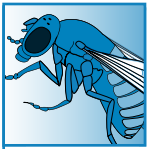


# WHAT GENETICS TELLS US ABOUT THE CAUSES AND MECHANISMS OF PARKINSON'S DISEASE

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Corti O, Lesage S, Brice A. What Genetics Tells Us About the Causes and Mechanisms of Parkinson's Disease. *Physiol Rev* 91: 1161–1218, 2011; doi:10.1152/physrev.00022.2010.—Parkinson's disease (PD) is a common motor disorder of mysterious etiology. It is due to the progressive degeneration of the dopaminergic neurons of the substantia nigra and is accompanied by the appearance of intraneuronal inclusions enriched in  $\alpha$ -synuclein, the Lewy bodies. It is becoming increasingly clear that genetic factors contribute to its complex pathogenesis. Over the past decade, the genetic basis of rare PD forms with Mendelian inheritance, representing no more than 10% of the cases, has been investigated. More than 16 loci and 11 associated genes have been identified so far; genome-wide association studies have provided convincing evidence that polymorphic variants in these genes contribute to sporadic PD. The knowledge acquired of the functions of their protein products has revealed pathways of neurodegeneration that may be shared between inherited and sporadic PD. An impressive set of data in different model systems strongly suggest that mitochondrial dysfunction plays a central role in clinically similar, early-onset autosomal recessive PD forms caused by *parkin* and *PINK1*, and possibly *DJ-1* gene mutations. In contrast,  $\alpha$ -synuclein accumulation in Lewy bodies defines a spectrum of disorders ranging from typical late-onset PD to PD dementia and including sporadic and autosomal dominant PD forms due to mutations in *SCNA* and *LRRK2*. However, the pathological role of Lewy bodies remains uncertain, as they may or may not be present in PD forms with one and the same *LRRK2* mutation. Impairment of autophagy-based protein/organelle degradation pathways is emerging as a possible unifying but still fragile pathogenic scenario in PD. Strengthening these discoveries and finding other convergence points by identifying new genes responsible for Mendelian forms of PD and exploring their functions and relationships are the main challenges of the next decade. It is also the way to follow to open new promising avenues of neuroprotective treatment for this devastating disorder.

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## I. INTRODUCTION

Although Parkinson's disease (PD) was already known in ancient India under the name of "Kampavata," the syndrome was first described in a monograph by James Parkinson, in 1817, in which he presented six cases of "shaking palsy" (292). His work went largely unrecognized for decades, until the neurologist Jean Martin Charcot recognized the importance of Parkinson's work and named the disorder "maladie de Parkinson" (Parkinson's disease).

PD is the second most common neurodegenerative disorder, after Alzheimer's disease, and is expected to impose an increasing social and economic burden on societies as populations age. The prevalence of the condition in industrialized countries is generally estimated at 0.3% of the entire

population, a percentage that increases with age; in persons over age 60, the percentage reaches 1–2%, in those over 80, 3–4% (464). Standardized incidence rates for PD, determined from prospective population-based studies, are estimated to be 8–18/100,000 person-years, with a lifetime risk of developing the disease of 1.5% (42, 105). In addition to age, gender also influences the incidence of PD as several of the prospective studies found evidence of a higher incidence in men than in women (104). PD is characterized clinically by a classic tetrad of motor symptoms: low-frequency resting tremor, rigidity of the skeletal muscles of the face and hands, reduced motor activity (bradykinesia), and, in later stages of the disorder, postural instability. The cardinal symptoms of PD result mainly from progressive and profound loss of neuromelanin-containing dopaminergic neurons in the substantia nigra pars compacta, associated with eosinophilic, intracellular proteinaceous inclusions, termed Lewy bodies, and dystrophic Lewy neurites in the brain stem and cortical areas. The basic components of these inclusions are  $\alpha$ -synuclein, neurofilament proteins, and

ubiquitin (151, 591). In addition, gliosis is often observed in the striatum and the substantia nigra of PD patients (473).

Motor impairment is often accompanied by nonmotor symptoms and signs, such as autonomic, cognitive, and psychiatric problems, related to the degeneration of other groups of neurons, including the serotonergic neurons of the raphe nucleus, noradrenergic neurons of the locus coeruleus, or cholinergic neurons of the nucleus basalis of Meynert. However, these motor dysfunctions do not become apparent until ~70–80% of nigrostriatal nerve terminals have undergone degeneration, suggesting the existence of an impressive compensatory mechanism in the earlier stages of the disease (30). Although slow in most cases, the progression of the disease is irreversible. At present, there is no treatment to arrest or retard the progression of neurodegeneration. Consequently, therapy is primarily symptomatic. Available pharmacological and surgical methods of treatment can alleviate some of the symptoms, but may be associated with serious side effects (546). Since the first description, PD has been the subject of intense investigation to understand its etiology and physiopathology and to develop new therapeutic strategies or preventive interventions based on reliable biomarkers.

Environmental factors were long thought to be the predominant cause of PD, particularly after the influenza pandemic of 1918, when a subset of affected individuals developed postencephalitic parkinsonism. Infectious agents in the environment were subsequently suspected to be the causal factors (514). This environmental hypothesis was further supported by the identification of *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the early 1980s, which causes selective degeneration of the nigrostriatal pathway by inhibiting mitochondrial complex I leading to a parkinsonian syndrome in rodents, primates, and humans (327, 579). Since then, a large number of environmental conditions and agents have been examined, including farming and rural life, industrial toxins, heavy metals, smoking, and drinking tea or coffee, although no conclusive links have been identified (122, 133).

Our ideas about the etiology of PD have changed considerably in the last decades. Although most patients (>85% of all cases) with idiopathic or late-onset PD do not appear to have inherited the disease, a positive family history is associated with a high risk of PD. Through the study of rare large families with clearly Mendelian inherited parkinsonism (<10%), several causative genes have been identified, showing that mitochondrial or lysosomal dysfunctions, protein aggregation, the ubiquitin-proteasome system, and kinase signaling pathways all play a major role in the pathogenesis of PD.

This review focuses on the genes and predisposing factors that have been conclusively associated with Mendelian or

multifactorial forms of the disease, as well as their contributions to our understanding of the underlying physiopathological mechanisms. Genes implicated in more atypical forms of parkinsonism are also reviewed.

## II. GENETIC BASES OF PARKINSON'S DISEASE

Our understanding of the mechanisms underlying the initiation and progression of PD began with the identification of mutations in the gene encoding  $\alpha$ -synuclein (SNCA) and the demonstration that  $\alpha$ -synuclein is the major component of filamentous Lewy bodies (512, 593). Since then, at least 16 loci (designated as PARK1 to PARK16) and 11 genes have been associated with inherited forms of parkinsonism (TABLE 1), including PARK1 and PARK4/SNCA, PARK2/*parkin*, PARK5/*ubiquitin COOH-terminal hydrolase L1 (UCHL1)*, PARK6/*PTEN-induced kinase 1 (PINK1)*, PARK7/*DJ-1*, PARK8/*Leucine-rich repeat kinase 2 (LRRK2)*, PARK9/*ATPase type 13A2 (ATP13A2)*, PARK11/*Grb10-interacting GYF protein 2 (GIGYF2)*, PARK13/*Omi/Htra2 (HTRA2)*, PARK14/*phospholipase A2 group VI (PLA2G6)*, and PARK15/*F-box protein 7 (FBXO7)*. The causal genes at four genetic loci have not yet been nominated (PARK3/chromosome 2p, PARK10/chromosome 1p, PARK12/chromosome Xq, and very recently PARK16/chromosome 1q). A recent genome-wide linkage screen of ~6,000 single nucleotide polymorphisms (SNP) in 278 families of European descent identified two novel loci on chromosomes 3 and 18 (172).

### A. The Genetic Contribution to PD Has Been Greatly Underestimated

Genetic research in the last decade, in particular the mapping and the subsequent cloning of genes that cause heritable forms of the disorder, has shown that PD is not a single clinical entity, but rather a heterogeneous group of diseases with different associated pathologies and a variable spectrum of clinical signs and symptoms. Thus some familial forms include atypical clinical features, such as young-onset, onset with dystonia, or the early occurrence of dementia or dysautonomia. However, despite excitement about these recent advances, only 5–10% of patients with a clinical picture of PD carry a mutation in one of the known genes that cause autosomal dominant or recessive forms of the disease. The lack of a clear family history in monogenic forms can result from recessive inheritance, a censored effect that may occur for multiple reasons, including death as the most common event prior to the observation of the disease or loss of follow-up, reduced penetrance, or a dominant de novo mutation. Alternatively, the disorder may result from a genetic predisposition to an environmental toxin, or to a combination of several genes that each increases the risk of the disease to only a modest extent.

**Table 1.** Summary of Parkinson's disease-associated loci and genes

PARK Loci	Gene	Map Position	Inheritance	Disease Onset	Mutations	Susceptibility Variants
<i>PD-associated loci and genes with conclusive evidence</i>						
PARK1/PARK4	<i>SNCA</i>	4q21	Dominant; rarely sporadic	Early onset	A30P, E46K, A53T genomic duplications/triplications	Promotor Rep1, 5' and 3' variants increase risk for PD
PARK8	<i>LRRK2</i>	12q12	Dominant; sporadic	Late onset	>80 Missense variants, >7 of them pathogenic, including the common G2019S	G2385R, R1628P increase risk for PD in Asian populations
PARK2	<i>parkin</i>	6q25-q27	Recessive; sporadic	Juvenile; early onset	Approximately 170 mutations (point mutations, exonic rearrangements)	Promoter polymorphisms increase risk for PD; heterozygous mutations may increase risk for late-onset PD
PARK6	<i>PINK1</i>	1p35-p36	Recessive	Early onset	Approximately 50 point mutations, rare large deletions	Heterozygous mutations may increase risk for late-onset PD
PARK7	<i>DJ-1</i>	1p36	Recessive	Early onset	Approximately 15 point mutations and large deletions	Heterozygous mutations may increase risk for late-onset PD
PARK9	<i>ATP13A2</i>	1p36	Recessive	Juvenile KRS, early-onset PD	>5 Point mutations	Heterozygous variants increase risk for PD
<i>PD-associated loci and genes with unknown relevance</i>						
PARK3	Unknown	2p13	Dominant	Late onset	Not identified	<i>SPR</i> variants may increase risk for PD
PARK5	<i>UCHL1</i>	4p14	Dominant	Late onset	One mutation in a single PD sibling pair	S18Y variant decreases risk for PD
PARK10	Unknown	1p32	Unclear	Late onset	Not identified	Unknown
PARK11	<i>GIGYF2</i>	2q36-q37	Dominant	Late onset	7 Missense variants	None
PARK12	Unknown	Xq21-q25	Unclear	Late onset	Not identified	Unknown
PARK13	<i>Omi/HTRA2</i>	2p13	Unclear	Late onset	2 Missense variants	Regulatory variants may contribute to risk for PD
PARK16	Unknown	1q32	Unclear	Unclear	Not identified	Polymorphic SNPs
<i>Loci and genes associated with atypical parkinsonism</i>						
PARK14	<i>PLA2G6</i>	22q12-q13	Recessive	Juvenile levodopa-responsive dystonia-parkinsonism	2 Missense mutations	Not investigated
PARK15	<i>FBXO7</i>	22q12-q13	Recessive	Early-onset parkinsonian-pyramidal syndrome	3 Point mutations	Not investigated
<i>PD-associated genes proposed by candidate gene approach</i>						
Not assigned	<i>SCA2</i>	12q24.1	Dominant for SCA2	Unclear	Low-range interrupted CAG expansions in <i>SCA2</i>	Not investigated
Not assigned	<i>GBA</i>	1q21	Recessive for GD	Unclear		Heterozygous GD-associated mutations increase risk for PD

PD, Parkinson's disease; GD, Gaucher's disease; SCA2, spinocerebellar ataxia type 2; KRS, Kufor Rakeb syndrome; SNCA,  $\alpha$ -synuclein; PINK1, PTEN-induced kinase 1; LRRK2, leucine-rich repeat kinase 2; SPR, sepiapterin reductase; UCHL1, ubiquitin COOH-terminal hydrolase 1; GIGYF2, GRB10-interacting GYF protein 2; PLA2G6, group VI phospholipase A<sub>2</sub>; GBA,  $\beta$ -glucocerebrosidase; SNP, single polymorphism nucleotide.

Although alterations in the genes identified so far account for only a small number of families, there is evidence that these same genes may also play a role in the much more common sporadic form of the disease. The possible role of variants in these PD-linked genes is intriguing. An illustration is offered by mutations in the *LRRK2* gene, which are found not only in familial forms of PD with late-onset autosomal dominant parkinsonism (477, 715), but also in a substantial number of idiopathic late-onset PD patients without a known family history of the disease (182, 346). These observations suggest that the contribution of genetics to PD may be greater than previously thought.

## B. Autosomal Dominant Forms of PD

Dominant genes are usually identified by positional cloning in large multigenerational kindreds. Causative mutations are mostly missense variations, the pathogenicity of which is difficult to prove, but can be supported by several lines of evidence: the mutation unequivocally segregates with the disease in family studies; the mutation is not found in a large group of healthy controls; the mutation is located in an important domain of the encoded protein; the mutation is highly conserved across different species; and there is in vitro and in vivo proof that the mutation dysregulates cel-

lular functions or increases cell death. However, the pathogenicity of missense variants in an isolated sporadic patient or in families that are too small to be informative in segregation analyses, is often uncertain, even if they are not found in a large number of controls (227). In addition, these dominant mutations may be found in clinically unaffected individuals, a phenomenon referred to as reduced penetrance. Dominant mutations often act through a gain-of-function mechanism. It has been speculated that they may also cause haploinsufficiency, as suggested for A53T and A30P *SNCA* mutations, for which mRNA abundance was found to be significantly lower than for the normal allele in blood cells or transformed lymphoblastoid lines (316); in this study, the ratio of the wild-type to mutant allele expression correlated with the severity of the clinical phenotype. However, the relevance of these observations is questionable, since the number of normal *SNCA* alleles also correlates with disease severity in PD (cf. sect. II B1). To date, at least two genes, *SNCA* and *LRRK2*, have been clearly shown to cause autosomal dominant PD, with an overall mutation frequency of ~5%. The pathogenic role of other dominant genes in PD, *UCHL1*, *GIGYF2*, *HTRA2*, is still controversial, because they have not been found in other patients (*UCHL1*, *GIGYF2*) or appear to act as genetic risk factors (*HTRA2*).

### 1. *α-Synuclein (SNCA)*, a direct link between genetic and sporadic PD

*SNCA* was the first PD gene to be mapped. It was identified in the Contursi kindred, a large family of Italian descent with dominantly inherited PD and Lewy body pathology (511). Since then, two categories of disease-causing mutations have been identified in the *SNCA* gene, which comprises six exons and spans 117 kb: point mutations leading to missense variations in the protein and whole-locus multiplications [originally designated PARK4 (580)], including duplications and triplications, leading to pathogenic overexpression of the wild-type protein. Point mutations are extremely rare: A53T, the most common, has been found in at least 15 Greek/Italian families that probably have a common ancestor (192, 491, 512, 594) and, more recently, in two PD families of Korean and Swedish origin, but on different haplotype backgrounds (297, 519). The A53T mutation has also been reported in an apparently sporadic Polish case with late-onset of PD (74 years), possibly due to reduced penetrance (427). Even in a large-scale screening of *SNCA* (27), only two additional point mutations, A30P and E46K, have been identified, each in a single family of German and Spanish origin, respectively (323, 705).

Clinically, patients with the *SNCA* A53T mutation have a broadly varying phenotype, ranging from typical late-onset PD to atypical PD with more severe features, including an earlier age at onset, more rapid progression, and a high prevalence of dementia, psychiatric problems, and autonomic dysfunction (192, 297, 399, 427, 492, 519). This

broad phenotypic spectrum and the clinical and neuropathological variability that has been observed within a given family suggest the existence of genetic and/or nongenetic modifiers of penetrance and expression (398). The clinical symptoms of patients with the *SNCA* A30P mutation closely resemble those with idiopathic PD, with a late age at onset and a mild phenotype (322). Carriers of E46K, however, have severe parkinsonism, with an early age at onset and diffuse Lewy body dementia (705).

Multiplications of *SNCA* appear to be more common than missense mutations in the gene, since 15 families, worldwide, have duplications and/or triplications of the *SNCA* locus; this represents ~2% of all familial forms of parkinsonism (7, 63, 143, 156, 253, 255, 258, 293, 463, 527, 580, 581). Genomic *SNCA* duplications are rarely identified in Asian and European sporadic PD patients (<1%), suggesting that such mutations may occur de novo or have reduced penetrance (7, 47, 566, 631).

The size of the genomic rearrangements varies among families and includes one to more than 20 adjacent genes, complicating genotype-phenotype comparisons for carriers of *SNCA* multiplications. However, the severity of the phenotype appears mainly to depend on dosage of the *SNCA* gene (255, 258, 527). The correlation between *SNCA* copy number and the phenotypic expression of PD is remarkably illustrated by an extensive Swedish/American family, the "Lister family complex," originally documented by Henry Mj6nes in 1949, in which one branch (branch J) had an *SNCA* duplication and a typical late-onset PD phenotype, whereas the other branch (branch I) had a triplication of the same genomic region and early-onset PD with dementia (156). It has been proposed that PD, parkinsonism with dementia, and dementia with Lewy bodies are causally related; they have been grouped under the term *synucleinopathy* disorders (633).

Consistent with the finding that overexpression of wild-type *SNCA* is sufficient to cause these disparate phenotypes, several groups, including a collaborative analysis of data from ~2,500 cases and matched controls, reported an association between the risk of PD and the longer allele of a complex dinucleotide repeat polymorphism in the promoter region of *SNCA* (NACP-Rep1), which increases expression of *SNCA* in vitro (218, 288, 392, 447, 486, 495, 607). In addition to the most studied Rep1 allele, more complete analyses of the *SNCA* gene have shown an association between specific haplotypes and sporadic PD, in particular in the 3'UTR (144, 198, 431, 442, 484, 486, 528, 674).

Human  $\alpha$ -synuclein was first identified as the precursor protein for the non-amyloid beta-component (NAC) of Alzheimer disease amyloid plaques (635).  $\alpha$ -Synuclein belongs to a family of 15- to 25-kDa proteins (282), three of which are

known:  $\alpha$ -synuclein,  $\beta$ -synuclein, and  $\kappa$ -synuclein (81), which are expressed in the brains of humans and rodents (354). Although the members of the synuclein family share considerable sequence homology,  $\alpha$ -synuclein is unique in that it contains a highly amyloidogenic domain in its midregion (NAC domain) that, by itself, has a high propensity to aggregate and initially to form an intermediate annular oligomeric structure or protofibrils, and ultimately insoluble polymers of fibrils (181). Structurally, this small 140-amino acid protein is also characterized by seven imperfect repeats (KTKEGV) in the NH<sub>2</sub> terminus, which forms an amphipathic  $\alpha$ -helical domain when the protein specifically associates with lipid-containing membrane microdomains known as lipid rafts (153), and an acidic COOH-terminal region (134) (FIG. 1). The protein is predominantly localized in presynaptic nerve terminals (85).

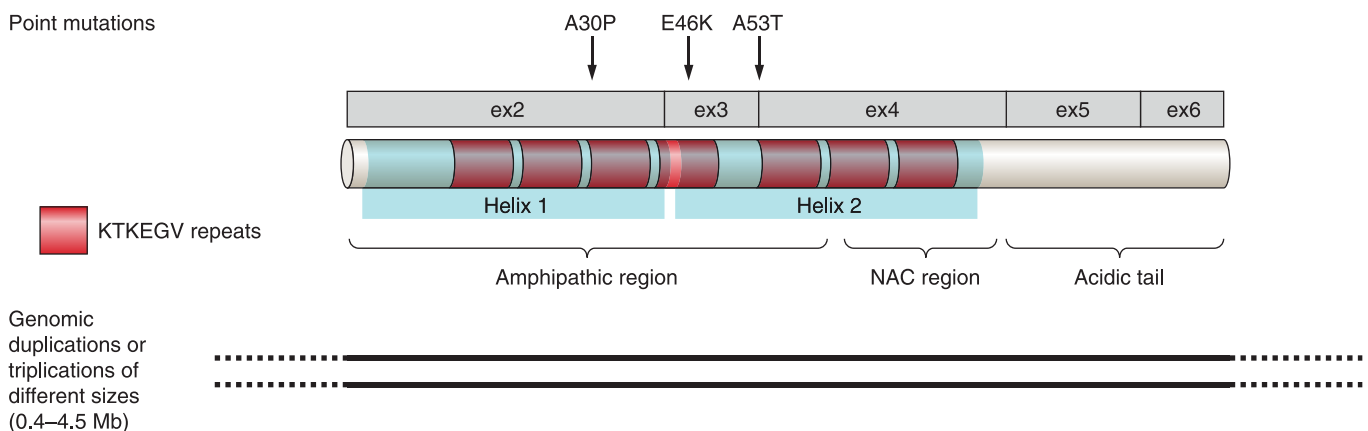
Although point mutations and genomic multiplications in *SNCA* are very rare, their identification led to the important discovery that the encoded protein is the major fibrillar component of the Lewy bodies, the pathological hallmark of PD in both familial and sporadic cases (592, 593). *SNCA* mutations might reduce the affinity of the protein for lipids, as demonstrated for the A30P variant (49), thus increasing the intracellular pool of proteins that, along with duplication and triplication of the gene, accentuates the tendency of the protein to form oligomers and later fibrillar aggregates. However, the precise relationship between protein aggregation, cellular dysfunction, and the cell death underlying PD is still unknown.

In addition, little is known of the biological function of  $\alpha$ -synuclein and of the potential contribution of its potential loss, due to sequestration of the proteins in LBs, to PD pathogenesis. Its localization at axon terminals strongly

suggests a role in synaptic transmission (270, 402), which has been corroborated by its involvement in the synaptic plasticity associated with song learning during juvenile development in male zebra finches (177). Consistent with this possibility, in mouse models lacking  $\alpha$ -synuclein, modest, although not always consistent effects on neurotransmitter release have been reported and correlated with changes in synaptic vesicle recycling and mobilization (3, 50, 691). In transgenic mice with a two- to threefold increase in  $\alpha$ -synuclein abundance, a deficit in neurotransmitter release due to alterations in synaptic vesicle pools and the failure of recycling vesicles to cluster in proximity of synaptic release sites was observed (454).  $\alpha$ -Synuclein is also suspected to have specific effects in dopaminergic neurons, where it may negatively regulate the activity of tyrosine hydroxylase, the rate-limiting enzyme in dopamine biosynthesis, as well as that of the dopamine transporter, responsible for the reuptake of the neurotransmitter from the synaptic cleft (571).

## 2. *Leucine-rich repeat kinase 2 (LRRK2)*, a common form in several populations

*LRRK2*, recently added to the list of PD causing genes, is the most important in terms of prevalence. The *PARK8* locus was originally mapped in a large Japanese family, the Sagami-hara kindred, with autosomal dominant asymmetrical, levodopa-responsive, late-onset PD (158), and confirmed in several European families (716). Several missense mutations were identified by positional cloning, by two independent groups, in a large gene, *Leucine-rich repeat kinase 2 (LRRK2)* (477, 715). This discovery was probably the most important step forward in our understanding of the pathogenesis of PD since the discovery of *SNCA*, as *LRRK2* mutations are frequent and are found in patients



**FIGURE 1.** Schematic representation of the  $\alpha$ -synuclein protein with the three pathogenic missense mutations above the protein organization and duplications or triplications of different genomic sizes below the protein (red lines).  $\alpha$ -Synuclein is a 140-amino acid protein with seven imperfect repeats (KTKEGV) in the NH<sub>2</sub> terminus, a central hydrophobic NAC (nonamyloid component) region, and an acidic COOH-terminal region. Numbers under the protein line indicate the boundaries of each domain. *SNCA* mutations might reduce the affinity of the protein for lipids, thus increasing the intracellular pool of proteins that, along with duplication and triplication of the gene, accentuates the tendency of the protein to form oligomers and later fibrillar aggregates.

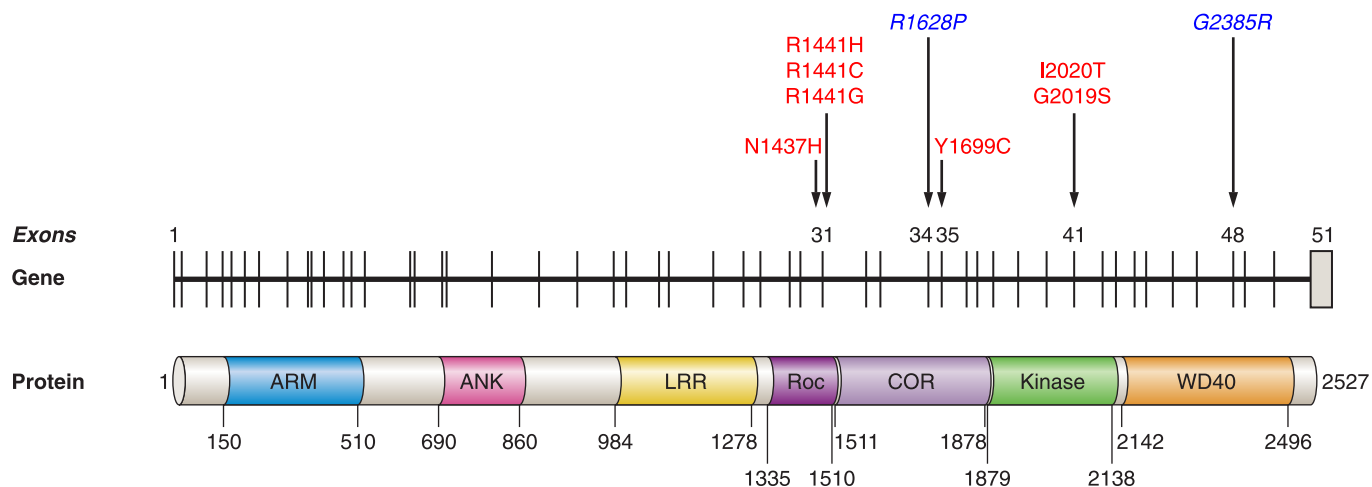
with typical, late-onset familial and sporadic PD. Since the first mutation in *LRRK2* was discovered in a Basque family with tremor as the presenting and initially predominant symptom, the encoded protein was named “Dardarin” from the Basque word “dardara” for “tremor” (477).

The *LRRK2* gene spans a genomic region of 144 kb, with 51 exons, encoding a large 2,527 amino-acid multi-domain protein. Sequence analysis indicates that the *LRRK2* protein comprises several independent domains (FIG. 2), including a ~900 residue NH<sub>2</sub> terminal predicted to adopt armadillo repeat folds, and ankyrin repeats, a leucine-rich repeat (LRR) domain, a Ras of complex protein (Roc) GTPase domain followed by its associated COOH terminal of Roc (COR) domain, a kinase domain of the tyrosine kinase-like (TKL) subfamily, homologous to other mitogen-activated protein kinase kinase kinase (MAPKKK), and a COOH-terminal WD40 domain (412). This combination of motifs is highly conserved in vertebrates and shares homology with the ROCO protein family (40). However, *LRRK2*, like the related *LRRK1*, is unusual in that it encodes two distinct enzymes, kinase and GTPase in the same molecule. Initial biochemical studies suggested that *LRRK2* is capable of undergoing both autophosphorylation and phosphorylation of a generic substrates such as moesin, 4E-BP, and myelin basic protein (MBP) (205, 259, 271, 667), and that the kinase activity is modestly regulated by the GTPase domain (211, 269, 367, 584). The presence of multiple protein interaction domains (armadillo, ankyrin, LRR, and WD40) suggests that *LRRK2*, in addition to its predicted protein kinase and GTPase activities, might serve as a scaffold for the assembly of a multiprotein signaling complex.

Given the large size of the gene, only a few systematic mutation screens of the entire gene have been performed in different populations. They show, however, that *LRRK2*

mutations are found in ~10% of patients with autosomal dominant familial PD (28, 120, 277, 294, 342, 409, 457, 500, 682), 3.6% of patients with sporadic PD, and 1.8% of healthy controls (479). It is, therefore, the most common genetic cause of the disease known so far. About 80 different probably pathogenic *LRRK2* variants have been identified (466) (FIG. 2). Except for rare splice site and nonsense variants (39, 277, 582, 715), all of them are missense variants, which, along with dominant inheritance, is consistent with a gain-of-function pathogenic mechanism. Because of reduced penetrance, the existence of phenocopies and, in most cases, late disease onset, parental genotypes are unknown and segregation analyses have not been performed; the pathogenicity of individual nonsynonymous, rare variants remains therefore uncertain (480).

So far, seven mutations (N1437H, R1441G/C/H, Y1699C, G2019S, and I2020T) in *LRRK2* are considered as “pathogenic” (FIG. 2) (2, 236). They appeared to be clustered in functionally important regions, which are highly conserved through species. The identification of a common c.6055 G>A base pair substitution resulting in the *LRRK2* G2019S mutation in the kinase domain of the protein, in both familial (4% worldwide) and apparently sporadic (1% worldwide) PD cases, and its very low frequency in healthy populations (<0.1% worldwide) (119, 182, 236, 459), have implications for genetic testing. Ethnicity greatly influences the prevalence of this mutation. Very rare in Asia (66, 162, 378, 518, 610, 702), South Africa (469), and Northern Europe (32, 433, 465, 500, 552), this mutation is frequent in PD patients from Italy, Spain, and Portugal (44, 73, 119, 120, 149, 166, 194, 196, 263, 401). Strikingly, it accounts for PD in ~30–40% of both familial and sporadic Arab patients from North Africa and 10–30% of Ashkenazi Jews (230, 250, 340, 344, 472, 475). Interestingly, a recent clinicogenetic study of this muta-



**FIGURE 2.** Schematic representation of the *LRRK2* gene and protein with the seven proven pathogenic mutations (in red) and the two Asian-specific risk factors (in blue) above the protein organization. *LRRK2* has 2,527 amino acids and contains several conserved domains: ARM (Armadillo), ANK (ankyrin repeat), LRR (leucine-rich repeat), Roc (Ras of complex proteins: GTPase), COR (COOH terminal of Roc), kinase domain, and WD40. Numbers under the protein line indicate the boundaries of each domain.

tion in a series of 63 PD patients of Yemenite Jewish origin detected no mutation carriers, suggesting a specific ancestral pattern of inheritance in Ashkenazi Jews (124).

At least three distinct haplotypes flanking the G2019S mutation have been reported (18, 194, 280, 347, 350, 626, 659, 699, 700): a common founder haplotype that is shared by most G2019S carriers in Europe, North Africa, and the Middle East, and a second very rare haplotype in five European-American families, suggesting that the G2019S mutation arose twice in these populations. The first haplotype was reported to derive from a common ancestor estimated to date back 1,525–2,600 years, using a maximum-likelihood method and a 25-year intergeneration interval (18, 659, 699), but was recently proven in a multiethnic study to have arisen at least 4,000 years ago (350). The second appeared more recently (699). The third, which seemed specific to the Japanese population (626, 700), has also been found in a Turkish family (508).

The high frequency of the *LRRK2* G2019S mutation in sporadic cases and in some familial forms of PD with unclear patterns of inheritance (346), but also in rare controls including subjects over 80 years of age (289), suggests an incomplete age-dependant penetrance, which must be taken into account for genetic counselling. The numerous estimates of the penetrance of this mutation range widely (~25–100% by age 80), possibly due to differences in study design (case-control or family-based methods) and recruitment, selection bias, inclusion of probands in the analyses, and methods of estimating penetrance (80, 195, 236, 250, 280, 330, 345, 475). The wide range of the estimates in these studies may be explained, however, by an ascertainment bias, since over-representation of families with multiple affected individuals can lead to an overestimation of penetrance (330). A recent study in an unselected series of patients from North Africa suggests that penetrance could be as low as 14% at the age of 80 (632). It will be of particular interest to identify the genetic or environmental factors that modulate penetrance in these families.

The clinical features of patients with the G2019S mutation are surprisingly uniform and resemble those of patients with other *LRRK2* mutations or with idiopathic PD. The mean age at onset is close to 60 years, with unilateral tremor as the initial sign of disease, a good response to treatment and slow progression (236).

It is interesting that, unlike the *SNCA* multiplications, no gene dosage effect has been observed for *LRRK2*; the ~30 homozygous mutation carriers that have been identified, mostly among North African Arabs, are clinically similar to those with heterozygous mutations (266, 340, 344). In addition, patients with *LRRK2* mutations and pathogenic variants in other PD-associated genes [*parkin*,  *$\beta$ -glucocerebrosidase* (*GBA*), *SCA2*] could not be distinguished from

patients with heterozygous *LRRK2* mutations in terms of an earlier age at onset or faster disease progression (62, 96, 168, 344). The identification of a healthy control (age 41 years) and three unaffected relatives (age 42, 45, and 70 yr) with homozygous G2019S mutations, and even a 52-yr-old unaffected carrier of heterozygous mutations in *parkin*, *LRRK2*, and *GBA*, confirms the reduced penetrance of *LRRK2* (266, 340, 478).

Three of the seven probable pathogenic variants in *LRRK2* affect the same residue, R1441, in the Roc GTPase domain (R1441C/G/H), which appears to be the second most common *LRRK2* mutation after G2019S. In addition to the R1441C (c.4321 C>T) and R1441G (c.4321 C>G) mutations first described (477, 715), an R1441H (c.4322 G>A) mutation has also been identified (149, 342, 409, 589, 701). The R1441G substitution appears to be geographically restricted to Northern Spain, particularly in the Basque population, where it represents ~20% of familial PD and results from a common founder dating back to the seventh century (196, 199, 408, 409, 477, 576). In contrast, R1441C and the less common R1441H variant appear to derive from multiple independent mutational events that occurred throughout the world (120, 465, 530, 570). The Y1699C (c.5096 A>G) and I2020T (c.6059 T>C) mutations have so far been found less frequently (28, 159, 294, 467, 477, 715), the latter in the original Japanese Sagami-hara family (159). The recently identified mutation N1437H (c.4309 A>C) in the Roc domain was identified in a large Norwegian four-generation family and an additional family from the same population, sharing the same haplotype (2).

In addition to these mutations that alone suffice to cause disease, two common nonsynonymous SNPs in *LRRK2* (G2385R and R1628P) (FIG. 2) appear to be true risk variants for PD in the Asian population. Assessment of the G2385R variant in large Asian populations showed associations with an overall disease risk of 2.55 (95% CI 2.10–3.10) in Chinese, Taiwanese, and Japanese populations (10, 60, 67, 121, 145, 160, 163, 353, 615, 702). G2385R is in the WD40 domain of the *LRRK2* protein thought to mediate protein-protein interactions.

The R1628P variant, located in the COR domain of the *LRRK2* protein, is the second major risk factor identified. It increases the risk of PD two- to threefold, but seems to be restricted to the Han Chinese population (379, 532, 612, 696, 711) and was not detected in any of the European, Japanese, Indian, and Malay individuals examined to date (532, 613, 702). Carriers of both G2385R and R1628P resemble patients with idiopathic PD (10, 60, 379).

Since accumulation of abnormal phosphorylated proteins is a common feature of many neurodegenerative diseases including PD, *LRRK2* might play a direct role in their patho-

genesis. Modulation of its kinase activities might therefore be an attractive therapeutic strategy. Although the function of the LRRK2 protein remains unclear, initial in vitro studies suggested that its kinase activities are increased by the PD-associated mutations, suggesting a gain of function (380). However, the conflicting results of the numerous studies on LRRK2 activity are more likely due to differences in experimental conditions than to the mutations (112, 188, 204, 211, 269, 271, 352, 356, 385, 388, 584, 667, 668). Only LRRK2 G2019S has consistently been shown to increase kinase activity; other mutations have only modest effects (203). There is generally good agreement that LRRK2 Roc domain mutations do not increase GTP binding but lower GTPase activity (211, 352, 356), suggesting that these mutations prolong the active GTP-bound state of the protein. In addition, it has been shown that several LRRK2 mutants are toxic to neurons, and that the kinase activity of the protein is required for cellular toxicity and neuronal death (204, 584).

### 3. Other forms of PD for which genetic validation is needed

The pathogenicity of several loci and genes originally associated with PD in genome-wide scans or candidate gene analyses has not been confirmed. *UCHL1* at the PARK5 locus appeared to be a good PD candidate gene, since it encodes a neuron-specific member of a family of deubiquitinating enzymes that cleave polymeric ubiquitin chains into monomers, and is also found in Lewy bodies. A heterozygous I93M missense mutation in the coding sequence of the gene was found in an affected sib pair (338). The mutations cause an ~50% decrease in the hydrolytic activity of the enzyme in vitro (338, 462). Neither I93M nor any other pathogenic mutations in *UCHL1* has been reported in other PD families. However, a common polymorphism in the *UCHL1* gene, the S18Y variant, has been controversially associated with a decreased risk of idiopathic PD in several studies, including a large meta-analysis (54, 132, 140, 394, 395, 609, 655, 676).

The mitochondrial serine protease *HTRA2*, at PARK13, is another good candidate gene for PD, the pathogenesis of which has been supported by in vitro and in vivo evidence (278, 287, 406). A heterozygous G399S mutation was identified in four German sporadic PD patients, but was found at the same frequency in patients and controls in other studies, suggesting that it may just be a rare variant in the German population (529, 578). Similarly, the A141S substitution in *HTRA2* was significantly over-represented in the group of PD patients in one study (600), but not in others (529, 578). Evidence for a causative role of *HTRA2* in PD is still lacking.

The PARK11 locus on chromosome 2q was identified in a mixed Caucasian population from the United States (487), but was not confirmed in a cohort of European families

(516). *GIGYF2* was proposed to be the causative gene at PARK11 (331). Recently, Giovannone et al. (185) found that the *GIGYF2*<sup>+/-</sup> mice began to exhibit motor dysfunction starting at 12–15 mo (185). *GIGYF2* encodes a 2,499-amino acid protein with a GYF motif that has been shown to interact with grb10 and consequently might regulate cellular response to insulin and insulin-like growth factor (184). We found seven sequence changes in this gene, four of which were evolutionary conserved, in two independent French and Italian PD groups but not in geographically matched controls. However, no mutations in the gene or associations with PD were found in subsequent analyses of the whole gene or tagging *GIGYF2* variants, in large series of both sporadic and familial PD cases of diverse origin and ethnically matched controls (37, 43, 52, 118, 210, 212, 343, 423, 458, 538, 608, 645, 710, 717), although one recent study identified nine novel variants in *GIGYF2* gene which might be associated with sporadic PD in the Chinese population (657). Collectively, these studies suggest that *GIGYF2* variations do not contribute significantly to sporadic or familial PD, at least in the populations examined. They also illustrate the difficulty of interpreting rare missense variations that are not found in the initial control group but are later found in larger independent series of controls.

Another dominant locus, PARK3, has been mapped to chromosome 2p13 in several large families, but the causative gene has not yet been identified. Interestingly, two independent studies suggest that PARK3 might be a modifying locus that influences age at onset (114, 489). Fine-mapping and investigation of candidate genes in the PARK3 locus identified the *sepiapterin reductase* (*SPR*) gene, the product of which is involved in dopamine synthesis (285, 560). This region might, however, harbor susceptibility genes for late-onset PD.

## C. Autosomal Recessive Forms of PD

Recessive loci can be identified by linkage mapping in nuclear families or, more easily, using autozygosity mapping in consanguineous families, in which the same chromosomal segments inherited from a common ancestor are transmitted through both the maternal and paternal lineages (658). Most recessive alleles result in the absence of the encoded protein or an inactive protein, and thus to a loss of function.

Homozygous or compound heterozygous mutations in the recessive genes *parkin* (PARK2), *PINK1* (PARK6), and *DJ-1* (PARK7) are unequivocally associated with heritable, levodopa-responsive parkinsonism with early age at onset and, generally, no atypical signs. A fourth gene, *ATP13A2* (PARK9), initially associated with an atypical multisystemic phenotype, might also play a role in rare cases with early-onset PD. So far, *parkin* and *PINK1* are the genes most frequently associated with autosomal recessive early-onset parkinsonism. However, penetrance might be re-



duced in rare cases, as suggested by the observation of a 56-year-old unaffected carrier with compound heterozygous mutations in the *parkin* gene (111). The penetrance of recessive genes is also age-dependent, however, and expression of the phenotype might simply be delayed. Apparently dominant, also termed “pseudo-dominant,” inheritance of a recessive disease-related gene has also been observed, particularly in consanguineous families (91, 381, 407).

### 1. *Parkin* is the prototype of early-onset PD

Mutations in the *parkin* gene at PARK2 are the most frequent known cause of early-onset (<40–50 yr) PD (10–20% worldwide; ~50% of recessive familial forms, ~15% of isolated cases in European populations) (383, 503) and have been found in numerous families with different ethnic backgrounds (238). However, the frequency of *parkin* mutations decreases significantly with increasing age at disease onset; ~80% in those with onset before age 20. It is very rare in those with onset after 50 years of age (309, 383, 410, 503). Exonic deletions in the *parkin* gene were first reported in Japanese families with autosomal recessive juvenile-onset parkinsonism (ARJP) (305); onset frequently occurred before the age of 20. The patients had a good response to levodopa, but developed levodopa-induced dyskinesias. More than 170 different mutations have since been identified throughout the sequence of this particularly large gene (1.35 Mb) including large deletions or multiplications, small deletions/insertions as well as missense mutations (466) (FIG. 3, A and B). Importantly, ~50% of *parkin* mutation carriers have exon rearrangements that, in the heterozygous state, are not detectable by sequencing alone (239). Rare deletions extending in the neighboring *parkin* coregulated gene (*PACRG*) result in the same phenotype (349).

*Parkin* mutation carriers have a clinical phenotype similar to that of sporadic patients, but also a number of specific clinical features. In addition to an earlier age at onset, they have more symmetrical onset, more frequently dystonias as the initial sign in addition to hyperreflexia, a relatively benign disease course with slower disease progression, sleep benefit, a better response to low doses of levodopa, but complicated signs with early motor fluctuations and the development of dyskinesias (267, 375, 376). Pyramidal signs, cerebellar features, and psychiatric disease have been reported, but dementia or dysautonomia seems to be rare (267, 376).

Pathologically, *parkin* mutations are associated with significant loss of dopaminergic neurons in the substantia nigra and moderate decrease of neurons in the locus coeruleus (438). Cell loss in the substantia nigra of patients with *parkin*-associated PD appeared to be caused by a loss of function of the protein. The Parkin protein contains an NH<sub>2</sub>-terminal domain homologous to ubiquitin (UBL) followed by three RING (really interesting new gene) finger domains (RING 0–2) separated by a 51-residue IBR (In-Between-Ring) domain in the COOH-terminal part, each of which

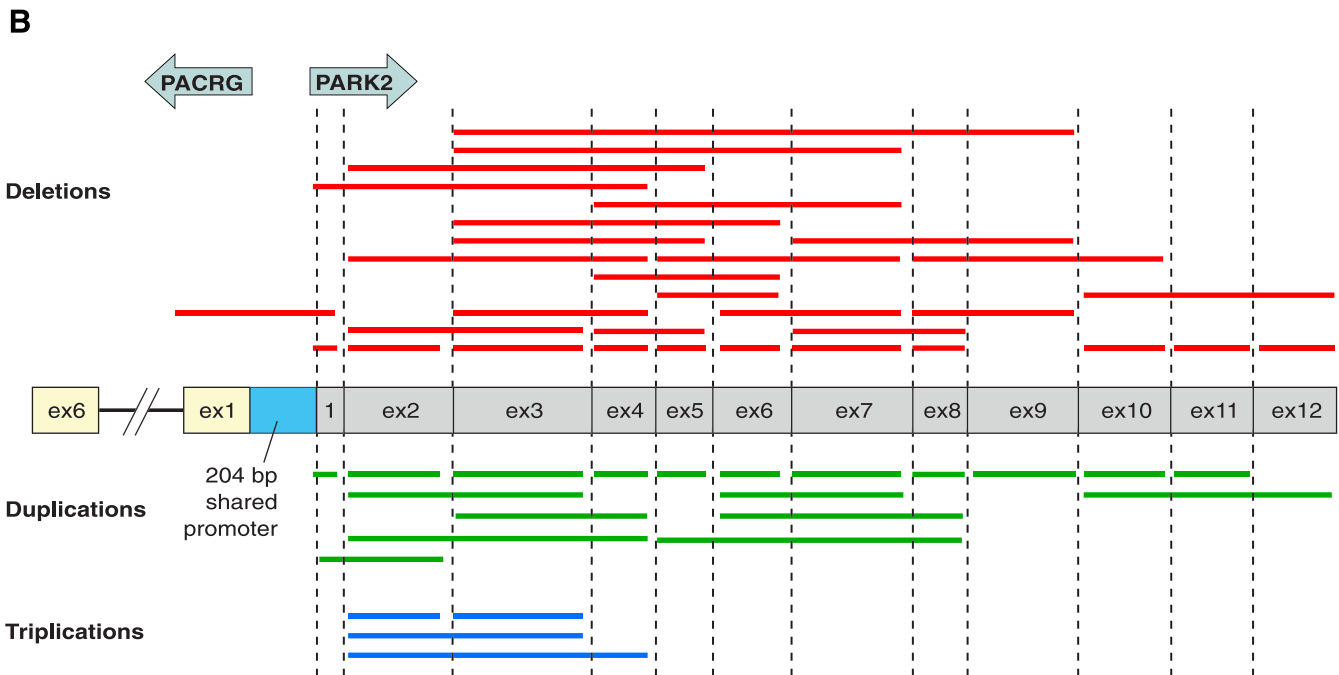
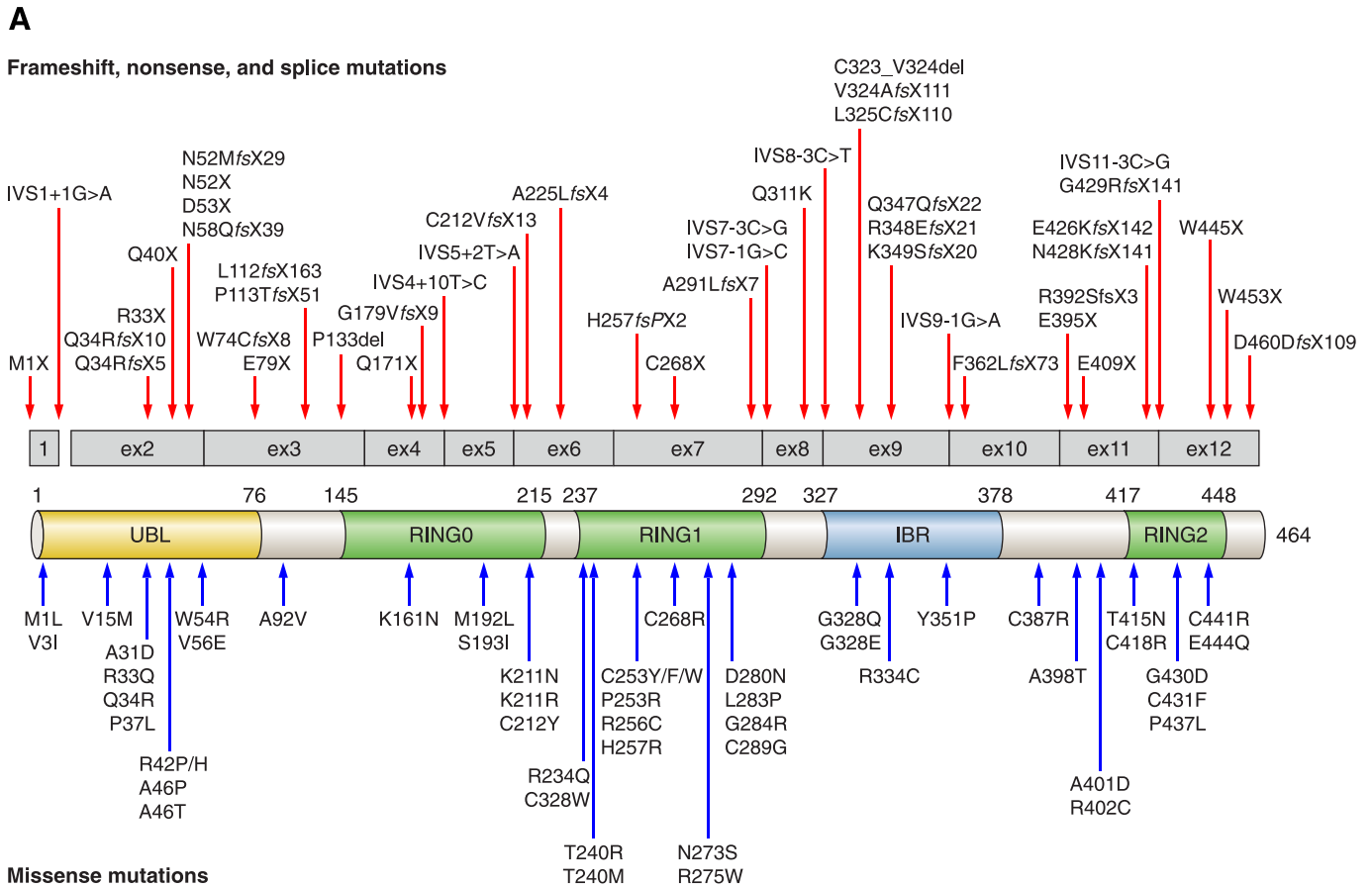
bind two Zn<sup>2+</sup> (FIG. 3) (247). Functionally, the Parkin protein is a member of a family of E3 ubiquitin ligases responsible for the transfer of activated ubiquitin molecules to a protein substrate (563). This process, termed ubiquitylation, may have various functional consequences, including proteasomal degradation of the modified protein (cf. sect. III B1). Mutations in *parkin* were hypothesized to impair the E3 ubiquitin ligase activity of Parkin, resulting in insufficient substrate clearance and subsequent aggregation (563). However, in vitro ubiquitylation assays showed that single amino acid substitutions only rarely affect the enzymatic activity of Parkin (223, 414), whereas they more often decrease its solubility, leading to formation of visible aggregates (reviewed in Ref. 89).

### 2. Other less common recessive genes: *PINK1*, *DJ-1*, and *ATP13A2*

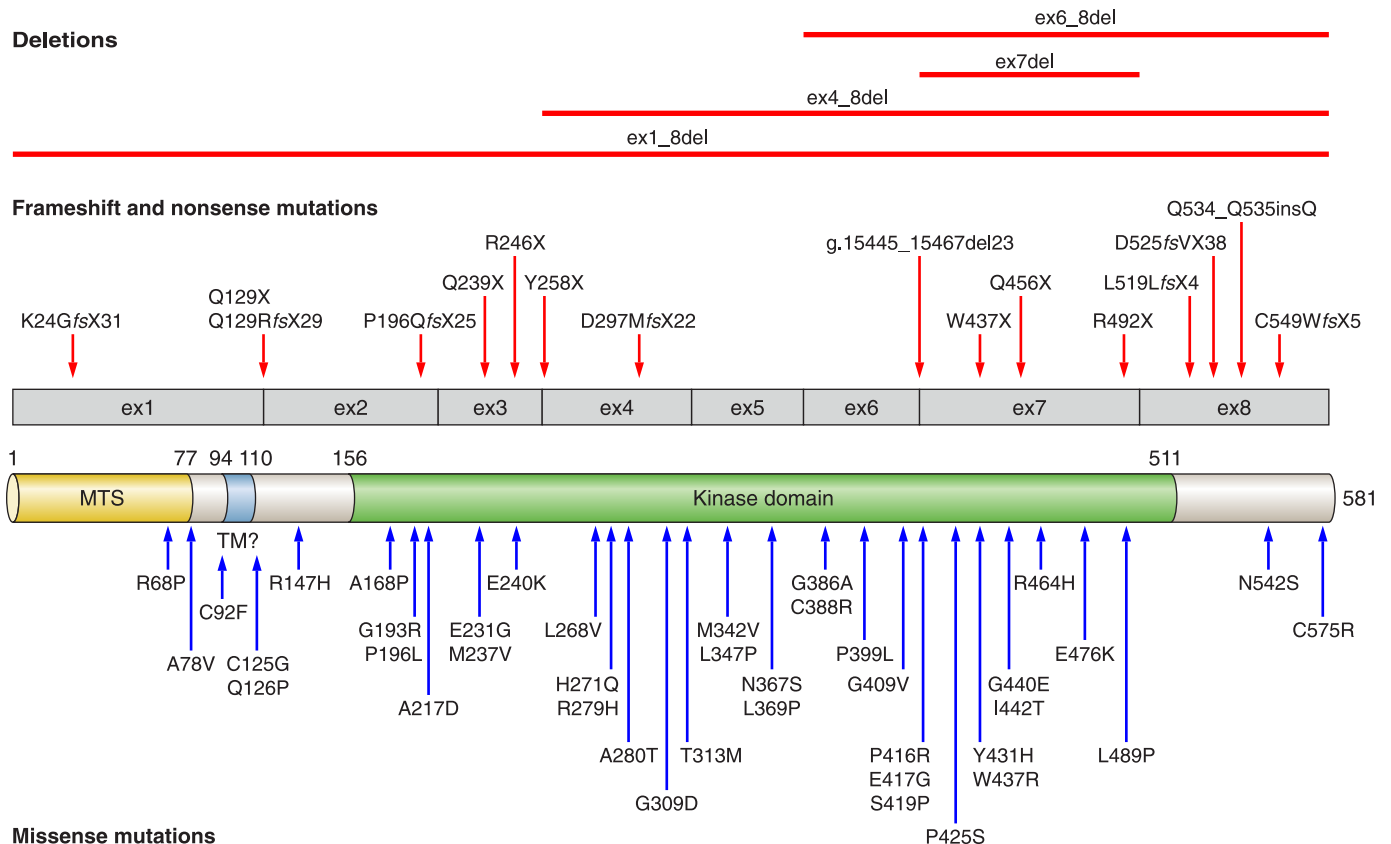
A homozygous G309D missense and a W437X nonsense mutation in the *PINK1* gene were initially detected in three consanguineous families with autosomal recessive early-onset PD previously linked to PARK6 on chromosome 1p35–36 (637, 638). Homozygous and compound heterozygous loss-of-function mutations in *PINK1* are the second most frequent cause of autosomal recessive early-onset parkinsonism; the mutation frequency varies geographically from 0 to 15% worldwide (108, 466). Most mutations in *PINK1* are point mutations or small insertions, or deletions detectable by sequencing, but genomic deletions, including a large deletion of the whole gene and a complex large rearrangement, have also been reported (57, 400), demonstrating the need to perform gene dosage analyses together with sequencing for sensitive mutation screening (FIG. 4). *PINK1* mutations are also a rare cause of sporadic early-onset PD (614, 639). No associations between sporadic PD and SNPs distributed throughout *PINK1* have been detected, however (74, 190, 207, 235).

The clinical phenotype of *PINK1*-related PD appears to be broadly similar to that of *parkin*- or *DJ-1*-related disease, although patients with *PINK1* mutations tend to have a better response to levodopa, a less severe disease, and longer mean disease durations (256). Interestingly, the presence of dystonia at onset and brisk reflexes, which were initially considered to be typical of *parkin* carriers, appear to be as frequent in patients with *PINK1* mutations. In addition, there are some indications that patients with *PINK1* mutations have an earlier disease onset and more frequent atypical symptoms, such as dystonia at onset, hyperreflexia, dyskinesias, and a higher prevalence of psychiatric disturbances (136, 357, 545, 596).

Digenic inheritance of *parkin* and *PINK1* has also been described in Asian populations and might be associated with psychiatric disorders (161).



**FIGURE 3.** Schematic representation of *parkin* on transcript level and the functional domains of the parkin protein with *A*) pathogenic frameshift mutations above the transcript and protein organizations and missense mutations below; *B*) exonic deletions above the transcript (red lines) and exonic duplications (green lines) or triplications (blue lines) below the transcript; a deletion of exons 1 of both *parkin* and the neighboring *parkin* coregulated gene (*PACRG*) is also shown. Only homozygous or compound heterozygous mutations are listed. Parkin is a 465-amino acid protein that contains an NH<sub>2</sub>-terminal ubiquitin-like (UBL) domain followed by three RING (really interesting new gene) finger domains (RING 0–2) separated by a 51-residue IBR (in-between-ring) domain in the COOH-terminal part. Numbers under the protein line indicate the boundaries of each domain.



**FIGURE 4.** Schematic representation of *PINK1* on transcript level and the functional organizations and missense mutations below the protein; rare deletions (above, red lines) including a deletion of the whole gene are also represented. Only homozygous or compound heterozygous mutations are listed. *PINK1* is a 581-amino acid protein with an NH<sub>2</sub>-terminal mitochondrial targeting signal (MTS) motif, a putative transmembrane (TM) region, and a serine-threonine kinase. Numbers under the protein line indicate the boundaries of each domain.

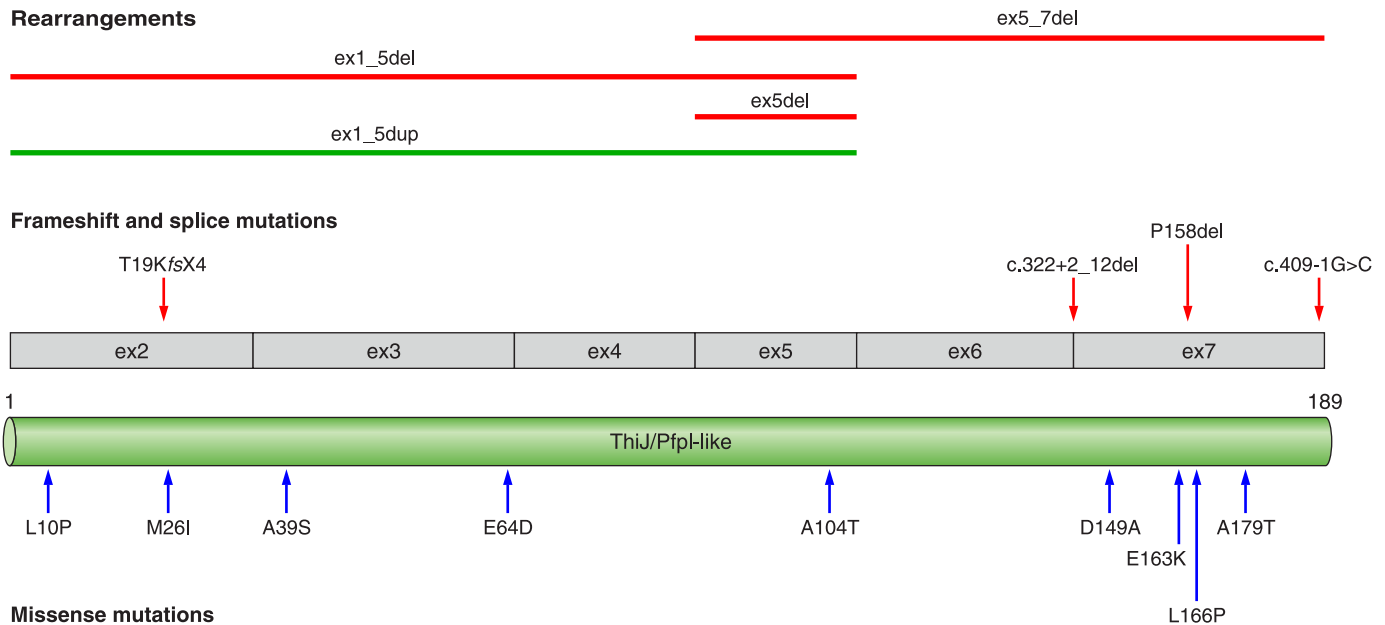
*PINK1* is a tumor suppressor with an NH<sub>2</sub>-terminal mitochondrial targeting signal (MTS) motif, a putative transmembrane (TM) region, and a serine-threonine kinase domain (FIG. 4), supporting the hypothesis that mitochondrial dysfunction and oxidative stress may play a role in the pathogenesis of PD. Some mutations destabilize the protein, whereas others may decrease kinase activity (23).

Mutations in the *DJ-1* gene are the least common of the known causes of autosomal recessive parkinsonism (~1% of early-onset PD). A large homozygous deletion and a homozygous missense mutation, L166P, were first identified in *DJ-1* at PARK7 in two consanguineous families from the Netherlands and Italy (38). Missense mutations in coding and promoter regions, frame-shift and splice site mutations, and exonic deletions have also been found in some (FIG. 5) (4, 126, 221, 242, 387, 619), but not in all studies in different populations (77, 237, 254, 373, 425, 488, 611, 627).

The *DJ-1*-related phenotype, with early-onset and slow disease progression, closely resembles that of patients with *parkin* or *PINK1* mutations, but genotype/phenotype cor-

relations could not be meaningfully performed, however, due to the small number of *DJ-1* patients. The presence of heterozygous mutations in the *DJ-1* and *PINK1* genes in two members of a Chinese family who developed PD in their 30s is suggestive of digenic inheritance; it was not fully penetrant, however, since a 42-year-old sibling with the same genotype was unaffected (618).

*DJ-1* was initially described in association with oncogenesis and male infertility in rats. It is a member of the ThiJ/Pfp1 family of molecular chaperones, which are induced during oxidative stress. Like the GAT superfamily members, human *DJ-1* has a highly conserved cysteine at position residue 106. The oxidation state of the Cys-106 residue appears to have an important role in the chaperone activity of *DJ-1*. Oxidative conditions induce formation of a sulfinic acid of Cys-106, the most sensitive cysteine residue to oxidative stress (12). In the presence of oxidative stress, *DJ-1* translocates from the cytoplasm to the outer mitochondrial membrane and is thought to play a role in neuroprotection (51). The L166P *DJ-1* mutant destabilizes the protein, inducing rapid proteasomal degradation, probably interfering with the neuroprotective mechanism (429, 435, 606).



**FIGURE 5.** Schematic representation of *DJ-1* on transcript level and the functional domains of the DJ-1 protein with pathogenic frameshift mutations above the transcript and protein organization and missense mutations below the protein; rare deletions (red lines) and duplications (green lines) (above) are represented. Only homozygous or compound heterozygous mutations are listed. DJ-1 has 189 amino acids with a single domain protein, and a critical cysteine residue [Cys106] can be modified under oxidative conditions to form a sulfinic acid. It is a member of the ThiJ/Pfp1 family of molecular chaperones, which are induced during oxidative stress.

The lysosomal *type 5 P-type ATPase* gene, *ATP13A2*, at PARK9, was associated with Kufor-Rakeb syndrome (KRS), a form of recessively inherited atypical parkinsonism. KRS is a levodopa-responsive juvenile parkinsonism, with akinesia, supranuclear gaze palsy, pyramidal signs, dementia, and progressive brain atrophy (449, 672). Homozygous or compound heterozygous truncating mutations in the *ATP13A2* gene were first described in two consanguineous KRS families from Jordan and Chile (521). A third patient of Japanese origin, with KRS-like disease and a later age at onset, had a homozygous *ATP13A2* F182L mutation (461). In a Brazilian sporadic patient with juvenile parkinsonism (<20 yr) and a homozygous G504R mutation, the atypical features were limited to an impaired upward gaze and moderate brain atrophy (116). In addition, seven heterozygous missense variations were identified in patients of Asian and European origin who had more typical early-onset PD (116, 125, 362). Recent association studies showed that neither genetic variability in *ATP13A2* nor gene dosage effects contribute substantially to idiopathic PD (148, 391, 520, 646).

The *ATP13A2* gene encodes a large transmembrane protein with putative ATPase activity located in lysosomes, linking abnormal lysosomal function to neurodegeneration. Functional studies showed that the wild-type *ATP13A2* protein is located in the lysosome membrane of transiently transfected cells, whereas the unstable truncated mutants were retained in the endoplasmic reticulum and degraded by the proteasome (521). The exact function of this protein re-

mains unknown, but, intriguingly, *ATP13A2* mRNA levels in the substantia nigra of patients with classical late-onset PD were ~10-fold higher than in control brains (521).

### 3. The controversial role of heterozygous mutations in recessive genes

Homozygous and compound heterozygous mutations in putatively recessive genes are unequivocally associated with early-onset PD. The role of heterozygous mutations is much more problematic, particularly for missense changes in the context of recessive inheritance. It is still not known whether heterozygous mutations are pathogenic in themselves. Haploinsufficiency, dominant-negative effects, or novel gain-of-function mechanisms have been suggested to explain the effects of these variants, but increasing evidence indicates that they are not mutations but rather susceptibility factors, defined as genetic alterations that are neither necessary nor sufficient to cause PD, but are associated with an overall higher risk of developing the disease (310). For example, asymptomatic *parkin* or *PINK1* carriers might have mild extrapyramidal signs, perhaps a behavioral disorder, as well as signs of nigrostriatal dysfunction on functional imaging (244, 295), hyperechogenicity of the substantia nigra on transcranial ultrasound images of the mid-brain (219, 220), discrete abnormalities in voxel-based morphometric analyses (34), and abnormal electrophysiological responses to transcranial magnetic stimulation (21, 106, 554). However, there is so far no evidence that these

abnormalities are progressive or that they could lead to overt PD.

Since PD is a common condition, the presence of these single mutations might be fortuitous and unrelated to their disease. This hypothesis cannot be confirmed, however, without knowledge of the frequency of carriers of the single mutations in the general population. A recent study of heterozygous *parkin* mutations in two European cohorts of healthy subjects found a mutation rate of <4% (48). Interestingly, during clinical follow-up, a 67-yr-old mutation carrier was found to have mild signs of parkinsonism, but did not fulfill the diagnostic criteria for definite PD. In most studies, controls are tested for specific mutations detected in patients. The results of seven studies in late-onset PD patients and healthy, age-matched controls (46, 76, 290, 348, 365, 485, 551) have been contradictory, possibly due to how the variants were defined as pathogenic and, thus, whether they were included in the statistical analyses. In addition, the frequency of heterozygous mutations in recessive genes in healthy controls might be overestimated in the absence of rigorous clinical examinations or follow-up. Some studies have shown that heterozygous mutations significantly influence age at onset of PD (76, 152, 485, 551, 602). Despite these findings, the association of heterozygous promoter and coding polymorphisms with susceptibility to late-onset PD remains inconclusive (311, 348, 382, 424, 470, 666).

#### 4. Other *PARK* genes associated with complex clinical features

A recent genome-wide scan in an eight-generation Amish family with parkinsonism, including progressive supranuclear palsy (PSP), detected markers on chromosomes 3, 7, 10, and 22 (337), but no associated genes have as yet been identified.

Homozygosity mapping followed by mutational analysis in two unrelated families with recessive adult-onset parkinsonism and levodopa-responsive dystonia led to the identification of homozygous mutations in a *phospholipase A<sub>2</sub>* gene (*PLA2G6*) encoding a calcium-independent group VI phospholipase A<sub>2</sub>, at PARK14 (476). Mutations in *PLA2G6* were known to cause infantile neuroaxonal dystrophy (INAD) and idiopathic neurodegenerative with brain iron accumulation (NBIA) (206, 296, 437). However, no mutation carriers were detected among patients with early-onset PD screened for mutations in the *PANK2* gene, which causes pantothenate kinase-associated neurodegeneration (PKAN) (712), also classified as NBIA type 1 (312).

A genome-wide SNP analysis in a large Iranian pedigree with a rare autosomal recessive parkinsonian-pyramidal syndrome (PPS) found linkage to chromosome 22 (569) at PARK15 and a disease-associated homozygous variation in the *F-box protein 7* (*FBXO7*) gene, a member of the F-box

family of proteins implicated in the ubiquitin-proteasome protein degradation pathway (245, 569). A homozygous truncating *FBXO7* mutation and compound heterozygous mutations have also been found in Italian and Dutch families with autosomal recessive early-onset parkinsonian-pyramidal syndrome (117).

#### 5. Other disease-causing genes associated with typical parkinsonism

Onset anticipation, as observed in some spinocerebellar ataxias (SCAs) caused by genetic repeat expansions, has also been described in familial parkinsonism (498), suggesting that repeat expansions might also cause familial PD. More than 30 genes or loci cause SCAs, a clinically and genetically heterogeneous group of autosomal inherited progressive neurodegenerative diseases (474, 597). The most frequent forms, SCA1, 2, 3, 6, 7, and 17, are caused by expansion of CAG repeats encoding polyglutamine (polyQ) tracts beyond a certain threshold. The CAG repeat expansions are usually unstable during transmission, with a tendency to increase further in size resulting in phenotypic variability and an increasingly earlier age of onset.

In SCAs, cerebellar ataxia is usually the predominant sign, but the phenotype often includes a variable association of pyramidal and extrapyramidal signs, deep sensory loss, slow ocular saccades, peripheral neuropathy, and cognitive signs. Extrapyramidal features, including parkinsonism, have been reported along with cerebellar ataxia in SCA1, 2, 3, 7, and 17 (555), but parkinsonism is sometimes pure, especially in patients with SCA2 and SCA3.

The frequency of SCA2 mutations in familial parkinsonism ranges from 1.5 to ~10%, and seems to be particularly high in patients of Asian origin (62, 214, 299, 361, 432, 499, 559, 575, 587, 656, 680). In these patients, parkinsonism may range from typical levodopa-responsive PD to Parkinson-plus phenotypes. The configuration of the SCA2 repeat expansion has recently been shown to play an important role in phenotypic variability. Whereas uninterrupted CAG repeat expansions are associated with ataxia, shorter expansions interrupted by CAA triplets, as in long normal alleles, are associated with parkinsonism (62, 299). These expansions are stably transmitted to offspring, suggesting that the interruption of a CAG stretch may confer stability during meiosis (68). In addition, CAA interruptions may prevent the formation of large expansions. Structural analyses of the SCA2 gene transcripts have shown that CAA or other interruptions facilitate the folding of CAG repeats, whereas uninterrupted expansions may form single hairpins that could be toxic if, for example, they sequester RNA-binding proteins (586). More rarely, repeat expansions in SCA3, 8, and 17 have also been associated with a phenotype resembling pure parkinsonism, without prominent ataxia (216, 300, 680).

The finding of parkinsonism and Lewy body pathology in patients with Gaucher's disease (GD) and their relatives has led to the screening of PD patients for mutations in the *GBA* gene, which in the homozygous or compound heterozygous state, cause GD, a recessive lysosomal storage disorder. Although classically divided into three types, this rare disorder has a continuum of phenotypes, including both nonneuronopathic and neuronopathic forms (572). Almost 300 *GBA* mutations have been identified in patients with GD: point mutations, insertions and deletions, as well as complex alleles derived from the recombination or gene conversion between the *GBA* gene and the highly homologous neighboring pseudogene that represent ~20% of the pathogenic mutations in *GBA* (248). These mutations are distributed over the entire coding regions, but the most frequent cluster in the COOH-terminal part of the gene that encodes the catalytic domain of the protein. The frequency and distribution of *GBA* mutations vary among populations. The most frequent mutation, N370S, which was previously considered to be associated exclusively with nonneuropathic GD, accounts for ~70% of mutant alleles in Ashkenazi Jews (573), but is rare in Asians (653). A second relatively frequent and panethnic mutation, L444P, exclusively associated with neuronopathic GD, is commonly found in non-Ashkenazi Jewish patients, either as point mutation or as part of a complex allele (573).

*GBA* carriers have a wide spectrum of phenotypes, ranging from classical, early-onset, levodopa-responsive PD to clinical features consistent with Lewy body dementia. Moreover, a recent neuroimaging study suggests that parkinsonian patients with *GBA* mutations, even in the heterozygous state, have presynaptic dopaminergic neuronal dysfunction as in PD (317). The brains of PD patients with *GBA* mutations contained widespread and abundant  $\alpha$ -synuclein pathology and prominent diffuse Lewy body-type pathology in the neocortex (455).

The first indication of a relationship between GD and parkinsonism came from autopsy studies, in which the frequency of *GBA* mutations was higher in PD patients, particularly those with earlier onset, than in age-matched controls without pathological evidence of PD (131, 386). These findings have since been replicated, mainly in Ashkenazi PD patients who have the highest mutation frequency (31 vs. 6% in ethnically matched controls) (5), but also in patients with clinically and pathologically diagnosed PD and Lewy body dementia in different populations. Despite differences in population size, diagnosis, and mutation rates, all of these independent studies show that the presence of one or two mutated *GBA* alleles is the most common genetic risk factor for the development of an  $\alpha$ -synucleinopathy, particularly early-onset PD (79, 131, 168, 341, 460, 544) and Lewy body disorders (78, 146, 191, 411). In contrast, a Norwegian study found similar mutation rates for the two most common mutations, N370S and L444P, in PD pa-

tients and controls (2.3 vs. 1.7%)(625). The mutation frequency in this and other studies was probably underestimated, however, since at least half of the mutant alleles can be missed, if only the two most common mutations are looked for (213, 573). Full exon sequencing must therefore be performed to accurately ascertain the frequency of *GBA* mutations in patients and controls, at least in non-Ashkenazi Jewish populations. A recent large meta-analysis that pooled genotyping data from 16 different *GBA* centers in the United States, Europe, Israel, and Asia, as well as the largest sequencing studies of *GBA* mutations in the French population, definitely confirm the role of heterozygous *GBA* mutations in the predisposition to PD (339, 573).

*GBA* mutations have been classified as mild when they cause GD type I with a slight *GBA* deficiency and severe when they produce GD type II or III (31). Similarly, a large study in Israeli Ashkenazi populations showed differential effects of severe versus mild *GBA* mutations on the risk of PD and the phenotype (168): severe mutations increased the risk of developing PD 13.6-fold, decreased the age at onset to 55.7 yr (compared with 60.7 yr in noncarriers of *GBA* mutations or carriers of *LRRK2* mutations), and was associated with cognitive symptoms in 55.6% of the patients; mild mutations increased risk only 2.2-fold, decreased the age at onset to 57.9 yr, and was associated with cognitive symptoms in 25% of the patients. The mechanism by which *GBA* mutations exert their pathogenic effects or act as risk factors for PD is not yet understood. Effect on lysosome function, ceramide metabolism, ubiquitin proteasome system, or lipid metabolism have been postulated, in relation to  $\alpha$ -synuclein clearance (113).

#### D. Recent Breakthroughs From Genome-Wide Association Studies

Although genes and mutations responsible for a growing number of rare Mendelian forms of parkinsonism have been identified, these monogenic models appear inadequate to explain common, typical PD, a complex disorder caused by the interplay of multiple genetic and nongenetic factors. *GBA* was identified as a susceptibility gene by a candidate gene approach, but genome-wide association studies (GWAS) have emerged as a powerful approach to identify susceptibility loci. These studies, involving testing of genetic polymorphisms in large series of cases versus controls, are able to identify low-penetrance alleles that cannot be detected by linkage studies. Genotyping platforms that can analyze hundreds of thousands of SNPs simultaneously make it possible to conduct association studies using sets of SNPs that tag most common variants in the genome, and hence to scan for associations without prior knowledge of function or position. Over the past 6 years, results from at least eight studies of PD have been published (164, 224, 393, 490, 535, 543, 577, 590). However, the success of the first association studies, which examined a relatively small

number of cases and controls (<1,000), was limited; no significant associations were identified (164, 393). A new generation of larger studies combined analyses across multiple scans and replication in tens of thousands of cases have provided consistent evidence implicating *SNCA* and *MAPT* and to a lesser extent *LRRK2* as susceptibility loci for idiopathic PD. They also led to the identification of four new risk loci: a risk locus on 1q32, designated as PARK16 and the *BST1* locus on 4p15 (543, 577), a risk locus on 12q24 (535), and the HLA region on chromosome 6p (224). In addition, a recent meta-analysis of datasets from five PD GWAS from the United States and Europe and replication analyses of significantly associated loci in an independent sample series have led to the identification of six known (*MAPT*, *SNCA*, *HLA-DRB5*, *BST1*, *GAK*, and *LRRK2*) and five new loci (*ACMSD*, *STK39*, *MCCC1/LAMP3*, *SYT11*, and *CCDC62/HIP1R*) (1).

The most immediate challenge, following GWAS, will be to identify genomic pathways related to PD and to understand the pathobiological consequences of risk variants (351, 595). A major aim will be to understand how genetic susceptibility factors interact with each other and with environmental factors to cause disease.

## E. Lessons From Neuropathology

Defined on the basis of clinical features that respond well to symptomatic treatment, PD is most often associated with Lewy bodies at the neuropathological level (249). Diagnosis requires the presence of two neuropathological stigmata: 1) loss of melanized dopaminergic neurons of the SNc and 2) Lewy bodies. Lewy bodies alone are not of diagnostic value, as they are found in the absence of nigral degeneration in other disorders with cognitive symptoms, such as Alzheimer's disease and diffuse Lewy body disease, which are part of a broader group of disorders characterized by  $\alpha$ -synuclein deposition and known under the term of synucleinopathies. Lewy bodies might therefore define a continuum of diseases with more or less widespread pathology; in the extreme cases, pathology may be restricted to neurons in the brain stem and associated with a pure movement disorder, or it may be diffusing throughout the neocortex in neurons and glial cells, in which case it presents clinically with profound dementia. The existence of such a relation has been strongly supported by the clinical and neuropathological correlation of disease severity with the number of *SNCA* allele copies. As discussed earlier in this review, the severity of the clinical presentation, whether compatible with typical late-onset PD or defined by early-onset PD with dementia, is clearly dependent on the number of *SNCA* alleles (cf. sect. IIB1). Post mortem analyses of cases with genomic duplications of *SNCA* have not been reported so far, but cases with *SNCA* triplications were associated with widespread cortical and subcortical LBs, vacuolar degeneration, massive neuronal loss, and gliosis (143, 215, 443,

660). Similar neuropathological presentations were reported for patients with point mutations in *SCNA* diagnosed with PD and dementia (130, 192, 594, 704).

Intuitively, diseases with similar neuropathological presentations should be studied together to understand their physiopathology. Genes unequivocally responsible for autosomal dominant forms of PD, *SNCA* and *LRRK2*, modulate the risk for PD, according to recent GWAS studies (1, 224, 535, 543, 577, 590) and lead to parkinsonism closely resembling sporadic PD, accompanied in most cases with Lewy body-related synucleinopathy. However, although *SNCA*-linked PD is exemplary in this respect, the case of *LRRK2*-linked PD complicates this picture, since despite the clinical homogeneity, the associated pathology is remarkably variable and not correlated with the type of mutation (87). Most patients with the G2019S mutation had  $\alpha$ -synuclein-positive Lewy bodies as in typical PD (179, 182, 531), but others did not (167, 179). Four different neuropathological profiles were found in the family from Western-Nebraska with the first described R1441C mutation: one of the patients had typical brain stem Lewy body pathology, the second diffuse Lewy body pathology, the other two tauopathy or pure nigral degeneration without Lewy body formation (679, 715). In two of the three patients from the German-Canadian family with the Y1699C mutation, nonspecific degeneration with ubiquitin-positive neuronal inclusions was observed in the substantia nigra, whereas Lewy bodies were present in the third patient (294, 715). Six patients from the original Sagamihara family that were later found to carry the *LRRK2* I2020T mutation, had pure nigral degeneration without Lewy bodies, another had Lewy bodies, still another had pathology consistent with multiple system atrophy, although all eight cases had similar clinical features and PET findings (158, 159, 228). Finally, in a single patient with the I1371V mutation analyzed post mortem, typical ubiquitin- and  $\alpha$ -synuclein-positive Lewy bodies were found (183).

PD with autosomal recessive inheritance differs generally from idiopathic PD, although cases with a clinical course indistinguishable from that of the typical disease have been reported. Autosomal recessive PD is characterized by 1) early disease onset, in most cases before age 40; 2) benign, slowly progressive disease course; 3) excellent response to levodopa but early levodopa-induced dyskinesias; and 4) minimal cognitive decline, minimal dysautonomia. It is consistent with neurodegeneration mainly restricted to the dopaminergic neurons of the SNc, as confirmed by the neuropathological analyses of the few cases that have come to autopsy. The only autosomal recessive forms of PD that have been examined post mortem for brain pathology are *parkin*- and, most recently, *PINK1*-linked diseases.

No Lewy bodies were found in the first *parkin* cases reported, who had homozygous exon 3 or exon 4 deletions, suggesting that *parkin*-linked PD is clinically distinct from typical PD with Lewy bodies, and that  $\alpha$ -synuclein does not

play a pathogenic role (87, 232, 438, 684, 685). This view has been challenged by the discovery of PD cases with *parkin* gene mutations and Lewy body pathology (142, 542) or Lewy body-like  $\alpha$ -synuclein-positive inclusions. Age at onset and disease duration were similar in *parkin* patients with and without  $\alpha$ -synucleinopathy, and Lewy body-like structures were observed in cases with homozygous gene deletions (542), compound heterozygous deletions (515), or a heterozygous deletion associated with a point mutation (142), suggesting the absence of biases related to clinical disease course or mutation type (87). However, the existence of additional susceptibility factors for PD was not excluded in the two families with typical Lewy pathology and *parkin* gene mutations: in one of the families, the affected son of the proband had only a heterozygous deletion (142), whereas in the second large family, several individuals with probable PD had heterozygous *parkin* gene mutations or no mutations (515). Lastly, Lewy bodies and Lewy neurites were found in a single case of PD due to a splicing mutation and an exon 7 deletion in *PINK1*, a young patient who died at 39 yr of age from causes independent of the disease only 8 yr after diagnosis (537). This patient belonged to a large Spanish family with levodopa-responsive early-onset parkinsonism in which all affected individuals carried the two segregating gene mutations either in the homozygous or in the compound heterozygous state.

In light of all these observations, it becomes increasingly clear that the subdivision of parkinsonian syndromes into two physiopathological groups with distinct neuropathology, Lewy body-PD-related autosomal dominant forms and recessive parkinsonism without synucleinopathy, is to a certain degree artificial and may be misleading (86, 87, 227).

Since Lewy bodies have been observed in all forms of PD, although not in each case examined, it can be argued that  $\alpha$ -synuclein is implicated in a series of complex pathological processes that cause the death of dopaminergic neurons, regardless of the form of PD. On the other hand, however, the absence of Lewy bodies in several cases affected by genetic forms of the disease indicates that  $\alpha$ -synuclein is not involved here, or that, in general, the formation of Lewy bodies may be an epiphenomenon rather than a primary event in the disease process. Paradoxically,  $\alpha$ -synuclein aggregation may be retarded in parkinsonian syndromes with autosomal recessive inheritance compared with autosomal dominant forms or sporadic PD. This might explain why Lewy bodies or Lewy body-like inclusion are more rarely observed and, in general, are less abundant; even if Lewy bodies are not observed, the possible accumulation of intermediate species in the aggregation processes should be considered in future studies. Of note, Lewy body pathology has also been reported in patients with GD associated with parkinsonism (677), and in a first autopsy case of SCA2 with parkinsonism (694).

### III. PARKINSON'S DISEASE GENES PROVIDE INSIGHT INTO PHYSIOPATHOLOGY

#### A. Recent Advances Reveal Major Links to Mitochondrial Physiology

The idea that mitochondrial dysfunction may be central to PD can be traced back to the discovery of the mechanism of action of MPTP in the early 1980s (328, 397) (reviewed in Ref. 675). It was demonstrated that MPTP crosses the blood-brain barrier and penetrates into glial cells where it is oxidized by monamine oxidase B into a pyridinium species, before being converted into the neurotoxin MPP<sup>+</sup> by further oxidation. MPP<sup>+</sup> is taken up by the dopamine transporter into monoaminergic neurons; here it concentrates in mitochondria where it inhibits specifically complex I of the respiratory chain, leading to ATP depletion, oxidative stress, and apoptotic cell death. This discovery inspired investigation of mitochondrial complex I activity in patients with sporadic PD (reviewed in Ref. 675). A moderate deficit in mitochondrial complex I has repeatedly been reported in the substantia nigra (272, 389, 549) of PD patients. Initially described as specific to this brain region (389, 550), it was also found in frontal cortex (291, 494) and platelets of patients (217, 321, 494, 547). Mitochondrial dysfunction may also affect other peripheral tissues, including skeletal muscle (33, 389, 501, 568, 620), and it may not be restricted to complex I (25, 217, 568).

In an attempt to provide the molecular mechanisms underlying mitochondrial defects in PD, cytoplasmic hybrid cells were generated to study the contribution of mitochondrial DNA isolated from platelets from PD patients. A few groups have reported that mitochondrial complex I defects can be "inherited" from patient-derived mitochondrial DNA by healthy recipient cells (209, 430, 603), but others have challenged these findings (14). In addition, the evidence that specific mitochondrial DNA haplogroups or point mutations are linked with PD is poor (reviewed in Ref. 547). However, the use of long-range and quantitative real-time or single-molecule PCR techniques to analyze this genome revealed an age-dependent accumulation of clonally expanded somatic mitochondrial DNA deletions, associated with respiratory defects, in human dopaminergic neurons from the substantia nigra (24, 319). Neurons in other brain regions were not affected by these alterations (24), providing a possible molecular basis to the vulnerability of dopaminergic neurons in PD.

Finally, a growing body of recent evidence provides strong support to the idea that mitochondrial dysfunction may be central to the physiopathology of familial PD, particularly to that of parkinsonian syndromes with autosomal recessive inheritance.



### 1. PD-related proteins have mitochondrial localizations

With the exception of PINK1, the products of PD-causing genes are not mitochondrial proteins per se. However, there is an extensive, although often contradictory, literature showing that all are, at some point, associated with mitochondria. PINK1, a potential mitochondrial serine/threonine kinase, is synthesized as a precursor of 66 kDa with a putative NH<sub>2</sub>-terminal mitochondrial targeting sequence and a possible transmembrane domain (574, 639). Ultrastructural and biochemical analyses of the overproduced protein initially showed it to be localized predominantly on mitochondrial cristae, facing the intermembrane space (IMS) (574). Other studies, however, have reported association of the endogenous protein with the inner (IMM) and outer mitochondrial membranes (OMM) in both human and rodent brain (169), or with the IMM and the IMS (444, 517), and occasionally the OMM (444) in cells. By analyzing the topology of a protein overproduced in various neuronlike cell lines, Zhou et al. (713) provided biochemical evidence that the COOH-terminal kinase domain of PINK1 faces the cytosol, whereas the NH<sub>2</sub> terminus of the protein is inside the mitochondrion. Recent evidence suggests that two alternative mitochondrial import/maturation pathways exist, leading either to direct insertion of full-length PINK1 within the OMM in uncoupled mitochondria, or to sequential two-step cleavage of the NH<sub>2</sub>-terminal sequence within the mitochondrion. This latter process, which depends on the mitochondrial membrane potential, involves a first cleavage by the matrix enzyme mitochondrial processing peptidase (MPP) to generate a 60-kDa protein, and a second cleavage performed by the protease presenilin-associated rhomboid-like protein (PARL) within the inner membrane, which liberates an unstable 52-kDa mitochondrial protein (107, 275). These results are consistent with previous observations in *Drosophila* cells demonstrating processing of PINK1 to a shorter isoform by the mitochondrial protease Rhomboid-7 (670). Intriguingly, despite its intramitochondrial generation, the 52-kDa PINK1 isoform is rapidly degraded by a protease sensitive to proteasome inhibitors (275). It remains to be clarified whether this finding hints at the existence of an intramitochondrial protease sensitive to such inhibitors, or whether it rather indicates that the shorter PINK1 species is exported to the cytosol where it is degraded by the proteasome.

There is indeed debate as to whether PINK1 is exclusively localized in mitochondria: the presence of extramitochondrial PINK1 isoforms with apparent molecular weights compatible with putative mitochondrial precursor and mature derivative proteins has been reported, particularly when the protein was overproduced in cell models (23, 506, 663, 713). Although this is possibly an artifact, since the overproduced protein might overwhelm the mitochondrial import machinery, this finding may also indicate that a proportion of the mature protein is exported from the or-

ganelle to the cytosol, or that alternative maturation pathways generate extramitochondrial pools of the protein (23, 363, 663) that may have physiological functions (226).

The processing, stability, and subcellular distribution of PINK1 isoforms are probably dynamically regulated; the Cdc37/Hsp90 chaperones and Parkin may be involved in these processes (363, 562, 636, 663). For some investigators, Parkin induces an increase in the mitochondrial pools of the protein (663). For others, Parkin stabilizes PINK1 pools sensitive to ubiquitylation and proteasomal degradation, an effect mediated by the RING2 domain and resulting in inhibition of PINK1 ubiquitylation and degradation by the ubiquitin-proteasome pathway (562, 636). Parkin is an essentially cytosolic protein, although its occasional association with various subcellular organelles, including the endoplasmic reticulum and the nucleus, has been reported (102, 564). In the adult mouse brain and in PC12 cells overproducing Parkin, a proportion of the protein was also found at the OMM (102, 598, 713), facing the cytoplasm, as suggested by limited proteolytic digestion of pure mouse brain mitochondrial fractions (102). Although some investigators have even suggested that Parkin has intramitochondrial localization (324), formal evidence in favor of this possibility is lacking, whereas it is generally admitted that Parkin associates with the OMM in a regulated manner. Recent studies have provided compelling evidence that loss of the electrical potential of the mitochondrial membrane or oxidative stress leads to the recruitment of Parkin to the OMM (176, 451, 452, 718).

Like Parkin, DJ-1 is a predominantly cytosolic protein, but some of the protein has been found in the mitochondrial fraction after subcellular fractionation and immunohistochemical analysis of transfected cells (429, 708) and mouse brain tissue (708). Furthermore, it appears to redistribute to the OMM under conditions of oxidative stress, a process dependent on the formation of a cystein-sulfinic acid at the conserved cysteine residue 106 (36, 51). However, the precise location of DJ-1 in the organelle is a matter of debate, since immunoreactivity to the endogenous protein was found associated with the IMS and the matrix, but not with the mitochondrial membranes (708).

Proteins encoded by genes involved in autosomal dominant forms of PD may also be recruited to the mitochondrion under some circumstances. Mitochondrial import assays suggested that  $\alpha$ -synuclein might be translocated into the organelle and associate with the IMM (115), a process that was dependent on the positively charged NH<sub>2</sub> terminus of the protein and required the OMM import channel TOM40, as well as a preserved mitochondrial membrane potential and ATP pool. However, using optical reporters to study the conformation of  $\alpha$ -synuclein, Nakamura et al. (450) showed that binding of the protein to purified rat brain mitochondria is instantaneous and independent of the

functional status of the organelles, suggesting that the protein is not imported into the organelle. Interestingly, these authors showed enrichment of endogenous  $\alpha$ -synuclein in purified rat brain mitochondria and were able to correlate the abundance of  $\alpha$ -synuclein to the amount of mitochondria contained in membrane fractions (450). As suggested for other PD-related proteins, translocation of  $\alpha$ -synuclein from the cytosol to the OMM may be dynamically regulated in response to oxidative or metabolic stress, but it is unclear to what extent this reflects a protective mechanism rather than a pathological process (82). Whether protective or pathological, mitochondrial accumulation of  $\alpha$ -synuclein may be relevant to the pathogenesis of PD, since it is higher in the substantia nigra and the striatum, but not the cerebellum, of PD patients compared with control subjects (115).

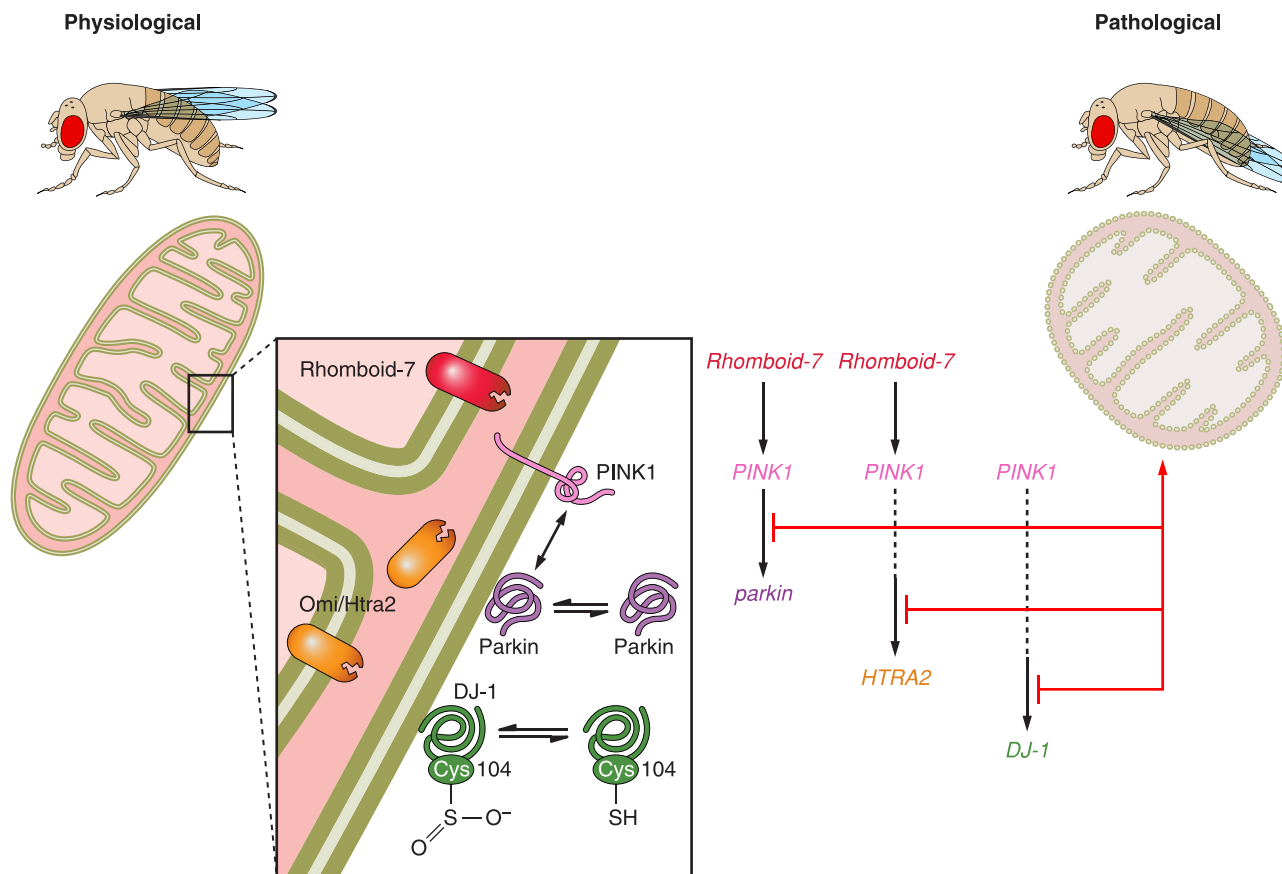
Finally, some LRRK2 was found associated with the OMM in mitochondria-enriched fractions of transfected cells (667); submitochondrial fractionation of mouse brain tissue also showed some LRRK2 immunoreactivity at the OMM, and in the mitoplast fraction (35). Colocalization with structures positive for Mitotracker or the nucleus-encoded polypeptide chain IV of cytochrome *c* oxidase was only minimal, however, in primary neuronal cultures (35), as well as in neurons from the adult human substantia nigra post mortem, where LRRK2 immunoreactivity was predominant in Nissl bodies (647).

## 2. *Drosophila* models reveal the existence of a molecular pathway centered on maintenance of the morphological integrity of mitochondria

The first hint that Parkin plays a role in the modulation of mitochondrial shape was provided by Darios et al. (102) in 2003, who observed that overproduction of the protein in nerve growth factor (NGF)-differentiated PC12 cells undergoing apoptosis following serum deprivation or treatment with the lipid second messenger C2-ceramide significantly delayed mitochondrial swelling, membrane rupture, and the release of proapoptotic molecules. Ultrastructural analysis in this model revealed a significant decrease in the mean cross-sectional area of mitochondria in cells overproducing Parkin, even under basal conditions, i.e., in the absence of proapoptotic stimuli. Compelling evidence in favor of such a role came subsequently from studies on *Drosophila* conducted in several independent laboratories. Flight muscle degeneration preceded by early mitochondrial pathology (ultrastructurally abnormal, swollen organelles with little electron-dense material and few cristae) led to abnormal wing posture (downturned wing phenotype) and reduced flight and climbing ability in *parkin* null mutant flies (202, 505). Male sterility in these flies was accompanied by defective individualization of spermatids, associated with severely disrupted Nebenkern, the specialized mitochondrial formation of *Drosophila* sperm; this observation was indicative of defects in mitochondrial morphogene-

sis during spermiogenesis (202, 526). Surprisingly similar phenotypes were described when the fly ortholog of *PINK1* was inactivated (75, 110, 493, 687) and, most recently, when the two *DJ-1* orthologs *DJ-1a* and *DJ-1b* were deleted (225). Although overproduction of Parkin reversed the anomalies caused by the *PINK1* deficiency, the reverse was not true; moreover, the phenotypes of double null *parkin/PINK1* mutant flies were no more severe than those of the single mutants, indicating that *PINK1* and *parkin* act in a linear pathway, in which *parkin* intervenes downstream of *PINK1* (FIG. 6). Strikingly, overproduction of DJ-1, whether of human or *Drosophila* origin, also rescued some of the defects found in *PINK1* but not *parkin* null mutant flies, particularly the faulty wing posture, structural abnormalities of the thoracic muscle, muscle degeneration, and loss of mitochondrial DNA (225); rescue was dependent on cysteine 104, corresponding to mammalian cysteine 106, suggesting that the cystein-sulfinic acid-modified DJ-1 protein might also function downstream of *PINK1*, possibly in a pathway parallel to the *PINK1/parkin* pathway (FIG. 6). Observations made in muscles of *Drosophila* mutants were, in part, confirmed in dopaminergic neurons. Some investigators reported neuronal atrophy (58, 202) or loss (493, 671, 687) in specific dopaminergic clusters, but these findings were not confirmed by others (75, 505). Park et al. (493) also reported the presence of abnormally enlarged and clustered organelles in dopaminergic neurons of *PINK1* null mutant flies, and rescue of these morphological alterations by overproduction of Parkin (493).

Interestingly, overexpression of *PINK1* in the visual systems resulted in a rough eye phenotype, indicating that excessive signaling through the *PINK1/parkin* pathway is deleterious (513). This phenotype was significantly attenuated on a *parkin* null background, but was dramatically accentuated when both genes were overexpressed, confirming involvement of *PINK1* and *parkin* in a common pathway of physiopathological relevance. Based on genetic interaction studies in the visual system, Whitworth et al. (670) identified two additional putative components of this pathway, the genes encoding the serine protease Omi/Htra2 and the intramitochondrial membrane protease Rhomboid-7 (670). Their analyses suggested that *rhomboid-7* acts upstream of *PINK1* and *parkin*, whereas *HTRA2* may be a downstream effector of *PINK1* intervening in a pathway parallel to that of *parkin* (FIG. 6). However, a genetic interaction between *PINK1* and *HTRA2* was not confirmed by Yun et al. (698) either in the visual system, in testes, or in muscle. Although some phenotypic similarities were observed between loss-of-function *omi/Htra2* mutants and *PINK1* or *parkin* mutants (604), major differences, i.e., absence of muscle degeneration or loss of dopaminergic neurons, suggest that *HTRA2* is not an essential component of the *PINK1/parkin* pathway (698). Moreover, flies overexpressing *omi* variants carrying PD-associated mutations previously suggested to compromise Omi/Htra2 protease



**FIGURE 6.** Genes responsible for autosomal recessive Parkinson's disease are involved in pathways that regulate mitochondrial morphology and integrity in *Drosophila*. Loss-of-function mutations in the *Drosophila* orthologs of *parkin* or *PINK1* lead to early mitochondrial pathology in flight muscles, associated with muscle degeneration, impaired flight and climbing abilities, and a peculiar wing phenotype (downturned wing). Similar phenotypes are observed in *DJ-1* mutant flies. Overexpression of *parkin* rescues the phenotype of *PINK1* mutant flies, whereas *PINK1* does not prevent the defects observed in *Parkin*-deficient flies, suggesting that these genes are involved in a common pathway in which *parkin* acts downstream of *PINK1*. Genetic interaction studies demonstrated involvement of the gene encoding the intramitochondrial membrane protease Rhomboid 7 upstream of *PINK1* in the *PINK1/parkin* pathway. The gene coding for the matrix serine protease Omi/Htra2 may act downstream of *PINK1* in a pathway parallel to the *PINK1/parkin* pathway. Overproduction of DJ-1 rescues some aspects of the phenotype caused by loss of *PINK1* function but does not affect the phenotype in *parkin* mutant flies, pointing to the existence of a pathway independent from the *PINK1/parkin* pathway, in which *DJ-1* acts downstream of *PINK1*; the effect of *DJ-1* depends on its ability to respond to oxidative stress with modification of cysteine 104 (the equivalent of cysteine 106 in mammalian DJ-1) to cysteine-sulfenic acid, followed by translocation of the protein to the OMM. The concerted effects of *PINK1* and *Parkin* in the *PINK1/parkin* pathway may be mediated by direct protein-protein interaction.

activity (600), or a mutation abolishing a putative PINK1-dependent phosphorylation site essential for this activity (510), behaved like those expressing the wild-type gene (698). These observations argue against a key role for *HTRA2* in the pathogenesis of PD, although they may also reflect functional differences between the human genes and their *Drosophila* counterparts.

Finally, analysis of the pathological phenotypes caused in the *Drosophila* visual system by concomitant manipulation of the expression levels of *LRRK2* and *pink1* or *parkin* revealed putative genetic interactions between these genes (643). However, the complex combination of phenotypes observed in these models, associated with reciprocal mod-

ulations restricted to only limited aspects of the global pathological picture, preclude straightforward interpretations and suggest that the degree of overlap between the biological functions regulated by the *PINK1/parkin* pathway and those controlled by *LRRK2* may not be significant.

### 3. The *PINK1/parkin* pathway regulates mitochondrial dynamics

Mitochondrial and cytosolic GTPases playing key roles in mitochondrial fusion and fission have been previously involved in human neurodegenerative disorders, highlighting the relevance of these processes to the physiology of the cell (359): mutations with autosomal dominant inheritance in

*opa-1* (*optic atrophy 1*), involved in fusion of the inner mitochondrial membrane, lead to retinal ganglion cell degeneration responsible for the most common form of inherited optic atrophy; autosomal dominant mutations in *mfn2* (*mitofusin 2*), coding for a pro-fusion protein embedded in the outer mitochondrial membrane, cause the common peripheral sensorimotor neuropathy Charcot-Marie-Tooth disease type 2A; the heterozygous A395D mutation in *drp1* (*dynamamin-related protein 1*), encoding a cytosolic GTPase involved in mitochondrial and peroxisomal fission, has been reported to cause abnormal brain development leading to early postnatal mortality.

Elegant studies in *Drosophila* provided evidence for genetic interactions between *parkin* and *PINK1* and genes encoding components of the mitochondrial fusion/fission machinery, suggesting an involvement of the corresponding proteins in processes regulating mitochondrial dynamics. Heterozygous loss-of-function alleles of *drp1* did not affect viability per se but were lethal when transferred onto a *parkin* or *PINK1* null background (110, 513). Conversely, an extra copy of *drp1* suppressed the morphological alterations of mitochondria and the degeneration of inverted flight muscles in *PINK1* (110, 513, 689) and *parkin* mutant flies (110), and rescued the related flight and climbing defects (513), suggesting that the *PINK1/parkin* pathway stimulates Drp1-mediated mitochondrial fission. Consistent with this possibility, RNAi-mediated knockdown or loss-of-function mutations of *opa1* (513, 689) or *mfn* homologs (110, 513) also had beneficial effects on the phenotypes induced by Parkin or *PINK1* deficiencies. These effects were observed not only in the inverted flight muscle (110, 513, 689) and in the testis (110), but also in the dopaminergic neurons of specific clusters, in which the abnormal mitochondrial aggregation induced by the mutation of *PINK1* was rescued by an extra copy of *drp1* or by removal of one *opa1* allele (689).

Some incongruencies complicate interpretation of the *Drosophila* data: 1) the defects in mitochondrial morphology in muscles and during sperm development in the testis of *PINK1* and *parkin* mutant flies overlap only to a certain degree with those caused by mutations in *drp1*; 2) overexpressing *PINK1* does not alter Nebenkern structure in onion-stage spermatids, in contrast to overexpressing *drp1* or to mutating the *mfn* homologue *fzo*; 3) decreasing *mfn* or *opa1* expression or overexpressing *drp1* in a *PINK1* mutant background, reverse alterations in mitochondrial morphology in the inverted flight muscles of *PINK1* mutant flies, but in addition push the system towards mitochondrial "hyper-fission" phenotypes; and 4) loss of function of genes encoding components of the mitochondrial fusion/fission machinery is lethal in flies, whereas *PINK1* and *parkin* null mutants are viable (110).

In addition, contradictory effects of the *PINK1/parkin* pathway have been reported in mammalian cells. Mitochondria did not present gross morphological abnormalities in mouse models (173, 186, 481). Consistent with the hypothesis that *PINK1* promotes mitochondrial fission, abnormally large mitochondria were more abundant in a *PINK1*-deficient mouse model (173). Furthermore, inhibition of the proteasomal machinery was less efficient in inducing fragmentation of the mitochondrial network in primary cortical neurons from *PINK1*-deficient mice than in neurons from wild-type mice, suggesting that mitochondrial fission related to apoptotic processes is altered (186).

Contrary to what was expected from the data obtained in *Drosophila* models, fibroblasts from PD patients carrying homozygous nonsense or missense *PINK1* mutations more often had truncated mitochondrial networks than control fibroblasts when they were cultured in medium with low glucose content, or in the presence of galactose to favor mitochondrial energy metabolism over glycolysis (138, 208). In fibroblasts from patients with *parkin* gene mutations or subjected to siRNA-mediated *parkin* gene silencing, Mortiboys et al. (439) observed increased mitochondrial interconnectivity, measured as branching, but no difference in organelle length compared with control cells (439). Consistent with the possibility that *parkin* deficiency renders cells more susceptible to insult-induced fission, mitochondria were significantly shorter in the patients' fibroblasts upon treatment with the mitochondrial complex I inhibitor rotenone. Although not always consistent across studies, these observations suggest that the *PINK1/parkin* pathway may indeed shift the balance of mitochondrial dynamics towards fission under basal conditions, but favor a higher degree of functional connectivity of the organelles under conditions of energy depletion or high energy demand. Interestingly, mitochondrial branching was more prominent after mitochondrial complex I inhibition in control fibroblasts, indicating that increasing mitochondrial connectivity may indeed represent a protective response of cells facing an energy crisis (439). Of note, DJ-1 deficiency resulted in a decrease in the complexity of the mitochondrial network, evaluated as mitochondrial branching and/or length, in immortalized embryonic fibroblasts and in primary cortical neurons from DJ-1-deficient mice, as well as in primary fibroblasts and lymphoblasts from *PINK1*-linked PD patients (265, 320). These defects were rescued by overproduction of Parkin or *PINK1*, suggesting that DJ-1 may be directly involved in the *PINK1/parkin* pathway, or at least regulate its activity (265). However, the possibility that independent pathways converge on maintenance of mitochondrial morphology and function should also be considered. Consistent with this idea, it was recently shown that  $\alpha$ -synuclein modulates mitochondrial dynamics by inhibiting fusion directly through its membrane-binding properties, independently from the fusion/fission machinery; again, *PINK1* and Parkin were able to rescue mitochon-

drial fragmentation caused by  $\alpha$ -synuclein overdosage (284).

Analyses in cells genetically modified to modulate expression of *PINK1* and *parkin* showed that the outcome depended on the cell model used. In overexpression and knock-down experiments in the simian kidney-derived COS7 cell line, Yang et al. (689) confirmed the pro-fission activity of *PINK1* first evidenced in *Drosophila*. As in *Drosophila*, this effect was mediated by Drp1, since it was counteracted by a dominant negative version of Drp1 defective in GTP binding (Drp1K38A). In HeLa cells or SH-SY5Y cells, however, the percentage of cells with a fragmented mitochondrial network was significantly higher after treatment with *PINK1*- (138, 384) or *parkin*-specific siRNAs than after transfection with control siRNA (384). Quantification of the length and interconnectivity of the mitochondrial network using standardized computer-automated image analysis techniques (97) or dynamic live imaging of a mitochondrially targeted YFP in a human dopaminergic cell line (540) confirmed that *PINK1* promotes maintenance of mitochondrial interconnectivity in SH-SY5Y or human dopaminergic neuroblastoma cells (97, 540). As in human fibroblasts from carriers of *parkin* gene mutations (439), fragmentation was enhanced in dopaminergic neuroblastoma cells depleted for *PINK1* (540).

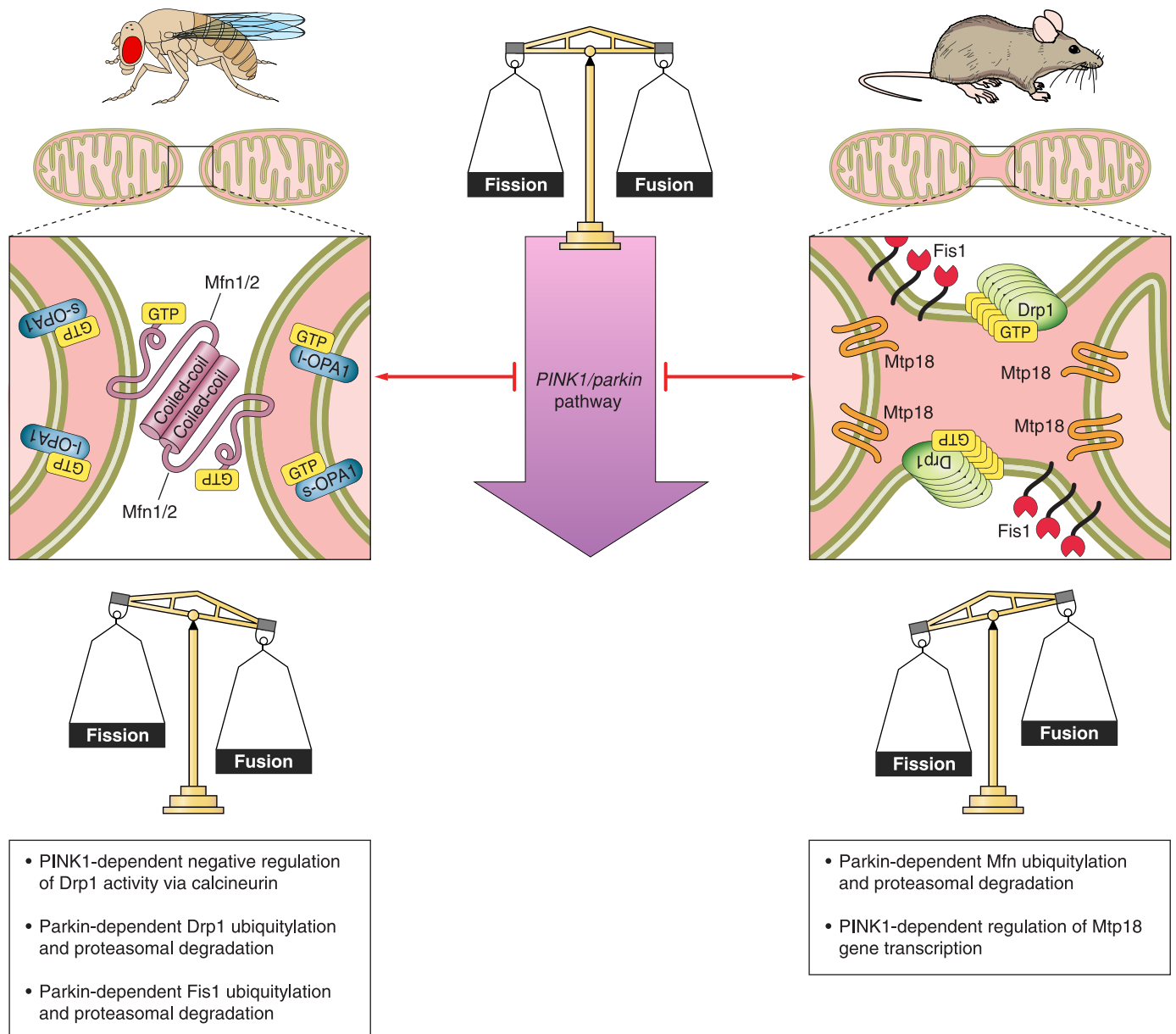
Whatever the final effect on mitochondrial interconnectivity when *PINK1* or Parkin levels were modulated in the different mammalian models examined, there was a general *consensus* across studies: 1) *PINK1* and Parkin are components of a common pathway in which Parkin acts as downstream effector (93, 138, 384, 689); and 2) Drp1 is a potential pivotal mediator of the regulatory activity of the *PINK1/parkin* pathway (93, 384, 540, 689). Sandebring et al. (540) provided first clues to the molecular mechanisms underlying regulation of Drp1 by the *PINK1/parkin* pathway. They showed that the decrease in mitochondrial interconnectivity observed in *PINK1*-depleted cells was associated, in an *in vitro* assay, with diminished Drp1 phosphorylation and the resulting increase in Drp1 GTPase activity. These changes were due to a net increase in calcineurin phosphatase activity in *PINK1*-deficient cells and were reversed by the calcineurin inhibitor FK506, identifying calcineurin as a putative target of the *PINK1/parkin* pathway. More recently, it was shown that Drp1 can itself be targeted by Parkin for proteasomal degradation in mammalian cells models (654). In addition, it was also shown that Parkin promotes the monoubiquitylation of the fission factor Fis1 (Fission 1); although this modification does not typically lead to proteasomal degradation, in this case, it triggered the breakdown of hFis1 by the proteasome (93). The above-mentioned mechanisms are consistent with negative regulation of mitochondrial fission by the *PINK1/*

*parkin* pathway (FIG. 7). However, both in *Drosophila* and in mammalian cells, it was also shown that Parkin promotes the ubiquitylation and proteasomal degradation of Mfn proteins, thus protecting the mitochondrial network from refusion of dysfunctional mitochondria destined to autophagic clearance (174, 616, 718) (FIGS. 7 and 8). Comprehensive analysis at the transcriptional level of the mammalian fission (Drp1, Fis1, Mtp18) and fusion (MfnI, MfnII, OpaI) factors in a *PINK1* knock-out mouse model detected a selective reduction in the *Mtp18* (mitochondrial protein 18) transcript, encoding a protein involved in the regulation of the mitochondrial translocation of Drp1 (359), suggesting that this pro-fission factor is positively regulated by the *PINK1/parkin* pathway (186) (FIG. 7).

Altogether, this pathway emerges as a pivotal upstream regulator of the balance between fusion and fission, with potential direct and indirect effects on the activity of several molecular components of the mitochondrial dynamics machinery (FIG. 7). Future studies will need to explain why the regulatory activity of the *PINK1/parkin* pathway affects differently mitochondrial interconnectivity in different model organisms and cell types. In addition to methodological differences in the assessment of mitochondrial morphology and dynamics, a number of intrinsic factors could influence the final outcome of this activity including 1) the intrinsic activity of the *PINK1/parkin* pathway and of potentially redundant pathways, 2) the degree of basal mitochondrial connectivity, 3) the kinetics of fusion and fission, 4) the size of active versus dormant pools of components of the fusion/fission machinery, 5) the efficacy and rapidity of potential compensatory mechanisms in the particular cell type/organism studied, and 6) the abundance or level of activity of proteins which, similarly to  $\alpha$ -synuclein (284), may modulate the properties of mitochondrial membranes independently from the mitochondrial dynamics machinery.

#### 4. The *PINK1/parkin* pathway regulates mitochondrial quality control

The involvement of *PINK1* and Parkin in processes leading to mitochondrial clearance may contribute to the reported changes in mitochondrial network complexity. Ultrastructurally abnormal mitochondria have been repeatedly reported in *PINK1* and Parkin-deficient models. Mitochondria in the flight muscles of both *parkin* and *PINK1* mutant flies appeared abnormally enlarged, with little electron-dense content and fragmented cristae (75, 202, 493, 687). Similar findings were reported in mouse models and in various human cell lines, in which *PINK1* depletion correlated with a higher frequency of abnormally swollen organelles (173, 540), fewer and disorganized cristae (540, 678), and/or a reduction in the length of cristae membrane relative to that of inner boundary membrane (97, 138). Thus accumulation of dysfunctional mitochondria may be a uni-



**FIGURE 7.** The *PINK1/parkin* pathway regulates mitochondrial dynamics. Studies in *Drosophila* models and in mammalian cells have provided evidence that the *PINK1/parkin* pathway modulates mitochondrial fusion and fission processes. In flies, the phenotypes caused by impairment of the *PINK1/parkin* pathway are rescued by overproduction of “profission” or depletion of “profusion” proteins, suggesting that it promotes mitochondrial fission. In mammalian cells, the complexity of the mitochondrial network is increased under the action of the *PINK1/parkin* pathway, whereas silencing of *PINK1* or *parkin* leads to mitochondrial fragmentation; here, the pathway appears to stimulate mitochondrial fusion and/or inhibit fission. It is likely that the *PINK1/parkin* pathway acts as an upstream regulator of the balance between mitochondrial fusion and fission, possibly affecting the abundance/activity of several core components of the mitochondrial dynamics machinery (Drp1, hFis1, Mfn, Mtp18), as suggested by a number of recent studies.

fyng feature of PINK1- and Parkin-deficient models across species and cell types, and may result from dysfunctional organelle clearance. The first hint that PINK1 is possibly involved in protein quality control in mitochondria was provided by the discovery of its relationship with two mitochondrial proteins suspected to be involved in the proper folding and in the degradation of misfolded proteins, the TNF receptor-associated protein TRAP1, and the serine

protease Omi/HtrA2, respectively (510, 517) (FIG. 8). By affinity-purifying proteins associated with PINK1 in mammalian cells, Pridgeon et al. (517) identified the molecular chaperone TRAP1 as the first direct protein substrate of the serine/threonine kinase activity of PINK1. They found the proteins to be colocalized at the IMM and in the IMS and demonstrated that phosphorylation of TRAP1 by normal PINK1, but not PD-causing PINK1 variants, is essential for

the protective activity of PINK1 against oxidative stress, although the underlying molecular mechanisms remain to be clarified (517). With a similar approach, it was also found that PINK1 is associated with Omi/HtrA2, the mammalian homolog of the bacterial heat shock endopeptidases Deg P and Deg S (139, 200). Although PINK1 was unable to phosphorylate HtrA2 directly, it enhanced the p38 MAPK-dependent phosphorylation of HtrA2 at serines 124 and 400, increasing its protease activity and protecting against 6-hydroxydopamine- and rotenone-induced cell death (FIG. 8).

More recently, it was demonstrated that Parkin is recruited selectively to dysfunctional mitochondria, in particular after impairment of the electrochemical membrane potential by uncoupling agents, e.g., the protonophore carbonyl cyanide *m*-chlorophenylhydrazone (CCCP), and thereby promotes the selective degradation of the organelles through autophagy (417, 451, 452) (FIG. 8). These findings have since been confirmed and extended by several investigators in different models, including neurons (176, 415, 648, 718). Because of the previously identified functional link between Parkin and PINK1 and the integration of a pool of intracellular PINK1 in the OMM, PINK1 emerged as a candidate receptor for Parkin at the mitochondrial surface. A number of studies provided evidence for a direct physical interaction between PINK1 and Parkin and reported complex, although not always consistent, reciprocal regulations of these proteins (302, 415, 557, 562, 636, 648, 681). Kim et al. (302) described, for the first time, massive relocalization of Parkin to mitochondria when it was coproduced together with PINK1 in different mammalian cell types, in the absence of a mitochondrial membrane-depolarizing stimulus (302). This phenomenon, associated with the perinuclear aggregation of mitochondria, was mediated by the RING1 domain of Parkin and dependent on a functional kinase domain of PINK1; it additionally appeared to require PINK1-dependent phosphorylation of two threonine residues in the recently identified RING0 domain of Parkin (247), T175 and T217. The instrumental role of PINK1 in the translocation of Parkin to the OMM was confirmed recently by several independent teams, who extended these observations by demonstrating that siRNA-mediated silencing or knockout of *PINK1* prevents association of Parkin with dysfunctional mitochondria and subsequent mitophagy in cells treated with CCCP or with paraquat, a toxin causing oxidative stress (176, 415, 453, 648, 718). These authors also generally agreed that the kinase activity of PINK1 was essential for recruitment of Parkin, although direct phosphorylation of Parkin by PINK1, whether at threonines T175 and T217 or at other residues, has been questioned (302, 453). Remarkably, it was shown that PINK1 accumulates on the OMM following = mitochondrial depolarization due to inhibition of its proteolytic digestion into a fragment sensitive to proteasomal degradation, and that this step is essential for Parkin recruitment

(415, 453). This finding adds another element to the complex dynamic regulations of the activity of the *PINK1/parkin* pathway in which, as for its impact on mitochondrial dynamics, *parkin* appears to act downstream of *PINK1*.

Interestingly, the perinuclear clustering of mitochondria observed following the corecruitment of exogenous PINK1 and Parkin at the OMM, even in the absence of mitochondrial membrane depolarization, was also associated with signs of mitophagy (648), and in the end with total clearance of the organelles (453). This provides a plausible explanation for toxic effects observed in *Drosophila* models when both proteins are overproduced (513). Preceding mitophagy, the PINK1-dependent association of Parkin with depolarized organelles was found to be accompanied by the corecruitment of ubiquitin and the ubiquitin-autophagy adaptor p62/SQSTM1, as well as the ubiquitin-binding protein deacetylase HDAC6 (176, 336) (FIG. 8). Although it was recently confirmed that VDAC1, but not VDAC2, is ubiquitylated in a Parkin-dependent manner following mitochondrial membrane depolarization, this modification did not appear to be mandatory for mitophagy to occur (275). Moreover, p62/SQSTM1 recruitment to the ubiquitylated mitochondria also appeared dispensable, suggesting that it is an epiphenomenon rather than an intrinsic part of the mitophagy execution program. As mentioned in section IIIA3, following mitochondrial uncoupling, which not only triggers mitophagy but also mitochondrial fusion arrest, Mfn1 and Mfn2 become additional targets for ubiquitylation by Parkin at the outer mitochondrial membrane (616). Ubiquitylation of Mfn1/2 leads to their proteasomal degradation dependent on the AAA+ ATPase, p97, previously involved in retrotranslocation of ubiquitylated endoplasmic reticulum membrane-spanning proteins destined for the proteasome (692). Impairment of this process, either by overproduction of a dominant negative p97 protein or by proteasomal inhibition, precluded Parkin-dependent mitophagy. However, Parkin was able to promote mitophagy in cells depleted for Mfn1/2, suggesting that while these proteins are not components of the mitophagy program, inhibiting fusion of damaged mitochondria facilitates autophagy-dependent mitochondrial clearance (616).

Two recent studies have provided strong evidence that the ubiquitin-proteasome system plays a role beyond Mfn1/2 degradation in Parkin-dependent mitophagy (61, 695): Parkin appears to activate the ubiquitin-proteasome system to promote the degradation of a series of proteins of the OMM of damaged mitochondria, leading to the rupture of the OMM, and only secondarily to the autophagic degradation of the disrupted organelles. These findings are consistent with the idea that the *PINK1/parkin* pathway may only be required for preparing mitochondria for mitophagy, a process termed “priming” and associated with ubiquitylation of the organelles, but not for induction of the process (123). In contrast, the BH3-only Bcl-2 family protein Nix, previ-

ously shown to be essential for elimination of mitochondria during erythroid cell maturation (541), appears to be required for mobilization of the autophagic machinery. Particularly, it was shown that Nix is required for membrane depolarization and generation of a burst of reactive oxygen species resulting in inhibition of mTOR signaling, mitochondrial translocation of Parkin, and induction of mitophagy (123).

It cannot be excluded that Parkin and PINK1 play multiple roles in the multistep process that culminates in the disappearance of dysfunctional mitochondria. This possibility is supported by the recently reported interaction between PINK1 and the tumor suppressor beclin 1, the regulatory subunit of the class-III PI3K complex crucial for phagophore elongation (428). Intriguingly, a recent report has provided evidence that mitochondria could supply membranes for autophagosome biogenesis, at least during starvation (222). This opens the way for exploration of the role of the *PINK1/parkin* pathway in this particular process which, if impaired, may compromise not only mitophagy but also the degradation of other cellular components and organelles. Despite these gaps in our understanding of the molecular mechanisms involved in the *PINK1/parkin*-dependent regulation of mitophagy, the physiopathological relevance of this regulatory activity is strongly supported by the observation that a series of *parkin* and *PINK1* gene mutations found in PD patients disrupt distinct steps of the chain of events triggered by mitochondrial membrane depolarization ultimately leading to clearance of dysfunctional organelles (176, 453).

Future studies will also have to examine a possible contribution of the *PINK1/parkin* pathway to processes that only secondarily affect mitochondrial clearance, in particular mitochondrial trafficking. Vives-Bauza et al. (648) have indeed proposed that Parkin and PINK1 may be part of a trafficking machinery responsible for the

delivery of damaged mitochondria to the lysosome-rich perinuclear region that may be a privileged site for their degradation. This process might involve the integral mitochondrial membrane GTPase Miro and the adaptor Milton which connect kinesin heavy chain to mitochondria and have previously been found in a complex containing PINK1 (664) (FIG. 8).

In addition, it will be essential to clarify some inconsistencies among studies. Several reports have shown that PINK1, in concert with Parkin, plays a key role in the autophagic clearance of dysfunctional mitochondria, whereas others have provided evidence that a stable PINK1 deficiency triggers compensatory autophagy of aberrant organelles, a process that might involve Beclin 1-dependent mechanisms and possibly compensatory increases in Parkin levels (69, 97). The question then inevitably arises: how can Parkin trigger mitophagy in the absence of PINK1, if PINK1 is absolutely required for it to be recruited to the OMM? It is not excluded that overdosage of Parkin may at least in part compensate for its requirement on PINK1 for mitochondrial recruitment. However, the existence of *PINK1/parkin*-independent, alternative pathways for organelle degradation is the most likely explanation for the observed compensatory autophagic response in the absence of PINK1. In addition, it should be considered that drawing conclusions on the status of the autophagic response may not be straightforward. Accordingly, a decrease in the steady-state levels of the autophagy marker, microtubule-associated protein light chain 3-II (LC3-II), was recently interpreted as indicative of reduced basal autophagy or as enhanced autophagic degradation by two independent groups who used different pharmacological approaches to dissect autophagic flux (265, 320).

Finally, the possible involvement of other PD-related genes in autophagic processes should also be investigated, partic-

**FIGURE 8.** The *PINK1/parkin* pathway regulates mitochondrial quality control. PINK1 may play roles in the proper folding and in the degradation of misfolded mitochondrial proteins by interacting with the protein chaperone TRAP1 and the serine protease Omi/Htra2. TRAP1 is directly phosphorylated by PINK1, and this modification mediates the protective functions of PINK1. Although PINK1 has affinity for Omi/Htra2, it promotes its phosphorylation indirectly, by activating the p38 MAPK signaling pathway. Phosphorylation of Omi/Htra2 at serine residues 124 and 400 activates the protein and its protective functions. PINK1 and Parkin have also concerted functions in priming mitochondria for mitophagy. Upon mitochondrial depolarization, the damaged organelles are separated from the healthy mitochondrial network through the action of the pro-fission GTPase Drp1. Parkin is recruited by PINK1 to the OMM, where it promotes, directly or indirectly, the ubiquitylation and proteasomal degradation of OMM proteins, including Mfn1/2 and VDAC1. Mfn1/2 degradation, facilitated by the retrotranslocation from the OMM to the cytosol mediated by the AAA+ ATPase p97, prevents refusion of depolarized mitochondria with intact organelles. Proteasomal degradation of OMM proteins leads to OMM rupture and is followed by autophagy-dependent degradation of the disrupted organelles. Mitophagy may be triggered by the BH3-only Bcl-2 family protein Nix, which contributes to mitochondrial membrane depolarization, leading to the generation of a burst of reactive oxygen species (ROS), followed by inhibition of mTOR signaling, and assembly of the phagophore. This structure may arise from the endoplasmic reticulum (231), kept in close proximity of mitochondria by protein-protein interactions between Mfn2 molecules embedded within endoplasmic reticulum and mitochondrial membranes (103); it may also originate directly from mitochondrial membranes, facilitating elimination of damaged mitochondrial portions. PINK1 participates in phagophore elongation by interacting with beclin 1, the regulatory subunit of the class-III PI3K (PI3KC3) complex which controls this process. Ubiquitylation of proteins at the OMM leads to recruitment of the ubiquitin-binding autophagic components, p62 and HDAC6; p62 interacts with lipidated LC3, an essential component of the autophagic machinery associated with the autophagosome membrane, while HDAC6 recruits the cortactin-dependent actin-remodeling machinery, leading to assembly of F-actin and facilitation of autophagosome-lysosome fusion. At the OMM, PINK1 also interacts with the GTPase Miro and the adaptor Milton, which is responsible for connecting damaged mitochondria to the microtubule motor machinery for delivery to the lysosome-rich perinuclear area and subsequent degradation.

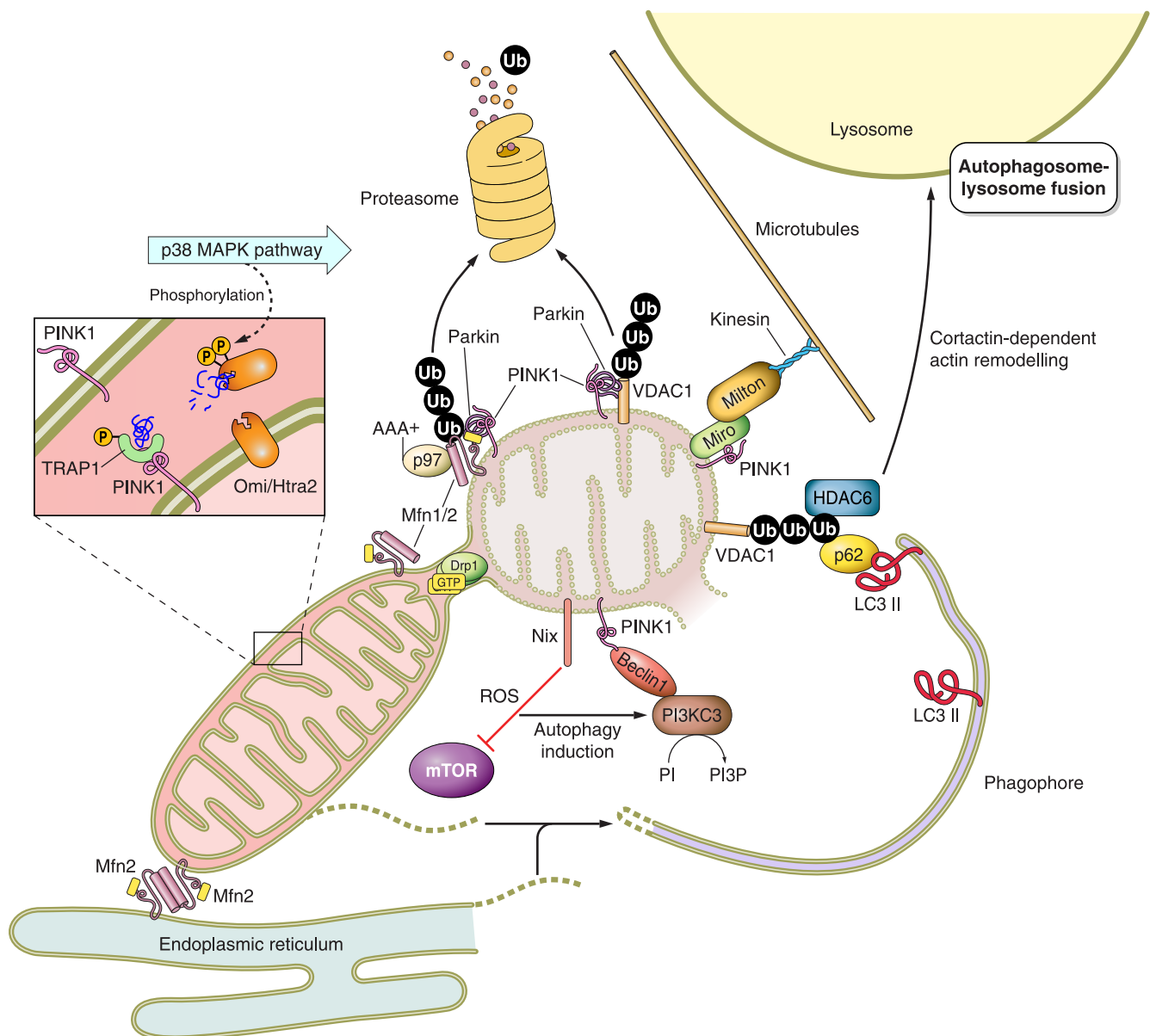


ularly of those involved in autosomal recessive PD, i.e., *DJ-1* and *APT13A2*. Of note, the extent of colocalization between mitochondrial and lysosomal markers was significantly reduced in immortalized primary embryonic fibroblasts from *DJ-1* knockout mice and in human primary fibroblasts from a PD patient with the *DJ-1* E64D mutation (320). In these cells, signs of defective autophagy-mediated lysosomal clearance were also observed, suggesting that DJ-1 might participate in these processes (320). Remarkably, accumulation of ultrastructurally abnormal mitochondria was also observed in transgenic mice overproducing  $\alpha$ -synuclein (364, 404, 599) and in neurons overproducing the PD-causing G2019S *LRRK2* variant (388). In addition, recent studies have provided support for the hypothesis that *LRRK2* directly regulates autophagic activity, although it is unclear whether it has positive or negative effects on this degradation pathway (8, 628). It is therefore

tempting to speculate that alterations in autophagy-dependent mitochondrial degradation pathways may be a unifying feature of models reproducing the genetic alterations found in familial forms of PD.

### 5. PD-related proteins affect intrinsic mitochondrial functions

There is abundant evidence that mutations in genes responsible for familial forms of PD cause defects in mitochondrial functions. Whether such defects are primary dysfunctions or are causally linked to alterations in the physiological processes controlling mitochondrial dynamics and clearance, or to other key upstream events, is unclear. Transgenic models provided the first evidence of mitochondrial respiratory dysfunction: reduced ATP levels were reported in Parkin-, PINK1-, or DJ-1-deficient *Drosophila* (75, 225,



493). Alterations in oxidative phosphorylation functions were described in *DJ-1* mutant *Drosophila* (225); in Parkin-depleted zebrafish (150); in mouse models in which the *parkin* (481), *PINK1* (173, 186), or *DJ-1* (320) genes were inactivated; or in cells or mice overproducing human  $\alpha$ -synuclein variants (374). Notably, deletion of *parkin* exon 3 in a knock out mouse model induced a nearly selective decrease in the abundance of proteins implicated in mitochondrial oxidative phosphorylation and oxidative stress control and was associated with an overall reduction in the respiratory capacity of mitochondria purified from striatum, in the absence of alterations in metabolic coupling (481). These changes were associated with reduced serum antioxidant potential and age-related signs of oxidative damage such as increased levels of protein carbonyls and the lipid peroxide 4-hydroxynonenal and are thus relevant to the physiopathology of the disease.

In addition to proteins involved in mitochondrial metabolism, the abundance of many other functional categories of proteins was altered in another *parkin* exon 3-deleted mouse model (502). Increased reduced glutathione (GSH) levels have been repeatedly observed in this model, possibly reflecting active compensatory antioxidant defenses (55, 268, 588). GSH is an abundant, multifunctional tripeptide with a reactive thiol capable of detoxifying 1) free radicals (superoxide and hydroxyl radicals, nitric oxide, carbon radicals) through direct interaction; 2) hydro and organic peroxides in conjugation with glutathione peroxidase; and 3) endogenous and exogenous toxins through the action of glutathione-S-transferases. It is also involved in protection of protein sulfhydryls against oxidation, and it binds to cysteine residues to modify protein activity. Since 1982 (504) several independent groups have reported a 40–50% decrease in glutathione levels specifically in the substantia nigra of PD patients but not in patients with multiple-system atrophy or progressive supranuclear palsy (reviewed in Ref. 706); it probably occurs early during disease development, since it is found in Incidental LB Disease, which is diagnosed at autopsy in normal individuals and may be the asymptomatic stage of PD. The loss of antioxidant capacity due to GSH depletion is therefore believed to contribute to the physiopathology of PD by exacerbating oxidative stress and mitochondrial dysfunction.

The functional capacity of striatal and cortical mitochondrial complexes is also decreased in PINK-deficient mice, although their abundance did not change, and ATP levels were not affected (173). Significant reductions in the enzymatic activity of aconitase, a key enzyme of the tricarboxylic acid cycle with an iron sulfide cluster sensitive to oxidative stress like mitochondrial complexes I and II, were observed in PINK1 and DJ-1-deficient mice (12, 173). Although markers of oxidative stress appeared unchanged in PINK1-deficient mice, hydrogen peroxide or heat shock challenges in primary cortical neurons induced more signif-

icant reductions in mitochondrial respiratory activities and membrane potential in the absence of PINK1 than in its presence, suggesting increased susceptibility to oxidative insults. Early and significant increases in mitochondrial hydrogen peroxide content were observed in DJ-1-deficient mice; they were paralleled by elevations in glutathione mitochondrial peroxidase activity, which compensated for a newly identified peroxiredoxin-like peroxidase activity of DJ-1 (12).

A decrease in mitochondrial membrane potential has been repeatedly, although not consistently (208), reported to be associated with 1) biallelic *PINK1* (138, 246) or *parkin* (439) gene mutations in human primary fibroblasts; 2) *PINK1* gene deletions in primary cortical and mesencephalic neurons (170, 186, 678), as well as at the synapse of the neuromuscular junction in *Drosophila* and in mouse embryonic fibroblasts (436); and 3) *PINK1* gene silencing in zebrafish embryos (13), PC12 cells (368), human neuroblastoma cells (175), and fetal mesencephalic stem cell-derived neurons (170, 678). More recently, it was observed in immortalized mouse embryonic fibroblasts from DJ-1-deficient mice (320). In some of these cell models, reduced membrane potentials were associated with decreased ATP synthesis (175, 186, 368, 439) and respiration (170, 175, 186, 246, 320, 439), altered glutathione homeostasis, and/or signs of oxidative stress (97, 170, 173, 208, 246, 320, 678). In some cases, alterations in oxygen consumption were attributed mainly to dysfunction of complex I (150, 246, 320, 374, 436, 439), which might be particularly vulnerable in familial PD, as it has long been suspected in sporadic PD. Of note, there was an inverse correlation between complex I activity and the degree of mitochondrial branching and length in fibroblasts from *parkin* mutation carriers, suggesting causal relationships between the morphological and functional alterations in these cells (439).

It has been proposed that Parkin modifies intrinsic properties of mitochondria, rendering them less susceptible to cytochrome *c* leakage induced by pro-apoptotic Bcl-2 family members and thus to downstream activation of caspases (29); whether these properties are linked to the reported alterations in oxidative phosphorylation, to defects in the clearance of dysfunctional organelles, or to other changes in mitochondrial physiology caused by Parkin deficiency (see below) remains to be determined. A few studies have suggested that Parkin and PINK1 might preserve mitochondrial biogenesis through maintenance of adequate mitochondrial pre-protein import efficacy (186) or by regulating mitochondrial DNA levels, transcription, and repair (175, 324, 533). PINK1 deficiency in mice was associated with a progressive reduction in the import of matrix-targeted pre-proteins, which probably contributed to the reported mitochondrial respiratory defects, but was possibly also the direct consequence of a reduction in inner membrane potential (186). PINK1 depletion in SH-SY5Y cells was

associated with lower mitochondrial DNA levels, less mitochondrial transcription factor A (TFAM), and reduced mitochondrial DNA synthesis (175). These alterations were not rescued by overproduction of Parkin, which is surprising given the findings of Rothfuss et al. (533), who reported enhancement of mitochondrial DNA synthesis and transcription in a cell line genetically modified to overproduce the protein. Chromatin immunoprecipitated with anti-Parkin antibodies was specifically enriched in mitochondrial DNA from native SH-SY5Y cells and, to a lesser extent, from mouse brain (533). Parkin was directly associated with several regulatory and coding regions of the mitochondrial genome, which were also covered by TFAM (533); these proteins might therefore cooperate during mitochondrial DNA transcription (324). Importantly, exogenous Parkin enhanced mitochondrial DNA repair under conditions of oxidative stress, whereas the loss of functional Parkin in fibroblasts from a patient with compound *parkin* gene mutations reduced repair capacity compared with cells from a control (533).

Finally, there is evidence that both PINK1 and Parkin are involved in maintenance of calcium homeostasis (170, 539). Gandhi et al. (170) recently provided spectacular insight into the potential mechanisms that underlie defects in mitochondrial respiration and loss of mitochondrial membrane potential in the absence of PINK1. They showed that the generalized impairment of respiration, the altered redox state, and the reduction in basal mitochondrial membrane potential caused by *PINK1* gene knockdown in mouse and human neurons were reversed with respiratory chain substrates, demonstrating that these were not primary defects. Remarkably, the major consequences of the PINK1 deficiency, mitochondrial calcium overload due to dysfunction of the mitochondrial  $\text{Na}^+/\text{Ca}^{2+}$  exchanger, were not corrected by respiratory chain substrates. Secondarily to this primary dysfunction, reactive oxygen species were produced at higher rates in the cytosol and in the mitochondria of PINK1-deficient neurons, leading to oxidative damage and inhibition of the glucose transporter, impairing glucose uptake (170). Loss of Parkin function may also impair intracellular calcium homeostasis: in human neuroblastoma cells lines overproducing pathogenic Parkin variants, but not normal Parkin, Sandebring et al. (539) recently observed that the basal hydrolysis of phosphatidylinositol (PI) increased in response to an increase in the activity of the Parkin substrate phospholipase C- $\kappa$  (PLC- $\kappa$ ), involved in the regulation of intracellular calcium (539). PLC- $\kappa$  activation increased basal intracellular calcium concentrations, which were directly responsible for the greater susceptibility of these cells to the pro-parkinsonian neurotoxin 6-hydroxydopamine. Surprisingly, normal Parkin did not have the expected inverse effects on PLC- $\kappa$  activity or intracellular calcium concentrations in transfected cells compared with nonmodified cells; it is therefore unclear whether the reported observations reflect unexpected dominant activi-

ties of pathogenic Parkin variants on PLC- $\kappa$  rather than loss of protein function. However, PLC- $\kappa$  levels were increased in brain homogenates of *parkin* knockout mice (109), and basal PI hydrolysis and calcium concentrations were increased in *parkin*-inactivated neuroblastoma cells (539), suggesting that altered intracellular calcium handling due to activation of PLC- $\kappa$  signaling may indeed contribute to the cellular vulnerability conferred by loss of Parkin function. It would be of value to explore, in neurons, the impact of overactivation of this pathway on intracellular ROS production, glucose uptake, mitochondrial membrane potential, and mitochondrial respiration to determine whether similar mechanisms underlie the increased vulnerability of Parkin- and *PINK1*-deficient neurons to calcium-induced cell death.

Of note, abnormal calcium handling may be particularly devastating for adult dopaminergic neurons in the substantia nigra, which, in contrast to the less vulnerable dopaminergic neurons in the ventral tegmental area (VTA), maintain their rhythmic pacemaker activity through calcium rather than sodium channels (59). The continuous exposure of this neuronal population to large influxes of cytosolic calcium might, if not appropriately buffered by mitochondria, increase their susceptibility to neurodegeneration. Dopaminergic neurons expressing high levels of calcium-binding protein such as calbindin are, indeed, spared in sporadic PD (101). Higher intracellular calcium concentrations in nigral compared with VTA neurons were also correlated with a greater susceptibility to L-dopa toxicity; the degree of vulnerability to L-dopa was proportional to intracellular dopamine concentrations, which were also higher in substantia nigra neurons than in VTA neurons, possibly reflecting a calcium-dependent regulation of aromatic amino acid decarboxylase (440). Since intracellular calcium is required for efficient degradation of proteins by the autophagy-lysosomal pathway and mitochondrial calcium overload may be part of a cascade of events leading to mitophagy (644), fruitful connections might be found between dysregulation of calcium homeostasis and impairment of autophagic/mitophagic processes in PINK1- or Parkin-deficient models.

## B. Evidence for Links to Protein Degradation Pathways

### 1. *Parkin, the ubiquitin-proteasome system and other ubiquitylation pathways*

As in other neurodegenerative disorders, the presence of hallmark inclusions filled with proteinaceous material in sporadic PD has fuelled speculation that failure of specific protein degradation pathways might play a primary role in the physiopathology of the disease. The involvement of ubiquitin-mediated processes has been suspected since immunoreactivity against this small protein was detected in Lewy bodies in patients with sporadic PD (325); identifica-

tion of the I93M mutation in *UCHL1* in a PD family supported this hypothesis, which, probably prematurely, gained considerable strength in 2000 with the discovery of the E3 ubiquitin-protein ligase activity of Parkin (262, 563, 709). Indeed, the role of UCH-L1 is questionable, as only one affected sib pair carrying the mutation has been reported in the literature (cf. sect. IIB3). In addition, the type of ubiquitylation promoted by Parkin has only relatively recently gained the interest of the scientific community, despite its relevance in determining the fate of the modified proteins, which is far from being systematically linked to proteasomal degradation.

Protein ubiquitylation is a complex and versatile process that begins with the ATP-dependent activation of the COOH-terminal group of an ubiquitin molecule by an E1 ubiquitin-activating enzyme, followed by the transfer of ubiquitin to specific E2 ubiquitin-conjugating enzymes and its final conjugation to the  $\epsilon$ -amino groups of one or several lysine residues of an acceptor protein by one of a multitude of E3 ubiquitin-protein ligases or ligase complexes with selective targets (693). A single ubiquitin molecule (mono/multimonoubiquitylation) or a chain (polyubiquitylation) can be attached to one or several lysines in the target protein. Ubiquitin chains may contain a single type of isopeptide linkage formed through homogeneous attachment of each successive ubiquitin to only one of the seven internal lysine residues of the preceding molecule, but the ubiquitin molecules may also contain mixed and forked linkages with ever-increasing numbers of combinations and topologies (693). Depending on the type of ubiquitin linkage, ubiquitylated proteins are recognized by a plethora of preferential “decoders,” i.e., proteins bearing ubiquitin-binding domains such as the ubiquitin-interacting motifs (UIM) or the ubiquitin-associated domains (UBA). These domains connect the ubiquitylation signal to downstream effectors of signaling pathways that have a variety of functions: regulation of receptor trafficking, cell cycle progression, gene transcription, and immune responses, in addition to the well-known protein degradation by the 26S proteasome (257). The mechanisms that govern the fate of proteins modified by specific ubiquitin chains, i.e., recognition by specific ubiquitin-binding proteins and coupling to particular biological processes remain poorly understood. Although ubiquitin chains formed via lysine-48 are known to regulate protein stability and are believed to be the dominant chain leading to proteasomal degradation (243), other types of chains may also serve this purpose (298, 693).

When the enzymatic activity of Parkin was discovered, its function was intuitively linked to the degradation of polyubiquitylated proteins by the 26S proteasome in the ubiquitin proteasome pathway (563). It was speculated that loss of Parkin function due to disease-causing mutations in its gene would lead to the abnormal accumulation of potentially

toxic substrates and, secondarily, to neurodegeneration. The absence of Lewy bodies in the first cases of *parkin*-linked PD analyzed post mortem (232, 438), the description of Parkin immunoreactivity in Lewy bodies (553), and the contribution of the protein to the formation of Lewy body-like inclusions in cell models (72) led to the hypothesis that Parkin-dependent ubiquitylation may be essential for the formation of these inclusions. However, typical Lewy bodies have since been found in patients with biallelic *parkin* gene mutations (87, 142, 515, 542; cf. sect. IIE), and the presence of Parkin in such inclusions has been brought into question (496, 703).

More than 20 putative Parkin substrates have been identified since it was discovered to be an E3 ubiquitin-protein ligase (for review, see Ref. 89), several of which appear to be aggregation-prone proteins that promote cell death when overproduced in cell, *Drosophila*, or rodent models (90, 127, 261, 308, 315, 634, 688). Some of these proteins were indeed found to be modestly upregulated in the brains of patients with *parkin* gene mutations or of *parkin* knock-out mice (109, 261, 314, 315, 502), in accordance with the “proteasomal hypothesis” for *parkin*-linked PD; there are discrepancies, however, across studies (cf. Ref. 89). Furthermore, some of these proteins have been detected in a proportion of the Lewy bodies in sporadic PD patients (90, 251, 396, 445, 652). According to a recent study, Parkin may interact with PINK1 and DJ-1 in a 200-kDa multiprotein complex with E3 ubiquitin-protein ligase activity that ensures the proteasomal degradation of misfolded Parkin substrates, particularly synphilin-1 and Parkin itself (681), consistent with the previously described coexistence of Parkin and DJ-1 in a large protein complex in the human brain (20). Parkin has also been found in a stable noncovalent 110-kDa complex *in vivo*, but none of the previously identified Parkin protein partners or substrates, including DJ-1, was detected in this complex (641). Finally, several studies have reported physical interactions between Parkin and proteasome subunits, suggesting mechanisms by which Parkin assembles with its substrates on the proteasome to promote their degradation or modulate proteasome activity (536). These discoveries have stimulated the search for proteasome dysfunction. Significant reductions in the proteasome activity and alterations in proteasome subunit composition (419, 420) have been found in the substantia nigra of patients with sporadic PD (165, 419, 421, 624), supporting the hypothesis that proteasome dysfunction may indeed play a role in the pathogenesis of PD. However, since these defects have only been found in the substantia nigra, dysfunction of this proteolytic machinery in sporadic PD is probably secondary to neuronal degeneration, rather than the primary defect that initiates the neurodegenerative process (165, 419, 624).

Nevertheless, the possibility that generalized proteasome dysfunction and the consequent accumulation of undegrad-

able substrates causes preferential degeneration of neuronal systems affected in PD has been explored *in vivo*. In a first exciting study, McNaught et al. (422) reported progressive nigrostriatal degeneration and Lewy body-like inclusions in rats treated with proteasome inhibitors, similar to pathology observed in PD (422). Some of these observations have been replicated (548, 707), but similar approaches in rodents or nonhuman primates have also failed to produce reliable effects (41, 318, 326, 413), even when proteasome inhibitors were combined with the mitochondrial neurotoxin MPTP (281, 567). Therefore, environmental compounds that are deleterious for the proteasome machinery are unlikely to play a determinant role in the physiopathology of sporadic PD. Whether genetic alterations that compromise the integrity of this machinery are involved deserves further investigation; spatially restricted conditional inactivation, in mice, of *Psmc1*, which encodes an essential subunit of the 26S proteasome, leads indeed to neurodegeneration and the formation of inclusions resembling precursors of Lewy bodies in the substantia nigra and forebrain (22).

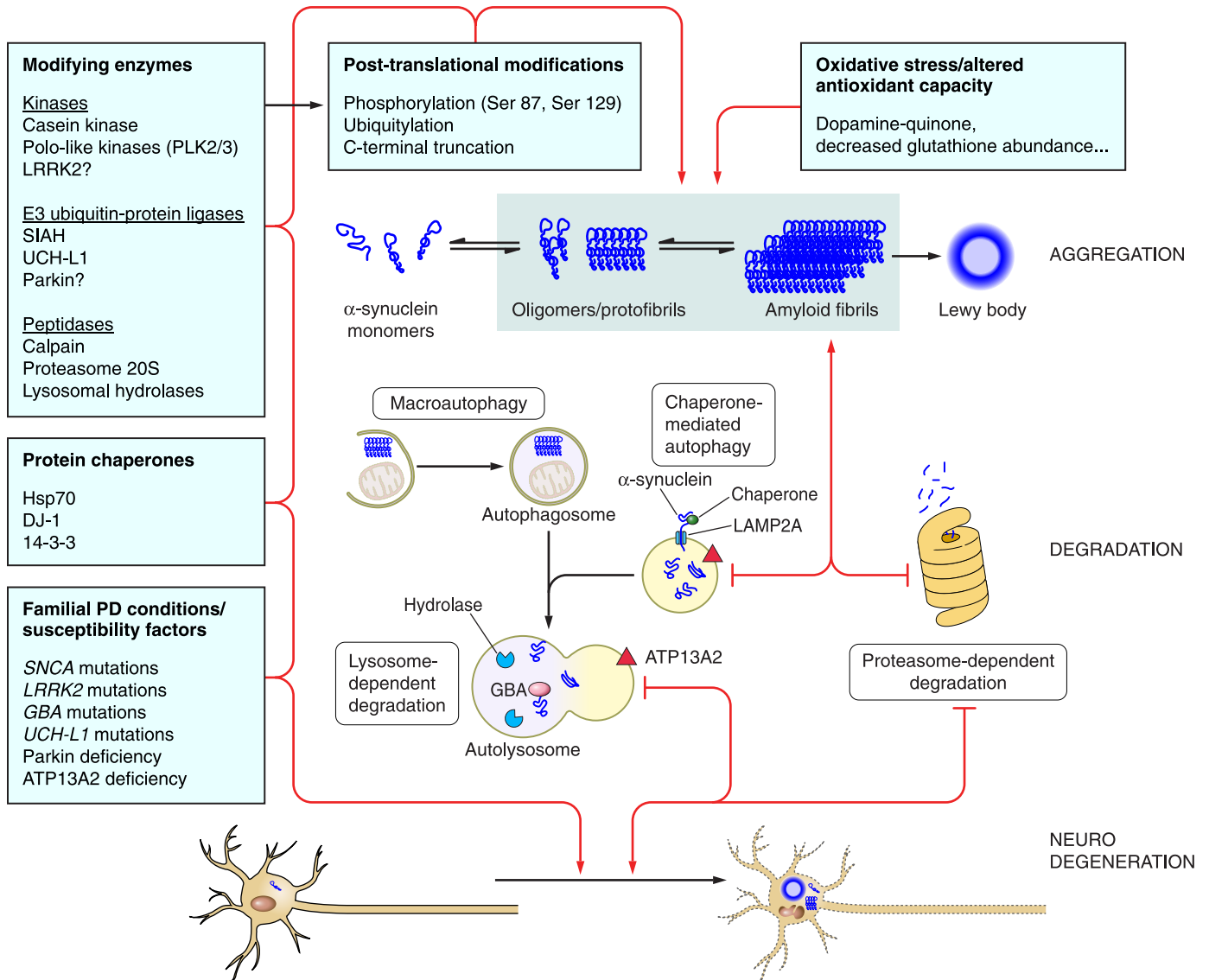
The exclusive involvement of the E3 ubiquitin-ligase Parkin in proteasomal functions is now being questioned. It is also becoming increasingly clear that this multifunctional protein does more than participate in the ubiquitin-proteasome pathway. *In vitro* studies have shown that Parkin preferentially monoubiquitylates its substrates (141, 223, 276, 366, 414, 434, 629), or performs K63-linked polyubiquitylation (241, 360, 471, 558). Protein chaperones and cofactors, like the E3/E4 protein, CHIP, or specific E2 enzymes, most likely modulate the different ubiquitylation activities of Parkin (128, 260, 558). These activities have revealed novel regulatory roles for Parkin in cell signaling that underlie its broad neuroprotective properties. Monoubiquitylation of the UIM adaptor protein Eps-15 by Parkin delayed endocytosis and degradation of the epidermal growth factor (EGF) receptor (EGFR) by interfering with the ability of Eps-15 to bind ubiquitylated EGFR, thus promoting EGF signaling through the PI(3)K-Akt pathway (141). Similarly, monoubiquitylation of the PDZ protein PICK1 suppressed PICK-dependent potentiation of the activity of acid-sensing ion channels, known to mediate excitotoxicity (276). Parkin contributes to the stress-induced activation of the neuroprotective nuclear factor (NF)- $\kappa$ B signaling pathway through K63-linked polyubiquitylation of two key negative regulators of this pathway, IKK $\kappa$ -NEMO and TRAF2 (241). Remarkably, this modification of IKK $\kappa$ -NEMO involved cooperation by the heterodimeric E2 enzyme UbcH13/Uev1 and enhancement of Parkin activity through direct phosphorylation by PINK1, a finding which further increases our understanding of the complex interactions between PINK1 and Parkin in biological processes (558). In several studies, Parkin negatively regulated the c-Jun NH<sub>2</sub>-terminal kinase (JNK) (58, 274, 366), previously found to be activated in MPTP- or 6-hydroxydopa-

mine-induced neurotoxic models of PD (98), possibly through the multimono-ubiquitylation-dependent modulation of the activity of Hsp70 (366). Finally, it was shown that Parkin is a transcriptional repressor of p53, probably independently of its E3 ubiquitin ligase activity (95). Of note, p53-dependent cell death is as a possible point of intersection between several specific PD-causing pathways: phosphorylation of p53 or reduction in its levels were shown to intervene in cell death caused by dopamine and 6-hydroxydopamine (100, 448), as well as in protective responses mediated by  $\alpha$ - and  $\beta$ -synuclein (9, 94) or DJ-1 (45, 178); moreover, p53 inhibitors are protective against MPTP (129). Parkin interacts physically with the p53 gene promoter, reducing p53 gene transcription and protein levels in a RING1-dependent manner and providing protection against 6-hydroxydopamine-induced caspase-3 activation and cell death. Consistent with these findings, Parkin deficiency or its alteration by PD-causing gene mutations correlated with higher amounts of p53 mRNA and protein in mouse and human brains, suggesting that p53-dependent processes may contribute to PD pathogenesis (95). Future studies will need to address the mechanisms that regulate the nuclear translocation of Parkin, which is primarily found in the cytoplasm under basal conditions. Despite these remarkable advances, the potentially intricate relationships between the multiple putative roles of Parkin and their causal links to the defects in synaptic transmission reported in *parkin* knockout animals (193, 240, 268, 306, 403) or to neurodegeneration in *parkin*-linked PD remain elusive.

## 2. $\alpha$ -Synuclein in PD: posttranslational modifications, aggregation, and degradation

Genetics has provided compelling evidence for the long suspected role of excess  $\alpha$ -synuclein in the physiopathology of PD (63, 253, 580); this has been extensively confirmed in animal models in which overproduction of normal or PD-causing variants of  $\alpha$ -synuclein cause degeneration of nigral dopaminergic neurons (137, 147, 303, 304, 371). Although there is still much debate as to the relevance of Lewy bodies to disease progression, it is recognized that  $\alpha$ -synuclein is one of the most abundant components of these inclusions, in which it accumulates under a variety of posttranslationally modified forms: phosphorylated at serine-129 (P<sup>129S</sup>- $\alpha$ -synuclein), ubiquitylated, COOH-terminally truncated, and nitrated (11, 17, 157, 180, 229, 593, 624). Whether and in what order these modifications cooperate to progressively assemble the protein into insoluble amyloid fibrils and modulate toxicity are controversial issues that are under intense investigation (FIG. 9).

The role of phosphorylation at serine-129, suspected to be the dominant pathological modification in human synucleinopathies (11, 157), has been studied in a variety of models, but with contradictory results (16, 64, 197, 418, 601). An  $\alpha$ -synuclein variant carrying a negatively charged residue as-



**FIGURE 9.** Regulation of the aggregation, degradation, and toxicity of  $\alpha$ -synuclein. The aggregation of  $\alpha$ -synuclein is a multistep process, involving the formation of assembly intermediates, oligomers, and soluble protofibrils, which precedes the formation of insoluble amyloid fibrils recruited into Lewy bodies. The cell antioxidant capacity, as well as byproducts of oxidative stress such as dopamine-quinone, affects this process. Several posttranslational modifications, particularly phosphorylation at serines 87 and 129, ubiquitylation and COOH-terminal truncations, are suspected to modulate  $\alpha$ -synuclein aggregation; their net effects and possible concerted or antagonistic actions in modulating  $\alpha$ -synuclein accumulation and toxicity are current topics of intense investigation. Several candidate enzymes for these posttranslational modifications have been identified, but their precise physiological and pathological roles remain to be determined. Protein chaperones, such as Hsp70 and DJ-1, antagonize the pathological accumulation of  $\alpha$ -synuclein, whereas mutations in the PD genes *SNCA*, *LRRK2*, *GBA*, *UCHL-1*, and *ATP13A2* are suspected to contribute to  $\alpha$ -synucleinopathy and  $\alpha$ -synuclein-dependent neurodegeneration. Loss of Parkin function may retard  $\alpha$ -synuclein aggregation and/or mitigate its toxicity, possibly through the establishment of neuroprotective compensatory mechanisms that lead to a less severe form of PD with slow progression. The degradation of  $\alpha$ -synuclein is mediated by both the proteasome machinery and the autophagy/lysosomal pathway. Macroautophagy may be responsible for degradation of  $\alpha$ -synuclein aggregates, whereas CMA degrades the soluble protein. The lysosomal uptake of PD-causing  $\alpha$ -synuclein variants, dopamine- $\alpha$ -synuclein adducts and possibly postranslationally modified and oligomeric  $\alpha$ -synuclein species is less efficient than that of soluble normal  $\alpha$ -synuclein. Mutant and possibly an excess of normal  $\alpha$ -synuclein impair the functions of the proteasome and the lysosome-dependent degradation pathways, which in turn promotes  $\alpha$ -synuclein build-up and toxicity.

partate at position 129 (S129D) mimicking constitutive phosphorylation enhanced toxicity in dopaminergic neurons of a transgenic *Drosophila* model, whereas a nonphosphorylatable alanine residue at position 129 (S129A) suppressed tox-

icity (64); in this study, there was no correlation between the propensity of the proteins to aggregate and their toxicity. Observations in SH-SY5Y cells were similar (601), but in two independent viral vector-based rat models, the

amino acid substitution S129A dramatically increased  $\alpha$ -synuclein toxicity, whereas S129D  $\alpha$ -synuclein was less toxic than the normal protein (16, 197). In a third study, viral vector-mediated delivery of normal, S129D, and S129A  $\alpha$ -synuclein to the rat SN induced similar pathological changes (418). In a mouse model transgenic for the A30P variant of human  $\alpha$ -synuclein, activation of the pro-apoptotic caspase-9 was preferentially associated with neurons in which P<sup>129S</sup>- $\alpha$ -synuclein accumulated (154). Furthermore, the solubility of P<sup>129S</sup>- $\alpha$ -synuclein decreased in relation to the appearance of neurodegenerative symptoms in this model, whereas  $\alpha$ -synuclein phosphorylated at S87 (another residue known to be modified) remained mostly soluble (154). In cell models, phosphorylation at S129 increased the tendency of  $\alpha$ -synuclein to form inclusions (583, 601). However, in vitro analysis of the structural properties of aggregating  $\alpha$ -synuclein by biophysical methods recently demonstrated that phosphorylation at serine-129 inhibits  $\alpha$ -synuclein fibrillization, indicating that P<sup>129S</sup>- $\alpha$ -synuclein in Lewy bodies may not correspond to the fibrillar species that accumulate in these models, or that other factors modulate P<sup>129S</sup>- $\alpha$ -synuclein fibrillization in vivo (483). Importantly, this study also provided compelling evidence that the phosphorylation mimics S129E/D do not faithfully reproduce the effects of phosphorylation so that caution should be used in drawing conclusions based on their use (483). Another point that is rarely taken into consideration when comparing the toxicity of the protein variants studied concerns their relative expression levels, which may well influence the experimental outcome per se, irrespective of the intrinsic protein properties. Identifying the natural kinases and phosphatases responsible for phosphorylating/dephosphorylating  $\alpha$ -synuclein will be essential for elucidation of the physiopathological relevance of these modifications and may also suggest valuable new therapeutic targets. Casein kinases can phosphorylate  $\alpha$ -synuclein in cell models (468, 601), but recently, in vitro and in vivo evidence has been provided that members of the Polo-like kinase (PLK) family, particularly PLK2 and PLK3, may be the major kinases involved in phosphorylation at residue S129 (264, 416) (FIG. 9). The relevance of phosphorylation at S87 is currently discussed.  $\alpha$ -Synuclein phosphorylated at S87 was not found by several authors in pathological inclusions in humans or in animal models (11, 154, 661). However, a recent study reported increased abundance of this  $\alpha$ -synuclein species associated with the membrane fraction in brain extracts from transgenic mouse models of synucleinopathies, or from patients with Alzheimer's disease, Lewy body disease, or multiple system atrophy; immunoreactivity against this protein was also found within Lewy bodies (482).

$\alpha$ -Synuclein is also modified by oligoubiquitylation and COOH-terminal truncation, although the function of these modifications is still unknown. Several studies have found ubiquitin molecules covalently attached to  $\alpha$ -synuclein in

Lewy bodies, perhaps secondary to aberrant deposition of  $\alpha$ -synuclein, since it only concerns a minor fraction of the total protein found in the inclusions (11, 229, 624). Liquid chromatography-mass spectrometry with peptide mass fingerprinting has shown P<sup>129S</sup>- $\alpha$ -synuclein to be the major ubiquitylated species in synucleinopathies; three major lysines, at positions 12, 21, and 23, are involved (11). Identification of a lysine-48 residue in the ubiquitin molecule by this approach strongly suggests that a brief ubiquitin chain attached to P<sup>129S</sup>- $\alpha$ -synuclein is extended via lysine-48 (11). Polyubiquitylated P<sup>129S</sup>- $\alpha$ -synuclein-species may be formed in vivo and rapidly degraded by the proteasome, explaining their absence in  $\alpha$ -synuclein preparations from the pathological human brain. It was shown that the E3 ubiquitin-protein ligase, seven in absentia homolog (SIAH), mono- or diubiquitylates  $\alpha$ -synuclein in cell models (335, 358). This modification concerns several  $\alpha$ -synuclein lysine residues, some of which at positions that are ubiquitylated in human synucleinopathies and promote the aggregation and toxicity of the protein (335, 534). Coimmunoprecipitation of  $\alpha$ -synuclein and SIAH from brain tissue and immunoreactivity to SIAH in a proportion of Lewy bodies in PD patients suggest that this molecular interaction is relevant to the physiopathology of the disease (358, 534). COOH-terminal truncations of  $\alpha$ -synuclein, some of which associated with S129 phosphorylation, also generate protein species that have been repeatedly found in lesions in patients with synucleinopathies (11, 17, 624). Although the mechanisms involved in their generation are unknown, some of these modifications may be produced under physiological conditions, since they have also been identified in healthy tissues (11). In vitro studies have provided evidence that truncated  $\alpha$ -synuclein assembles faster into filaments than the full-length protein, whether wild-type or mutated (446, 556). Studies in transgenic mice have shown that COOH-terminal truncations may also contribute to the formation of  $\alpha$ -synuclein fibrils in vivo and contribute to the pathological changes initiating neurodegenerative processes in dopaminergic neurons (99, 622).

In addition to posttranslational modifications, other factors are suspected to increase the propensity of  $\alpha$ -synuclein to aggregate (FIG. 9). One is the neurotransmitter dopamine (683) and its oxidation products, quinones, which have been shown to react with  $\alpha$ -synuclein in vitro and to form adducts that prolong the lifetime of protofibrils but inhibit fibrillization, providing a clue to the mysterious molecular mechanisms that govern the specificity of the lesions in PD (84). The specific role of each molecular species formed during  $\alpha$ -synuclein aggregation, particularly soluble oligomers and protofibrils, or insoluble fibrils in mediating the neurotoxic effects of the protein, remain poorly understood. Because acceleration of in vitro oligomerization but not fibril formation seems to be a common effect of the PD-causing A53T and A30P  $\alpha$ -synuclein substitutions (83), it has been speculated that the soluble oligomers may be the

toxic species; however, this property does not seem to be shared by the E46K variant (155). This hypothesis has been supported, however, by the demonstration that annular protofibril intermediates of the aggregation process form pores that permeabilize biological membranes (329, 650), although the relevance of these to PD pathogenesis *in vivo* remains unclear.

The degradation of  $\alpha$ -synuclein is a debated issue, and it is likely that both the ubiquitin-proteasome system and pathways of lysosomal degradation intervene in regulating the steady-state levels of the protein under physiological conditions. Degradation of  $\alpha$ -synuclein by the proteasome (26, 623) and the formation of proteinaceous inclusions in neuronal cells treated with proteasome inhibitors has been described (524, 525), but the involvement of autophagy and lysosomes has also been demonstrated (65, 334, 497, 662). There is evidence that mutant, and possibly excessive normal  $\alpha$ -synuclein, impairs the function of both of these protein degradation pathways, facilitating its own pathological accumulation (92, 507, 585, 617) (FIG. 9).

In 2004, Cuervo et al. (92) identified, in the  $\alpha$ -synuclein sequence, the pentapeptide motif required to target cytosolic proteins to lysosomal degradation via chaperone-mediated autophagy (CMA); they also showed that  $\alpha$ -synuclein can be taken up and degraded through CMA in isolated liver lysosomes, and that general lysosome inhibitors stabilize the monomeric protein in neuronal cells (92). In cell models, as in the rodent brain,  $\alpha$ -synuclein was shown to interact physically with lysosome-associated membrane protein 2A (LAMP-2A), a transmembrane receptor of substrates for lysosomal degradation involved in their translocation into the organelle, providing support for the idea that CMA is involved in its clearance (92, 649). Consistently, LAMP-2A gene silencing slowed the degradation of monomeric and oligomeric  $\alpha$ -synuclein species in several different types of neurons, including primary neurons from the ventral midbrain (649). However, in addition to CMA, macroautophagy also intervened in  $\alpha$ -synuclein degradation, although there is debate as to whether the normal protein and PD-causing variants are equally sensitive to this process (649, 662, 697). PD-causing substitutions in  $\alpha$ -synuclein dramatically increased their affinity for LAMP-2A and blocked CMA, resulting in inhibition of their own uptake as well as that of other CMA substrates (92). The S129E  $\alpha$ -synuclein variant, as well as oligomeric species of  $\alpha$ -synuclein, bound to lysosomal membranes but were less efficiently translocated across the membranes, although they did not interfere with the degradation of other CMA substrates (405). In contrast, dopamine- $\alpha$ -synuclein adducts formed *in vitro* blocked CMA in isolated lysosomes, like PD-causing variants. Consistently, exposure of primary ventral midbrain neurons to cytosolic dopamine concentrations identical to those required to produce dopamine- $\alpha$ -synuclein adducts *in vitro* reduced CMA activity by 50%

(405), an effect which was not observed in neurons from  $\alpha$ -synuclein-deficient mice. These observations provide another potential clue to the specificity of the lesions in PD. As mentioned in section II B1, moderate elevations in  $\alpha$ -synuclein levels, related to aging (70, 355) or to genetic alterations, may have inhibitory effects on neurotransmitter release (454). The resulting excess in cytosolic dopamine in nigral neurons, if not compensated by efficient vesicular storage (377), may in turn promote the accumulation of  $\alpha$ -synuclein, thus perpetuating a vicious circle that may further increase the vulnerability of this neuronal population and, in the end, lead to PD.

### 3. Is there functional interplay between Parkin and $\alpha$ -synuclein?

Since  $\alpha$ -synuclein in Lewy bodies is in part oligoubiquitylated (11, 229, 624), it was suggested that the E3 ubiquitin-protein ligase Parkin may be directly involved in the ubiquitylation and possibly the degradation of the protein. The finding, in 2001, that a new O-glycosylated form of  $\alpha$ -synuclein, exclusively found in the human brain, increased in abundance in PD patients with *parkin* gene mutations and was directly ubiquitylated by Parkin, constituted an exciting indication that a physiopathological pathway might be shared among diseases with apparently distinct etiologies (565). Unfortunately, other researchers have failed to detect O-glycosylated  $\alpha$ -synuclein in the diseased human brain (229, 624) or to demonstrate an enzyme-substrate relationship between Parkin and  $\alpha$ -synuclein (72). Today it is generally accepted that Parkin does not interact directly with  $\alpha$ -synuclein, but overproduction of Parkin provides protection against the deleterious effect of  $\alpha$ -synuclein in various models, including neuronlike cell lines (301), primary mesencephalic neurons (507), *Drosophila* (233, 234, 688), and rodents (372). These studies have provided support for the idea that Parkin and  $\alpha$ -synuclein may intervene in a common pathogenic pathway, although whether and where they interact in this pathway is still unclear.

Lo Bianco et al. (372) suggested that Parkin might regulate the deposition of  $\alpha$ -synuclein phosphorylated at S129, since they observed a correlation between the formation of inclusions of phosphorylated  $\alpha$ -synuclein and neuroprotection by Parkin codelivered with  $\alpha$ -synuclein to the rat substantia nigra by lentiviral vector-mediated gene transfer (372). It should be noted, however, that, in the above-mentioned studies, Parkin was overproduced, although Parkin function is lost in autosomal recessive PD caused by *parkin* gene mutations, and perhaps in sporadic PD through age-related or oxidative and nitrosive stress-dependent changes in its activity (71, 332, 496, 690). It was therefore essential to determine whether Parkin depletion would exacerbate the deleterious effects of  $\alpha$ -synuclein in models of  $\alpha$ -synucleinopathy. In 2006, von Coelln et al. (651) analyzed a transgenic mouse carrying the human A53T variant of  $\alpha$ -synuclein in which *parkin* was also inactivated. In this model,



Parkin deficiency had no effect on the abundance or distribution of human  $\alpha$ -synuclein, its solubility, or ubiquitylation. In addition, the age-dependent, lethal neurodegenerative phenotype caused by expression of the human  $\alpha$ -synuclein transgene was similar in the presence or absence of Parkin (50% of the animals severely affected at  $\sim$ 12 mo of age). These observations did not support a major role for endogenous Parkin in the modulation of  $\alpha$ -synuclein aggregation or toxicity.

Surprisingly, however, by using a similar approach, we recently revealed an unexpected relationship between Parkin deficiency and  $\alpha$ -synucleinopathy: in a longitudinal behavioral study in *parkin* knockout mice crossbred with mice transgenic for the A30P variant of human  $\alpha$ -synuclein (hA30P $\alpha$ -syn), we observed a significant delay in the development of motor impairment in the absence of Parkin, and a later manifestation of the neurodegenerative disorder caused by overproduction of  $\alpha$ -synuclein (154). The disorder in hA30P $\alpha$ -syn mice was less aggressive than in the model studied by von Coelln et al. (651), since it did not manifest before 15 mo of age, suggesting that the relatively moderate disease-modifying effect of Parkin may have been masked in mice transgenic for the A53T  $\alpha$ -synuclein variant. At the end stage of the disease, the neuropathology of hA30P $\alpha$ -syn mice with or without Parkin was similar, suggesting that the absence of Parkin delays disease without affecting the nature of neuropathological events associated with  $\alpha$ -synuclein deposition: whether or not Parkin was present, deposits of ubiquitin and  $\alpha$ -synuclein, particularly P<sup>129S</sup>- $\alpha$ -synuclein, were observed throughout the brain stem and spinal cord of affected but not healthy mice. Interestingly, immunoreactivity to ubiquitin was less abundant than staining for P<sup>129S</sup>- $\alpha$ -synuclein, although they were systematically associated, suggesting that a fraction of phosphorylated  $\alpha$ -synuclein is directly modified by ubiquitylation, as observed in human synucleinopathies (11). In end-stage Parkin-deficient mice producing A30P  $\alpha$ -synuclein, the proportion of P<sup>129S</sup>- $\alpha$ -synuclein-immunoreactive deposits associated with ubiquitin tended to be lower than in mice with normal *parkin* alleles; since we did not observe Parkin-dependent ubiquitylation of phosphorylated  $\alpha$ -synuclein in a purely in vitro ubiquitylation assay, this finding may be indicative of less advanced synucleinopathy. Since only a fraction of  $\alpha$ -synuclein is ubiquitylated in Lewy bodies, it has indeed been suggested that ubiquitylation could be secondary to pathological modification and/or deposition of the protein, in an attempt to direct it towards ubiquitin-proteasome or lysosomal degradation (229, 624). Altogether, our study suggested that loss of Parkin function may beneficially reduce  $\alpha$ -synuclein build-up in the slowly progressing *parkin*-related parkinsonian syndromes, in which  $\alpha$ -synucleinopathy is generally less severe than in sporadic disease, if not absent (87). Future studies will need to explore this possibility further, by addressing the underlying mechanisms, particularly in do-

paminergic neurons, which we were unfortunately unable to analyze due to lack of A30P  $\alpha$ -synuclein gene expression in this neuronal population (154). These mechanisms are most probably indirect and may be sought among the compensatory neuroprotective responses triggered by Parkin deficiency. For example, Parkin-deficient mice had elevated brain levels of reduced glutathione (268), an established antioxidant substantially lowered in abundance in the substantia nigra of PD patients (706; cf. sect. IIIA5), increasing the resistance of Parkin-deficient primary midbrain neurons to nitric oxide, L-dopa, or proteasome inhibitors (55, 56, 588). That such changes in glutathione homeostasis may also have beneficial effects on synucleinopathy is suggested by the observation that inactivation of genes involved in glutathione synthesis or conjugation enhances  $\alpha$ -synuclein toxicity in yeast cells and in dopaminergic neurons in transgenic *Drosophila*, whereas genetic or pharmacological activation of these pathways is protective (630, 673) (FIG. 9).

A number of additional clues to possible indirect functional interactions between Parkin and  $\alpha$ -synuclein are found in the literature, although they must be validated and their physiological roles and pathological implications for PD clarified: 1) overproduction of Parkin led to activation of the cysteine-protease calpain, which cleaves  $\alpha$ -synuclein, reducing  $\alpha$ -synuclein-mediated cell death in mammalian cells (301); 2) Parkin ubiquitylated the  $\alpha$ -synuclein protein interactor synphilin and contributed, in concert with synphilin and P<sup>129S</sup>- $\alpha$ -synuclein, to the formation of ubiquitylated Lewy body-like inclusions in cell models (72, 360, 583) [of note, however, we did not detect any immunoreactivity to synphilin in the deposits of P<sup>129S</sup>- $\alpha$ -synuclein in hA30P $\alpha$ -syn mice (154)]; 3) in cells genetically modified to overproduce Parkin and  $\alpha$ -synuclein, Parkin accumulated as an insoluble protein and insoluble Parkin was observed in brain extracts from patients with Lewy body disease (286) [however, Parkin did not accumulate in the insoluble brain fractions from diseased hA30P $\alpha$ -syn mice with wild-type *parkin* alleles (154)]; 4) the neuronal chaperone 14-3-3 $\alpha$  interfered with the ability of Parkin to interact with synphilin by inhibiting its ubiquitin-protein ligase activity, whereas  $\alpha$ -synuclein but not the PD-causing A30P and A53T variants relieved this inhibitory effect by associating physically with 14-3-3 $\alpha$ ; 5) Parkin has been reported in complexes containing Hsp70 (260, 283, 634), in which it might regulate Hsp70 activity (366, 434) and thus modulate  $\alpha$ -synuclein aggregation and toxicity (15, 313); 6) Parkin and  $\alpha$ -synuclein both interact physically with the dopamine transporter, with potentially antagonistic effects on its expression at the cell surface and its activity, modulating dopamine-induced toxicity (273, 333, 441, 665) (FIG. 9).

#### 4. Other PD-related proteins may modulate $\alpha$ -synuclein accumulation and toxicity

In search of evidence that parkinsonian syndromes with distinct etiologies share common pathogenic mechanisms,

several investigators have explored the possibility that  $\alpha$ -synuclein interacts functionally with other PD-related proteins (FIG. 9). Although there is agreement that there is little colocalization between DJ-1 and  $\alpha$ -synuclein in Lewy bodies (426, 456), DJ-1 was found to interact with  $\alpha$ -synuclein in a large molecular complex of more than 2,000 kDa in brains of unaffected individuals and patients with Pick's disease or multiple system atrophy (426). Interestingly, DJ-1 associated directly with  $\alpha$ -synuclein in vitro and in neurons under oxidative conditions, counteracting  $\alpha$ -synuclein aggregation with its redox-sensitive chaperone activity (561); loss of this interaction in DJ-1 knockout neurons differentiated from mouse embryonic stem cells led to a more dramatic accumulation of  $\alpha$ -synuclein under oxidative stress. Others have suggested that upregulation of Hsp70 may be an indirect mechanism through which DJ-1 regulates  $\alpha$ -synuclein aggregation and toxicity (19, 714). However, DJ-1 deficiency did not modify the disease course in transgenic mice overproducing the PD-causing A53T variant of human  $\alpha$ -synuclein, although moderate disease-modifying effects may have been masked by the severity of the neurodegenerative phenotype linked to synucleinopathy in this particular model (50% mortality at 10 mo of age) (522).

Overproduction of PINK1 mitigated  $\alpha$ -synuclein-induced phenotypes in *Drosophila*, but effects of PINK1 depletion were not reported (621). Overexpression of YPK9 (*Yeast Park9*), the yeast ortholog of the ATP13A2 gene, at PARK9, suppressed  $\alpha$ -synuclein toxicity in yeast cells. In addition, although its knockdown did not enhance  $\alpha$ -synuclein toxicity, deletion of the closely related *SPF1* gene, encoding a protein with 30% identity and 49% similarity to the P-type ATPase encoded by ATP13A2, was lethal in cells with a single  $\alpha$ -synuclein gene copy (187). Remarkably, YPK9 suppressed the  $\alpha$ -synuclein phenotype synergistically with *Ypt1*, the yeast homolog of the GTPase Rab1A, involved in the regulation of vesicle trafficking from the ER to the Golgi and previously shown to rescue  $\alpha$ -synuclein toxicity in yeast and in dopaminergic neurons from various organisms (88). Similarly to *Ypt1*, YPK9 rescued defective vesicle trafficking caused by  $\alpha$ -synuclein expression, restored  $\alpha$ -synuclein to the plasma membrane, and prevented the formation of inclusions associated with clusters of mislocalized transport vesicles in yeast cells; in addition, overproduction of ATP13A2 protected dopaminergic neurons from the rat embryonic mesencephalon against  $\alpha$ -synuclein-mediated toxicity. Whether the neuroprotective mechanisms are conserved in yeast and mammals remains to be determined (187), but the relevance of the above-mentioned findings to PD pathology is supported by the localization of the YPK9 gene product to the membrane of the vacuole, the yeast equivalent of the mammalian lysosome to which the type 5 P-type ATPase encoded by ATP13A2 is targeted (521). Intriguingly, the human and yeast proteins are both predicted to be cationic transmem-

brane metal transporters, and it was indeed shown that YPK9, but not variants reproducing mutations found in PARK9 patients, protects cells against excess  $Mn^{2+}$  exposure, revealing a potential cross-talk between genetics and an environmental risk factor for PD (187).

An elegant genetic study in mice identified strong functional interplay between  $\alpha$ -synuclein and LRRK2 (364). Lin et al. (364) generated transgenic mice overproducing human A53T  $\alpha$ -synuclein or various forms of LRRK2, including the normal protein, the common G2019S variant, and a kinase-dead (KD) variant generated by deletion of amino acid residues 1887 to 2102, under the control of the tetracycline sensitive *tet-off* gene regulatory system and the *calcium/calmodulin-dependent protein kinase II-alpha* promoter; in addition, they crossed these lines to generate double transgenic mice overproducing LRRK2 and A53T  $\alpha$ -synuclein. Neurodegeneration was not observed in single transgenic LRRK2 mice up to 20 mo of age, whereas, in agreement with previous studies, overproduction of A53T  $\alpha$ -synuclein induced progressive neuropathological alterations in the forebrain, observable at 12 mo of age, including astrogliosis, microglial activation, and neurodegeneration. Coproduction of A53T  $\alpha$ -synuclein with LRRK2, G2019S LRRK2, or KD LRRK2 dramatically accelerated the progression of this neuropathological phenotype, which was already observable at 1 mo of age; its severity depended on LRRK2 dosage rather than on the LRRK2 variant overproduced. This observation is intriguing, particularly since, in contrast to  $\alpha$ -synuclein-dependent PD, gene dosage effects do not appear to be involved in PD linked to LRRK2 mutations (266). LRRK2 overproduction accelerated the pathological accumulation of A53T  $\alpha$ -synuclein in neuronal somata, although it had only modest effects on  $\alpha$ -synuclein levels in soluble and insoluble brain fractions. Remarkably, the structure of the Golgi complex was altered in neurons of mice overproducing normal or G2019S LRRK2 and more moderately in single A53T  $\alpha$ -synuclein transgenic mice; this phenotype was dramatically exacerbated in double transgenic mice, in which severe fragmentation of the Golgi apparatus correlated with the degree of somatic accumulation of  $\alpha$ -synuclein, possibly reflecting dysfunction of ER-Golgi-mediated protein/vesicle trafficking. Unfortunately, the relevance of these observations to the degenerative processes affecting nigral dopaminergic neurons in PD remain unclear, since the promoter used to drive the expression of the transgenes in the mouse lines studies did not allow for consistent expression in midbrain neurons. Nevertheless, the possible implication of LRRK2 and  $\alpha$ -synuclein in a common pathway crucial to PD development is further supported in this study by the observation that LRRK2 deficiency significantly mitigated all the pathological aspects of  $\alpha$ -synuclein-dependent disease in A53T  $\alpha$ -synuclein transgenic mice, whereas LRRK2 overproduction did not modify amyloid precursor protein-induced neurodegeneration (364). Paradoxically, however, loss of LRRK2 function

alone led to age-dependent apoptotic renal degeneration, accompanied by dramatic accumulation of soluble and insoluble, monomeric and high-molecular-weight  $\alpha$ -synuclein species observed on western blots, and  $\alpha$ -synuclein and P<sup>129S</sup>- $\alpha$ -synuclein immunoreactive inclusions detected by immunohistochemical methods (628). These changes were associated with signs of impairment of the autophagy-lysosomal pathway: decreased abundance of the autophagosomal membrane-linked lipidated isoform II of microtubule-associated protein 1 light-chain 3 (LC3), increased abundance of p62, and accumulation of lipofuscin granules. Although none of these changes was observed in the brains of aged animals, this study suggests that loss of function mechanisms may intervene in LRRK2-dependent PD and point to a role of LRRK2 in the regulation of autophagy-lysosomal protein degradation (628). Previous studies reported enhancement of autophagy upon LRRK2 knockdown in cell models (8) and suggested that PD-causing LRRK2 mutations deregulate the autophagy-lysosomal pathway through which LRRK2 appears to modulate neurite process morphology (8, 388, 509).

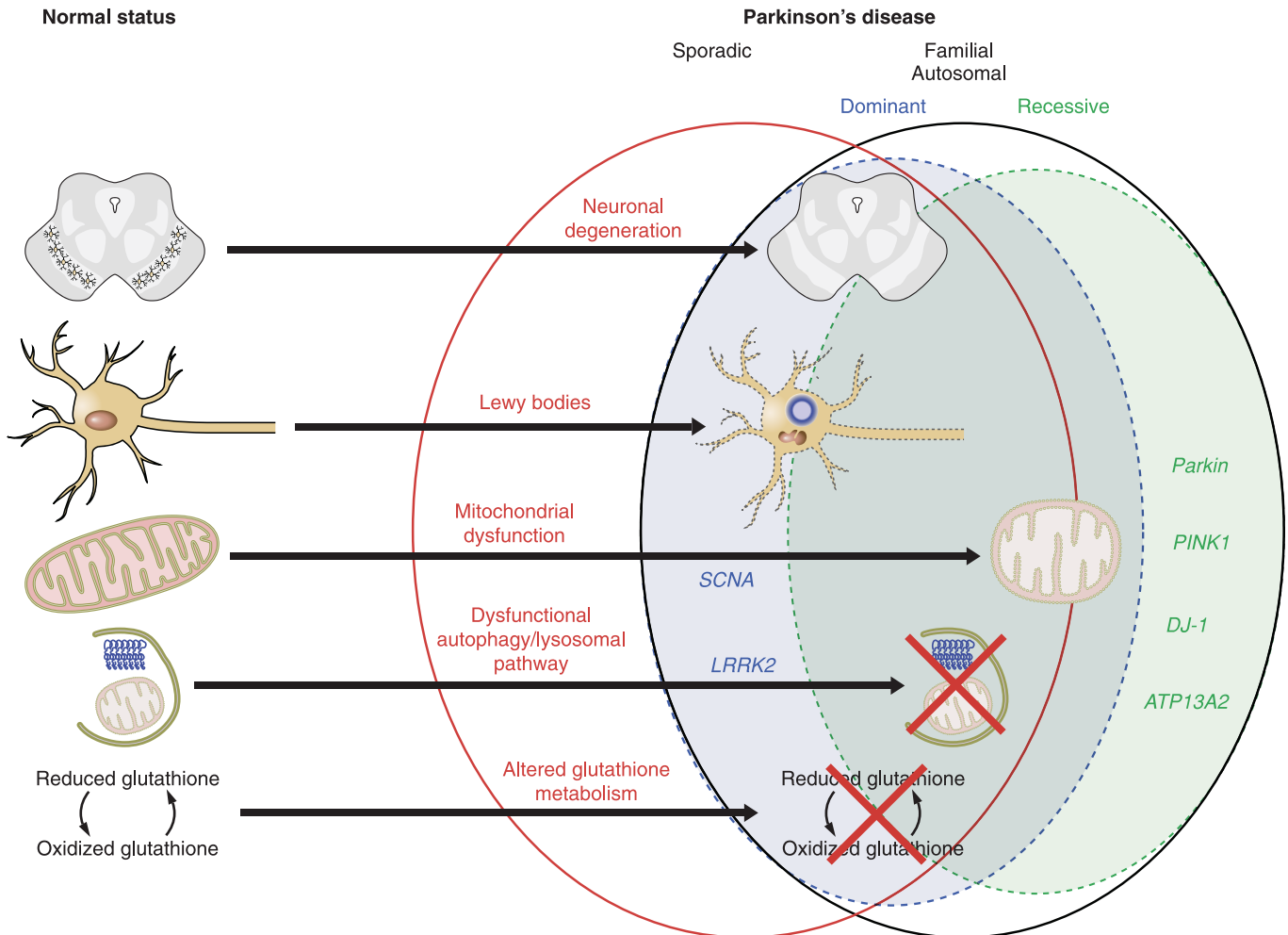
There are also indications of potential functional interplay between  $\alpha$ -synuclein and the ubiquitin hydrolase UCHL1, which complement the relatively weak genetic findings in support of the implication of this protease in the physiopathology of PD. In particular, UCHL1, in addition to its recognized hydrolase activity, possesses noncanonical dimerization-dependent ubiquitin ligase activity *in vitro* (369). This activity led to the polyubiquitylation of  $\alpha$ -synuclein, a modification which was not recognized by the proteasome for degradation but instead caused the accumulation of the protein in cell models. Interestingly, the polymorphic S18Y variant of UCHL1, associated in some studies with a reduced risk of developing PD, did not alter the hydrolase activity of the protein but attenuated its ubiquitin ligase function, which may therefore play a deleterious role in PD pathogenesis by promoting  $\alpha$ -synuclein aggregation. Although the authors provided evidence for a physical association between UCHL1 and  $\alpha$ -synuclein in a synaptic vesicle fraction isolated from rabbit brain, the physiopathological relevance of their findings remains to be clarified, particularly since  $\alpha$ -synuclein appears to be modified by two or three ubiquitin molecules rather than by polyubiquitylation in human synucleinopathies (11, 229, 624). It is not excluded that synuclein species carrying a chain of more than four ubiquitins are generated, but these chains are most likely formed through K48 isopeptide bonds (cf. sect. III B2) (11) and may therefore be rapidly targeted to the proteasome, which again is not consistent with the proposed proteasome-independent polyubiquitylation of  $\alpha$ -synuclein by UCHL1. Nevertheless, the functional link between these proteins was recently strengthened by the demonstration that the effects of UCHL1 on the accumulation of  $\alpha$ -synuclein are mediated by a COOH-terminal farnesylation; a significant proportion of UCHL1 in rodent and

human brain, as well as in cell models, associates with membranes through this modification (370). In various cell models, overproduced farnesylated UCHL1 was associated with ER membranes, where it promoted the accumulation and toxicity of  $\alpha$ -synuclein, although unfortunately, the authors did not determine how these effects relate to the ubiquitin-ligase activity of the protein. It would also be valuable to determine how farnesylation of UCHL1 affects proteasomal and/or autophagic degradation of  $\alpha$ -synuclein. There is indeed recent evidence that UCHL1 interacts with components of the CMA pathway, particularly the lysosome receptor LAMP-2A, and with the chaperones, Hsc70 and Hsp90, and that pathological enhancement of these interactions by the putatively PD-causing I93M substitution inhibits degradation of  $\alpha$ -synuclein by CMA (279).

Finally, based on genetic evidence indicating that GD may be linked to PD, the possibility that pharmacological inhibition of the GBA protein alters  $\alpha$ -synuclein homeostasis was recently explored (390). Short-term treatment of differentiated SH-SY5Y cells or mice with the GBA inhibitor conduritol B epoxide led to moderate accumulation of  $\alpha$ -synuclein protein without altering mRNA levels. Enhanced immunoreactivity to  $\alpha$ -synuclein was observed within the cytoplasm and nucleus of neurons and in the substantia nigra pars compacta but not the cortex or the hippocampus, 48 h after a single administration of the drug. These changes were accompanied by an astroglial response associated with increased  $\alpha$ -synuclein immunoreactivity in reactive astrocytes. Although these observations provide a first proof of principle that GBA activity and  $\alpha$ -synuclein protein levels may be linked, they do not provide clues to the molecular mechanisms involved. In addition, although severe neuronopathy was associated with GBA gene deletion in the mouse, the presence of  $\alpha$ -synucleinopathy in this model was not reported (135).

### C. Concluding Remarks: Molecular Pathways Linking Idiopathic and Genetic Forms of PD

Mendelian inheritance accounts for no more than 10% of PD cases examined in the clinic. Nevertheless, the discovery of genes involved in familial forms of PD has brought great hope that understanding the functions of their products will shed light not only on the pathogenic mechanisms involved in each of these specific genetic diseases, but possibly also on the physiopathology of sporadic PD. Investigating the relationships between these proteins is therefore a current research focus in the field that might unravel pathways of convergence between different PD forms. The probability of convergence will be highest in late stages of active dopaminergic neuronal death, which occurs whatever the specific disease cause. However, it will be most relevant if it hints at early events that may tip the scales towards pathology.



**FIGURE 10.** Is Parkinson's disease (PD) a single disease entity? PD is in most cases a sporadic disorder caused by the preferential, progressive loss of the neuromelanin-containing dopaminergic neurons in the substantia nigra pars compacta and associated with Lewy bodies. No more than 10% of the cases are caused by mutations in genes with autosomal dominant or recessive inheritance. Most cases with autosomal recessive PD are due to mutations in genes with mitochondrial functions. Autosomal recessive PD has unique clinical features, including early onset, slow progression, excellent response to levodopa, and early levodopa-induced dyskinesia; at the neuropathological level, it most often presents as pure nigral dopaminergic cytopathy without Lewy bodies. However, in some cases, autosomal recessive PD may be clinically indistinguishable from sporadic PD; in addition, cases with typical Lewy bodies have been reported. Autosomal dominant PD, caused by mutations in the  $\alpha$ -synuclein gene *SCNA* and in *LRRK2*, is clinically similar to sporadic PD and most often presents with typical Lewy body pathology. Whether sporadic PD and familial PD with distinct genetic causes are separate clinical and etiological entities is under vivid debate. Nevertheless, mitochondrial dysfunction, impaired autophagy/lysosomal degradation of proteins/organelles, altered glutathione homeostasis, and abnormal  $\alpha$ -synuclein build-up are pathogenic mechanisms that may be shared between these diseases.

Post mortem examination of more cases will be necessary to draw reliable conclusions as to the nature of the neuropathological changes associated with autosomal recessive parkinsonism (cf. sect. III E). However, the similarities among the clinical features of PD linked to the loss of Parkin, PINK1, and DJ-1 function; their unique characteristics; as well as research discoveries identifying key functions of these genes within common biological processes, strongly support the idea that these disorders are related physiopathologically. As illustrated in the previous sections of this review, the evidence that *parkin*- and *PINK1*-linked diseases are caused by dysfunction of a common multifunc-

tional pathway centered on maintenance of mitochondrial functions is strong. Although it is unclear whether DJ-1 intervenes directly in the *PINK1/parkin* pathway, a number of observations suggest that DJ-1 dysfunction may primarily affect mitochondrial physiology. In addition, the finding that, like single gene deletions, the triple deletion of *parkin*, *PINK1*, and *DJ-1* genes in mice does not cause dopaminergic neurodegeneration supports the idea that the three proteins intervene in a single pathway (307). It is therefore justified to consider the human parkinsonian syndromes due to *parkin*, *PINK1*, or *DJ-1* gene mutations to be pure nigral mitochondrial cytopathies (6, 86) (FIG. 10).

A possibly shared pathway has also emerged for dominant Lewy body-associated parkinsonism with the discovery of functional interplay between LRRK2 and  $\alpha$ -synuclein. PD-causing *LRRK2* mutations may contribute to the accumulation of  $\alpha$ -synuclein, although the underlying molecular mechanisms, particularly the relative contribution of loss and gain of function, will need to be investigated (53, 364, 628). The *LRRK2* kinase activity-dependent upregulation of *SCNA* gene transcription, mediated by activation of the MAPK/ERK cascade, may turn out to be central (53). Future studies will have to reconcile the appearance of  $\alpha$ -synucleinopathy associated with apoptotic cell death in the kidney of *LRRK2* knockout mice (628) with the exacerbation of  $\alpha$ -synucleinopathy and neurodegeneration observed when *LRRK2* is inactivated in the brains of transgenic mice overproducing the A53T variant of  $\alpha$ -synuclein (364).

Despite great efforts to identify other direct interactions between the protein products of PD-causing genes, whether of autosomal dominant or recessive inheritance, the pathophysiological relevance of most of them remains to be proven. Nevertheless, as mentioned throughout this review, alterations in autophagy-lysosome pathways, which intervene both in the degradation of  $\alpha$ -synuclein and in the clearance of dysfunctional mitochondria, have emerged as a common theme in models for autosomal dominant and recessive forms of PD. These protein/organelle degradation pathways may, therefore, be at the crossroad of the pathological processes triggered by disease-causing mutations in different inherited parkinsonian syndromes. The causative involvement of these pathways in dopaminergic neuron degeneration in PD is strongly supported by the close genetic relationship between the lysosomal storage disorder GD and PD, as well as by the identification of mutations in the gene encoding the lysosomal type 5 P-type ATPase ATP13A2 responsible for rare autosomal recessive PD cases. Depending on the specific molecular steps of the autophagy-lysosome pathways targeted and on the severity of the elicited functional changes, it is conceivable that different genetic alterations cause a continuum of phenotypes, ranging from pure mitochondrial cytopathies to predominant  $\alpha$ -synucleinopathy (FIG. 10).

Other possible points of convergence between the pathways involved in autosomal dominant and recessive PD have also been uncovered. Early compensatory mechanisms aimed at counteracting the primary genetic alterations in autosomal recessive parkinsonian syndromes may modulate  $\alpha$ -synuclein aggregation and toxicity. Changes in glutathione metabolism exemplify this situation remarkably well: abnormally high levels of reduced glutathione have been reported in Parkin-deficient mice (268) or in response to paraquat treatment in human fibroblasts from carriers of PD-causing *PINK1* gene mutations (208); upregulation of endogenous glutathione-S-transferase (GST) genes occurred early during muscle degeneration in Parkin mutant *Drosophila* (201); inactivation of these genes exacerbated

cell death in a yeast model of  $\alpha$ -synuclein toxicity (673) and promoted dopaminergic neurodegeneration in Parkin mutant (671) and in  $\alpha$ -synuclein transgenic *Drosophila* (630). Similarly, pharmacologically or genetically induced glutathione depletion decreased viability in DJ-1 mutant *Drosophila* (640) and enhanced dopaminergic neuron loss in  $\alpha$ -synuclein transgenic *Drosophila* (630). Conversely, overexpression of GST or treatment with chemical agents favoring glutathione replenishment protected dopaminergic neurons in Parkin mutant and in  $\alpha$ -synuclein transgenic *Drosophila* (630, 671).

Less surprisingly, convergence may also be observed in later stages of neuronal degeneration, at the level of prosurvival or pro-death cell signaling pathways. For example, several lines of evidence suggest that Parkin negatively regulates the JNK pathway, possibly by distinct mechanisms (58, 252, 274, 366, 523); LRRK2 may also regulate this pathway, although whether its net effect is enhancement or downregulation is unclear (189, 669). A Parkin deficiency appeared to interfere with EGFR-mediated upregulation of the phosphoinositide 3 kinase-Akt pathway (141), and Akt signaling was mitigated by stable DJ-1 knockdown in *Drosophila* (686). In this organism, LRRK2 interacted genetically and physically with the 4E-BP target of the TSC/Rheb/TOR/4E-B downstream branch of the Akt pathway; excessive LRRK2-dependent phosphorylation and inherent inactivation of 4E-BP, a negative regulator of the translation initiation factor eIF4E sensitized animals and dopaminergic neurons to oxidative stress (259). Intriguingly, 4EBP was also found to interact genetically with the *PINK1*/parkin pathway: compensatory reductions in phosphorylated 4E-BP were observed in *PINK1* and *parkin* mutant *Drosophila*; in contrast, overexpression of 4E-BP or its activation by the mTOR inhibitor rapamycin, or by loss of LRRK2 function, rescued the phenotypes related to deletion of *PINK1* or *parkin* (605), but also those caused by overproduction of LRRK2 or PD-causing LRRK2 variants (259). Moreover, 4E-BP activity correlated with increased levels of the detoxifying enzyme GstS1, suggesting that the 4E-BP pathway may, at least in part, mediate its protective effects by increasing glutathione conjugation (605).

Of note, most of the above-mentioned processes, mitochondrial complex I dysfunction, alterations in autophagy-lysosomal pathways, and impairment of glutathione homeostasis, are suspected to play a role in the pathogenesis of sporadic PD. As already mentioned, recent GWAS studies have provided support to the hypothesis that common variants in genes responsible for autosomal dominant parkinsonian syndromes represent risk factors for sporadic PD (1, 224, 535, 543, 577, 590). Such approaches cannot possibly identify rare variants as risk factors, and indeed, none of the GWAS studies identified *GBA*, which has been recognized by several independent groups as the most common genetic risk factor for the development of PD. As previously dis-

cussed in section IIC3, the association of heterozygous polymorphisms with disease susceptibility remains a matter of debate. Future reassessments of these rare variants by whole genome sequencing might uncover positive associations, although this remains speculative. In addition, failure in identifying such associations does not exclude the possibility that rare heterozygous polymorphic variants increase the risk of developing PD in conjunction with other genetic or environmental factors. It is envisageable that, at some stage of disease progression, factors that promote deposition or toxicity of  $\alpha$ -synuclein may impair the functions of the neuroprotective autosomal recessive PD genes, ultimately leading to dopaminergic neurodegeneration. The suggestion that oxidative stress-induced nitrative damage or catechol modification might modulate the aggregation of  $\alpha$ -synuclein and promote its toxicity (84, 171) is consistent with this hypothesis; nitrosylated and catechol-modified Parkin species have been detected in brain tissue from sporadic PD patients and were shown to be less active in vitro (71, 332, 690). Similarly, age-related processes in the human brain have been linked both to  $\alpha$ -synuclein stabilization (70, 355) and diminished Parkin solubility (496). Valuable insight into possible overlapping pathogenic processes in forms of PD with distinct etiologies may be provided in the future by coupling high-performance micro-dissection techniques with the thorough examination of post mortem tissue for the existence of somatic gene variants by sensitive next generation sequencing techniques. Abundant somatic mitochondrial DNA deletions associated with respiratory chain deficiencies have been discovered in individual cells from the substantia nigra, but not other brain regions, in PD patients and during aging in normal individuals (24, 319). Somatic mutations in the *parkin* gene have recently emerged as a frequent cause of nonneuronal cell-derived cancers (642). To contribute to neurodegeneration, such mutations would probably have to occur early during development of neuronal lineages. Applied to the study of genomic DNA, in-depth sequencing of post mortem tissue should help advance our still fragmentary understanding of the mechanisms underlying the preferential vulnerability of specific neuronal population in PD.

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## DISCLOSURES

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# What Genetics Tells us About the Causes and Mechanisms of Parkinson's Disease

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**A Dimeric PINK1-containing Complex on Depolarized Mitochondria Stimulates Parkin Recruitment**

Kei Okatsu, Midori Uno, Fumika Koyano, Etsu Go, Mayumi Kimura, Toshihiko Oka, Keiji Tanaka and Noriyuki Matsuda

*J. Biol. Chem.*, December 20, 2013; 288 (51): 36372-36384.

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**DJ-1 Associates with lipid rafts by palmitoylation and regulates lipid rafts-dependent endocytosis in astrocytes**

Kwang Soo Kim, Jin Soo Kim, Ji-Young Park, Young Ho Suh, Ilo Jou, Eun-Hye Joe and Sang Myun Park

*Hum. Mol. Genet.*, December 1, 2013; 22 (23): 4805-4817.

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**DISC1 complexes with TRAK1 and Miro1 to modulate anterograde axonal mitochondrial trafficking**

Fumiaki Ogawa, Elise L.V. Malavasi, Darragh K. Crummie, Jennifer E. Eykelenboom, Dinesh C. Soares, Shaun Mackie, David J. Porteous and J. Kirsty Millar

*Hum. Mol. Genet.*, October 2, 2013; .

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Elisabeth Stogmann, Alexander Zimprich and Fritz Zimprich

*Brain*, October , 2013; 136 (10): e254.

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