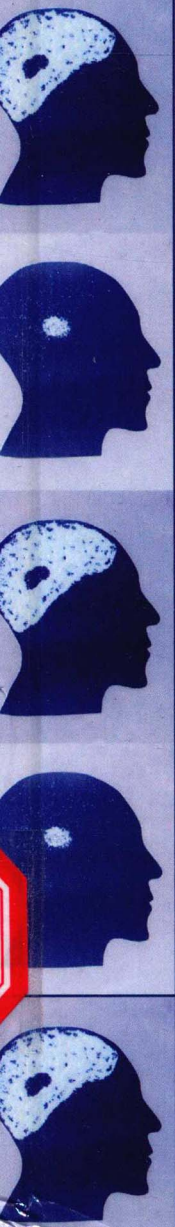
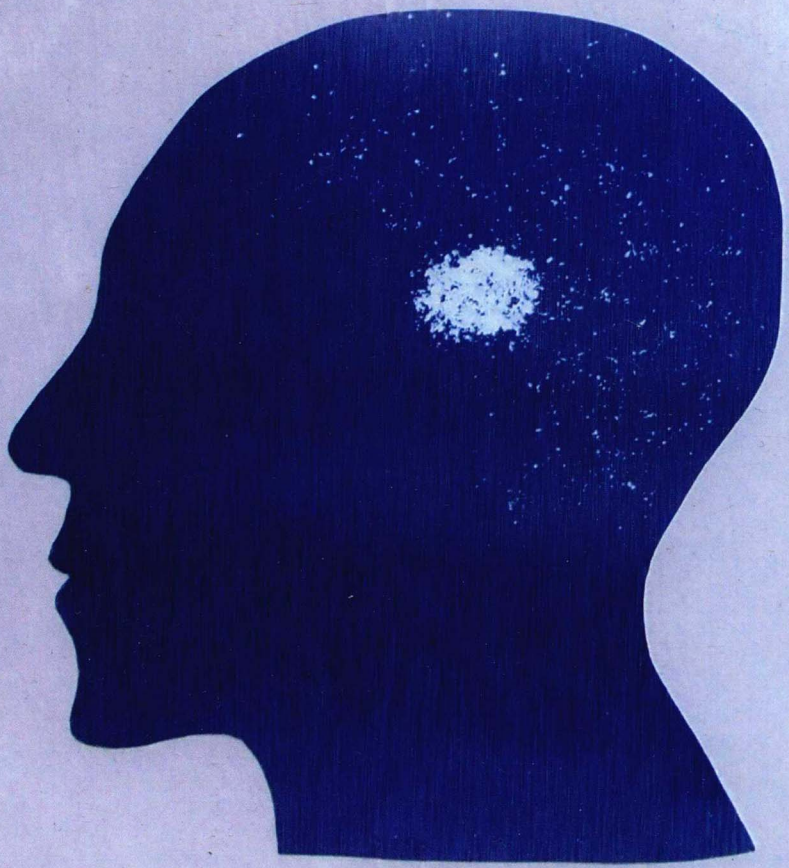
PARKINSON'S DISEASE

MOLECULAR MECHANISMS UNDERLYING PATHOLOGY





Edited by Patrik Verstreken

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Molecular Mechanisms Underlying Pathology

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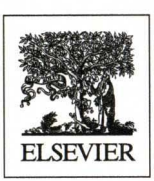

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Preface

Parkinson's disease, first described as the "shaking palsy," was originally described in 1817 by James Parkinson. Now 100 years later, we have learned a great deal about the etiology of this very common disease, but a cure still does not exist. In this book, the leading scientists in the field of Parkinson's disease discuss key aspects of molecular and cellular dysfunction associated with the disease and we highlight potential therapeutic avenues that may be explored.

Parkinson's disease is the second most common neurodegenerative disorder and millions of people around the world have been diagnosed with this disease. A number of "typical" features are associated with Parkinson's that include difficulties to initiate movements and a loss of automatism in moving, shaking, rigid muscles, posture changes as well as difficulties to smell, sleep, swallow, constipation etc. Pathologically, several of these dysfunctions are ascribed to the loss of dopaminergic neurons in the substantia nigra pars compacta but the disease is much more systemic and other neurons suffer as well. While several books on the clinical and pathological aspects of Parkinson's disease have been published, compendia on critical molecular and cellular defects associated with Parkinson's are much scarcer, yet understanding the underlying molecular and neuronal dysfunction will be important when developing therapeutic interventions.

While only decades ago it was thought that Parkinson's disease was a purely sporadic disease, caused by environmental causes, scientists have discovered numerous genetic factors, causative genes, and risk loci in the genome, that are strong and important contributors to the disease. The genetic and genomic era in Parkinson's disease has brought (and will bring in the future) many important breakthroughs that are being discussed in this volume. In many instances, the discoveries made regarding these genetic factors are also important to understand how environmental factors contribute to the disease. This book therefore takes off with a classification of the genetic factors involved in Parkinson's disease and continues with a discussion on the different molecular and cellular pathways that have been implicated in the disease. This knowledge will be critical to eventually understand how Parkinson's disease manifests itself at the level of neuronal circuits and the brain.

This book is build up around different key pathways and cellular defects that have been connected to Parkinson's disease and not around

individual genes or environmental stress factors causative to the disease. It integrates the data obtained with different in vivo and in vitro systems, from cultured cells and yeast to nematodes, flies, mice, rats, and where applicable humans. The time is right for this book as we are at the brink of taking the molecular and cellular discoveries to the next level for the benefit of patients and society.

Patrik Verstreken
Professor, KU Leuven
Group Leader, VIB

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CHAPTER

1

The Neurogenetics of Parkinson's Disease and Putative Links to Other Neurodegenerative Disorders

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OUTLINE

Parkinson's Disease. http://dx.doi.org/10.1016/B978-0-12-803783-6.00001-8

1 INTRODUCTION

Two decades after the discovery of the first gene causing a monogenic form of Parkinson's disease (PD), that is, *alpha-synuclein* (*SNCA*),[1] the etiology of classical PD remains an imperfectly understood complex puzzle of genes and the environment. Although only a minority (ie, ~5%) of cases is due to well-defined genetic causes, important clues about the more common, "idiopathic" PD (iPD) can be garnered from these monogenic model diseases, which will be discussed in more detail in the first part of this introductory chapter. The idiopathic form of PD constitutes the majority (>90%) of all PD cases and typically shows no or a less pronounced family history than monogenic PD. Importantly, iPD cannot be attributed to a single genetic mutation but rather the combination and interaction of dozens to hundreds of genetic risk variants and few environmental factors (such as pesticide exposure, history of head injury, and possibly coffee consumption and smoking history)[2].

Postencephalitic and MPTP-induced parkinsonism lack of convincing concordance rates among monozygotic and dizygotic twins—except for those with an early age of onset[3]—and the identification of environmental risk factors[2] had initially all supported the hypothesis of an exogenous cause of PD. Thus, the identification of monogenic forms of PD has revolutionized this previously held view of a largely nongenetic etiology for this progressive movement disorder. The genetics have clearly established

the existence of several distinct entities of PD, and has greatly advanced our understanding of both monogenic and iPD.

Major findings in this context include but are not limited to the discovery of SNCA as the main component of Lewy bodies in both *SNCA* mutation-linked and iPD[4] and the intriguing observation that *SNCA* mutations can not only be causative of PD but also that variants in the very same gene confer risk to iPD.[5–7]

Detailed multimodal analyses of individuals with monogenic forms of PD have provided unique opportunities to pursue the mechanisms of neuronal degeneration in PD highlighting the "Bermuda triangle" of PD pathogenetic mechanisms with (1) impaired protein turnover, (2) mitochondrial dysfunction, and (3) disturbances in synaptic and endosomal vesicle and protein trafficking and recycling[8] in postmitotic neuronal cells (Fig. 1.1).

An improved understanding of monogenic PD and of the genetic contribution to iPD is highly imperative, as it is conceivable that at least a subset of PD may be causally treatable. In this context, neurogenetics provides a unique opportunity to identify and study individuals at risk of this neurodegenerative disorder in its earliest stages, which likely are the ones most amenable to neurorestaurative or even preventive treatment. Although causative PD mutations are rare, all monogenic forms combined and considered across different ethnic populations constitute a significant proportion (~5%) of all PD.

Althogether, the numbers of people with PD in the most populous nations worldwide have been estimated at ~4 million in 2005 and are

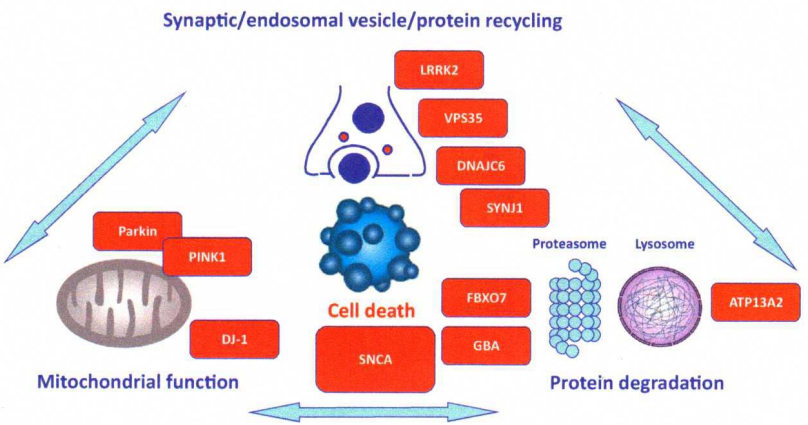

FIGURE 1.1 **"Bermuda triangle" of disease mechanisms implicated in monogenic (and idiopathic) Parkinson's disease highlighting the role of confirmed genes for monogenic PD and parkinsonism, as well as for the *GBA* gene in the context of protein degradation, mitochondrial function, and synaptic and endosomal vesicle and protein recycling.**

expected to more than double to ~9 million by the year 2030,[9]. These figures clearly highlight the need for continued research efforts to tackle monogenic forms and iPD, which will constitute an increasing health problem and socioeconomic burden in the upcoming years.

Although the research community, neurologists, as well as PD patients have been rightfully excited about the rapid advances in gene discovery and improved understanding of the mechanisms underlying PD, success in translational research is in danger to fall behind the high expectations that have been raised by these new discoveries. In this chapter, we will review important research questions and data gaps and highlight some of the burning issues related to the genetics of PD, including the definition and classification of genetic PD, promises and pitfalls of recent genetic insights and genetic testing, the role of reduced penetrance in disease manifestation, genetic susceptibility, and lessons learned from other neurodegenerative diseases that may relate to PD.

2 DEFINITION OF (GENETIC) PARKINSON'S DISEASE

As the discovery of different monogenic forms of PD has challenged the previous concept of a single clinical and nosological entity, it is important to reconsider the definition of PD and to clarify the nomenclature and categorization used in the remainder of this and the other chapters of this book. The following paragraph is based on and contains verbatim quotes from recommendations of the Task Force on the "Definition of Parkinson's Disease," which published their landmark consensus paper in *Movement Disorders*,[10] the official journal of the International Parkinson and Movement Disorder Society (MDS), in 2014: "Most clinicians would endorse the diagnostic gold standard (of PD) as a combined clinical and pathological syndrome, consisting of the following: (1) a motor clinical syndrome, with levodopa-responsive parkinsonism, typical clinical characteristics, and an absence of markers suggestive of other disease. (2) Pathologic confirmation of alpha-synuclein deposition and dopamine neuronal loss in the substantia nigra pars compacta (SNpc). Only at this point is the diagnosis termed "definite." If typical synuclein pathology is not found, the clinical diagnosis is considered incorrect. Likewise, the pathology is "incidental" in the absence of clinical symptoms or attributed to another disease if parkinsonism did not dominate the clinical picture (eg, diffuse Lewy body disease or primary autonomic failure). Therefore, a motor clinical syndrome is the entry point, and pathology is the arbiter of diagnosis."[10]

However, clinico-pathological findings in monogenic forms of PD have called this definition into question in several ways. For example, although the majority of mutation carriers in the *Leucine-rich repeat kinase 2* (*LRRK2*) gene show typical SNCA-positive Lewy bodies,[11] there are reports on

variable *postmortem* findings, even among members of the same LRRK2 family who showed different pathologies, with and without SNCA deposition.[12] Even more strikingly, while most carriers of Parkin (*PARK2*) mutations meet typical clinical criteria of PD,[13] SNCA deposition and Lewy bodies are frequently lacking.[14] To account for these emerging challenges in definition, the MDS Task Force proposed a separate "clinico-genetic" category irrespective of the occurrence of SNCA deposition: "This category would refer specifically to highly penetrant mutations in which the majority of affected meet clinical PD criteria, regardless of whether autopsy specimens of patients with this mutation find SNCA pathology. In research studies, this diagnostic subcategory could be included or not according to the context. For example, an autopsy study validating clinical diagnostic criteria might exclude such patients, a randomized trial of symptomatic dopaminergic therapy might include them, and a neuroprotective trial may elect to include or exclude, depending upon the mechanism of the agent."[10]

Of further note, the umbrella term "parkinsonism" is often used in conjunction with monogenic forms of PD and refers to the typical clinical hallmarks of PD, that is, bradykinesia, resting tremor, rigidity, and postural instability, of which usually at least two have to be present. However, parkinsonism is observed in multiple clinical contexts beyond PD and is, for example, found in patients with multiple system atrophy or progressive supranuclear palsy (PSP), is a common feature in the dystonia–parkinsonisms, and may be encountered as a clinical syndrome in patients with other neurologic conditions, such as stroke or neuroinflammatory disease.

3 CLASSIFICATION AND NOMENCLATURE OF MONOGENIC PARKINSON'S DISEASE

The discovery of monogenic forms of PD did not only pose challenges to the definition of PD but also to its classification and the nomenclature of genetic forms of PD, as the old naming system became increasingly faulty and obsolete. This system of locus (ie, the "PARK" locus system) was originally established to specify chromosomal regions that had been linked to a familial form of PD where the gene was yet unknown. According to this scheme, a number suffix was assigned to each PARK locus according to the chronological description of these loci in the literature (eg, "PARK1," "PARK2," etc.). This system has been adopted by clinicians and researchers to provide names for the condition and is often used synonymously for the chromosomal region.[15] However, as techniques of genetic research and our knowledge have evolved—especially in the light of next-generation sequencing (NGS)—a number of problems have arisen with this system including (1) the inability to distinguish disease-causing

genes from genetic risk factors, (2) an inconsistent relationship between list membership and PD phenotypes including those with very atypical features, (3) missing locus symbols for some established monogenic PD genes, (4) more than one symbol being assigned for the same disorder (eg, PARK1 and PARK4 both designating *SNCA*), and (5) unconfirmed reports of a putative PD gene or locus. This state of affairs led to the foundation of the MDS Task Force for Nomenclature of Genetic Movement Disorders in 2012, which very recently published their international consensus recommendations for a new system for naming of genetically determined PD and other movement disorders.[16]

The newly proposed system takes into account the two key notions derived from the neurogenetics of PD: First, there are multiple clinically different forms of PD caused by the same genotype and second, multiple PD genes may cause a similar clinical picture. The Task Force recommendations for the inclusion of genes into the list of confirmed PD genes are as follows: (1) genes should only be included when genetic testing is possible. Accordingly, a disorder should only be listed once the causative gene is identified. The exception to this recommendation is when a founder haplotype is diagnostic, as in the case of X-linked dystonia–parkinsonism. (2) Previously used number suffixes should be replaced by the gene name, that is, the PARK designation should be followed by the name of the disease-causing gene (eg, PARK-*SNCA* [currently PARK1 and PARK4]). (3) Only disease-causing genes should be considered in this naming system, whereas genetic risk loci should not be included. For the latter, the PDGene website (http://www.pdgene.org) provides a genome-wide catalog of genetic association results in PD and highlights established as well as putative PD genetic risk factors.[6,7] (4) To avoid inaccuracies and redundancies that currently permeate the lists of locus symbols, the threshold of evidence should be raised before assigning locus symbols according to the guidelines of the US National Human Genome Research Institute: (1) presence of the variant in multiple unrelated affected individuals. (2) Evidence for segregation. (3) The variant should be conserved across different species. (4) The variant should be predicted to alter the normal biochemical effect of the gene product, if possible as supported by functional evidence in human tissue or well-established cellular or animal models or by other biochemical or histological abnormalities.[17] In the following, these criteria will be applied to monogenic PD.

4 MONOGENIC FORMS OF PARKINSON'S DISEASE AND PARKINSONISM

A total of 23 genes and loci have currently been assigned a "PARK" designation (Table 1.1).

TABLE 1.1 The Current List of Locus Symbols for Hereditary PD and Parkinsonism

Symbol	Gene locus	*Gene*	Inheritance	Status and remarks
PARK1	4q21-22	*SNCA*	AD	Confirmed
PARK2	6q25.2-q27	*PARK2 (Parkin)*	AR	Confirmed
PARK3	2p13	*Unknown*	AD	Unconfirmed; Causative mutation and gene not identified since locus description in 1998
PARK4	4q21-q23	*SNCA*	AD	Erroneous locus (identical to *PARK1*)
PARK5	4p13	*UCHL1*	AD	Unconfirmed (could not be replicated by independent studies
PARK6	1p35-p36	*PINK1*	AR	Confirmed
PARK7	1p36	*PARK7 (DJ-1)*	AR	Confirmed
PARK8	12q12	*LRRK2*	AD	Confirmed; Variations in *LRRK2* gene include risk-conferring variants and disease-causing mutations.
PARK9	1p36	*ATP13A2*	AR	Confirmed
PARK10	1p32	*Unknown*	Risk factor	Unconfirmed. This locus did not show robust association signals in the most recent GWAS.
PARK11	2q36-27	*Unknown*	AD	Initially described mutations in *GIGYF2* later also found in controls; replication studies could not confirm *GIGYF2* as causative of PD
PARK12	Xq21-q25	*Unknown*	Risk factor	Unconfirmed. This locus did not show robust association signals in the most recent GWAS.
PARK13	2p12	*HTRA2*	AD or risk factor	Could not be confirmed by independent studies
PARK14	22q13.1	*PLA2G6*	AR	Confirmed. The majority of cases do not include parkinsonism but present as infantile neuroaxonal dystrophy

(*Continued*)