

# Translational Models of Parkinson's Disease and Related Movement Disorders

Edited by  
**WAEEL MOHAMED**



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Edited by

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I extend my heartfelt gratitude and deep appreciation as I dedicate this work to my wife, Dr. Rehab Ismaeil. Your unwavering support and limitless love have consistently served as pillars, guiding me through my academic journey and beyond. I am truly thankful for the love and motivation you bring into my life, acknowledging that none of this would have been attainable without you by my side. Your culinary expertise, featuring easy and delicious recipes in your homemade meals, not only satisfies my appetite but also nourishes my mind, providing food for thought.

**Wael Mohamed**  
Pahang, Malaysia

# Contents

Contributors	xv
Preface	xvii
Acknowledgments	xix

## Section I Understanding PD and related movement disorders

### 1. Neuroinflammation, glymphatic system, and Parkinson's disease

*Sohaila Mohammed Salah Saleh, Nada Nasser,  
Engy K. Tharwat, Tasneem Elbehiry and  
Hagar Ismail Helmy*

List of abbreviations	3
1. Parkinson's disease: exploring the interplay of neuroinflammation and the glymphatic system	4
2. Neuroinflammation	5
2.1 Definition and types of neuroinflammation	5
2.2 The cellular and molecular mechanisms	5
2.3 Crucial routes involved in neuroinflammation comprise	5
2.4 Astrocyte participation	6
2.5 The relationship between neuroinflammation and neurodegeneration	6
3. The glymphatic system	6
3.1 Waste clearance pathways	7
4. Microglia role in PD neuroinflammation	7
5. Monocyte role in neuroinflammation	8
6. Astrocyte role in PD neuroinflammation	9
7. Peripheral immune cell-mediated inflammation role in PD	10
8. Biomarkers of neuroinflammation in Parkinson's disease	11
9. Interleukins	11
10. NF- $\alpha$ /sTNFRs	12

11. Beta-amyloid 1–42, tau, p-tau	12
11.1 Alpha-synuclein	12
11.2 Genetic biomarkers in PD	13
11.3 Imaging biomarkers	14
12. The importance of early diagnosis	15
13. Clinical biomarker	15
14. Hyposmia	16
15. REM behavior sleep disorder	16
15.1 Neuroimaging analysis	16
16. Diffusion tensor imaging	16
17. Positron emission tomography	16
18. single-photon emission computed tomography	16
19. Therapeutic approaches of neuro- inflammation and glymphatic system disturbance in Parkinson disease	17
19.1 Challenges with neurotrophic factors	17
19.2 Antiinflammatory therapies in PD	17
19.3 Current clinical trials for antiinflammatory disease modification in PD	18
20. Conclusion	18
References	19

### 2. Pharmacotherapy of PD and related movements disorders and their limitations

*Malak M. Soliman*

1. Introduction to Parkinson's disease and related movement disorders	29
1.1 Definition and overview of Parkinson's disease and related disorders	29
1.2 Epidemiology and prevalence	29
1.3 Pathophysiology	29
1.4 Symptoms of PD and related disorders: Distinguishing motor and nonmotor	30
1.5 Progression of the disease and its impact on treatment decisions	30
2. Pharmacotherapy for Parkinson's disease	30
2.1 Overview of pharmacological agents used in PD	30

2.2	Levodopa: Mechanism of action, benefits, and side effects	31	2.	<b>Diagnosis of Parkinson's disease</b>	40
2.3	Dopamine agonists and MAO-B inhibitors in Parkinson's disease: Efficacy, usage, and safety	32	2.1	Clinical diagnosis	40
2.4	MAO-B inhibitors: Role in PD management, efficacy, and safety concerns	32	2.2	Differential diagnosis	40
2.5	Anticholinergics, other medications, and personalized medicine in Parkinson's disease treatment	33	2.3	Imaging and laboratory tests	41
2.6	Other medications: Amantadine and NMDA receptor antagonists	33	3.	<b>Biomarkers in Parkinson's disease</b>	42
2.7	Personalized medicine approach in PD treatment	33	3.1	Biochemical biomarkers	42
3.	<b>Treatment of related movement disorders: Differentiating pharmacotherapy</b>	34	3.2	Neuroimaging biomarkers	45
3.1	Essential tremor	34	3.3	Genetic biomarkers	46
3.2	Dystonia	34	3.4	Multimodal biomarkers	48
3.3	Huntington's disease	34	3.5	Non-invasive biomarkers	48
4.	<b>Limitations and challenges in pharmacotherapy</b>	34	4.	<b>Biomarkers in other movement disorders</b>	49
4.1	Drug resistance and diminishing efficacy	34	4.1	Huntington's disease	49
4.2	Side effects management, nonmotor symptoms challenges and managing advanced PD and related disorders	35	4.2	Dystonia	49
5.	<b>Adjunct therapies and multidisciplinary approach in Parkinson's disease and related movement disorders</b>	35	4.3	Essential tremors	53
5.1	Role of physical, occupational, and speech therapy	35	5.	<b>Challenges and future directions</b>	54
5.2	Psychosocial support	35	5.1	Limitations and challenges of current biomarkers	54
5.3	Diet and lifestyle modifications	36	5.2	Potential new biomarkers	54
6.	<b>Emerging treatments and future directions in Parkinson's disease</b>	36	5.3	Future implications of biomarkers	55
6.1	New pharmacological agents and strategies	36	6.	<b>Conclusion</b>	55
6.2	Gene therapy and stem cell therapy	36		<b>References</b>	55
6.3	Technology in treatment management	36	4.	<b>OMICS and bioinformatics in Parkinson disease and related movements disorders</b>	
7.	<b>Conclusion</b>	37		<i>Engy K. Tharwat, Hossam Hatem, Ahmed Sameh, Basmala A. Sultan, Salma Yehia and Omnia A. Abdelazeem</i>	
	<b>References</b>	37		<b>List of abbreviations</b>	65
3.	<b>Diagnosis and biomarkers of Parkinson's disease and related movement disorders</b>		1.	<b>Introduction and Background</b>	66
	<i>Mahmoud A. Ebada, Adel Mouffokes, Muhammad Imran, Mahmoud Tarek Hefnawy, Youssef Soliman, Mohamed El-Samahy, Ateeba Kamran, Tungki Pratama Umar, Basma Ehab Amer, Maged Elsayed and Mrinmoy Kundu</i>		1.1	Introduction	66
1.	<b>Introduction</b>	39	1.2	PD gene mutations that are passed from generation to generation	67
			2.	<b>High-throughput sequencing techniques are being used to discover the causative genes related to PD disease</b>	67
			2.1	The use of GWAS in PD	69
			2.2	The use of WES in PD	69
			2.3	Using WGS in PD	70
			3.	<b>Parkinson's disease and omics</b>	70
			3.1	Lipidomics	70
			3.2	Genomics	71
			3.3	Metabolomics	72
			3.4	Proteomics	74
			3.5	Challenges encountered in utilizing omics technologies in the study of the genetics of Parkinson's disease and other related movement disorders	74
			4.	<b>Other movement-related disorders</b>	77
			4.1	Urge phenomenon	77
				<b>References</b>	77

## 5. Modeling Parkinson's disease with the alpha-synuclein protein

*Engy K. Tharwat, Ahmed Sameh, Hossam Hatem, Omnia A. Abdelazem and Sohaila Mohammed Salah Saleh*

List of abbreviations	83
1. Historical overview	84
2. Structure and function of alpha-synuclein	84
2.1 Structure of alpha-synuclein	84
3. Function of alpha-synuclein	85
4. Neuroprotective, synaptic functions, and neurotransmitter release	85
5. Metabolic regulation and calcium signaling	86
6. Chaperone activity and interaction with heat shock proteins (HSPs)	86
6.1 Synucleinopathies: Key role in neurodegenerative disorders	86
7. Other functions	87
8. Genetic aspects of alpha-synuclein	87
8.1 SNCA gene	87
9. Polymorphism within the SNCA locus	88
9.1 Other genes at SNCA locus	88
10. Therapeutic interventions of alpha-synuclein's protein	89
11. Therapeutic strategies for Parkinson's using alpha-synuclein	89
12. Targeting $\alpha$ Syn accumulation: Pros and cons	91
13. $\alpha$ Syn targeted therapies	91
14. Alpha-synuclein model	91
15. Alpha-synuclein aggregation formation	91
16. Conclusion	94
References	94

## 6. $\alpha$ -Synuclein seeding assay and analysis

*Eman Alwakil*

1. Introduction	97
2. Parkinson's disease	97
3. Alpha-synuclein structure and its physiological function	99
4. Development of $\alpha$ -syn seeding assays	101
5. $\alpha$ -Syn seed amplification assays in CSF	101
5.1 AbbVie $\alpha$ -syn-SAA method	101
5.2 PMCA by Amprion lab	102
5.3 RT-QuIC by Caughey laboratory	103
6. $\alpha$ -Synuclein seeds as serum biomarkers	103
7. Conventional assays for $\alpha$ -syn detection	104
8. Conclusion	107
References	107

## Section II Mammalian models of Parkinson's disease

### 7. SHH, nurr1, pitx3, and en1 models for Parkinson's disease

*Ganna Ameen, Heba Fahmy, Amal Gaber, Fatima, Mohamed Abbas and Rana I. Soliman*

1. Introduction	113
2. SHH	113
2.1 Pathway of Sonic Hedgehog signaling in Parkinson's disease	114
2.2 Primary cilia pathway related to SHH	114
3. Nurr1	114
3.1 Role of Nurr1 in Parkinson's disease	115
3.2 The involvement of NURR1 in the inflammatory response mediated by $\alpha$ -Synuclein	115
3.3 The influence of NURR1 on neuroinflammation resulting from mitochondrial dysfunction and oxidative stress	117
3.4 Nurr1 in the treatment of Parkinson's disease	117
4. Pitx3	117
5. En1	118
5.1 Engrailed	119
5.2 Significance statement	120
6. Conclusion	120
References	120

### 8. Stem cell for PD: Technical considerations

*Sara S. Ibrahim, Esraa Elmligy and Engy K. Tharwat*

1. Historical milestones in stem cell research	125
2. Overview of Parkinson's disease and stem cell therapy	125
3. Technical considerations in stem cell therapy	129
4. Human and induced pluripotent stem cells	129
5. Mesenchymal stem cells	130
6. Meta-analysis in Parkinson's disease	131
7. Challenges and risks	135
7.1 Addressing immune response and minimizing risk of rejection	135
8. Legal and ethical frameworks guiding stem cell research	137
9. Current research and clinical trials	138



10. Future directions and innovations	138	10.1 The inhibition of complex I results in an increase in ROS superoxide generation	180
References	139	10.2 MitoPark mice startle	180
Further reading	145	10.3 Electrophysiological parameters in the Mitropark mouse	181
<b>9. Deep brain stimulation using animal models of Parkinson's disease</b>		<b>11. PD in Mitopark mouse model and its correlation to neuroinflammation</b>	181
<i>Amena S. El-Feky, Fatma M. Ali, Fatima Mohamed Abbas and Hend H. Mahmoud</i>		<b>12. Treatment response</b>	181
1. Introduction	147	<b>13. Conclusion</b>	182
2. Deep brain stimulation	148	References	182
2.1 Deep brain stimulation history	149	Further reading	184
3. Parkinson disease and subtypes of Parkinson disease	149	<b>11. The beta-sitosterol beta-D-glucoside (BSSG) rat model of Parkinson's disease</b>	
4. Animal models of Parkinson disease	150	<i>Rana I. Soliman, Nourhan S. Sultan, Hagar Lokman, Yomna Elkaramany, Shima Mohamed Ibraheem and Hagar Ismail Helmy</i>	
4.1 Brain-first subtype animal models	151	1. Introduction	187
4.2 Body-first animal models	155	2. Parkinson's disease	187
5. Mechanism of deep brain stimulation and Parkinson disease	156	2.1 Pathogenesis of Parkinson's disease	188
6. Conclusion	158	2.2 Symptomatic treatment for Parkinson's disease	190
References	158	3. The BSSG model	191
Further readings	165	3.1 Background	191
<b>10. The MitoPark mouse model of Parkinson's disease</b>		3.2 Motor characteristics	192
<i>Nada Yasser, Aya Haggag, Nourhan Abdelfatah Ahmed, Briksam S. Mohamed, Jaya Kumar and Hend H. Mohamed</i>		3.3 Prodromal traits	192
1. Introduction	167	3.4 Cognitive impairments	193
1.1 Parkinson's disease (PD)	167	3.5 $\alpha$ -Synuclein pathology	193
1.2 Animal models used for PD	168	3.6 Effectivity of action	194
2. Parkinson's disease models	169	3.7 The advantages of the BSSG model	195
2.1 Nonmammalian species	170	4. Neuroprotective therapies using the BSSG model	196
2.2 Rodents	171	5. Limitations of using the BSSG model for PD	196
2.3 Nonhuman primates (NHP)	171	6. Conclusion	196
2.4 Induced pluripotent stem cell (iPSC)-derived PD model	171	References	197
3. Mechanisms of Parkinson's disease (PD) models	171		
3.1 Neurotoxin models	171	<b>Section III</b>	
3.2 Genetic models	173	<b>Invertebrate models of Parkinson's disease</b>	
4. PD correlation to the mitochondria	175	<b>12. SCA1 zebrafish model</b>	
5. The role of mitochondrial DNA mutations and complex I deficiency	176	<i>Nourhan Sabri Sultan, Hagar Mostafa Lokman, Basant Mohamed Osama and Mohammed Ibrahim Kh</i>	
6. Mitochondrial dysfunction and oxidative stress	177	1. Introduction	205
7. The role of mitochondrial DNA	178	2. Spinocerebellar ataxia type 1 (SCA1)	205
8. Establishing the MitoPark mouse	178		
9. Characterization of the MitoPark mouse	179		
10. MitoPark mouse impaired respiratory chain function	179		

3. Molecular mechanisms of neurodegeneration	206	8. Neurotoxin-induced zebrafish model of PD	222
4. The role of protein aggregates	206	8.1 Transgenic zebrafish models of PD	222
5. Neurobehavioral phenotyping	207	8.2 PINK1 gene mutation	222
6. Paresis and paralysis	207	8.3 DJ-1 gene mutation	223
7. Balance and coordination	208	8.4 $\alpha$ -synuclein (SNCA) gene	223
7.1 Evidence for links to protein to neurodegenerative disorder	208	8.5 Parkinson's disease protein 2 (PARK2) gene	223
7.2 Alpha-synuclein	208	8.6 Parkinson's disease protein 7 (PARK7) gene	224
7.3 Parkin and PINK1	208	8.7 LRRK2 gene	224
7.4 DJ-1	209	9. Defined toxins associated with PD	225
7.5 LRRK2	209	9.1 Rotenone	225
8. Hypokinetic movement disorders	209	9.2 Paraquat	225
9. Parkinsonism in spinocerebellar ataxia	209	9.3 Ziram	225
10. PD-related proteins affect intrinsic mitochondrial functions	210	9.4 Benomyl	225
10.1 Mitochondrial dysfunction in autosomal dominant Parkinson's disease	210	9.5 Diesel exhaust particle extracts	226
10.2 Mitochondrial dysfunction in autosomal recessive Parkinson's disease	211	10. Use of gene editing technology in zebrafish	226
11. Modeling of SCA1 in zebrafish	212	11. Zebrafish models for the functional genomics of neurogenetic disorders	226
12. Plasmid vectors for microinjection	213	12. Conclusion	227
12.1 pA-4xmir181aT-GAPmScarlet-E1b-8xca8-E1b-4xmir181aT-pA (stock no. #5158)	213	References	227
12.2 pA-4xmir181aT-GAPmScarlet-E1b-8xca8-E1b-HA:Atx1[30Q]-4xmir181aT-pA (stock no. #3417)	213		
12.3 pA-4xmir181aT-GAPmScarlet-E1b-8xca8-E1b-HA:Atx1[82Q]-4xmir181aT-pA (stock no. #5187)	213		
13. Microinjection of nucleic acids	213		
13.1 Results	214		
14. Conclusion	216		
References	217		
		<b>14. Drosophila PD model</b>	
		<i>Fatma E. Sayed, Aya Khaled Mahmoud, Omaima Ali Mostafa Mohammed, Rana I. Soliman and Mariam Abdur-Rahman</i>	
		1. Introduction	231
		2. Parkinson's disease	231
		3. Symptoms	232
		4. Current symptoms relief medications	232
		5. Mechanism	233
		6. Causes and risk factors	233
		7. The history of Drosophila as a model organism	234
		8. Chromosomes of Drosophila	234
		9. Advantages of using <i>D. melanogaster</i> as a model organism	235
		10. Drosophila as a PD model	235
		10.1 Alpha-synuclein models	235
		10.2 Parkin mutation	236
		10.2 DJ-1	236
		11. Advanced therapeutic approaches of PD using the Drosophila model	236
		11.1 Therapeutic approaches based on natural products	236
		11.2 Therapeutic approaches based on herbal products	238
		12. Chemotherapeutic approaches	238
		13. Gene therapy	239
		14. Conclusion	239
<b>13. Various zebrafish models of Parkinson's disease: What gives us hope</b>			
<i>Al-Hassan Soliman Wadan and Wael Mohamed</i>			
1. Introduction	219		
2. Available animal models to study and conduct research on PD	219		
3. What are zebrafish?	220		
4. Understanding the behavioral neuroscience of zebrafish animals	220		
5. Using zebrafish as an animal model: Advantages and disadvantages	220		
6. Challenges of the zebrafish model	220		
7. Zebrafish as a model for Parkinson's disease	221		

References	240	2. The LRRK2 gene	268
Further reading	245	3. Structure and physiological functions of LRRK2 protein	268
<b>15. <i>Caenorhabditis elegans</i> models of tauopathy</b>		3.1 Enzymatic domains	268
<i>Bassant Hossam Abd El Hady and Mohanned Mohsen</i>		3.2 Protein-protein interaction domains	269
List of abbreviations	247	4. Animal models of LRRK2 mutations	269
1. <i>C. elegans</i>	247	4.1 Cellular cultures	269
1.1 Natural history of the life <i>C. elegans</i>	247	4.2 Rodent models	269
2. <i>C. elegans</i> nervous system and developmental plasticity	249	4.3 Drosophila models	269
2.1 Genetics	250	4.4 <i>Caenorhabditis elegans</i> models	269
3. Tau protein and tauopathies	250	5. <i>Caenorhabditis elegans</i> neurobiology	270
3.1 Physiology	250	5.1 Taxonomy, anatomy and habitat	270
3.2 Localization	250	5.2 Life cycle	270
3.3 Tau protein conformational changes in neurodegenerative diseases	251	5.3 Reproduction	270
3.4 The role of MAPT gene mutations in tauopathies	251	5.4 Why it is used as a disease model	270
3.5 Tau aggregates and toxicity in <i>C. elegans</i> neurons	251	5.5 Usage as a disease model	271
3.6 <i>C. elegans</i> as a model for protein misfolding diseases: Investigating the role of PTL-1 in neuronal function and regulation	252	6. <i>Caenorhabditis elegans</i> as a model to study LRRK2 in Parkinson disease	271
4. The utilization of <i>C. elegans</i> as a valuable experimental tool	252	6.1 <i>Caenorhabditis elegans</i> LRRK1 knock-off models	271
4.1 Transgenic <i>C. elegans</i> as a model organism for investigating neurodegenerative diseases	252	6.2 <i>Caenorhabditis elegans</i> LRRK2 transgenic overexpression models	272
4.2 Expression system choices for <i>C. elegans</i> models of tauopathies	254	References	272
5. PRE- and postsynaptic abnormalities	258		
6. Therapeutic interventions tested in <i>C. elegans</i>	259		
7. Exploring the potential of <i>C. elegans</i> as a tauopathy model: Future directions, advantages, and limitations	260		
7.1 Advances and challenges in CRISPR-Cas genome editing technology in <i>C. elegans</i>	260		
7.2 Advantages and limitations	261		
8. Conclusion	262		
References	262		
<b>16. LRRK2 in <i>Caenorhabditis elegans</i> model</b>			
<i>Yasser Mecheri and Soundous Malek Behloul</i>			
1. Introduction	267		
		<b>Section IV</b>	
		<b>Ethics and regulations related to translational PD models</b>	
		<b>17. Confounding factors for validation of PD models</b>	
		<i>Alaa Oraby</i>	
		1. Introduction	281
		2. The problem of confounding factors in animal models	281
		3. Embedded confoundings in PD modeling	282
		3.1 Biological and model related confounding factors	282
		3.2 Phenotypic differences	282
		3.3 Disease onset and progression	283
		3.4 Genetic differences	283
		3.5 Genetic variability	283
		3.6 Comorbidities of human PD	284
		4. Validation of animal models	284
		4.1 Internal validity and external validity	284
		4.2 Experimental confounding factors	285
		4.3 Application of validation on PD models	285
		5. Conclusion	286
		References	286

## 18. Neurobehavioral characterization of PD models

*Sara Ayman Al-Hafiry, Fahda Ziad Albaba, Nada Waheed Yassin, Fatima Mohamed Abbas and Rama Jamal Eddin Haboush*

1. Introduction	291
2. Characterization of motor symptoms	291
2.1 Tremors	292
2.2 Forelimb akinesia	293
2.3 Bradykinesia	293
2.4 Rigidity	293
3. Characterization of nonmotor symptoms	294
3.1 Depression	294
3.2 Anxiety	294
3.3 Cognitive impairment	295
3.4 Sleep disorders	295
3.5 Autonomic dysfunction	297
3.6 Pain	298
3.7 Olfactory dysfunction	299
3.8 Blink reflex abnormality	299
4. Conclusions and perspectives	300
References	300

## 19. Ethical regulations for induction and validation of PD models

*Alaa Oraby*

1. Introduction	307
2. Optimal Parkinson's model	308
3. Validation of animal models	308
4. Regulation of animal models	308
4.1 Replacement	308
4.2 Reduction	309
4.3 Refinement	312
5. Pros and cons of different PD models	312
5.1 Biochemical and cellular models	312
6. Mammalian models	313
6.1 6-OHDA, MPTP, and rotenone rodent model of PD	313
6.2 $\alpha$ -Synuclein mouse models	314
6.3 MitoPark mouse model	314
6.4 The BSSG rat model of Parkinson's disease	314
6.5 Marmoset ( <i>Callithrix jacchus</i> ) model of $\alpha$ -synuclein	314
6.6 Invertebrate models	314
7. Conclusion	315
References	315

## 20. The OMICS and PD models: Hopes or hypes

*Kholoud Elsamman*

1. Introduction	321
-----------------	-----

1.1 Omics trend and progression	321
1.2 Genetic models of PD	326
2. Transcriptomics in PD models	331
2.1 Proteomics	333
2.2 Proteomics in PD models	334
3. Metabolomics for PD models	334
4. Microbiomics in PD models	334
4.1 Multiomics approaches for identifying Parkinson disease mechanisms and biomarkers	335
4.2 Potential for omics-based personalized medicine for PD	336
5. Conclusion	336
References	336

## 21. Parkinson's disease from an Ayurveda perspective: Opportunities and challenges for further research

*Satyajit Pandurang Kulkarni*

1. Introduction	345
1.1 Introduction to Parkinson's disease	345
1.2 Dopamine and its altered role in PD	346
1.3 Causes of PD	346
1.4 Current treatment of PD	346
1.5 Need for new treatment modalities	346
2. Ayurveda and PD	347
2.1 Ayurveda	347
2.2 Correlates to PD	347
2.3 Kampavata	348
2.4 Case studies in Ayurveda	348
3. Ayurveda for PD	349
3.1 Single herbal drugs	349
3.2 Ayurvedic panchakarma for prevention of PD	352
3.3 Massage and hot fomentation for PD	354
3.4 Panchakarma for PD	354
3.5 Strengths and limitations of Ayurveda modalities	355
4. Challenges for Ayurvedic interventions in PD	356
4.1 Lack of evidence	356
4.2 Multiple interventions	356
4.3 Lack of standardization	357
5. Current models used in PD	358
6. Conclusion	358
References	358

Index	361
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# Preface

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*Navigating the complexities of illness without the guidance of books is like sailing into the unknown, yet studying books without the experience of patients is to stay anchored in the harbor.*

**Sir Thomas Browne (1605–1682)**

Welcome to the “Translational Models of Parkinson’s Disease and Related Movement Disorders.” In the realm of neuroscience, the study of neurodegenerative disorders stands at the forefront of scientific inquiry and medical innovation. This comprehensive book serves as a vital resource for researchers, clinicians, and students seeking a profound understanding of the intricate complexities surrounding Parkinson’s disease.

Neurodegenerative disorders, characterized by the progressive degeneration of the structure and function of the nervous system, pose significant challenges to both affected individuals and the global healthcare landscape. The ever-growing prevalence of these conditions necessitates a multidisciplinary approach that spans basic science, clinical research, and therapeutic development.

This book is crafted with the intention of providing a state-of-the-art compendium that not only reviews the current knowledge on the mechanisms underlying Parkinson’s disease but also delves into cutting-edge diagnostic methodologies and therapeutic interventions. Each chapter is meticulously curated to offer a blend of foundational concepts and the latest advancements in the field.

The journey through this book begins with a comprehensive exploration of the molecular and cellular mechanisms driving Parkinson’s disease. From the intricate interplay of genetic and environmental factors to the cascading events leading to neuronal demise, readers will gain insights into the intricate tapestry of neurodegenerative processes.

Moving forward, the book meticulously examines the evolving landscape of diagnostic approaches. In an era of precision medicine, understanding the early indicators and developing accurate diagnostic tools is crucial for timely intervention. The exploration encompasses a variety of modalities, from advanced imaging techniques and biomarker discovery to innovative neuroimaging technologies.

The latter sections of the book are dedicated to the horizon of therapeutic possibilities. From traditional pharmaceutical interventions to emerging gene and cell-based therapies, this section provides a comprehensive overview of the current and potential future strategies for managing and, ultimately, halting the progression of Parkinson’s disease.

Parkinson’s disease and related movement disorders pose profound challenges to individuals, families, and societies worldwide. The quest to understand, treat, and ultimately conquer these conditions has been a journey marked by perseverance, collaboration, and innovation. In this volume, “Translational Models of Parkinson’s Disease and Related Movement Disorders,” we embark on a comprehensive exploration of the intricate landscape of these neurological conditions.

The genesis of this book stems from the collective efforts of dedicated researchers, clinicians, and advocates who have committed their expertise and passion to unraveling the complexities of Parkinson’s disease and related disorders. Through translational research—bridging the gap between basic science and clinical practice—we aim to illuminate the underlying mechanisms, identify novel therapeutic targets, and pave the way for more effective treatments.

Each chapter in this volume represents a milestone in our understanding of Parkinson’s disease and related movement disorders. From elucidating the molecular pathways implicated in neurodegeneration to developing cutting-edge animal models that faithfully recapitulate the clinical manifestations, the contributions herein offer invaluable insights into the pathogenesis, diagnosis, and management of these conditions.

Importantly, this book underscores the interdisciplinary nature of translational research, highlighting the indispensable role of collaboration across diverse fields—from neurobiology and genetics to pharmacology and clinical medicine. By fostering dialogue and synergy among researchers and practitioners, we aspire to accelerate the translation of scientific discoveries into tangible benefits for patients and their families.

As we delve into the pages of “Translational Models of Parkinson’s Disease and Related Movement Disorders,” let us reflect on the collective determination to confront these formidable challenges. May this volume serve as a beacon of hope, guiding us toward a future where Parkinson’s disease and related disorders are not merely managed but conquered.

In assembling this book, my aim is to foster a deeper understanding of Parkinson’s disease and to inspire collaborative efforts across disciplines. I extend our gratitude to the contributors who have shared their expertise and experiences, making this handbook an asset for researchers and practitioners navigating the intricate landscape of Parkinson’s disease.

May this book serve as a beacon for those dedicated to unraveling the mysteries of PD and related movement disorders, offering a roadmap toward advancements in diagnosis and innovative therapeutic strategies, ultimately bringing us closer to a future where these devastating disorders can be effectively treated and, perhaps, prevented.

**Editor:**

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# Acknowledgments

The completion of this book, “Translational Models of Parkinson’s Disease and Related Movement Disorders,” represents a collaborative endeavor that would not have been possible without the contributions and support of numerous individuals and organizations. First and foremost, I express my deepest gratitude to the researchers, clinicians, and experts in the field of Parkinson’s disease and movement disorders whose dedication and insights have enriched the content of this volume. Your relentless pursuit of knowledge and commitment to improving patient outcomes serve as an inspiration to us all.

I extend my appreciation to the editors, reviewers, and contributors whose meticulous attention to detail and scholarly rigor have ensured the quality and accuracy of the information presented in this book. Your expertise and scholarly contributions have been instrumental in shaping its content and scope.

I also thank the publishing team for their professionalism, guidance, and support throughout the editorial and production process. Your expertise and dedication have been invaluable in bringing this project to fruition.

Lastly, I express my gratitude to our families, friends, and colleagues for their unwavering encouragement, understanding, and patience during this project. Your support has been a source of strength and motivation, enabling us to overcome challenges and achieve our goals.

Together, we have endeavored to create a comprehensive resource that advances our understanding of Parkinson’s disease and related movement disorders and fosters collaboration and innovation in translational research. It is our sincere hope that this book will serve as a valuable reference for researchers, clinicians, students, and stakeholders dedicated to improving the lives of individuals affected by these conditions.

**Editor:**  
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# Various zebrafish models of Parkinson's disease: What gives us hope

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## 1. Introduction

The selection of appropriate animal models to study neurodegenerative and neurodevelopmental disorders, including Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease, schizophrenia, and epilepsy, depends on various criteria and limitations (Pienaar et al., 2010). An ideal animal model of PD should demonstrate histopathological characteristics such as progressive loss of dopaminergic neurons and nondopaminergic neurons, with symptoms appearing in adulthood (Barnhill et al., 2020). These models should also mimic clinical manifestations of PD, including motor features responsive to L-DOPA therapy, like bradykinesia, rigidity, postural instability, and resting tremor (Breger & Fuzzati Armentero, 2019; Pienaar et al., 2010). Rodent and primate models have been developed to explore disease mechanisms and enhance therapeutic outcomes using neurotoxic substances or genetic manipulation. Various toxins, such as 6-hydroxydopamine (6-OHDA), rotenone, paraquat, and 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP), have been used to selectively destroy nigrostriatal DA neurons, resulting in PD-like symptoms in animals (Burns et al., 1983; McKinley et al., 2005). Rotenone models are preferred for assessing neuroprotection due to their independent mechanism of neurotoxicity from the DA uptake transporter (DAT) (Pienaar et al., 2009; Tapias et al., 2010). Though these models offer valuable insights, they do not fully replicate all human PD symptoms. Transgenic approaches involving gene manipulation, such as overexpression, knock-out, knock-in, and knock-down of PD genes, have been used to study PD (Sfar et al., 2009; Xiong et al., 2009). However, high-throughput screenings for genetic interactions or pharmacological therapies can be costly and time-consuming when using murine or nonhuman primate models (Faust et al., 2009). As alternatives, models involving zebrafish (ZF), fruit flies, nematodes, and anurans have gained attraction due to their efficiency and contribution to understanding disease mechanisms and novel therapeutic strategies (Pienaar et al., 2010).

## 2. Available animal models to study and conduct research on PD

Furthermore, when selecting an animal model for preclinical research, specific criteria must be met, including information accessibility, tractability, and comparative translational potential (Dietrich et al., 2020). Model organisms are chosen based on their comparable physiology, anatomy, genetic homogeneity, and response to treatments similar to humans (Barré-Sinoussi & Montagutelli, 2015; Pienaar et al., 2010). Throughout history, researchers have introduced various animal species as study models in scientific research, including roundworms (*Caenorhabditis elegans*), fruit flies (*Drosophila melanogaster*), ZF (*Danio rerio*), rodents (*Mus musculus* and *Rattus norvegicus*), and nonhuman primates (Chia et al., 2020). In neuroscience research, conducting human-based studies is challenging and limited, mainly because experiments on the brain need to be done in vitro, often only feasible postmortem (Shamoo, 2010). Therefore, animals with significant functional similarities to humans, such as fruit flies, rodents, and ZF, offer excellent alternatives for comprehensive nervous system studies, benefiting from their impressive heart physiology and anatomy. ZF, scientifically known as *Danio rerio*,

has been a prominent model for neuroscience-related studies for the past 3–4 decades (Razali et al., 2021). As a freshwater teleost of the Cyprinidae family, ZF's use in neuroscience research has been optimized by developing methodologies and techniques (Razali et al., 2021). Due to its close neurofunctional and behavioral similarities to humans, ZF has become an excellent model for neurodegenerative, neurodevelopmental, and neuropharmacological studies (Razali et al., 2021). Its well-characterized nervous system positions ZF as a promising replacement for rodent models in studying PD, the second most common neurodegenerative disease after Alzheimer's (Poewe et al., 2017). As we focus on ZF in neuroscience research, particularly regarding PD studies, these aquatic creatures have gracefully established themselves as a potent animal model for investigating and combatting this chronic and progressive neurodegenerative disease.

### 3. What are zebrafish?

The involvement of ZF in the research world traces back to the 1950s when molecular biologist George Streisinger, based at the University of Oregon, recognized its potential (Barnhill et al., 2020). Over the subsequent decade, researchers delved into numerous investigations, mainly focusing on the development of the nervous system, leading to profound insights (Razali et al., 2021). In 1998, the National Institute of Health (NIH) established the groundbreaking Trans-NIH Zebrafish Initiative, formally acknowledging ZF as a valuable animal model in scientific studies (Razali et al., 2021). Since then, ZF have played pivotal roles as model organisms in diverse research domains, encompassing neurodegeneration, neurodevelopment, neurobehavior, toxicology, and drug discovery (Razali et al., 2021).

### 4. Understanding the behavioral neuroscience of zebrafish animals

Zebrafish stands out as an ideal model for behavioral neuroscience due to its diverse cognitive processes, mirroring those of humans, encompassing learning, memory, fear, anxiety, perception, social skills, and even sleep patterns (Biase et al., 2013; Pisco et al., 2013). ZF with high anxiety levels exhibit distinct behavior, spending more time at the edges and bottom of a novel tank, indicating thigmotaxis (Razali et al., 2021). Regarding learning and memory functions, ZF demonstrate remarkable capabilities in associative learning, avoidance learning, object discrimination learning, spatial learning, and more (Razali et al., 2021). For instance, the object discrimination test assesses their memory retention by introducing a novel object and observing their recognition after specific time intervals (Razali et al., 2021). Studies have revealed the involvement of specific brain regions, such as the ZF telencephalon and thalamus, in processing visual discrimination (Messina et al., 2020). Another insightful behavioral task is the avoidance learning test, where ZF learn to avoid electric shocks by refraining from swimming into a dark compartment. This test demonstrates ZF's ability to acquire avoidance learning and encode it into long-term memory (Blank et al., 2009). Through such comprehensive cognitive assessments, ZF has proven to be a valuable model in unraveling intricate behavioral processes relevant to neuroscience research.

### 5. Using zebrafish as an animal model: Advantages and disadvantages

Zebrafish exhibit behaviors and phenotypes that closely resemble human behaviors. Neurotoxin-induced ZF display movement impairments like decreased swimming speed and abnormal swimming behavior, akin to bradykinesia-like symptoms observed in PD patients (Blank et al., 2009). Notably, genomic analysis reveals that the ZF genome shares 70% similarity with the human genome, with 80% of genes located in the same chromosome order, indicating conserved synteny between the two species (Blank et al., 2009). ZF's unique attributes make it an exceptional model for research. External and transparent embryo development allows real-time study of the developmental process (Ali et al., 2011), and their embryos readily absorb compounds or neurotoxins (d'Amora Silvia, 2018). Advantages over other animal models include high fecundity, with ZF laying 200–300 eggs per week, enabling larger sample sizes and more significant results (Hoo et al., 2016). ZF also reach sexual maturity in just 3–4 months and have an average lifespan of 3–4 years, contributing to shorter experimental timelines and reduced costs (Gilbert et al., 2013; Njiwa et al., 2004). Furthermore, ZF husbandry and maintenance protocols are simpler and less complicated compared to rodents and nonhuman primates (Avdesh et al., 2012). These combined advantages underscore ZF's exceptional value as a model organism, offering profound insights into various research areas with potential implications for understanding human health and disease.

### 6. Challenges of the zebrafish model

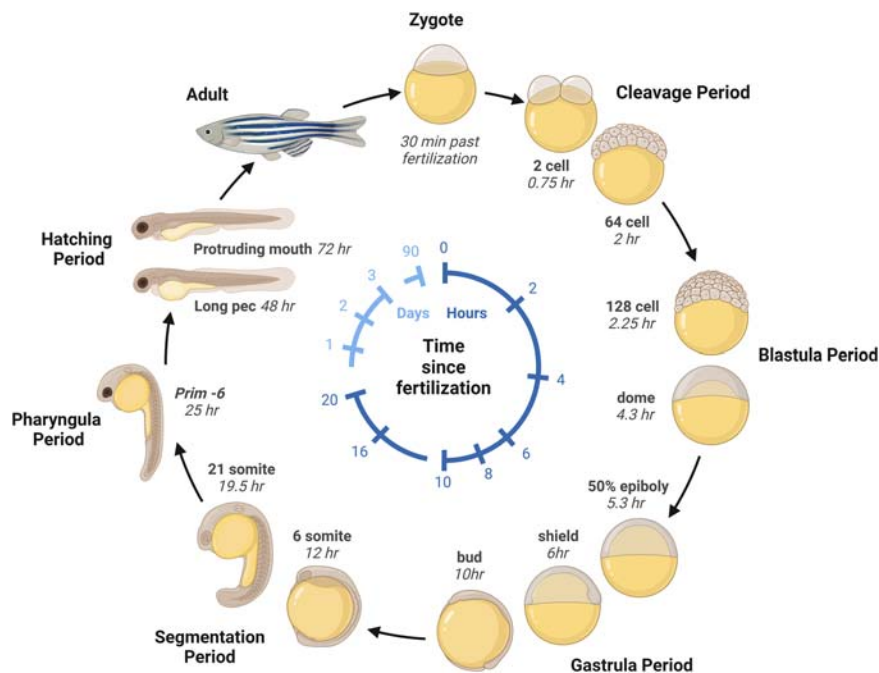
While ZF offer numerous advantages for research, it is essential to acknowledge their limitations as a model organism. One significant drawback is the relative scarcity of accessible information regarding ZF strains and transgenic models compared

to widely studied organisms like rodents. The availability of validated reagents, such as test kits and antibodies, that react with ZF is also limited, which can hinder postsacrifice molecular analyses. When evaluating drug efficacy, the external development of ZF embryos allows real-time observation, but variations in drug uptake, especially when administered orally, can lead to heterogeneous results. Additionally, differences in metabolism pathways and uptake rates of drugs or chemicals in ZF embryos compared to humans need careful consideration to avoid result misinterpretations (Ali et al., 2011). ZF's natural ability for regeneration and neurogenesis poses challenges for PD studies, as it complicates the establishment of a stable PD model. For instance, the dopaminergic neuronal population in the olfactory bulb of adult ZF can regenerate to normal levels within 45 days after ablation. While this regenerative ability is disadvantageous for degenerative studies, it offers valuable insights into regenerative pathways that could be potentially applied to humans.

These animals have proven to be powerful model organisms, but researchers must be aware of these limitations and consider them while designing experiments and interpreting results. By recognizing and addressing these shortcomings, the scientific community can harness the full potential of ZF research while making informed and meaningful discoveries.

## 7. Zebrafish as a model for Parkinson's disease

Extensive research on ZF has enabled the detailed mapping of their dopaminergic nervous system (Fig. 13.1) since their recognition as a model organism in 1998. ZF, and vertebrates like humans, share anatomical features that make them suitable for studying PD-related mechanisms. In ZF embryos, dopaminergic neurons appear as early as 19 h post-fertilization in the posterior tuberculum of the ventral diencephalon, equivalent to the human substantia nigra, and these neurons project to the ventral telencephalon, equivalent to the human striatum, resembling the nigrostriatal dopaminergic nervous system (Flinn et al., 2008). This system's resemblance to human PD pathology makes ZF a valuable model for studying related molecular mechanisms.



**FIGURE 13.1 Zebrafish lifecycle and development.** This figure illustrates the life cycle and developmental stages of zebrafish (*Danio rerio*). From fertilized embryos, zebrafish undergo rapid and transparent embryogenesis, progressing through various developmental stages, including gastrula, segmentation, and hatching. The larvae eventually mature into adult zebrafish with fully formed organs and systems, enabling researchers to study the complexities of various biological processes. Recent research advances have been integrated to researching on zebrafish such as (A) CRISPR technology: Zebrafish has become a powerful model organism for utilizing CRISPR/Cas9 gene editing technology. The precise and targeted gene manipulation facilitated by CRISPR has allowed researchers to create specific genetic modifications in zebrafish, mimicking human disease mutations and investigating gene function. (B) Drug libraries: Zebrafish has emerged as an ideal platform for high-throughput drug screening due to its transparent embryos and fast development. Researchers can efficiently test large libraries of compounds to identify potential drug candidates for various neurological disorders, including Parkinson's disease. (C) Analysis of phenotypes: Zebrafish's ease of genetic manipulation and rapid development has enabled the analysis of phenotypic changes associated with neurodegenerative diseases. By inducing specific genetic modifications or exposing zebrafish to environmental factors, researchers can study various phenotypic changes, contributing valuable insights into the pathogenesis of neurological disorders.

Zebrafish Parkinson's models encompass two main types: the neurotoxin-induced model and the transgenic model. The neurotoxin MPTP is commonly used to induce PD-like symptoms in ZF, causing the degeneration of DA neurons and reducing dopamine, norepinephrine, and serotonin levels in the brain, particularly in the posterior tuberculum of the ventral diencephalon. The ZF PD model induced by MPTP displays motor dysfunctions, including reduced swimming speed and abnormal swimming behaviors, analogous to bradykinesia in PD patients. Another frequently used neurotoxin is 6-hydroxydopamine (6-OHDA), which, as an oxidative dopamine analog, leads to mitochondrial dysfunctions and the death of DA and noradrenergic neurons (Soliman & Abdellatif, 2023; Tolba et al., 2023; Wadan & Liaquat, 2024; Wadan et al., 2024). In contrast, the transgenic model utilizes ZF with targeted mutated genes to mimic autosomal dominant or recessive PD in humans. The wealth of information on ZF dopaminergic neuronal projections and their compatibility with experimental manipulations provide this species a distinct advantage for investigating molecular mechanisms associated with PD (Mohamed et al., 2023; Sayed et al., 2024; Sanaeifar et al., 2024).

## 8. Neurotoxin-induced zebrafish model of PD

MPTP, 6-OHDA, paraquat, and rotenone are commonly used neurotoxins to induce PD-like symptoms in ZF. MPTP causes degeneration of dopaminergic neurons and motor dysfunction. 6-OHDA leads to selective dopaminergic and noradrenergic neuron loss and decreased locomotion and dopamine levels. Paraquat enhances oxidative stress in dopamine neurons, resulting in variable effects on behavior and dopamine levels in ZF. Rotenone acts as a redox cycler and has mixed effects on dopaminergic neurons and locomotion in ZF.

### 8.1 Transgenic zebrafish models of PD

Parkinson's disease does not naturally occur in animals, and due to its slow progression in humans, no single animal model can fully replicate all aspects of the disease. However, different animal models can be used to study specific aspects of PD. For instance, rodents can be used to selectively kill dopamine neurons, resulting in some motor features of PD, making them suitable for testing medicines to alleviate symptoms. Other models focus on investigating underlying molecular mechanisms, such as  $\alpha$ -syn aggregation and dopaminergic cell loss. ZF offers distinct advantages over many other models (Barnhill et al., 2020; Guo, 2004). The transparency of ZF embryos and larvae allows noninvasive imaging techniques to study neuronal integrity, proteostasis, mitochondrial functions, and microglial activity using fluorescent reporters. ZF is also a prolific external breeder, enabling easy genetic modification without injuring the parent, reducing variation, and increasing experimental replicates. High-throughput behavioral assays can be performed in ZF larvae, serving as a powerful screening tool, although the range of behaviors that can be measured is limited (Guo, 2004).

Both genetic and toxin-induced ZF models have been utilized for PD research, but certain considerations are essential. Researchers often use embryos and larvae for their transparency, but they should be aware that the study involves a degenerative disease in a developing organism. The timing of toxin exposure is crucial due to rapid embryo development. Factors like chorion integrity and the formation of the blood–brain barrier should also be taken into account during experimentation. When conducting and reviewing ZF studies, careful consideration of these factors maximizes the benefits of using this model organism (Barnhill et al., 2020). While no model is perfect, the use of ZF in PD research has provided valuable insights and advanced our understanding of the disease.

### 8.2 PINK1 gene mutation

Mutations in the PINK1 gene are the second most common cause of autosomal-recessive early-onset PD. PINK1 is a ubiquitously expressed protein that contains an N-terminal mitochondrial targeting motif and a conserved serine/threonine kinase domain. PINK1 protects neurons against mitochondrial dysfunction and apoptosis induced by stress. In *Drosophila*, pink1-deficient mutants have mitochondrial defects that lead to degeneration of flight muscles and mild loss of dopamine (DA) neurons (Clark et al., 2006; Park et al., 2006). However, similar defects were not observed in mice with targeted null mutations in pink1 (Gautier et al., 2008; Kitada et al., 2007). In ZF, pink1 is expressed ubiquitously, and the predicted protein has 54% amino acid sequence identity to human PINK1. A previous study reported that MO knockdown of pink1 in ZF resulted in an approximate 40% reduction in the number of DA neurons in the ventral tegmental area (vDC) (Anichtchik et al., 2008). However, this phenotype has not been replicated by other studies. A study has shown that MO knockdown of pink1 in ZF does not cause large alterations in the number of DA neurons in the vDC. However, it was observed that the patterning of these neurons and their projections are perturbed (Xi et al., 2010). The pink1 morphants also show impaired response to touch stimuli and reduced swimming behavior (Xi et al., 2010). The knockdown of pink1 in ZF

also causes mitochondrial defects, such as the loss of cristae and a reduced number of mitochondria, thus affecting mitochondrial function. In addition, the DA neuron clusters of pink1-deficient ZF are more sensitive to 1-methyl-4-phenyl-1,2,3,6-tetrapyridine (MPTP) toxicity (Sallinen et al., 2010). These results indicate that PINK1 plays a role in DA neuron development and function in ZF. Developmental defects in DA neurons, resulting from PINK1 mutations, may also render DA neurons more susceptible to environmental stress. A ZF line with a nonsense mutation in exon seven of the pink1 gene was found in ENU-mutagenesis libraries (Bandmann et al., 2010). This mutation is predicted to result in a partial Pink1 protein with loss of its C terminus and part of its kinase domain. Although there were no obvious behavioral abnormalities, the larvae of this line showed a significant decrease in the number of DA neurons and a reduction in mitochondrial complex I activity. These phenotypes are similar to those observed in parkin-deficient ZF. These latter observations further support the notion that PINK1 and Parkin are in the same pathway in regulating DA neuron development and mitochondrial functions, as was previously suggested by Drosophila PD models. Hence, PINK1 plays a critical role in DA neuron development and function. Mutations in PINK1 can lead to developmental defects in DA neurons and make them more susceptible to environmental stress. This may contribute to the increased risk of PD in individuals with PINK1 mutations.

### 8.3 DJ-1 gene mutation

Mutations in the DJ-1 gene are a rare cause of autosomal-recessive early-onset PD. DJ-1 is a member of the ThiJ/Pfpl/DJ-1 protein family and is involved in various functions, including its role as a redox-sensitive chaperone and in mitochondria protection against oxidative stress. In Drosophila models, RNA interference-knockdown of DJ-1 led to varying degrees of degeneration of dopamine (DA) neurons and hypersensitivity to oxidative stress (Dawson et al., 2010). However, similar to parkin- or PINK1-null mice, DJ-1-null mice did not show any major abnormality in the number of DA neurons in the substantia nigra pars compacta and in the levels of striatal dopamine (Dawson et al., 2010). The ZF Dj-1 protein shows 83% overall amino acid identity to human DJ-1 (Bai et al., 2006). The amino acids affected by pathogenic mutations in PD patients are especially well conserved in ZF Dj-1. It is expressed through embryogenesis and transcripts are ubiquitously found in all adult tissues with a relatively higher abundance in the brain. MO knockdown of dj-1 in ZF did not cause a decrease in the number of DA neurons. However, DA neurons in dj-1 morphants were more sensitive to hydrogen peroxide or to the proteasome inhibitor MG132. They were also more susceptible to programmed cell death. Upregulation of dj-1 was reported in the brain of ZF subjected to oxidative stress. These findings suggest that DJ-1 has conserved functions in ZF and humans. Mutations in DJ-1 may impair the response of DA neurons to environmental stress and eventually lead to cell death. Therefore, DJ-1 plays a critical role in DA neuron protection against oxidative stress. Mutations in DJ-1 can lead to increased sensitivity of DA neurons to environmental stress and may contribute to the increased risk of PD in individuals with DJ-1 mutations (Baulac et al., 2009).

### 8.4 $\alpha$ -synuclein (SNCA) gene

The discovery of a mutation in the  $\alpha$ -synuclein gene as a cause of autosomal dominant PD (AD PD) shed light on the significance of  $\alpha$ -synuclein in the formation of Lewy bodies (LBs), a hallmark of PD pathology (Fig. 13.2). Increased  $\alpha$ -synuclein expression due to gene duplication is sufficient to cause PD. While ZF lack  $\alpha$ -synuclein expression, they do express  $\beta$ -,  $\gamma$ 1-, and  $\gamma$ 2-synuclein proteins, with  $\gamma$ 1-synuclein shown to function similarly to human  $\alpha$ -synuclein. Through genetic technology, researchers have created ZF transgenic models expressing human wild-type  $\alpha$ -synuclein. Overexpression and aggregation of  $\alpha$ -synuclein in these models led to reduced mitochondrial activity, increased reactive oxygen species (ROS), neuronal apoptosis, and cell death. Recent studies have indicated that intracellular LBs progressively disrupt dopamine neurons by affecting mitochondrial function and inducing oxidative stress, potentially contributing to early-onset PD. ZF transgenic models offer valuable insights into the role of  $\alpha$ -synuclein in PD pathology and provide a powerful tool to study disease mechanisms and potential therapeutic interventions.

### 8.5 Parkinson's disease protein 2 (PARK2) gene

Mutations in the PARK2 gene are linked to early-onset PD and are the most common cause of autosomal recessive PD. The PARK2 gene encodes the Parkin protein, which functions as a ligase responsible for targeting damaged proteins for degradation through autophagy and breakdown processes. Parkin is also involved in mitophagy, degrading damaged mitochondria, and targeting  $\alpha$ -synuclein proteins for degradation. In pathological conditions with mutated PARK2 genes, Parkin loses its degrading ability, leading to mitochondrial dysfunction,  $\alpha$ -synuclein aggregation, and LB formation, contributing to the development of PD. ZF Parkin protein shares homology and functional similarity with the human

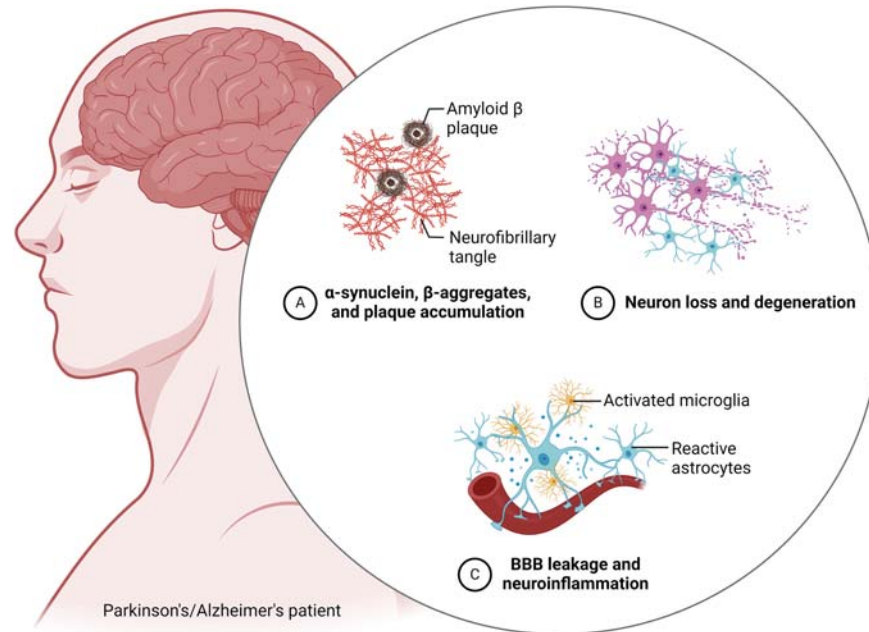


FIGURE 13.2 The hallmarks of Parkinson's disease.

counterpart. Knockdown of the PARK2 gene in ZF disrupted the mitochondrial respiratory chain, reduced dopamine (DA) neurons in the diencephalon, and increased sensitivity to toxic metabolites. The ZF model of PD with a mutated PARK2 gene indicates that the loss of Parkin function disrupts mitochondrial regulation, leading to the loss of DA neurons and perturbation of the DA system. This model offers valuable insights into the role of Parkin in PD pathology and its contribution to the disease mechanism.

### 8.6 Parkinson's disease protein 7 (PARK7) gene

Mutations in the PARK7 gene are associated with early-onset autosomal recessive PD. This gene encodes the DJ-1 protein, which plays a crucial role in human physiology by regulating genes involved in oxidative stress response mechanisms. DJ-1 helps cells survive oxidative stress by controlling the transcription of genes with antioxidant and antiapoptotic properties. Inactivation of DJ-1 induces the expression of genes responsible for cell apoptosis. In PD patients with inactivated DJ-1 protein, symptoms like young-onset motor disability, muscle rigidity, and tremors are observed. The ZF PARK7 gene is highly similar to human DJ-1, sharing 83% identical sequence. ZF expressing mutated DJ-1 protein exhibit characteristics resembling PD motor symptoms in humans, such as reduced swimming velocity and increased freezing bouts. Knockdown of the PARK7 gene in ZF increases ROS (ROS) production and makes DA neurons more susceptible to oxidative stress. Moreover, the knockdown of PARK7 indirectly leads to DA neuron death by not only increasing ROS levels but also inhibiting proteasomal activity necessary for the mitophagy process. The functional annotations of DJ-1 protein provide important insights into the significance of redox regulation in preventing cellular degeneration and maintaining cell survivability, contributing to a better understanding of PD pathology.

### 8.7 LRRK2 gene

Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are a prominent cause of autosomal dominant PD, accounting for 1% of sporadic cases and 4% of familial cases. The G2019S mutation is the most common, especially in Ashkenazi Jewish people or North African Berbers, along with other pathogenic variants. Although the penetrance of LRRK2 mutations is generally low (approximately 25%), patients with these mutations exhibit similar symptoms to idiopathic cases and often have α-synuclein-containing LBs. LRRK2 is a protein with several functional domains, including a serine/threonine kinase and a GTPase domain. Most pathogenic mutations in the LRRK2 gene are believed to result in a toxic gain-of-function increase in kinase activity. Thus, inhibiting the kinase activity is considered a potential therapeutic target for both LRRK2-induced and idiopathic PD.

Zebrafish have a homolog of the human LRRK2 (hLRRK2) gene, with the protein containing all the functional domains of the human counterpart. The kinase domain is particularly conserved in ZF, sharing 71% homology with the human LRRK2 protein. While gain-of-function increase in kinase activity is the most likely mechanism leading to PD in LRRK2 mutations, ZF researchers have focused on knocking down the ZF LRRK2 (zLRRK2) gene. Morpholino (MO) knockdown of zLRRK2 in ZF results in embryonic lethality with severe morphological and neuronal defects, including the loss of tyrosine hydroxylase (TH)-positive neurons. However, the effects of targeted deletion of the Trp-Asp-40 (WD) domain of zLRRK2 using MO are less clear, with conflicting results reported by different research groups. Some studies have observed a Parkinson's phenotype with loss of TH + neurons and locomotive dysfunction, while others could not reproduce these findings despite using the same reagents. These discrepancies warrant further investigation to better understand the role of LRRK2 in ZF and its implications for PD research.

## 9. Defined toxins associated with PD

Zebrafish have been a valuable tool in investigating if the associations between exposure to environmental toxins, especially pesticides, and an increased risk of developing PD represent causality.

### 9.1 Rotenone

Rotenone, a mitochondrial complex I inhibitor, has been linked to an increased risk of PD. In rats, systemic administration of rotenone leads to  $\alpha$ -syn accumulation, loss of dopamine neurons, and motor deficits. However, when administered systemically to adult ZF, it did not affect dopamine neurons or locomotion in one study (Breitaud et al., 2004), but other studies reported decreased dopamine levels, locomotion, and olfaction when exposed to water (Wang et al., 2017; Ünal et al., 2020). Exposure of ZF embryos to rotenone resulted in a moderate loss of dopamine neurons, decreased locomotion, and occasional cardiac defects, but the selectivity of the neuronal loss was not determined (Kalyn et al., 2019).

### 9.2 Paraquat

Paraquat, similar to MPTP in structure, was initially studied due to its resemblance. However, it was later discovered that, unlike MPTP, paraquat does not act as a substrate for DAT or a complex I inhibitor. Instead, it functions as a redox cyclor, leading to increased oxidative stress in dopamine neurons (Bus & Gibson, 1984). Mammalian exposure to paraquat results in approximately 20% dopaminergic neuron decrease and evidence of oxidative stress. When combined with the fungicide maneb, the loss of dopamine neurons is significantly enhanced (Thiruchelvam et al., 2000). Epidemiological studies also suggest an increased risk of PD when exposed to both maneb and paraquat (Wang et al., 2011).

Studies involving ZF and paraquat have yielded mixed results. Some experiments showed no effect on embryos when treated with paraquat up to a certain concentration (Breitaud et al., 2004), while others observed decreased locomotion, dopamine, serotonin, and evidence of oxidative stress (Nellore & Nandita, 2015). Treatment with paraquat at different developmental stages of ZF resulted in a 16% decrease in dopamine neurons and altered expression of DAT and TH (Kalyn et al., 2019). In adult ZF, intraperitoneal injection of paraquat led to decreased locomotion, increased dopamine concentration, and decreased DAT expression, but no change in TH expression (Bortolotto et al., 2014). However, when adult ZF were exposed to paraquat in water for 4 weeks, no significant effects were observed (Breitaud et al., 2004).

### 9.3 Ziram

Exposure to ziram has been linked to an increased risk of PD (Wang et al., 2011; Chou et al., 2008). To investigate the plausibility of this association, ZF embryos were exposed to 50 nM of ziram at 24 h postfertilization (hpf), resulting in a specific loss of dopaminergic neurons and altered swimming behavior in the dark, similar to dopamine blockage (Lulla et al., 2016). Notably, the loss of dopamine neurons was found to be dependent on  $\gamma$ 1-synuclein, as knockdown with MO provided protection. Additionally, the drug CLR01, which breaks apart  $\gamma$ 1-synuclein fibrils, also showed a protective effect (Lulla et al., 2016).

### 9.4 Benomyl

Benomyl, another fungicide, has also been linked to an increased risk of developing PD. Like ziram, it selectively killed dopamine neurons in ZF (Fitzmaurice et al., 2013, 2014). The toxicity mechanism was attributed to the inhibition of aldehyde dehydrogenase, an enzyme responsible for detoxifying the dopamine metabolite DOPAL (Fitzmaurice et al., 2013, 2014).



## 9.5 Diesel exhaust particle extracts

Diesel exhaust particle extracts (DEPe), commonly used as a surrogate model of air pollution in health effects studies, were employed to investigate the biological plausibility and mechanisms of toxicity associated with this exposure. ZF embryos treated with DEPe for 24 h (from 24 to 48 h postfertilization) and analyzed at 5 days postfertilization showed a loss of both dopaminergic and nondopaminergic neurons, along with altered behavior (Barnhill et al., 2020; Ritz et al., 2016). Using a transgenic ZF line that measures neuronal autophagic flux (Khiansuwan et al., 2019), it was observed that DEPe inhibited autophagic flux, and enhancers of autophagy were found to be protective against neuronal loss (Alshial et al., 2023).

## 10. Use of gene editing technology in zebrafish (Ünal & Emekli-Alturfan, 2019)

Recent genetic advancements have made ZF an excellent model for studying neurological diseases, including PD, AD, Huntington's disease, and schizophrenia (Doğanli et al., 2013). Morpholino antisense oligonucleotide microinjection is a widely used technique for transient gene silencing in ZF. By hybridizing to the ATG initiation codon or binding to the exon–intron insertion signal before mRNA, Morpholino halts the translation of specific target mRNA in early development stages. It enables high-throughput gene silencing, but its effectiveness diminishes rapidly after 3 days and is completely lost after 5 days. However, despite being powerful and potentially efficient, morpholino microinjections may have some common issues, such as nonspecific toxicity and nontarget effects on different genes, including triggering a p53-dependent cell death pathway (Bandmann & Burton, 2010; Robu et al., 2007). The toxic effects of p53-induced morpholino exposure in ZF embryos manifest as small heads and eyes, somit and notochord abnormalities, and craniofacial disorders. Due to the limitations of the morpholino approach, interest has grown in alternative strategies for stable silencing. One such strategy is TILLING (targeting local lesions in genomes), adapted from Arabidopsis to ZF, providing stable mutant lines but with low efficiency. Zinc finger nucleases (ZFNs) are DNA-binding proteins that create double-strand breaks in specific genes for targeted genome regulation. ZFNs are injected into ZF embryos at the single-cell stage, and each ZFN contains three genetic finger tails to bind to the target gene on both strands. The FokI restriction endonuclease in the ZFN head results in double-strand breaks within the targeted gene, but it is a high-cost technique (Foley et al., 2009). The DNA repairs occur through nonhomologous ends (NHEJ) and homologous recombination (HR) pathways. While NHEJ causes silencing of the repaired region, HR enables genome integration. However, the inability to precisely target desired sequences remains a limitation for all ZFN-based methods (Osakabe & Osakabe, 2014).

An alternative to the ZFN system is transcriptional activator-like effector nucleases (TALENs), which require a pair of TALENs connected to the DNA strands to make cuts at the desired region. When TALENs are mutually bound, the FokI endonuclease cuts the targeted DNA sequence, activating DNA repair mechanisms. However, despite high specificity, nontarget mutations have been reported in genome regulation using TALENs (Joung & Sander, 2013). In ZF, the CRISPR/Cas9 system, based on periodically divided palindromic clusters, can achieve very high levels of gene silencing (Irion et al., 2014). In CRISPR technology, the Cas9 endonuclease, along with the targeted RNA sequence, is sufficient for the DNA cut. By creating the Cas9-RNA (SgRNA)-DNA complex, double-strand breaks occur in the target region (Ellakwa et al., 2024). The only prerequisite for this cut is the presence of the NGG sequence called PAM (Protospacer adjacent motif) at the 3' ends of the target region. In a transgenic ZF model (Tg (dat: CFP-NTR)) generated by Godoy et al. (2015), which expresses cyan fluorescent protein-nitroreductase fusion protein (CFP-NTR) under DAT cis-regulatory elements' control, prodrug metronidazole exposure in 5-day-old larvae resulted in caspase three activation in CFP-positive neurons and reduction in DAT-positive cells.

## 11. Zebrafish models for the functional genomics of neurogenetic disorders

Zebrafish have been utilized as a model for PD research (Flinn et al., 2008; Kabashi et al., 2011). MPTP treatment in ZF embryos mimicked some PD effects, showing dopaminergic neuron loss, which could be rescued with deprenyl (Breteau et al., 2004; Lam et al., 2005; McKinley et al., 2005). Several PD-related genes, including UCH-L1, DJ-1, and Parkin, have been studied in ZF. Knockdown of DJ-1 in ZF increased susceptibility to oxidative stress and elevated SOD1 levels, while combined knockdown of DJ-1 and p53 caused dopaminergic neuronal loss. Parkin knockdown led to a significant decrease in ascending dopaminergic neurons in the posterior tuberculum, similar to the substantia nigra in humans (Flinn et al., 2009). ZF models provide opportunities for screening compounds that promote or prevent the Parkinsonian phenotype (Boehmler et al., 2009), aided by GFP-expressing enhancer trap lines (Wen et al., 2008).

## 12. Conclusion

Animal models are indispensable for understanding disease mechanisms, identifying causes, and advancing treatments. ZF stands out among mammalian models due to its cost-effectiveness, transparency, and genetic manipulability. This review highlights ZF studies investigating the genetic and environmental aspects of PD, offering valuable insights transferable to mammalian models. Future ZF research is likely to involve high-throughput screenings to identify PD-associated environmental toxins and novel therapeutics. Particularly in neurodevelopmental research, *Danio rerio* has proven to be a valuable platform, benefiting studies on neurodegenerative diseases like PD, Alzheimer's, and Huntington's. ZF's transparent embryos, easy genetic manipulations, and short life cycles have facilitated molecular investigations, including omics studies, surpassing the limitations of primates and rodents.

Currently, ZF serves as an excellent model for studying neurobehavioral aspects relevant to humans and is widely utilized in various fields such as biology, neuroscience, pharmacology, and toxicology research. In this manuscript, we highlight its significance as a model for screening novel drugs targeting neurological disorders. Recent advancements in using ZF to analyze the pathology of PD are discussed. By manipulating the expression of orthologous ZF genes or introducing pathogenic genes linked to human neurodegenerative disorders, researchers have successfully induced morphological, physiological, and biochemical defects in specific neuronal classes, demonstrating functional conservation between human neurodegenerative disease-related genes and ZF. This supports the use of ZF as an alternative model for investigating the molecular basis of PD. With its unique attributes, ZF holds great potential as a high-throughput drug-screening vertebrate platform. Embracing the concept of precision medicine, a comprehensive understanding of disease omics (genomics, proteomics, metabolomics) can aid healthcare practitioners in tailoring treatments to individual PD patients. This patient-centered approach is believed to enhance treatment efficacy by considering each patient's specific needs. Given that most PD cases are sporadic, precision medicine knowledge can guide the selection of the most appropriate therapeutic strategies for individual patients. Although extensive research is ongoing to comprehend PD's etiology and pathophysiology, much remains to be explored, particularly at the molecular genomic and proteomic levels. In this regard, ZF has been and will continue to be an invaluable PD model, especially in studies demanding molecular investigations.

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# Index

Note: 'Page numbers followed by f indicate figures, t indicate tables, and b indicate boxes.'

## A

AbbVie  $\alpha$ -syn-SAA method, 101–102  
Adeno-associated viral (AAV)-induced asyn overexpression, 153–154  
Adenosine triphosphate (ATP), 326  
Adipose-derived stem cells (ADSCs), 134  
Adult stem cells (ASCs), 126–127  
Aggregation-prone regions (APR), 91  
Alpha-synuclein ( $\alpha$ -Syn), 12–13, 67, 173, 210  
    aggregation formation, 91–93, 92f–93f  
    beta-sitosterol beta-D-glucoside (BSSG), 189, 193–194  
    chaperone activity, 86–87  
    Drosophila model, 233, 235–236  
    function of, 85, 87  
    genetic aspects, 87–88  
    heat shock proteins (HSPs), 86–87  
    history, 84  
    metabolic regulation and calcium signaling, 86  
    model, 91  
    neuroprotective, synaptic functions, and neurotransmitter release, 85–86  
    nuclear receptor-related factor1 (Nurr1), 115–116  
    omics, 326–327  
    polymorphism, 88–89  
    spinocerebellar ataxia type 1 (SCA1), 208  
    structure of, 84–85, 85f  
    targeting, 91  
    therapeutic interventions, 89  
    therapeutic strategies, 89–90  
    zebrafish (ZF) models, 223  
 $\alpha$ -synuclein seeding assays  
    amplification  
        AbbVie  $\alpha$ -syn-SAA method, 101–102  
        protein-misfolding cyclic amplification (PMCA), 102–103  
        real-time quaking-induced conversion (RT-QuIC), 103  
        side-by-side method, 102t  
    clinical symptoms, 97  
    conventional assays, 104–106, 106t  
    development of, 101  
    ethical regulations, 312  
    medications, 97–99  
    pathogenesis, 99  
    serum biomarkers, 103–104

    structure and physiological function, 98f–99f, 99–100  
Alzheimer's disease (AD), 12, 66, 212  
Amantadine, 33  
Amprion lab, 102–103  
Amyotrophic lateral sclerosis (ALS), 212  
Ankyrin (ANK) domain, 269  
Anti-Parkinson activity  
    Ashwagandha (*Withania somnifera*), 350  
    Bala (*Sida cordifolia*), 351  
    Bramhi (*Bacopa monnieri*), 350  
    Mucuna pruriens, 349  
Anxiety, 294–295  
Ashwagandha (*Withania somnifera*), 350  
Astrocytes, 5–6, 9  
Autonomic dysfunction, 297–298  
Ayurvedic medicine  
    case studies in, 348–349  
    causes of, 346  
    correlation, 347–348  
    definition, 347  
    dopamine, 346  
    incidence and prevalence, 345  
    Kampavata, 348  
    lack of evidence, 356  
    lack of standardization, 357–358  
    massage and hot fomentation, 354  
    multiple interventions, 356–357  
    panchakarma therapies, 352, 352t–355t  
    single herbal drugs  
        Ashwagandha (*Withania somnifera*), 350  
        Bala (*Sida cordifolia*), 350–351  
        Bramhi (*Bacopa monnieri*), 350  
        Mucuna pruriens, 349  
        Parisak Yavani, 351–352, 351t  
    strengths and limitations of, 355–356  
    substantia nigra, 345  
    treatment of, 346

## B

Benomyl, 225  
Beta-sitosterol beta-D-glucoside (BSSG)  
    advantages of, 195  
     $\alpha$ -synuclein pathology, 193–194  
    cognitive impairments, 193  
    effectivity of action, 194–195  
    ethical regulations, 314  
    history, 191–192  
    limitations of, 196  
    motor characteristics, 192  
    neuroprotective therapies, 196  
    overview, 187  
Parkinson's disease  
    diagnostic tests, 188  
    environmental factors, 187–188  
    pathogenesis of, 188–190  
    symptomatic treatment for, 190–191  
        symptoms, 187–188  
    prodromal traits, 192–193  
Biochemical biomarkers  
    biofluid, 42–43  
    microRNAs (miRNAs), 43, 44t–45t  
Bioinformatics, 67  
Biomarkers  
    biochemical  
        biofluid, 42–43  
        microRNAs (miRNAs), 43, 44t–45t  
    definitions, 42  
    genetic  
        Mendelian mutations, 47  
        risk alleles, 47  
        risk scoring, 47  
        testing and counseling, 46–47  
    implications, 55  
    limitations and challenges of, 54  
    movement disorders, 50t–52t  
        dystonia, 49–53  
        essential tremor (ET), 53–54  
        Huntington's disease (HD), 49  
    multimodal, 48  
    neuroimaging, 45–46  
    non-invasive, 48–49  
    protein misfolding cyclic amplification (PMCA), 54  
    real-time quaking-induced conversion (RT-QuIC), 54  
Bladder dysfunction, 297  
Blink reflex abnormality, 299  
Blood-based metabolomics, 73–74  
Body-first animal models, 155–156  
Bone marrow-derived mesenchymal stem cells (BMSCs), 128  
Bradykinesia, 291–293  
Brain-first subtype animal models  
    fibrillar forms of asyn, 154  
    neurotoxins, 151–153  
    transgenic models, 154–155  
    viral vector-mediated asyn overexpression, 153–154

Brain function, 9

Bramhi (*Bacopa monnieri*), 350**C***Caenorhabditis elegans* models

ethical regulations, 315

history, 247–248, 248f

leucine-rich repeat kinase 2 (LRRK2). *See*  
leucine-rich repeat kinase 2 (LRRK2)

nervous system and developmental

plasticity, 249–250, 249f

pre- and postsynaptic abnormalities,  
258–259

tau protein and tauopathies

advantages and limitations, 261–262

aggregates and toxicity, 251

conformational changes, 251

CRISPR-Cas genome editing technology,  
260–261

development, 254

localization, 250

MAPT gene mutations, 251

mechanosensory gene expression

regulation, 257–258, 258t

pan-neuronal gene expression regulatory  
models, 254–256

physiology, 250

PTL-1, 252

therapeutic interventions, 259–260

transgenic model, 252–254, 253f

*Callithrix jacchus*, 314

Cardiovascular dysfunction, 297

Caughey laboratory, 103

Cell death, 326

Chaperone activity, 86–87

Chromosomes, 234

Cognitive impairments, 193, 295

Complementary and Alternative Medicines  
(CAM), 347

Complex I deficiency, 176–177

Confounding factors, model validation

animal models

problem of, 281–282

validation of, 284–285

biological and model-related, 282

disease onset and progression, 283

genetic differences, 283

genetic variability, 283–284

human, 284

personalized medicine, 281

phenotypic differences, 282

Construct validity, 285

CRISPR-Cas genome editing technology,  
260–261**D**

Deep brain stimulation (DBS)

animal models

body-first animal models, 155–156

brain-first subtype, 151–155

ethical issues, 150–151

overview, 150

beta-sitosterol beta-D-glucoside (BSSG),  
190

characteristics, 148

definition, 148

electrodes, 147

history, 149

mechanism of, 156–158

subtypes of Parkinson disease, 149–150

symptoms, 147

Dementia with Lewy bodies (DLBs), 12

Depression, 294

Diesel exhaust particle extracts (DEPE), 226

Diet, 36

DJ-1 gene mutation, 67, 209, 223, 236

Dopamine agonists, 32

Dopamine receptor D2 (Drd2), 9

Dopaminergic (DA) cells, 127

Dopamine transporter single-photon emission  
computed tomography (DAT  
SPECT), 14*Drosophila* model, 170

alpha-synuclein models, 235–236

causes and risk factors, 233–234

chemotherapeutic approaches, 238

chromosomes of, 234

clinical problems, 231–232

DJ-1, 236

*Drosophila melanogaster*, 235

ethical regulations, 315

gene therapy, 239, 239t

genetic analysis, 235, 235t

history of, 234

incidences, 231

leucine-rich repeat kinase 2 (LRRK2), 269

mechanism, 233

parkin mutation, 236

symptoms, 232–233

therapeutic approaches

herbal products, 238

natural products, 236–238, 237t

Drug resistance and diminishing efficacy, 34

Dysfunctional protein clearance systems, 189

Dystonia, 34, 49–53

**E**

Electrical sensitivity, 298

Engrailed (En1), 118–120, 313

Enzymatic domains, 268

Epigenomics, 330–331

Essential tremor (ET), 34, 53–54

Ethical regulations

beta-sitosterol beta-D-glucoside (BSSG),  
314

biochemical and cellular models, 312–313

clinical manifestations, 307

mammalian models

 $\alpha$ -synuclein mouse models, 314*Caenorhabditis elegans*, 315*Drosophila* model, 315

6-hydroxyamine (6-OHDA), 313–314

1-methyl-4-phenyl-1, 2, 3, 6-

tetrahydropyridine (MPTP), 313–314

Mitopark mouse model, 314

rotenone rodent model, 313–314

zebra fish model, 312–313

Marmoset model, 314

optimal Parkinson model, 308

prevalence, 307

regulation of animal models

advantages and disadvantages, 308,

310t–311t

reduction, 309–312

refinement, 312

replacement, 308–309

rules of, 308, 309f

validation of animal models, 308

Eye movements, 48–49

**F**

Face validity, 284

Fecal microbiota transplantation (FMT),  
335

Flavonoids, 236

Forelimb akinesia, 293

**G**

Gait analysis, 48

GAPmScarlet fluorescence, 215

Gas chromatography-mass spectrometry  
(GC-MS), 73

Gastrointestinal (GI) tract, 18, 297–298

Genetic biomarkers

Mendelian mutations, 47

risk alleles, 47

risk scoring, 47

testing and counseling, 46–47

Genome-wide association studies (GWAS),  
68, 68f

Genomics, 71–72, 329–330

Glucocerebrosidase (GBA1), 67

Glucocorticoids (GCs), 8

Glymphatic system

definition, 6–7

therapeutic approaches, 17–18

waste clearance pathways, 7

Gut dysbiosis, 357

Gut microbiome, 11

**H**

Heat shock proteins (HSPs), 86–87

Herpes simplex virus (HSV), 327

High-sensitivity C-reactive protein (hsCRP),  
13

High-throughput methods, 328

High-throughput sequencing techniques

clinical settings, 67

genome-wide association studies (GWAS),  
68, 68f

next-generation sequencing (NGS)

strategies, 68, 68f

whole-exome sequencing (WES), 69

whole-genome sequencing (WGS), 70

Human Ataxin-1 in the stable transgenic  
zebrafish strains, 215

Human embryonic stem cells (hESC), 128

Human pluripotent stem cells (hPSCs),  
128–129, 135–136  
Huntington's disease (HD), 34, 49  
6-Hydroxydopamine (6-OHDA), 151, 172,  
292–293, 313–314, 325  
Hyoscamus niger, 351–352  
Hypokinetic movement disorders, 209  
Hyposmia, 16

## I

Induced pluripotent stem cells (iPSCs),  
128–129, 133–134, 171, 325  
Interleukin-6 (IL-6), 11  
Interleukin-10 (IL-10), 12  
Itrifal Muqawwi-e-Dimagh (IMD), 238

## K

Kaempferol (KPF), 236–237  
Kampavata, 348

## L

Leucine-rich repeat kinase 2 (LRRK2), 67,  
174, 209, 211, 224–225, 327  
animal models, 267–268  
*Caenorhabditis elegans*  
characteristics, 270–271  
knock-off models, 271–272  
life cycle, 270  
reproduction, 270  
taxonomy, anatomy and habitat, 270  
transgenic overexpression models, 272  
usage, 271, 271t  
ethical regulations, 312–313  
history, 268  
prevalence, 267  
structure and physiological functions,  
268–269  
Levodopa/Carbidopa Intestinal Gel (LCIG),  
232–233  
Levodopa (L-dopa), 31–32, 349, 356  
Lifestyle modifications, 36  
Lipidomics, 70–71  
Liquid chromatography-mass spectrometry  
(LC-MS), 73  
Liver x receptor (LXR), 194–195  
Luteolin, 237

## M

Machado-Joseph disease, 209–210  
MAPT gene mutations, 251  
Marmoset model, 314  
Massively parallel reporter assays (MPRAs),  
328  
Mechanical sensitivity, 298  
Mechanosensory gene expression regulation,  
257–258, 258t  
Mesenchymal stem cells (MSCs), 127,  
130–131, 133  
Metabolomics, 72–74, 334  
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine  
(MPTP), 151–152, 172, 313–314,  
322–323, 326

Microbiomics  
fecal microbiota transplantation (FMT), 335  
mechanisms and biomarkers, 335–336  
personalized medicine, 336  
Microglia, 7–8  
Microinjection  
nucleic acids, 213–216  
plasmid vectors for, 213  
MicroRNAs (miRNAs), 43, 44t–45t, 330  
Midbrain dopaminergic neurons, 313  
Mitochondria, 175–176  
Mitochondrial DNA (mtDNA)  
mutations, 176–177  
role of, 178  
Mitochondrial dysfunction, 117, 177–178,  
189  
in autosomal dominant Parkinson's disease,  
210–211  
in autosomal recessive Parkinson's disease,  
211  
MitoPark mouse model  
characteristics, 168, 169t  
characterization, 179  
complex I deficiency, 176–177  
dopaminergic neurons, 167–168  
establishing, 178–179  
ethical regulations, 314  
genetic models, 173–175, 173t, 175t  
induced pluripotent stem cell (iPSC), 171  
mitochondria, 175–176  
mitochondrial DNA (mtDNA)  
mutations, 176–177  
role of, 178  
mitochondrial dysfunction and oxidative  
stress, 177–178  
neuroinflammation, 181  
neurotoxin models, 171–173  
nonhuman primates (NHP), 171  
nonmammalian species, 170–171  
progressive neurodegeneration and  
Parkinsonism phenotype, 168–169,  
170f  
respiratory chain function, 179–181  
rodents, 171  
toxin-induced models, 168  
treatment response, 181  
Monoamine oxidase B (MAO-B) inhibitors, 32  
Monocytes, 8  
Movement disorders  
biomarkers, 49–54  
omics, 77  
pharmacotherapy. *See* Pharmacotherapy  
*Mucuna pruriens*, 349  
Multimodal biomarkers, 48

## N

Nasal administration, 357–358  
Neural progenitor cells (NPCs), 115  
Neural stem cells (NSCs), 131  
Neurobehavioral characterization  
definition, 291  
motor symptoms  
beam walking test, 292  
bradykinesia, 291–293

forelimb akinesia, 293  
rigidity, 293–294  
tremors, 292–293  
neurotoxins and genetics, 291  
nonmotor symptoms  
anxiety, 294–295  
autonomic dysfunction, 297–298  
blink reflex abnormality, 299  
cognitive impairment, 295  
depression, 294  
olfactory dysfunction, 299  
pain, 298–299  
sleep disorders, 295–296  
Neurobehavioral phenotyping, 207  
Neuroimaging biomarkers, 45–46  
Neuroinflammation, 189–190  
astrocyte participation, 6  
astrocyte role, 9  
biomarkers of, 11  
cellular and molecular mechanisms, 5  
crucial routes, 5–6  
definition, 5  
microglia role, 7–8  
monocyte role, 8  
*vs.* neurodegeneration, 6  
therapeutic approaches, 17–18  
types of, 5  
Neuromelanin-sensitive magnetic resonance  
imaging (NM-MRI), 14  
Neurotoxin models, 325  
compounds, 153  
6-hydroxydopamine (6-OHDA), 151, 172  
1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine  
(MPTP), 151–152, 172  
paraquat (PQ), 152–153, 172  
rotenone, 152, 173  
zebrafish (ZF) models, 222–225  
Neurotrophic factors (NFs), 17  
N-methyl-D-aspartate (NMDA) receptor, 33  
Non-A $\beta$  component (NAC), 84  
Nonhuman primates (NHP), 171, 323–324  
Non-invasive biomarkers, 48–49  
Nuclear magnetic resonance spectroscopy  
(NMR), 72–73  
Nuclear receptor-related factor1 (Nurr1)  
 $\alpha$ -synuclein, 115–116  
definition, 114–115  
ethical regulations, 313  
minocycline, 115  
mitochondrial dysfunction and oxidative  
stress, 117  
neural progenitor cells (NPCs), 115  
role of, 115  
treatment of, 117

## O

Olfactory bulb (OB), 149–150  
Olfactory dysfunction, 299  
Olfactory testing, 49  
Oligodendroglia, 10  
Omics  
challenges, 74–75, 75f–76f, 76t  
complex disease primary tissues, 322–323,  
323f, 324t



Omics (*Continued*)

- definition, 321
  - diagnosis, 321
  - emerging models, 325
  - etiology, 321
  - genetics
    - $\alpha$ -synuclein, 326–327
    - leucine-rich repeat kinase 2 (LRRK2), 327
    - parkin, 327
    - protein deglycase, 327
    - pten-induced kinase 1 (PINK1), 327–328
    - in vitro modeling, 328–329, 329t
  - genomics, 71–72, 329–330
  - 6-hydroxydopamine (6-OHDA), 325
  - induced pluripotent stem cells (iPSC), 325
  - lipidomics, 70–71
  - metabolomics, 72–74, 334
  - 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 326
  - microbiomics
    - fecal microbiota transplantation (FMT), 335
    - mechanisms and biomarkers, 335–336
    - personalized medicine, 336
  - movement disorders, 77
  - nonhuman primates (NHP), 323–324
  - nonmammalian species, 324–325
  - paraquat, 326
  - proteomics, 74, 333
  - rodents, 323
  - rotenone, 326
  - transcriptomics, 330–334
- Oxidative stress, 18, 117, 177–178, 351

**P**

- p53-dependent cell death pathway, 226
- Pain, 298–299
- Panchakarma therapies, 352, 352t–355t
- Pan-neuronal gene expression regulatory models
  - genome-wide RNAi screen, 255–256
  - molecular models, 255
  - mutant and wild-type forms of human MAPT, 255
- phosphorylation, 256
- rab-3 and tau fragments, 256
- SOD1 expression and neuronal activity, 256
- Paralysis, 207
- Paraquat (PQ), 152–153, 172, 225, 326
- Paresis, 207
- Parisak Yavani, 351–352, 351t
- Parkin, 174, 208–209, 211, 236, 327
- Parkinson's disease (PD)
  - alpha-synuclein ( $\alpha$ -Syn). *See* Alpha-synuclein ( $\alpha$ -Syn)
  - antiinflammatory disease modification, 18
  - antiinflammatory therapies, 17–18
  - astrocyte role, 9
  - Ayurvedic medicine. *See* Ayurvedic medicine
  - beta-amyloid 1–42, tau, p-tau
    - alpha-synuclein, 12–13

- Alzheimer's disease (AD), 12
- analysis, 12
- cerebral spinal fluid (CSF), 12
- vs. dementia, 12
- dementia with Lewy bodies (DLBs), 12
- genetic biomarkers, 13–14
- imaging biomarkers, 14–15
- beta-sitosterol beta-D-glucoside (BSSG). *See* Beta-sitosterol beta-D-glucoside (BSSG)
- biomarkers, 11, 15. *See also* Biomarkers *Caenorhabditis elegans*. *See* *Caenorhabditis elegans* model
- clinical diagnosis, 40, 40t
- deep brain stimulation (DBS). *See* Deep brain stimulation (DBS)
- definition, 4
- differential diagnosis, 40–41, 41f
- diffusion tensor imaging (DTI), 16
- Drosophila. *See* Drosophila model
- early diagnosis, 15
- Engrailed (En1), 118–120
- ethical consideration. *See* Ethical regulations
- hyposmia, 16
- imaging and laboratory tests, 41
- immune cell-mediated inflammation, 10–11
- microglia role, 7–8
- MitoPark mouse model. *See* MitoPark mouse model
- monogenic and idiopathic, 66
- motor and nonmotor symptoms, 66
- mutations, 67
- neurobehavioral characterization. *See* Neurobehavioral characterization
- neurotrophic factors (NFs), 17
- nuclear receptor-related factor1 (Nurr1), 114–117
- omics. *See* Omics
- Pitx3, 117–118
- positron emission tomography (PET), 16
- REM sleep behavior disorder (RBD), 16
- single-photon emission computed tomography (SPECT), 16
- Sonic Hedgehog (SHH), 113–114
- stem-cell therapy. *See* Stem-cell therapy
- TNF- $\alpha$ /sTNFRs, 12
- Parkinson's disease protein 2 (PARK2) gene, 223–224
- Parkinson's disease protein 7 (PARK7) gene, 224
- Perturbing Regulatory Interactions by Synthetic Modulators (PRISM), 328
- Pharmacotherapy
  - adjunct therapies and multidisciplinary approach, 35–36
  - anticholinergics, 33
  - definition and overview of, 29
  - dopamine agonists, 32
  - dystonia, 34
  - epidemiology and prevalence, 29
  - essential tremor, 34
  - gene therapy and stem cell therapy, 36
  - Huntington's disease (HD), 34
  - levodopa, 31–32

- limitations and challenges, 34–35
- medications, 33
- monoamine oxidase B (MAO-B) inhibitors, 32
- motor and nonmotor, 30
- new pharmacological agents and strategies, 36
- overview, 30–31
- pathophysiology, 29–30
- personalized medicine, 33
- progression, 30–33
- technology, 36–37
- treatment, 34
- Phosphorylation, 256
- Physical, occupational, and speech therapy, 35
- PINK1-Parkin, 313
- Pitx3, 117–118, 313
- Polymorphism, 88–89
- Predictive validity, 284
- Primary cilium (PC), 114
- Protein deglycase, 174, 327
- Protein-misfolding cyclic amplification (PMCA), 54, 102–103
- Protein-protein interaction domains, 269
- Protein with tau-like repeats (PTL-1), 252
- Proteomics, 74, 333
- Psychosocial support, 35
- PTEN-induced kinase 1 (PINK1), 174–175, 208–209, 211, 222–223, 327–328
- Purkinje cell-specific SCA1, 214
- PyMOL molecular Graphics system (PyMOL), 92f

**R**

- Real-time quaking-induced conversion (RT-QuIC), 54, 103
- Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES), 13
- REM sleep behavior disorder (RBD), 16
- Respiratory chain function, 179–181
- Restless leg syndrome (RLS), 348
- Rigidity, 293–294
- Rotenone, 152, 225, 313–314, 326

**S**

- Saliva metabolomics, 74
- Sebum, 74
- Seed amplification assays (SAAs), 13
- Serum biomarkers, 103–104
- Single nucleotide variations (SNVs), 70
- Sleep disorders, 295–296
- SMPD1 mutation, 67
- Sonic Hedgehog (SHH)
  - ethical regulations, 313
  - primary cilium (PC), 114
  - signaling system, 114
- Spinocerebellar ataxias (SCA), 209–210
- Spinocerebellar ataxia type 1 (SCA1)
  - balance and coordination, 208–209
  - definition, 205–206
  - history, 205

hypokinetic movement disorders, 209  
 intrinsic mitochondrial functions, 210–211  
 microinjection  
   of nucleic acids, 213–216  
   plasmid vectors for, 213  
 neurobehavioral phenotyping, 207  
 neurodegeneration, 206  
 paresis and paralysis, 207  
 Parkinsonism in, 209–210  
 protein aggregates, 206–207  
 in zebrafish, 212  
   behavioral performance of, 216  
   genetic modeling, 214–215  
   Purkinje cell layer integrity, age-related progressive disturbances, 215–216  
 Spinocerebellar ataxia type 3 (SCA3), 209–210  
 Stem-cell therapy  
   challenges and risks, 135–137  
   history, 125  
   human and induced pluripotent stem cells, 129  
   innovations, 138–139  
   legal and ethical frameworks, 137–138  
   mesenchymal stem cells (MSCs), 130–131  
   meta-analysis in, 131–135  
   overview of, 125–128  
   research and clinical trials, 138  
   technical considerations in, 129  
 Substantia nigra (SN), 345  
 Synucleinopathies, 86–87

## T

Tau protein and tauopathies  
 advantages and limitations, 261–262  
 aggregates and toxicity, 251  
 conformational changes, 251  
 CRISPR-Cas genome editing technology, 260–261

development, 254  
 localization, 250  
 MAPT gene mutations, 251  
 mechanosensory gene expression regulation, 257–258, 258t  
 pan-neuronal gene expression regulatory models, 254–256  
 physiology, 250  
 PTL-1, 252  
 Tfam disruption, 178–179  
 Thermal sensitivity, 298–299  
 Thiobarbituric acid reactive substance (TBARS), 351  
 Time to threshold (TTT), 101–102  
 Toxin-induced models, 168  
 Transcranial magnetic stimulation (TMS), 190  
 Transcranial sonography (TCS), 46  
 Transcriptional activator-like effector nucleases (TALENs), 226  
 Transcriptomics, 330–334  
 Transgenic models, 154–155  
 Tremors, 292–293  
 Type 2 diabetes (T2D), 86

## U

Ubiquitin-proteasome system (UPS), 189  
 Urine metabolomics, 74

## V

Validation, Parkinson's disease (PD) models  
 confounding factors  
   application of, 285  
   definition, 284  
   experiment, 285  
   internal and external validity, 284–285  
   ethical regulations, 308  
 Voice and speech analysis, 48

## W

Whole-exome sequencing (WES), 69  
 Whole-genome sequencing (WGS), 70

## Z

Zaprinast (ZAP), 238  
 Zebrafish (ZF) models, 170–171, 212  
   advantages and disadvantages, 220  
   behavioral neuroscience of, 220  
   challenges of, 220–221  
   clinical manifestations, 219  
   definition, 220  
   ethical regulations, 312–313  
   functional genomics of, 226  
   gene editing technology, 226  
   lifecycle and development, 221, 224f  
   neurotoxin-induced model, 222–225  
   spinocerebellar ataxia type 1 (SCA1)  
     behavioral performance of, 216  
     genetic modeling, 214–215  
     Purkinje cell layer integrity, age-related progressive disturbances, 215–216  
   study and research, 219–220, 221f  
   toxins, 225–226  
   transgenic models  
      $\alpha$ -synuclein (SNCA) gene, 223  
     DJ-1 gene mutation, 223  
     leucine-rich repeat kinase 2 (LRRK2) gene, 224–225  
     Parkinson's disease protein 2 (PARK2) gene, 223–224  
     Parkinson's disease protein 7 (PARK7) gene, 224  
     PINK1 gene mutation, 222–223  
     transparency of, 222  
   types, 222  
 Zinc finger nucleases (ZFNs), 226  
 Ziram, 225

# Translational Models of Parkinson's Disease and Related Movement Disorders

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The second most prevalent neurodegenerative condition following Alzheimer's disease is Parkinson's disease, marked by the loss of midbrain dopaminergic neurons and age-related motor impairments. To enhance predictability and management of Parkinson's disease risk, experimental investigations rooted in epidemiological and genetic studies are imperative. ***Translational Models of Parkinson's Disease and Related Movement Disorders*** examines the state-of-the-art methodologies for developing and validating contemporary translational experimental models of Parkinson's disease. It scrutinizes various attributes of these models, including the prion-like properties of  $\alpha$ -synuclein, mitochondrial functions associated with the PINK1-Parkin pathway/CHCHD2, and the endolysosomal pathway linked to LRRK2, VPS35, and ATP13A2, employing cultured cells such as patient-derived induced pluripotent stem (iPS) cells. This book emphasizes the potential for introducing novel models for Parkinson's disease and related movement disorders, while also highlighting current advancements, preclinical and clinical developments, and future prospects concerning numerous model systems.

## Key features

- Emphasizes the induction and validation of various existing experimental models of Parkinson's disease.
- Offers a comparative overview of different experimental models of Parkinson's disease.
- Explores the advantages and drawbacks of each model, including associated limitations.



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