-of-function mutations in PINK1 are associated with autosomal recessive early-onset PD and impair its role in mitochondrial homeostasis and autophagic regulation [55,57,60,61].

3.4.2. The Limitations and the Developments in PINK1 Transgenic Mouse Models

Similar to PRKN knockout models, deletion of exons 2–5 or 4–7 in PINK1-deficient mice does not lead to dopaminergic neurodegeneration [239,240]. Although a decrease in dopamine levels and inflammatory cytokines were detected in exon 4-5 knockout-induced PINK1-deficient C57BL/6 mice, no TH+ neurodegeneration was observed [241]. Filograna and colleagues also reported no PD-like phenotype in PINK1 knockout C57BL/6N mice [242]. Transgenic models expressing the PINK1^{G309D} mutation showed α-synuclein aggregation in the midbrain without TH+ neurons loss in the SN in 129/SvEv mice [243].

The development and investigation of PINK1 mouse models are ongoing. Recent studies suggest that PINK1-related phenotypes may be more nuanced and develop with age. For example, Sliter and colleagues reported a 20% reduction in TH+ neurons in PINK1 knockout mice at the age of 40 weeks [244]. Despite the initial lack of an identified motor phenotype, more recent re-examinations revealed non-motor symptoms like depression and anxiety in aging PINK1-deficient mice [245,246]. Moreover, age-dependent changes in primary cilia morphology have been observed in striatal and cholinergic neurons of PINK1 knockout mice, similar to the observations in LRRK2^{R1441C} and LRRK2^{G2019S} mouse models, suggesting shared pathogenic pathways [182,183,247]. These findings highlight the emerging role of PINK1 in PD pathogenesis and emphasize the need for further refinement of PINK1 transgenic mouse models to more faithfully replicate both motor and non-motor aspects of the disease.

3.5. DJ-1 (PARK7)

3.5.1. The Role of DJ-1 in Oxidative Stress and PD

The human DJ-1 gene (NLM, gene ID 11315), located on chromosome 1p36.23, encodes a 189-amino acid protein. Homodimeric DJ-1 is present in the cytoplasm, mitochondria, and nucleus. It functions as an oxidative stress sensor, contributing to the elimination of reactive oxygen species such as hydrogen peroxide [248,249]. This suggests that DJ-1 plays a neuroprotective role in the brain [250]. Pathogenic mutations in DJ-1 are associated with autosomal recessive early-onset parkinsonism [251]

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and are typically loss-of-function mutations, implicating DJ-1 in the pathogenic mechanism of PD [64–69].

3.5.2. Behavioral and Cellular Changes in DJ-1 Mouse Models

The existing DJ-1 mono-transgenic mouse models poorly recapitulate notable parkinsonian phenotypic features [252–258]. However, some subtle changes have been reported in these animals. While no changes in the substantia nigra were observed, noticeable TH+ neurodegeneration was found in the retinas of DJ-1 exon 2 knockout C57BL6/J mice, leading to increased light sensitivity of the eyes [253,258]. Although typical neuropathological features cannot be reproduced in mouse models, behavioral phenotypes have emerged in recent studies. For example, in DJ-1 exon 2 knockout B6/129 mice, reduced locomotor activity was observed in open field test at an age of three months [259]. Similarly, on the C57BL/6J background, the knockout of DJ-1 exon2 led to motor deficits (at 10 months) [260], gait abnormalities and decline of grip strength (at 16 months) [254]. These findings suggest that DJ-1 plays a role in motor function and oxidative stress regulation, although its dopaminergic impact in current mouse models appears modest.

Beyond behavioral alterations, DJ-1 mouse models have provided insights into underlying mechanisms of PD, particularly inflammation and mitochondrial function. Excessive activation of the apoptosis-related p53 pathway was reported and contributed to apoptosis and inflammation in the colon after DJ-1 knockout in C57BL/6 mice [261]. Increased microglial activation caused by the NF-κB pathway was observed in DJ-1 exon2 knockout C57BL/6J mice [262]. DJ-1 deficit attenuated the proliferation of astrocytes and monocyte infiltration, and delayed the recovery from brain injury, further contributing to PD [263]. Through proteome analysis and further research, Ozawa found that the DJ-1 protein is essential for the nitrosylation of parkin, which is important for maintaining mitochondrial function [264]. These findings suggest that DJ-1 plays a critical role in regulating inflammatory responses and mitochondrial mechanisms.

3.6. Modeling Gene-Environment and Gene-Gene Interactions in the Aetiology of PD

3.6.1. PD and Environmental Factors: Neurotoxin Models and Gene Interactions

PD is a multifactorial disorder caused by complex interactions among genetic, environmental, and lifestyle factors. The influence of environmental factors on PD is significant but often overlooked. Exposure to certain environmental factors, such as pesticides, has been strongly linked to increased PD risk [8,265,266]. Combining different models to study the interaction between environmental factors and PD-associated PD genes, either individually or in combination, is providing new insights into the disease. In peer-reviewed publications, neurotoxin-induced PD mouse models occupy the largest proportion of published animal research articles. These models include those induced by 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), pesticides, and other neurotoxins [29,267].

MPTP, 6-OHDA, rotenone, and paraquat are the most used neurotoxins in PD research to induce PD-like pathological phenotypes in mouse models. MPTP crosses the blood-brain barrier rapidly due to its high lipophilicity [268,269]. Its active metabolite MPP^+ has a high affinity for dopamine, norepinephrine, and serotonin transporters on the plasma membrane, allowing it to accumulate in dopaminergic neurons. Once inside the cell, MPP^+ accumulates in the mitochondrial matrix, inducing ATP depletion and oxidative stress, which cause mitochondrial dysfunction and eventually neuronal death [270–273]. Similarly, 6-OHDA, a dopamine analog, is taken up by dopaminergic and noradrenergic neurons, where it causes neuronal damage through oxidative stress and iron-mediated catalysis [274]. Rotenone is a highly toxic chemical. It functions as a potent mitochondrial complex I inhibitor, inducing oxidative stress and cell death by inhibiting ATP synthesis [267,275]. Paraquat is also a highly toxic herbicide. It selectively induces neuronal cell death in the SNpc by participating in redox cycling and activating mitochondrial apoptosis [267]. These neurotoxins provide valuable tools for modeling PD pathology and studying its underlying mechanisms in rodents.

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3.6.2. Interactions Between MPTP and SNCA

Several studies have examined how *SNCA* mutations influence susceptibility to MPTP. Yu and colleagues reported that $SNCA^{A30P}$ transgenic mice exhibited significantly higher mortality compared to WT mice following MPTP exposure, with all deaths occurring in males— consistent with gender differences observed in PD prevalence [276]. However, subsequent studies found when compared with control WT animals, neither $SNCA^{A53T}$ nor $SNCA^{A30P}$ mutations significantly increased dopaminergic neuron loss in SNpc and striatum due to MPTP exposure [277–279]. Despite the lack of significant dopaminergic neurodegeneration, apoptotic markers were elevated. For example, expression of Bax and Bcl-2 in the nucleus basalis magnocellularis-substantia innominate was significantly higher in $SNCA^{A30P}$ mice than in WT mice following MPTP treatment [280,281]. In addition to affecting neuron survival, *SNCA* mutations also impair neuronal regeneration and dopamine metabolism. Transgenic *SNCA* expression significantly impaired the regeneration of dopaminergic neurons and fibers after MPTP treatment [282,283]. Notably, HPLC-electrochemical analysis revealed a more pronounced decrease in dopamine levels in the olfactory bulbs of $SNCA^{A53T}$ mice compared to WT mice after MPTP treatment [282].

3.6.3. Interactions Between MPTP and LRRK2/PINK1

The interaction between MPTP and LRRK2 is particularly noteworthy. Similar to SNCA, overexpression of both WT LRRK2 and $LRRK2^{G2019S}$ leads to increased mortality when exposed to a standard dose of 10 mg/kg MPTP [284]. Neurodegeneration severity directly correlates with the level of LRRK2 expression, irrespective of the specific variant [181,284,285], supporting a gain-of-function role for LRRK2 variants in PD. Functionally, $LRRK2^{G2019S}$ mice showed reduced motor performance on the rotarod after MPTP treatment compared to WT mice, indicating a synergistic gene-environment effect [284].

Similarly, PINK1 loss-of-function variants increase neuronal vulnerability to MPTP. WT PINK1 has also been shown to protect about 15% more primary neurons than $PINK1^{-/-}$, or loss-of-function mutants ($PINK1^{G309D}$ and $PINK1^{K219M}$) in response to MPTP treatment [286]. This highlights the protective role of PINK1 in mitigating MPTP-induced neuronal damage. The $PINK1^{-/-}$ mice demonstrated an exacerbation of the usual MPTP-induced motor dysfunction, accumulation of α-synuclein, and gliosis, as shown by elevated GFAP+ astrocytes and Iba1+ microglia in the midbrain substantia nigra [287].

3.6.4. Interactions Between Other Neurotoxins and Genetic Mutations

Similar to the results reported on the combined effects of SNCA mutation and MPTP exposure, $SNCA^{A30P}$ mice exhibited an increased mortality rate compared to WT controls when exposed to rotenone, despite showing no significant differences in dopaminergic neuron death [278]. However, exposure to other neurotoxins, such as 6-OHDA and paraquat, showed variability in their interactions with SNCA gene variants. For example, 6-OHDA induced reductions in TH fiber density in the midbrain were more pronounced in $SNCA^{A30P}$ mice than in WT controls [288]. When exposed to paraquat and maneb, overexpression of SNCA significantly exacerbated loss of neural progenitors [289].

The mutations not only affect the neurons' susceptibility to neurotoxins but also influence which brain regions are impacted. For example, under the treatments of rotenone, $SNCA^{A30P}$ mice older than 9 months exhibited a more significant reduction in hippocampal-cortical network gamma oscillations, which is an electrophysiological marker of attention and memory, compared to WT mice [290]. Additionally, the interaction of $SNCA^{A53T}$ and paraquat treatment led to significantly enhanced α-synuclein pathologies in the cerebellar cortex, hippocampus, somatosensory and auditory cortices [291].

Other PD-linked genes also modulate neurotoxins sensitivity. For instance, the $LRRK2^{G2019S}$ mutation can further exacerbate rotenone-induced mitochondrial dysfunction and impaired

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neurotransmission [292]. Moreover, studies using SN neurons dissected from PINK1 KO mice highlighted the essential role of PINK1 in maintaining normal mitochondrial membrane potential and protecting against neurodegeneration under rotenone treatment [293].

3.7. The Potential Interactions of Multiple PD Genes

The evidence summarized above demonstrates that when exposed to exogenous neurotoxins, mice with PD-related gene mutations exhibit worse outcomes than WT mice. These outcomes include higher mortality, increased neurodegeneration, impaired neurogenesis and neurotransmission, and deficits in the motor system. A critical next step is to examine potential interactions between different *PARK* genes. Accumulation of insoluble misfolded α-synuclein proteins can cause the attenuation of proteasome activity, lysosomal dysfunction, blocking of tubulin polymerization, inhibition of mitochondrial complex I and oxidative stress [20,103]. Therefore, it is hypothesized that *SNCA* causal variants that induce aggregation of α-synuclein may have a high likelihood of interacting with the pathological effects of other *PARK* gene mutations.

Initially, aggregated α-synuclein may trigger proteasome- and lysosome-mediated cellular protein degradation pathways. As previously noted, LRRK2 is also involved in regulating the function of lysosomal proteases [205]. When these degradation systems are overwhelmed by excess misfolded proteins, cellular health is further compromised. The inhibition of mitochondrial complex I by α-synuclein and the resulting oxidative stress may interact with proteins parkin, PINK1, and DJ-1 [105,210,211,213,236,237,264]. Increased expression of α-synuclein as been linked to elevated levels of pink1 protein, contributing to enhanced pS65-Ub-mediated mitophagy [294]. DJ-1 may also have connections with α-synuclein via its role in apoptosis, astrocyte proliferation, and inflammation [262,263,295,296].

Beside the synergistic effect with SNCA, there is emerging evidence for potential interactions among other *PARK* genes. PINK1 and LRRK2 both contribute to the morphological development of primary cilia in striatal neurons and cholinergic neurons [182,183,247]. Additionally, glutamatergic synaptic transmission requires the involvement of both LRRK2 and parkin [207,221]. These results indicate the pathway connections and functional convergence among PD-related genes themselves and suggest that multiple interconnected molecular pathways underlie PD pathogenesis. Therefore, the application of combined transgenic models, such as double knockout and multiple mutations, is becoming a popular approach moving forward.

3.8. Clinical PD and Related Mouse Behavioral Assessments

When evaluating a novel animal model of PD, a crucial criterion is assessing the model's ability to faithfully reproduce the hallmarks of the disease, including both pathological and neurological features. Current behavioral assessments in PD models heavily emphasize motor dysfunction, reflecting their ease of quantification and alignment with diagnostic criteria for parkinsonism. However, this emphasis risks overlooking early prodromal symptoms and non-motor comorbidities that define PD's preclinical and clinical trajectory in humans. Table 4 summarises the mouse behavioral tests which are widely used to evaluate both motor and non-motor symptoms associated with PD. The following sections described the specific manifestations of frequently reported symptoms in PD patients and the corresponding behavioral assessments in mouse models. The tested capacities and parameters were summarized to illustrate how behavioral tests are used to quantify outcomes of animal behavior. By bridging gaps between clinical PD manifestations and preclinical modeling, this integrated analysis aims to refine behavioral phenotyping strategies, ultimately strengthening the translational power of PD mouse models.

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Table 4. Examples of classical mouse behavioral assessments in PD research.

Mouse Assessments	Classification	PD-Related Symptoms
Open field test	Comprehensive	Parkinsonian syndromes and Anxiety [297,298,345]
Rotarod test	Motor	Parkinsonian syndromes [308–311]
Pole test		Parkinsonian syndromes [305–309]
Beam walking test		Parkinsonian syndromes and Gait disturbance [307,308,311–313]
Hanging test		Dystonia [81,308,314]
DigiGait test		Gait disturbance [318–320]
EEG and EMG	Non-motor	Sleep and Circadian rhythms disorder [324,325]
Buried food-seeking test		Olfactory disorder [328–330]
Voiding spot assay		Urinary dysfunction [333]
Metabolic cage assay		Constipation, GI and Urinary dysfunction [334]
Whole gut transit time		GI [125]
Forced swim test		Depression [298,338]
Elevated maze test		Anxiety and fear [339]
T/Y maze test		Cognitive impairment [340–342]
Barnes maze		Learning and Memory dysfunction and Bradykinesia [343]
Morris water maze		Learning and Memory dysfunction [298,344]
Open field test		Parkinsonian syndromes and Anxiety [297,298,345]
Rotarod test		Parkinsonian syndromes [308–311]
Pole test		Parkinsonian syndromes [305–309]
Beam walking test		Parkinsonian syndromes and Gait disturbance [307,308,311–313]

3.8.1. Assessing Bradykinesia and Tremor in PD Models

A variety of assessments have been developed to measure motor deficits based on performance evaluation. Rest tremor, characterized by involuntary shaking of a limb or head at rest, is a common motor symptom of PD. Visual observation in daily checks can be used to assess tremors without the need for a specialized behavioral assessment. Bradykinesia, which refers to slowness of movement and difficulty initiating movements, is another key motor symptom of PD. Locomotor function is often used as an indicator of bradykinesia. The open field test, where mice are placed in an open arena to freely explore, is a commonly used assessment to determine levels of locomotor activity, general anxiety levels, and exploratory tendencies [297,298]. Various open field test arenas, such as home-cage, square-arena, and round-arena open fields, can be used as long as the mice can freely move and explore around [299–301]. Nevertheless, compared with the home-cage open field test, the standard arenas can provide more locomotor space without limitations and support the collection of more behavioral readouts [302]. Parameters such as total travel distance and average speed are notable indicators of bradykinesia. Additionally, the open field test can provide insights into the anxiety levels of mice based on their thigmotaxis (tendency to stay close to walls) behavior [303,304].

3.8.2. Evaluating Rigidity and Comprehensive Motor Capacity

The characteristic rigidity of PD is characterized by intensified muscle stiffness and evident resistance to passive movement. It manifests as a persistent hindrance to limb mobility, resulting in rigid and inflexible muscle tone. This rigidity affects multiple muscle groups, making the initiation and execution of voluntary movements challenging. To assess rigidity and overall motor function,

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tests like the pole test and rotarod are commonly employed. The pole test involves placing a mouse face-up on a rough-surfaced pole, and the time it takes for the mouse to reorient itself and land on the ground reflects its overall motor capacity [305,306]. Compared with control mice, PD mice with motor deficits needed more than 50% more time to complete the reorientation and landing [307–309]. The accelerating rotarod test assesses motor coordination, learning, and cardiopulmonary endurance. Mice are placed on a rotating rod that gradually increases in speed. Time spent on the rotarod reflects their balance, coordination, and endurance [310,311]. PD mice generally show reduced latency to fall due to motor impairment [308,309].

3.8.3. Effective Assessment of Balance and Strength

Two simple yet effective tests include the beam walking test and hanging test are typically employed for balance and strength assessment. For example, in the beam walking test, mice walk across a narrow beam to reach a darkened safety box, thereby their dynamic balance and motor coordination are evaluated. Performance is quantified by the time it takes for the mouse to reach the dark box and the number of foot slips during the assessment [311–313]. Increased beam crossing latency and the number of foot slips indicate significant motor deficits in PD mouse models [307,308]. Similarly, in the wire mesh grip strength test, or hanging test, mice are simply required to hang onto an upside-down mesh for as long as possible, and the hanging time is used to assess muscle strength and motor deficits [81]. PD neurotoxin-induced mice show significant grip strength deficits in this test [308,314]. These tests collectively highlight the multifaceted motor impairments in PD, contributing to gait impairments, including movement velocity, stride length, turning ability, and limb coordination [315].

There has been significant progress in the development of technologies capable of comprehensively evaluating motor functions. Two notable digital platforms in this regard are DigiGait [316] and CatWalk [317], which enable an objective assessment of motor functions by yielding an array of gait-related parameters. Both tests analyze posture and kinematics of mice through dynamic fingerprint signals generated from all four limbs, thereby offering valuable information about gait characteristics related to strength, balance, and coordination [318–320].

3.9. Non-Motor Behavioral Assessments

3.9.1. Measuring Sleep Disorder

Certain assessments have been developed to measure non-motor deficits based on performance evaluation. It is evident that modulating sleep and circadian rhythms can effectively address disease progression in PD [321]. Sleep disorders in PD patients include excessive daytime sleepiness, insomnia, and fragmented sleep during the night [322]. Electrophysiological studies have indicated that dopaminergic neurons mediate arousal behavior through communication with the striatum, basal forebrain, and cerebral cortex [323]. In mouse models, the implantation of electroencephalogram and electromyogram electrodes is commonly used to record and quantify the sleep-wake cycle [324,325].

3.9.2. Assessing Olfactory Dysfunction

Approximately 90% of PD patients experience olfactory impairments, including difficulties in identifying, detecting and discriminating odors [326]. Olfactory decline has been suggested as an indicator of neurodegeneration beyond the striatum in PD [327]. The buried food-seeking test is an assessment designed to evaluate mouse olfaction, where the time taken by the mouse to find buried food under bedding can be used as a measure of olfactory capacity [328–330]. Furthermore, fasting before the buried food-seeking test has been shown to enhance the performance of mice in the assessment, improving the sensitivity of the test [331].

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3.9.3. Evaluating Autonomic Dysfunction

PD patients are often troubled by prodromal symptoms, such as constipation, urinary incontinence, and gastrointestinal dysfunction, sometimes many years before formal clinical diagnosis [19,26,332]. Various methods are available to monitor urinary dysfunction in mouse models. For example, the voiding spot assay allows for visualizing and quantifying urinary function in mice through urine stains on filter paper, without invasive procedures [333]. The metabolic cage assay is a specialized housing unit that enables continuously monitoring and measuring various physiological parameters, including metabolic rate, food and water intake, and waste output [334].

3.9.4. Measuring Psychiatric and Cognitive Symptoms

Meta-analytic studies have reported that approximately 38% of PD patients experience depression, while 40% and 26.3% are diagnosed with mild cognitive impairment and dementia, respectively [335–337]. Accordingly, several assessments have been designed to measure the emotional and cognitive capacities of mice. Forced swim tests continue to be widely used to assess the level of depression in mice [298,338]. The elevated maze test focuses on anxiety-related behavior and introduces fear of heights to modify the exploratory behavior of mice [339]. Various mazes, such as the T-maze, Y-maze, Barnes maze, and Morris water maze, are designed to evaluate the cognitive capacity, memory, and learning in mice. In these tests, mice are trained to remember targets under the motivation of food rewards or shelter, with the ability to recognize targets and complete memory tasks serving as key indicators of spontaneous alternation, spatial learning, memory retrieval, and cognitive flexibility [298,340–344].

While there continues to be much progress in the development of behavioral phenotyping methods for use to explore Parkinsonian symptoms in mice, there remains a need to formalize and harmonize these methods so that direct comparisons can be made between studies.

4. Conclusions

4.1. Reducing Inconsistencies

The use of genetic mouse models has significantly advanced our understanding of the molecular mechanisms underlying PD. However, based on our extensive review of literature, various experimental variables have been identified as critical contributors to significant discrepancies in the measured experimental outcomes (Table 5). These discrepancies can cloud data interpretation and limit the research community's ability to find consensus.

Table 5. Variables contributing to experimental discrepancies in mouse models of PD.

Variable	Comment
Mouse strain used	Variation in genetic background and behavior
Genetic variants introduced	Different variants have differential effects
Transgenic technology used	Impacts expression levels, tissue distribution and cellular specificity of pathology
Age of the animals	Age-related differences in biological effects
Period of phenotypic examination	Required to assess progressive nature of the pathology
Protocols used for phenotyping	Different assessment methods measure different aspects of pathology, motor, non-motor and cognitive behavior.

For example, while C57BL/6 and FVB are the two most widely used mouse strains for genetically modified mice, the differences in genetic background and stress responses between these strains profoundly influence phenotypic outcomes, such as neurodegeneration patterns and behavioral deficits. For specific genes, unique pathogenic mutations lead to distinct protein dysfunction and further affect the specificity and severity of PD-like phenotypes. The choice of transgenic methods

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(e.g., PAC, BAC, AAV, CRISPR-Cas9), and promoters (e.g., PDGFB, Thy1, CMV) directly impacts transgene expression levels and spatial distribution. Moreover, although most PD-like symptoms, including motor deficits, α-synuclein aggregation, and neurodegeneration, manifest progressively in aged mice, studies are not regularly performed at different ages, emphasizing the need for longitudinal studies to better model human disease progression. Finally, the existing motor and non-motor behavioral tests lack standardized protocols, with variations in equipment design, testing parameters, and scoring criteria, complicating cross-study comparisons. These variables contribute to inconsistencies that hinder reproducibility across studies.

4.2. Recommended Strategies for Improving Models in the Future

Collectively, our study highlights the urgent need for developing an optimized approach to examining genetic mouse models for PD. We need to better harmonize experimental guidelines, consider strain selection, formulate the use of standardized genetic tools, age windows, and behavioral protocols that will enhance reproducibility, improve model validity, and accelerate the translation of preclinical findings to clinical applications. Establishing and characterizing transgenic modifications across diverse mouse strains offers may provide insights into the differential susceptibility of specific pathways to perturbation (including toxic insults). An example is the known preference of using C57BL/6 mice for MPTP-induced PD models due to their higher toxin susceptibility compared to other strains [346–350]. Employing consistent transgenic models would benefit and facilitate data integration across diverse research. As a minimum, quantifying the expression level and anatomical distribution of the mutated genes on RNA and protein level, for comparison with other mice models carrying similar mutations would serve to reduce variability in findings. Using age stratification consistently is another recommendation. We suggest categorizing behavioral test outcomes into age cohorts (2, 6, 12, and 18 months) to track progressive pathology and improve data consistency. Finally, the necessity to establish and refine a standard behavioral phenotyping protocol with consistent data analysis methods tailored to the study's objectives, would improve outcomes. Selecting commonly used behavioral assays, such as the rotarod or open field test, can provide a standardized foundation for experimental design, including age, strain, and testing conditions. This standardization can establish a base for cross-model comparisons and ensure data reproducibility. A shared foundation in experimental protocols will also facilitate collaborative refinement of methods and enable more direct comparisons between studies. In addition, employing an integrated multi-omics approach together with this standardized phenotyping could unravel complex gene-gene and gene-environment interactions to provide new disease insights. Such efforts will be crucial for translating mechanistic insights into therapeutic strategies that address PD's multifactorial nature and lead to better outcomes for preclinical studies and meaningful translation of this information into valuable results that help people living with conditions like Parkinson's.

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Abbreviations

The following abbreviations are used in this manuscript:

6-OHDA	6-Hydroxydopamine
AAV	Adeno-Associated Virus
ATP	Adenosine Triphosphate
ATP13A2	ATPase 13A2
BAC	Bacterial Artificial Chromosome
Bax	Bcl-2–Associated X Protein
Bcl-2	B-Cell Lymphoma 2
BIIB054	human-derived α-syn antibody
C57BL/6J	Inbred Laboratory Mouse Strain
ChAT	Choline Acetyltransferase
CMV	Cytomegalovirus
CRISPR-Cas9	Genome Editing System
DaT-SPECT	Dopamine Transporter SPECT
DJ-1	Protein Deglycase DJ-1
DNAJC6	DnaJ Homolog Subfamily C 6
EAAT2	Excitatory Amino Acid Transporter 2
EEG	Electroencephalography
EMG	Electromyography
ER	Endoplasmic Reticulum
FVB/N	Inbred Laboratory Mouse Strain
GFAP	Glial Fibrillary Acidic Protein
GI	Gastrointestinal
GIGYF2	GRB10 Interacting GYF Protein 2
HPLC	High-Performance Liquid Chromatography
HTRA2	High Temperature Requirement Protein A2
IL	Interleukin
JIP4	JNK-Interacting Protein 4
JNK	c-Jun N-terminal Kinase
KO	Knockout
LRRK2	Leucine-Rich Repeat Kinase 2
MDS-UPDRS	Movement Disorder Society United PD rating scale
MOM	Mitochondria outer membrane
MPP+	1-Methyl-4-Phenylpyridinium
MPTP	1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine
mRNA	Messenger RNA
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NF-κB	Nuclear Factor kappa-light-chain-enhancer of B cells
NLRP3	NLR Pyrin Domain Containing 3
PAC	P1-Derived Artificial Chromosome
PARK	Parkinsonism-Associated Gene Loci
PD	Parkinson's Disease
PDGFB	Platelet-Derived Growth Factor Subunit B
PGC-1α	PPAR Gamma Coactivator 1-Alpha
PINK1	PTEN-Induced Kinase 1
PLA2G6	Phospholipase A2 Group VI
PRKN	Parkin
SNARE	Soluble NSF Attachment Protein Receptor
SNCA	Alpha-Synuclein
SNpc	Substantia Nigra pars compacta
Syn9048	pan-α-synuclein antibody
SYNJ1	Synaptojanin 1
TH	Tyrosine Hydroxylase
TNF	Tumor Necrosis Factor
UCH-L1	Ubiquitin C-terminal Hydrolase L1
VPS35	Vacuolar Protein Sorting 35

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