F1000Reports MEDICINE

Published: 01 April 2011

Molecular insights into Parkinson's disease

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F1000 Medicine Reports 2011, **3**:7 (doi:10.3410/M3-7)

Abstract

Parkinson's disease is a neurodegenerative movement disorder characterized by loss of midbrain dopaminergic neurons leading to motor abnormalities and autonomic dysfunctions. Despite intensive research, the etiology of Parkinson's disease remains poorly understood leaving us with no effective therapeutic options. However, the recent identification of genes linked to heritable forms of Parkinson's disease has revolutionized research in the field and has begun to provide new clues to disease pathogenesis. Here we discuss these recent genetic advances and highlight their significance in our quest to better understand common underlying disease mechanisms that will help us identify innovative neuroprotective therapies for Parkinson's disease.

Introduction

Parkinson's disease is the second most common neurodegenerative disorder, affecting 1–2% of the population over the age of 65 [1]. It is a chronic movement disorder caused by relentless degeneration of specific neuronal populations in the brain, most notably the dopamine-producing neurons of the substantia nigra pars compacta region of the basal ganglia, which helps control voluntary movement. Patients generally suffer from the cardinal symptoms of slowness of movement, tremors while at rest, rigidity, and poor balance, and often also show autonomic, cognitive, and psychiatric disturbances. Parkinson's disease is progressive and may last 10–20 (or more) years after diagnosis. It is typically partially treatable (mainly with dopamine-replacement therapy) for a few years after diagnosis, but this is generally followed by years of decline during which there is no effective therapy, eventually leading to premature death. Parkinson's disease is usually a sporadic disorder with onset in later life and the causes of this disease are incompletely understood. For most of the twentieth century, genetic predisposition was thought to play a negligible role in the disease, but in the past 15 years the identification of distinct genetic loci responsible for (both the dominant and recessive) inherited forms of Parkinson's disease has provided us with numerous clues to understanding its molecular causes. To date, about 16 Parkinson's disease-related genetic loci (the PARK loci) and 11 genes associated with these PARK loci have been described (see Table 1). Among these genes, 5 have been studied extensively: α-*synuclein* (also known as *SNCA*), *parkin* (*PARK2*), *PINK1* (*PARK6*), *DJ-1* (*PARK7*), and *LRRK2* (*PARK8*) [2]. Consequently, these will be the main focus of this review. Recent genome-wide association studies (GWAS) have found that having particular variants of these genes greatly increases the chance of developing Parkinson's disease [3,4], suggesting perhaps that in the cases where the functions are known, the products of these genes are often proteins involved in the way brain cells cope with oxidative stress, mitochondrial dysfunction, and removal of misfolded proteins. A commonly held view is that Parkinson's disease may result from environmental factors (such as toxins) damaging dopamine-producing neurons of the substantia nigra in an accumulative way in individuals who have defects in pathways dealing with oxidative stress, mitochondrial dysfunction, and either the ubiquitin proteasome system or the autophagy-lysosome pathway, which remove misfolded proteins (Figure 1). However, some of the implicated proteins have functions that do not necessarily

Table 1: Gene loci identified for Parkinson's disease and their probable functions

Locus	Gene	Chromosome	Inheritance	Probable function
PARK1 & PARK4	*α-synuclein*	4q21	Dominant	Presynaptic protein, Lewy body, lipid and vesicle dynamics
PARK2	*parkin*	6q25.2-27	Recessive	Ubiquitin E3 ligase, mitophagy
PARK3	Unknown	2p13	Dominant	Unknown
PARK5	*UCHL1*	4p14	Dominant	Ubiquitin C-terminal hydrolase
PARK6	*PINK1*	1p35-36	Recessive	Mitochondrial kinase
PARK7	*DJ-1*	1p36	Recessive	Oxidative stress
PARK8	*LRRK2*	12p11.2	Dominant	Kinase signaling, cytoskeletal dynamics, protein translation
PARK9	*ATP13A2*	1p36	Recessive	Unknown
PARK10	Unknown	1p32	Dominant	Unknown
PARK11	*GIGYF2*	2p37	Dominant	IGF-1 signaling
PARK12	Unknown	Xq21-q25	X-linked	Unknown
PARK13	*Omi/HtrA2*	2p13	Unknown	Mitochondrial serine protease
PARK14	*PLA2G6*	22q13	Recessive	Phospholipase enzyme
PARK15	*FBXO7*	22q11	Recessive	Ubiquitin E3 ligase
PARK16	Unknown	1q32	Unknown	Unknown

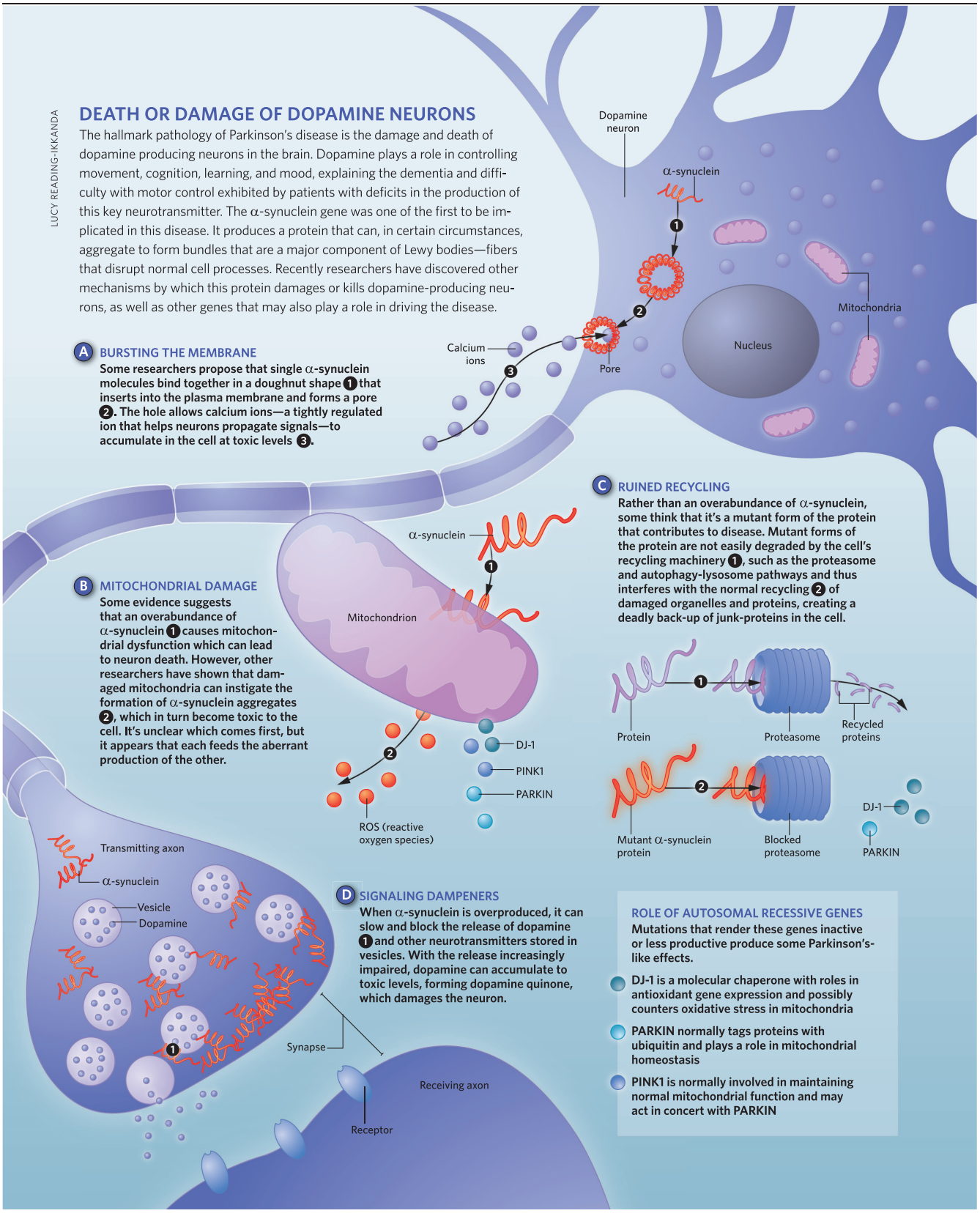
ATP13A2, ATPase type 13A2; FBXO7, F-box protein 7; GIGYF2, GRB10 interacting GYF protein 2; HtrA2, HtrA serine peptidase 2 (also known as Omi); IGF-1, insulin-like growth factor 1; LRRK2, leucine-rich repeat kinase 2; PINK1, PTEN-induced putative kinase 1; PLA2G6, phospholipase A2, group VI (cytosolic, calcium-independent); UCHL1, ubiquitin carboxyl-terminal esterase L1. Adapted from *Hum Mol Genet* [68], © 2007.

fit into this model, making the scenario somewhat complicated. Here, we provide a brief overview of how genetic research and the ensuing molecular insights have led to substantial advances in our understanding of disease pathogenesis and in experimental approaches to study the disorder.

Genetic breakthroughs

The first big breakthrough came in studying the inherited autosomal-dominant form of Parkinson's disease, when mutations of the α-synuclein gene locus were reported in several families with a history of Parkinson's disease. Both point mutations (three point mutations) and multiplications [5-7], in addition to triplications [8] and duplications [9,10] in the α-synuclein gene cause Parkinson's disease. Those with a family history of triplications tend to be younger at disease onset compared to those with duplications, and the fact that even one copy of the faulty gene is sufficient to cause the disease suggests that the increased levels of α-synuclein are in some way toxic [8,11]. Although our knowledge about the normal function of α-synuclein is limited (we know that it modulates synaptic plasticity and regulates neurotransmitter release), recent studies elucidating the structural properties of this protein have shed considerable light on its pathogenic involvement in Parkinson's disease. Both pathogenic mutations and elevated concentrations will give α-synuclein a propensity to develop a β-sheet structure which readily polymerizes into oligomers and higher order aggregates such as fibrils [12]. α-synuclein aggregation was worsened by various types of post-translational modifications such as Ser-129 phosphorylation, calpain-mediated cleavage, *O*-glycosylation, tyrosine nitration, methionine oxidation, and C-terminal truncation [2], although the mechanisms are not clear. Insoluble α-synuclein fibrils are a key component of Lewy bodies (cytoplasmic bodies containing aggregated proteins), which are the pathogenic hallmark of Parkinson's disease. There is some controversy as to whether Lewy bodies are a cause or a consequence of Parkinson's disease, with some evidence suggesting that they play a protective role by sequestering toxic α-synuclein oligomers [13]. However, emerging evidence from in-vitro studies [14] and animal models [15-18] suggests that both the oligomer and fibrillar forms of α-synuclein aggregates are toxic to neurons. However, the precise roles of α-synuclein aggregation in mediating cell death in Parkinson's disease remain elusive, although there is no shortage of hypotheses. One suggestion is that α-synuclein oligomers may alter plasma membrane stability or permeability by forming membrane pores that increase intracellular Ca^{2+} to toxic levels [20] (Figure 1). Another suggestion is that because α-synuclein is found at mitochondrial membranes of dopaminergic neurons [21], its overexpression may induce mitochondrial dysfunction (by inhibiting complex I), and since mitochondria are a major source of reactive oxygen species, this would result in increased oxidative stress, leading to neurodegeneration [22,23] (Figure 1). Yet another potential mechanism of α-synuclein toxicity is suggested by the observation that increased or mutant *α-synuclein* expression in synaptic vesicles interferes with synaptic transmission by causing the accumulation of docked vesicles at the presynaptic membrane [24], reducing the recycling vesicle pool [25] and thereby increasing cytosolic dopamine to toxic levels [26] (Figure 1). Finally, there is the suggestion that as mutant species of α-synuclein are poor substrates for proteasomal degradation, they inhibit proteolysis [27], block lysosomal function [28] (Figure 1) and chaperone-mediated autophagy [29], and disrupt endoplasmic reticulum-Golgi trafficking [30,31], causing toxicity.

Figure 1. Underlying mechanism of dopaminergic neurodegeneration in Parkinson's disease



Whatever the exact mechanism(s) involved, it is clear that α-synuclein aggregates exert toxic effects on several important cellular functions necessary for survival of dopaminergic neurons.

The second gene mutation identified as causing the autosomal-dominant form of Parkinson's disease is that of *LRRK2*. *LRRK2* mutations cause early-onset Parkinson's disease in families from diverse ethnic backgrounds, with a clinical profile identical to sporadic late-onset Parkinson's disease. Leucine-rich repeat kinase 2 (LRRK2) is a large multidomain protein [32], but mutations associated with Parkinson's disease are concentrated in the central catalytic regions of the GTPase and kinase domains, and most of them result in increased kinase activity in vitro [32]. Increased kinase activity is known to promote cell death in Parkinson's disease, but the mechanisms are not yet known. LRRK2 undergoes autophosphorylation and also phosphorylates a number of protein substrates, so it is significant that the toxicity of disease-causing mutant forms of LRRK2 is related to their enhanced kinase activity and GTP binding [32-34]. Unsurprisingly, a great deal of effort has been focused on identifying the normal function of LRRK2, including studying its phosphosubstrates, binding partners, and regulators of its kinase and GTPase activities, in order to determine how it causes disease. LRRK2 is thought to play a role in neuronal outgrowth [35,36], protein translation by phosphorylation of the translation inhibitor eukaryotic initiation factor 4E (eIF4E) [37,38], and in cytoskeletal dynamics via phosphorylation of moesin, which anchors the cytoskeleton to the plasma membrane [39]. Mice that harbor *LRRK2* mutations develop the cardinal abnormalities of Parkinson's disease in the nigrostriatal system (one of the major dopaminergic pathways conveying impulses from the substantia nigra), such as stimulated dopamine neurotransmission or behavioral deficits [40]; others show progressive age-dependent motor deficits that can lead to immobility but are responsive to the dopaminergic drugs L-DOPA and apomorphine, and develop axonal spheroids in striatal and cortical projections composed of phosphorylated tau despite an absence of nigrostriatal dopaminergic neurodegeneration [41]. Strikingly, there is an additive effect of expressing mutant forms of *LRRK2* and *α-synuclein* in mice, whereas deficiency of LRRK2 limits the toxic effects of mutant α-synuclein [42], suggesting that the two proteins interact. Until recently, it was unclear whether the neurological features in mice with mutant *LRRK2* result from altered kinase activity. Recent studies elegantly demonstrated that viral-mediated overexpression of G2019S mutant *LRRK2* in nigrostriatal dopaminergic neurons (those located in the substantia nigra pars compacta and striatum) resulted in marked neurotoxicity caused by LRRK2 kinase activity. By contrast, overexpression of normal LRRK2 or a "kinase-dead" version of the enzyme did not have this adverse effect [43]. What's more, the mutant-LRRK2-mediated nigrostriatal dopaminergic neurotoxicity was blocked by selective LRRK2 kinase inhibitors GW5074 and indirubin-3′-monoxime [43]. This is encouraging as it suggests that LRRK2 kinase inhibitors could become a new treatment for Parkinson's disease.

There have also been advances in understanding from studying the recessive form of the disease. There is compelling evidence suggesting that mutations causing a loss of function in three genes, *parkin*, *PINK1*, and *DJ-1*, underlie the autosomal-recessive Parkinson's disease (and also a few cases of sporadic Parkinson's disease) [44]. Recent studies have demonstrated that products of all three genes preserve mitochondrial function and protect against reactive oxygen species. Patients homozygous for loss-of-function *parkin* mutations or having compound heterozygous *parkin* mutations account for about 50% of all familial early-onset cases of Parkinson's disease, with point mutations being the most frequent genetic lesion and deletions, duplications, and exonic rearrangements also contributing to disease [45]. Mutations in *PINK1*, the second most common autosomal-recessive mutation (following *parkin*) contribute to between 1% and 7% of early-onset Parkinson's disease [46], whereas mutations in *DJ-1* are a rare cause of Parkinson's disease [47]. There has inevitably been much study of what the protein products of these genes do. Parkin tags protein lysine residues with ubiquitin, either targeting them for destruction via the 26S proteasome (by adding polyubiquitin chains via lysine K48) or influencing other signaling pathways such as DNA repair, endocytosis, transcriptional regulation, and protein trafficking (by ubiquitination via lysine K48 or K63) [48]. Disease-causing mutations in *parkin* lead to a loss of this E3 ubiquitin ligase activity [48], but although numerous substrates for parkin have been identified to date, no consensus has emerged on which of these may (if not ubiquitinated) lead to neurodegeneration in Parkinson's disease (Figure 1).

Several *PINK1* mutations are also thought to lead to a loss of function [49]. PTEN-induced putative kinase 1 (PINK1) is found in the mitochondrial intermembrane space and membranes of the mitochondria [50], with its serine/threonine kinase domain facing the cytosol [51], suggesting that its substrates may reside here. Several studies point towards both parkin and PINK1 having a prominent role in preserving mitochondrial function (Figure 1). This can be seen vividly in *parkin* or *PINK1*-mutant/deficient flies, which exhibit abnormal mitochondria together with enhanced sensitivity to oxidative stress, apoptotic

muscle degeneration, and significant loss of a subset of dopaminergic neurons [52-54]. Furthermore, mice lacking *parkin* and *PINK1* exhibit nigrostriatal deficits (without degeneration) and mitochondrial dysfunction (indicated by reduced activity of multiple respiratory chain complexes) [55,56]. Interestingly, increased expression of *parkin* improved dysfunctions in flies lacking *PINK1*, but increased expression of *PINK1* had no effect on dysfunctions in flies lacking *parkin* [54,57]. This neatly puts parkin and PINK1 in a common pathway, with PINK1 functioning upstream from parkin. This is also consistent with recent studies where PINK1 was shown to act upstream of parkin to regulate degradation of damaged mitochondria by a process known as mitophagy [58,59]. Together these data provide compelling evidence by which both parkin and PINK1 play a crucial role in mitochondrial quality control for Parkinson's disease. These further reinforce the similarities between sporadic and familial forms of the disease, which both implicate mitochondrial dysfunction as a common pathogenic mechanism.

Parkinson's disease-associated mutations in the third gene, *DJ-1*, produce an inactive molecule that can't form a dimer, or lead to no expression at all [60,61]. DJ-1 is a molecular chaperone with a variety of functions and is found in the cytosol, the mitochondrial matrix, and mitochondrial intermembrane space [62]. In cellular models, it regulates oxidation-reduction-dependent signaling pathways and acts as a regulator of antioxidant gene expression [63], and gene deletion studies show that it counters oxidative stress in mitochondria [64]. Recent studies indicate that DJ-1 deficiency is associated with apoptosis, perturbed mitochondrial dynamics, and autophagic dysregulation [65-67], linking it with functions mediated by both parkin and PINK1 (Figure 1). Future studies focused on the interplay between PINK1, parkin, and DJ-1 will hopefully greatly advance the understanding of how mutations in these genes cause Parkinson's disease and what the common underlying mechanisms are.

Future directions

The identification and characterization of familial Parkinson's disease-linked genes has sparked an extremely fruitful line of research, delineating molecular pathways that are involved in the pathogenesis of Parkinson's disease. Although the genetic mutations in known genes account for only a limited fraction of the heritable forms of Parkinson's disease, the use of high-throughput exome and genome sequencing in the future are likely to identify additional rare variants that will further expand our knowledge of pathogenic disease mechanisms. So far, the proteins that have been linked to Parkinson's disease by genetic studies have roles in lipid and vesicle dynamics (α-synuclein), the ubiquitin-proteasome system (parkin), cytoskeletal dynamics, protein translation, abnormal kinase function (LRRK2), oxidative stress, and mitochondrial dysfunction (DJ-1, PINK1, parkin). Evidently, these disparate functions must overlap as they lead to the dysfunction and death of dopaminergic neurons characteristic of Parkinson's disease. As discussed above these molecular pathways and functions are not only relevant for the rare familial variants of Parkinson's disease, but also to the more common sporadic version of the disease.

However, while we have made great strides in understanding, the relationships between these functions are not direct and the connections between them are not immediately apparent. Therefore, the major focus in the future should be to identify common underlying mechanisms by which familial Parkinson's disease-linked genes affect dopaminergic neuronal survival, to hopefully provide the basis for new and tractable targets for new drugs to prevent and treat Parkinson's disease.

Abbreviations

GWAS, genome-wide association studies; LRRK2, leucine-rich repeat kinase 2; PINK1, PTEN-induced putative kinase 1.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

BT is supported by National Institutes of Health grants NS060885 and NS062165 and a grant from the Michael J. Fox Foundation for Parkinson's Research. MFB is supported by National Institutes of Health grant ES017295, and grants from the Parkinson's Disease Foundation, Department of Defense, and Michael J. Fox Foundation for Parkinson's Research.

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