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The Impact of Genetic Research on Our Understanding of Parkinson's Disease

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Abstract

Until recently, genetics was thought to play a minor role in the development of Parkinson's disease (PD). Over the last decade, a number of genes that definitively cause PD have been identified, which has led to the generation of disease models based on pathogenic gene variants that recapitulate many features of the disease. These genetic studies have provided novel insight into potential mechanisms underlying the etiology of PD. This chapter will provide a profile of the genes conclusively linked to PD and will outline the mechanisms of PD pathogenesis implicated by genetic studies. Mitochondrial dysfunction, oxidative stress and impaired ubiquitin-proteasome system function are disease mechanisms that are particularly well supported by genetic studies and are therefore the focus of this chapter.

Introduction

Parkinson's disease (PD) is the most common neurodegenerative movement disorder, affecting approximately 1% of the population at 65 years of age, increasing to 5% at 85 years (Van Den Eeden et al, 2003). Clinically, PD is characterized principally by symptoms of resting tremor, bradykinesia, rigidity and postural instability although additional dysfunction of non-motor systems is frequently present (Savitt et al., 2006). The primary symptoms, which together constitute Parkinsonism, arise from a profound degeneration and loss of dopaminergic neurons in the substantia nigra pars compacta, which leads to a marked depletion of the neurotransmitter dopamine in the striatum, a key region of the basal ganglia that regulates movement (Dauer and Przedborski, 2003).

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Identifying a role for genetics in PD

Until the end of the twentieth century, PD was predominantly considered a non-genetic disease caused by environmental factors and aging (Farrer, 2006). This notion was propagated early-on by the emergence of Parkinsonism in survivors of the encephalitis epidemic that occurred from 1917–1928 (Poskanser and Schwab, 1963) and later fuelled by discoveries from epidemiological studies that Parkinsonism is associated with exposure to certain pesticides and to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) via narcotic use (Langston et al., 1983; Elbaz and Moisan, 2008). A major contribution of heredity to development of the disease was thought unlikely due to epidemiological studies which indicated no effect of heritability on life-time risk of developing PD (Cookson et al., 2005). A role for genetics in PD was also not supported by cross-sectional twin studies that suggested low concordance rates in monozygotic and dizygotic twins (Ward et al., 1983; Martilla et al., 1988). This was despite the fact that since as early as the 1880's, clinicians had been noting familial aggregation of Parkinsonism (Leroux, 1880; Gowers, 1900) and that numerous families inherited PD in a Mendelian fashion (Bell and Clark, 1926) suggesting a genetic contribution to disease. For example, studies on multiple populations in the mid-twentieth century indicated that the emergence of many cases of Parkinsonism were consistent with an autosomal dominant mode of inheritance (Allen, 1937; Mjones, 1949). Finally, over the last decade, linkage mapping studies have resulted in the identification of distinct genetic loci that definitively cause familial PD (Farrer, 2006). These discoveries have resulted in a paradigm shift in perceptions towards the contribution of genetics to PD that extend beyond early-onset familial disease, since variants in α-synuclein and leucine rich repeat kinase 2 (LRRK2) contribute to the lifetime risk of sporadic PD in the population (Cookson et al., 2005; Satake et al., 2009). Importantly, recent advances in the genetics of PD have led to cell and animal models of disease that promote our understanding of molecular pathways underlying the pathogenesis of PD (Dawson et al., 2002; Moore and Dawson, 2008). Although monogenic and sporadic forms of PD are not clinically or pathologically identical, they exhibit common core features such as Parkinsonism and loss of nigral dopamine neurons suggesting that they share common mechanisms of disease and that genetics should, therefore, provide clues to the etiology of sporadic PD (Cookson et al., 2005). The following section describes the genes that have been definitively linked to PD, the normal function of their gene products and how pathogenic mutations are thought to impact cell systems. This outline will form the basis for a subsequent discussion of how genetics has impacted our understanding of PD pathogenic mechanisms.

Dominantly Inherited Mutations

α-synuclein

Studies on a large family of Italian descent (the Contursi kindred) with apparent autosomal dominant PD, led to the discovery of a PD susceptibility locus on the long arm of chromosome 4 (Polymeropolous et al., 1996) that was later identified as the SNCA gene that encodes α-synuclein (Polymeropolous et al., 1997). The 209G>A (Ala53Thr) mutation found in this family was followed by the discovery of two further PD-associated SNCA missense mutations: 88G>C (Ala30Pro) (Kruger et al., 1998) and 188G>A (Glu46Lys)

(Zarranz et al., 2004). Patients with SNCA point mutations typically develop prominent dementia and an earlier onset of Parkinsonism than in sporadic PD (Farrer, 2006). In addition to point mutations, duplication or triplication of SNCA have been found in kindreds with classic PD or sometimes, Parkinsonism with autonomic dysfunction and dementia (Singleton et al., 2003; Chartier-Harlin et al., 2004). The strong association between SNCA mutations or multiplications and PD suggests a central role for α-synuclein in PD pathogenesis (Moore et al., 2005). Furthermore, comparison of patients with duplications and triplications of SNCA reveals that age of onset is younger and disease progression faster with gene triplication (which results in an approximate doubling of plasma α-synuclein levels) (Farrer et al., 2004; Miller et al., 2004; Ross et al., 2008) suggesting that α-synuclein expression level and disease severity are related. This correlation between α-synuclein expression levels and PD susceptibility is further supported by studies in patients with sporadic PD in which allelic variability in regions of the SNCA promoter (especially the Rep1 region) is associated with risk of developing PD (Tan et al., 2000; Farrer et al., 2001; Pals et al., 2004), although this remains somewhat controversial (Spadafora et al., 2003; Tan et al., 2003; DeMarco et al., 2008).

α-Synuclein exists mainly as a 140 amino acid protein whose precise function is unknown (Moore et al., 2005). α-Synuclein is expressed in neurons throughout the mammalian nervous system where it resides predominantly at presynaptic terminals associated with vesicles and membranes (Kahle et al., 2000; Fortin et al., 2004; Bonini and Giasson, 2005). Interestingly, α-synuclein is natively unfolded in solution although it adopts an alpha-helical rich conformation when associated with membranes (Ferreon et al., 2009).

The precise function of α-synuclein is unclear, although its association with synaptic vesicles suggests a possible role in neurotransmission. Indeed, studies in yeast and mammalian systems suggest that α-synuclein may regulate synaptic vesicle trafficking via binding to lipids (Jenco et al., 1998; Outeiro and Lindquist, 2003; Nemani et al., 2010). A recent report describes a possible role for α-synuclein in assembly of the SNARE complex between vesicle and presynaptic membranes, which is crucial for priming and recycling of synaptic vesicles (Chandra et al., 2005; Bonini and Giasson, 2005). Deletion of the co-chaperone cysteine-string protein-α in mice results in neurodegeneration with underlying impairment in SNARE complex assembly (Chandra et al., 2005). The authors further report that transgenic expression of α-synuclein attenuates inhibition of SNARE complex formation and prevents neurodegeneration. Despite this, genetic knock-out studies in mice have indicated that the absence of α-synuclein has no significant effect on the pool size of recycling synaptic vesicles, synaptic plasticity or dopamine uptake and release from nerve terminals (Chandra et al., 2004) suggesting that α-synuclein may not be required for regulating synaptic vesicle release or uptake under normal conditions and may, instead, be protective following exposure to certain cell stressors.

Mutations and multiplications in the SNCA gene may cause PD through a gain-of-toxic-function mechanism as suggested by their dominant inheritance pattern. When mutated or at elevated concentrations, α-synuclein has a propensity to develop a β-sheet-rich structure that readily polymerizes into oligomers (Sharon et al., 2003) and higher-order aggregates such as fibrils (Conway et al., 1998) in cells, animal models and human brain (Lee et al., 2002;

Outeiro et al., 2008; Sharon et al., 2003; Miller et al., 2004). Insoluble α-synuclein fibrils are a major component of hallmark PD inclusions called Lewy bodies and Lewy neurites, present in perikarya and neurites, respectively. In PD, Lewy bodies and neurites can be found in both dopaminergic and non-dopaminergic neurons of the brainstem and in the cortex (Farrer, 2006). Importantly, Lewy bodies are found in a number of neurodegenerative diseases involving SNCA mutations including PD, parkinsonism with dementia and dementia with Lewy bodies (MartÌ et al., 2003). This establishes a link between these diseases with distinct clinical features but shared pathology. Controversy exists as to whether Lewy bodies and neurites are a cause or consequence of PD, and some evidence suggests they might actually have a protective role by acting to sequester toxic α-synuclein oligomers (Tanaka et al., 2004; Olanow et al., 2004). Fueling this controversy are the findings that certain SNCA mutations (A53T and A30P) promote oligomerization but not fibrillization of α-synuclein and moreover that Lewy bodies are frequently absent from the brains of PD patients with genetic mutations (Conway et al., 2000; Gaig et al., 2007; Ahlskog, 2009). Accordingly, emerging evidence suggests that prefibrillar oligomers and protofibrils are the toxic species responsible for PD pathology (Conway et al., 2000; Goldberg and Lansbury, 2000, Masliah et al., 2000; Kayed et al., 2003; Danzer et al., 2007). α-Synuclein oligomers, akin to other amyloidogenic oligomers cause elevated Ca^{2+} influx into cells *in vitro*, possibly by altering membrane stability or permeability by forming membrane pores (Demuro et al., 2005; Danzer et al., 2007). Elevated intracellular Ca^{2+} levels may promote cellular toxicity through increased generation of reactive oxygen species and resultant oxidative damage.

Whether the pathogenic α-synuclein species is oligomeric, fibrillar or both, it is reasonably clear that aggregates of this protein are toxic in primary neuronal cultures (Xu et al., 2002; Tanaka et al., 2001; Zhou and Freed, 2005 Petrucelli et al., 2002), invertebrate animal models (Feany and Bender 2000; Park and Lee, 2006; periquet et al., 2007; Kuwahara et al., 2006; Lakso et al., 2003) and in rodent (St Martin et al., 2007; Lo Bianco et al., 2002) and non-human primate models involving viral vectors to deliver α-synuclein to the substantia nigra (Kirik et al., 2003; Yasuda et al., 2007). Aggregation may be promoted by numerous factors including mitochondrial complex I inhibitors paraquat and rotenone (Manning-Bog et al., 2002; Sherer et al., 2002; Sherer et al., 2003). Evidence linking exposure to these compounds with the occurrence of sporadic PD suggests a possible role for α-synuclein aggregates in sporadic disease. Additionally, oxidative and nitrative damage, which accumulate in the brains of many species including humans during aging, may promote aggregation of α-synuclein to toxic species (Ostrerova-Golts et al., 2000; Cole et al., 2005; Qin et al., 2007; Leong et al., 2009). Tyrosine nitration of α-synuclein is found in the PD brain and has been shown to accelerate α-synuclein aggregation *in vitro* (Giasson et al., 2000) by a mechanism that may include reduced efficiency of α-synuclein degradation by calpain I and 20S proteasome (Hodara et al., 2004). Lastly, the interaction of α-synuclein with other amyloidogenic proteins such as tau (Giasson et al., 2003) or amyloid-β (Masliah et al., 2001) may synergistically drive fibrillization of these proteins. For example, amyloid-β peptides were shown to promote intraneuronal α-synuclein aggregation in cell cultures and transgenic mice expressing both α-synuclein and amyloid-β neuronally developed more α-synuclein-immunoreactive inclusions than singly α-synuclein transgenic mice. These double

transgenic mice also exhibited motor deficits and impaired learning and memory before mice expressing transgenic α-synuclein only (Masliah et al., 2001). A clear relevance of this stimulatory effect on α-synuclein aggregation applies to patients with clinical and pathological features of both PD and Alzheimer's disease (e.g. those with the Lewy body variant of Alzheimer's disease).

While α-synuclein is seen to undergo aggregation and post-translational modifications, and these events may lead to its toxicity to neurons, the effects of α-synuclein responsible for causing cell death are not yet clear. Nevertheless, several theories have been put forth to explain α-synuclein toxicity and are briefly outlined here. As already mentioned, α-synuclein oligomers can form pore-like structures and annular rings of α-synuclein were previously observed in brains of patients with multiple system atrophy, a synucleinopathy. Neural cells expressing mutant forms of α-synuclein (A53T and A30P) exhibited non-selective cation pores that increased both basal and depolarization-induced intracellular Ca^{2+} levels (Furukawa et al., 2006). Furthermore, cells expressing mutant α-synuclein were more sensitive to iron generated reactive oxygen species, unless treated with Ca^{2+}-chelating agents, suggesting that elevated intracellular Ca^{2+} levels were responsible for the increased vulnerability of these cells to toxic insults. Given that a portion of α-synuclein has been observed to localize to mitochondrial membranes of dopamine neurons (Li et al., 2007; Nakamura et al., 2008), and the central involvement of mitochondria in PD pathogenesis, an obvious question is whether such pores form in mitochondrial membranes to promote mitochondrial dysfunction. Overexpression of α-synuclein in cells was reported to induce abnormal morphology and dysfunction of mitochondria together with increased oxidative stress (Hsu et al., 2000). Since there was little change in cell viability, this suggests that mitochondrial deficits were not secondary to cell death, but a direct consequence of α-synuclein overexpression.

Another potential mechanism of α-synuclein toxicity supported by the interaction of α-synuclein with synaptic vesicles is that increased or mutant α-synuclein expression interferes with synaptic neurotransmission. Wild type or A30P α-synuclein was shown to impair catecholamine release from chromaffin and PC12 cells associated with an accumulation of 'docked' vesicles at the presynaptic membrane (Larsen et al., 2006). Furthermore, α-synuclein overexpression to levels predicted to result from gene multiplication impaired neurotransmitter release in mice through a mechanism involving reduced size of the recycling vesicle pool (Nemani et al., 2010). Uptake of dopamine into synaptic vesicles may also be perturbed by α-synuclein. Mutant α-synuclein overexpression was reported to downregulate the vesicular monoamine transporter 2 which may lead to increased cytosolic levels of dopamine (lotharius et al., 2002). Pathogenic species of α-synuclein are not good substrates for proteasomal degradation and aggregates can directly bind to 20/26S proteasomal subunits inhibiting proteolytic activity (Snyder et al., 2003). α-Synuclein may also affect protein degradation through inhibiting lysosomal function (stefanis et al., 2001) and chaperone-mediated autophagy (Cuervo et al., 2004). Recent data suggests that chaperone-mediated autophagy is important in the regulation of the neuronal survival factor MEF2D (myocyte enhancer factor 2D) and that α-synuclein expression can disrupt this leading to cell death (Yang et al., 2009).

Hence, α-synuclein aggregates appear to exert toxic effects on numerous cell functions. The relative contributions of these effects to neuronal cell death is not well understood and may vary depending on cell type and other circumstances such as the type and amount of α-synuclein pathogenic species present. Teasing apart primary effects of α-synuclein toxicity from secondary will be important for identifying therapeutic targets for preventing cell death (Cookson, 2009).

Leucine-rich repeat kinase 2 (LRRK2)

Since the first identification of pathogenic LRRK2 mutations in 2004 (Paisan-Ruiz et al., 2004; Zimprich et al., 2004a; Zimprich et al., 2004b), mutations in this gene are now the most common known cause of familial PD worldwide (Webber and West, 2009). Autosomal dominantly inherited LRRK2 mutations exist in families from diverse ethnic backgrounds and mostly give rise to PD phenotypes that are highly similar to those of typical late-onset PD. This suggests that understanding the effects of mutant LRRK2 on disease pathogenesis has the potential to generate substantial insight into sporadic PD mechanisms. Interestingly, despite consistency of clinical phenotypes, LRRK2 mutant carriers can exhibit diverse neuropathology occasionally lacking Lewy bodies, even between individuals with the same mutation (Zimprich et al., 2004; Gaig et al., 2007).

LRRK2 encodes a large, 280 KDa protein with initial studies indicating potential roles in cytoskeletal dynamics, protein translation control, mitogen-activated protein kinase pathways, and apoptotic pathways. LRRK2 contains numerous domains, namely ankyrin-like repeats, leucine-rich repeats, COR (C-terminal of ROC) WD-40 domain and a catalytic GTPase/kinase region. Interestingly, LRRK2 kinase activity appears to require a functional GTP-ase domain (West et al., 2007) and possibly LRRK2 dimer formation (Sen et al., 2009). LRRK2 undergoes autophosphorylation and phosphorylates a number of protein substrates *in vitro*. Analysis of the human kinome indicates that the kinase domain of LRRK2 and its homolog LRRK1 are most similar in sequence to the receptor-interacting protein kinase and death-domain containing interleukin receptor-associated kinase families and to a lesser extent, MAP (mitogen-activated protein) kinase kinase kinases. Several of the most clear and common pathogenic mutations (G2019S, I2020T, R1441C/G) are found in the central catalytic region and may result in increased kinase activity *in vitro* (West et al., 2007) although it is important to note that not all PD-associated LRRK2 mutations increase kinase activity and only the G2019S mutation has consistently been found to increase kinase activity to date (Greggio and Cookson, 2009).

Much effort is currently focused on attempting to identify kinase substrates and pathogenic mechanisms linked to altered kinase activity. A role for LRRK2 in protein translation control has been put forth by the identification of the translational inhibitor 4E-BP (eukaryotic initiation factor 4E-binding protein) as a LRRK2 substrate both *in vitro* and in a *Drosophila* model (Imai et al., 2008; Tain et al., 2009). 4E-BP in its non-phosphorylated state interacts with eIF4E (eukaryotic initiation factor 4E), preventing activity of eIF4E within the protein translation machinery thereby inhibiting protein translation (Khalegpour et al., 1999). Phosphorylation of 4E-BP disrupts its interaction with eIF4E and stimuli that affect 4E-BP phosphorylation such as oxidative stress and activation of the mTOR

(mammalian target of rapamycin) pathway can impact protein translation indicating that 4E-BP phosphorylation is associated with increased protein translation. Overexpression of human LRRK2 in mammalian cells or a *Drosophila* ortholog (dLRRK) in flies was shown to result in increased 4E-BP phosphorylation at two threonine sites (Thr37/Thr46) leading to secondary phosphorylation by additional kinases at other sites including Ser65/Thr70 (Imai et al., 2008). The authors also reported that RNAi-mediated silencing of LRRK2 in cells or loss-of-function dLRRK mutation in flies led to a decrease in 4E-BP phosphorylation at these sites supporting the possibility that 4E-BP is a kinase substrate of LRRK2. Finally, the authors showed that dopamine neuron pathology associated with dLRRK mutations was suppressed via overexpression of 4E-BP suggesting that increasing 4E-BP activity might attenuate PD pathology. Another recent study in *Drosophila* has strengthened a potential link between LRRK2, 4E-BP activity and PD pathology (Tain et al., 2009). Increased 4E-BP activity resulting from loss of dLRRK or administration of rapamycin was sufficient to suppress pathology in PINK1 (PTEN-induced putative kinase 1) and Parkin mutants raising the possibility that an involvement of general protein translation in PD pathology might be relevant to other PD-associated genes.

Another candidate substrate for LRRK2 kinase activity is moesin (Jaleel et al., 2007). Moesin is a member of the ERM (ezrin/radixin/meosin) protein family whose primary role is to anchor the cytoskeleton to the plasma membrane. Jaleel et al. found that Moesin could be phosphorylated by LRRK2 at Thr558 and to a lesser extent at Thr526. One caveat is moesin phosphorylation could only be observed after denaturating moesin via heating and even then, phosphate was minimally incorporated suggesting that moesin may be a weak kinase substrate of LRRK2. Despite this, a recent study on developing neurons supports the possibility that moesin is a LRRK2 substrate *in vivo* (Parisiadou et al., 2009). Phosphorylated ERM protein accumulated more in developing neurons from G2019S LRRK2 transgenic mice and less in LRRK2 knock-out mice than controls (Parisiadou et al., 2009). Furthermore, the extent of ERM phosphorylation correlated negatively with neurite outgrowth suggesting that LRRK2 mutations may perturb normal neuronal development.

Based on sequence similarity between LRRK2 and MAPKK kinases, which are involved in the MAPK signaling pathway and important to cellular stress responses, Gloeckner et al, recently used *in vitro* studies to probe MAPK kinases as potential substrates for LRRK2 kinase activity (Gloeckner et al., 2009). These studies revealed phosphorylation of MKK3, -4, -6 and -7 by LRRK2 and moreover, that PD-linked G2019S or I2020T mutations in LRRK2 exhibit increased phosphotransferase activity as well as enhanced autophosphorylation. Whether these changes are due to LRRK2 kinase activity is not clear since the authors did not use kinase-dead versions of LRRK2 as a control. Since phosphorylation of MAPK kinases within their activation loop is linked to increased downstream phosphorylation of c-Jun N-terminal kinase (JNK) and c-Jun, it might be expected that increased LRRK2 kinase activity would lead to higher phosphorylated JNK and/or c-Jun levels. However this is inconsistent with prior studies in cell system (West et al., 2007) in which LRRK2 overexpression does not appear to increase levels of phosphorylated JNK or c-Jun. Hence, the simplest explanation here is that there exists disparity between kinase activity observed *in vitro* and that found in intact cells.

For any putative LRRK2 kinase substrate identified *in vitro*, it will be imperative to determine its relevance as a substrate *in vivo* where conditions affecting protein localization, activity and structure are far more complicated. Moreover, since existing studies largely support an increase in kinase activity following certain mutations in LRRK2 (e.g. G2019S), it will be important to assess whether the phosphorylation of any putative substrate is enhanced in the presence of mutant LRRK2 relative to wild-type LRRK2.

Numerous studies show that expression of mutant LRRK2 causes cell death. Overexpression of mutant LRRK2 in primary neuronal cultures leads to rapid cell death possibly by apoptosis, while comparable expression of wild-type LRRK2 has only subtle effects on cell viability (Smith et al., 2005; Greggio et al., 2006; MacLeod et al., 2006; Smith et al., 2006; Iaccarino et al., 2007; West et al., 2007; Ho et al., 2009.). A proposed link between increased LRRK2 kinase activity and neuronal death in PD requires further investigation *in vivo*, although a dominant mode of inheritance (consistent with a toxic-gain-of-function) and preliminary studies in cell culture are supportive of this. Multiple investigators have discovered that pathogenic LRRK2 mutants engineered to ablate kinase activity are substantially less toxic in cultured cells than kinase-active counterparts (West et al., 2007; Gregio et al., 2006; Smith et al., 2006) indicating that kinase activity contributes to cellular toxicity. One caveat is that not all pathogenic LRRK2 mutations appear to result in elevated kinase activity based on measurements of autophosphorylation or generic kinase substrate phosphorylation. A possibility to consider here is that pathogenic LRRK2 mutations might alter kinase activity towards specific substrates that are key to LRRK2-mediated toxicity but not a universal increase in kinase activity to all substrates. Perhaps identification of true *in vivo* LRRK2 substrates will permit definitive assessment of the role of kinase activity in LRRK2-mediated PD pathogenesis. Despite considerable recent progress, much remains to be understood about the contribution of mutant LRRK2 to PD pathogenesis. Given the pervasiveness of these mutations in PD, unlocking these mysteries will surely have broad implications in understanding fundamental mechanisms of PD development and for therapeutic strategies aimed at LRRK2.

Recessive mutations

Compelling evidence implicates loss-of-function mutations in three genes; Parkin, PINK1 (PTEN-induced putative kinase 1) and DJ-1, in autosomal recessive PD and some sporadic cases (Dodson and Guo, 2007). Recent work has demonstrated key roles for all three gene products in preserving mitochondrial function and protecting against reactive oxygen species. This underscores the central role of mitochondrial dysfunction and oxidative stress in PD pathogenesis, reinforcing previous studies linking sporadic PD cases with mitochondrial poisons such as MPTP and paraquat. Recessively inherited mutations in a fourth gene, ATP13A2, are linked to Kufor-Rakeb syndrome, a pallidopyramidal syndrome featuring Parkinsonism together with behavioral and cognitive disorders (Najim al-Din et al., 1994). Large-scale association studies showed that ATP13A2 genetic variants do not segregate with PD within families indicating that these mutations likely do not contribute to disease risk (Vilarino-Guell et al., 2009).

Parkin

Mutations in Parkin were originally linked with autosomal recessive juvenile-onset Parkinsonism (AR-JP) in three unrelated Japanese families in 1997 (Kitada et al., 1998). Homozygous loss-of-function or compound heterozygous Parkin mutations account for approximately 50% of all familial early-onset cases of PD with point mutations being the most frequent genetic lesion, and deletions, duplications and exonic rearrangements also contributing to Parkin-linked PD (Mata et al., 2004). Although the majority of Parkin-associated PD is inherited in an autosomal recessive manner, there is some evidence to suggest that Parkin haploinsufficiency due to polymorphisms in the promoter or coding regions may associate with increased susceptibility to late-onset PD (Farrer, 2006). Clinically, patients with Parkin mutations are L-Dopa responsive and exhibit slower disease progression often accompanied by early-onset dystonia. Interestingly, Parkin-linked disease may be associated with an absence of Lewy body pathology, a finding that is inconsistent with these being causal in disease pathogenesis. However, Lewy body pathology is observed in some cases of Parkin-linked PD.

Parkin encodes a protein of 465 amino acids consisting of an N-terminal ubiquitin-like (UBL) domain, central linker region and a C-terminal RING domain containing two RING-finger domains (Moore et al., 2005). Parkin demonstrates E3 ubiquitin protein ligase activity, tagging protein lysine residues with ubiquitin. Attachment of Poly-ubiquitin chains to proteins via lysine K48 usually targets them for degradation via the 26S proteasome whereas monoubiquitylation and poly-ubiquitination through K48 or K63 can influence other pathways such as intraellular signaling, DNA repair, endocytosis, transcriptional regulation and protein trafficking (Mukhopadhyay et al., 2007; Sandebring et al., 2009).

While the majority of the Parkin pool is localized to the cytoplasm and vesicular structures (Shimura et al., 2000; kubo et al., 2001), a portion is found associated with the outer mitochondrial membrane (Darios et al., 2003). Several recent studies on *Drosophila* and mice have revealed a key role for Parkin in regulating mitochondrial function and protection against oxidative stress (Greene et al., 2003; Park et al., 2006; Yang et al., 2006; Deng et al., 2008; Palacino et al., 2004), which is discussed further in a subsequent section. Most mutations in Parkin appear to impair its E3 ligase activity or interactions with E2 enzymes such as UbcH7 and UbcH8 (Shimura et al., 2000; Zhang et al., 2000). Although it is not definitively known that loss of Parkin's E3 ligase activity is sufficient for development of PD, a prominent hypothesis is that Parkin mutations lead to toxic accumulation of its substrates due to impaired ubiquitin-proteasome function (Dodson and Guo, 2007). Through extensive *in vitro* investigations, a number of putative Parkin substrates have been identified including the aminoacyl-tRNA synthase cofactor p38 (Corti et al., 2003), far upstream element-binding protein-1 (Ko et al., 2006) cyclin E (Staropoli et al., 2003), the parkin-associated endothelin receptor-like receptor (Pael-R) (Imai et al., 2001), synphilin-1 (Chung et al., 2001), synaptotagmin XI (Huynh et al., 2003), CDCrel-1 (Zhang et al., 2001) and alpha/beta-tubulin (Ren 2003). From this set, only the p38 subunit of aminoacyl tRNA synthase and far upstream element-binding protein-1 have been demonstrated to accumulate in the brains of both patients with Parkin mutations and Parkin-null mice (Ko et al., 2005; Ko et al., 2006) highlighting the importance of determining the authenticity of all other

putative substrates *in vivo*. Further studies will also be required to determine the roles of these substrates in PD pathogenesis.

PINK1

A second locus for autosomal recessive early-onset Parkinsonism was discovered initially in a large Sicilian family mapped to the short-arm of chromosome 1p35-p36 (Valente et al., 2001) and later extended to eight additional families from four European countries (Valente et al., 2002). Subsequent work revealed that within this locus, mutations in PINK1 are linked to PD (Valente et al., 2004). Atypical clinical phenotypes have been reported in PINK1-linked PD, including dystonia, psychiatric disturbances and sleep benefit (Hatano et al., 2004; Tan and Dawson, 2006; Valente et al., 2004). PINK1 is a cytosolic and mitochondrially-localized protein kinase which contains an N-terminal mitochondrial targeting sequence followed by a predicted transmembrane domain, suggesting that PINK1 may be an integral transmembrane protein possibly in the mitochondrial inner membrane with which it closely associates (Silvestri et al., 2005). However, a recent study indicates that the kinase domain of PINK1 faces out into the cytosol (Zhou et al., 2008). Existing evidence from cell and animal models suggests that PINK1 is important for protection against cell death related to mitochondrial dysfunction and oxidative stress (Exner et al., 2007; Clark et al., 2006; Deng et al., 2008;, Hoepken et al., 2007; Wood-Kaczmar et al., 2008). Although several PD-associated mutations reduce PINK1 kinase activity, it is not clear whether loss of kinase activity is required for PD pathogenesis, since disease-associated mutations are found both within and outside of the kinase domain. It seems, however, that kinase activity is required for the protective function of PINK1 against pro-apoptotic agents since staurosporine-induced cell death was substantially reduced by wild type PINK1 overexpression whereas an equivalent increase in kinase-inactive PINK1 mutant had no protective effect (Petit et al., 2005). Additionally, recent *in vivo* data suggests that phosphorylation of the mitochondrial chaperone TRAP1 (TNF receptor-associated protein 1) by PINK1 is important for the protective action of PINK1 against oxidative stress-induced cell death (Pridgeon et al., 2007). The authors also reported that the ability of PINK1 to phosphorylate TRAP1 is impaired by PD-associated G309D, L347P and W437X PINK1 mutations suggesting a possible connection between these mutations, impaired PINK1 substrate phosphorylation and cell death. PINK1 was recently demonstrated to regulate mitochondrial Ca^{2+} efflux in mammalian neurons and loss of PINK1 was associated with mitochondrial Ca^{2+} overload and consequent respiration inhibition via increased reactive oxygen species generation and opening of the mitochondrial permeability transition pore (Ghandi et al., 2009).

DJ-1

Mutations in DJ-1 were originally associated with early-onset PD in 2003 (Bonifati et al., 2003) and are known to be very rare, accounting for less than 1% of early-onset cases. The DJ-1 protein is a member of the ThiJ/PfpI family of molecular chaperones that are induced by oxidative stress (Dodson and Guo, 2007). Consistent with this, DJ-1 deficiency in Drosophila increases cell death caused by ROS-generating species linked to PD in humans (Muelener et al., 2005). Additional studies revealed that a conserved cysteine residues in

human (Canet-Aviles et al., 2004), mice (Andres-Mateos et al., 2007) and *Drosophila* (Meulener et al., 2006) DJ-1 is modified under conditions of oxidative stress and this modification is necessary for the protective effects of DJ-1. Furthermore, evidence in mice indicates that DJ-1 acts as an atypical peroxiredoxin-like peroxidase to scavenge H_2O_2 produced by mitochondria (Andres-Mateos et al., 2007). Accordingly, DJ-1 knock-out mice exhibit elevated mitochondrial H_2O_2 and reduced activity of mitochondrial aconitase activity levels although the pathological consequences of this are uncertain since there was an absence of dopaminergic neuron degeneration in these mice (Andres-Mateos et al., 2007). Hence, DJ-1 may act as a cellular redox-sensor, which becomes activated under oxidative conditions to provide protection against ROS-mediated damage. Numerous functions have been ascribed to DJ-1, including protease, transcriptional coactivator and molecular chaperone functions, although which of these, if any, contribute to its protective role in PD remains to be determined.

Impact of genetic research on understanding mechanisms of PD pathogenesis

Genetic studies over the last decade have resulted in the identification of pathogenic gene variants that underlie familial PD and in some cases contribute to the lifetime risk of developing sporadic PD. By linking these genes to PD and understanding the biological roles of the products they encode, a wealth of insight has been generated into mechanisms of PD pathogenesis. These pathogenic genes also yield understanding of possible relationships between PD and disorders with overlapping clinical or neuropathological features that may share common mechanisms. For example, neuronal α-synuclein accumulation often in Lewy bodies can be found in a number of neurodegenerative disease including PD, dementia with lewy bodies, multiple system atrophy and pure autonomic failure (Kramer and Schulz-Schaeffer, 2009; Goldstein and Sewell, 2009; Kövari et al., 2009) suggesting that α-synuclein aggregation is a common mechanism in these diseases. Genetic studies have in some instances corroborated pathogenic mechanisms indicated by environmental factors such as a central involvement of oxidative stress and mitochondrial dysfunction in PD etiology. Additionally, genetic studies have implicated protein mishandling due to dysfunction of the ubiquitin proteasome system in development of PD. Since perturbations in the ubiquitin proteasome system or mitochondrial function both lead to the same pathological outcome, i.e. loss of dopamine neurons and development of PD, it is likely that an important relationship exists between these functions that converges on dopamine neuron viability. The model presented in Figure 3 illustrates molecular pathways in PD pathogenesis implicated by genetic studies and how these pathways may be connected.

Mitochondrial dysfunction and oxidative stress

A role for mitochondrial dysfunction in PD pathogenesis is supported by studies on a number of gene products linked to PD. Knock-out studies in animals clearly indicate that two PD-linked genes, Parkin and PINK1, have key roles in preserving mitochondrial function and that loss-of-function mutations in these genes can lead to PD. *Drosophila* Parkin null mutants exhibit mitochondrial pathology marked by enlarged size and rarified cristae, as well as enhanced sensitivity to oxidative stress, apoptotic muscle degeneration,

significant (albeit slight) degeneration of a subset of dopamine neurons and reduced life span (Greene et al., 2003; Pesah et al., 2004). Parkin null mice, which exhibit nigrostriatal deficits without nigral degeneration, do not have gross changes in striatal mitochondrial morphology but do experience mitochondrial dysfunction evidenced by reduced activity of multiple respiratory chain complexes along with decreased antioxidant capacity that results in increase oxidative damage (Palacino et al., 2004). Intriguingly, complete loss of PINK1 function in flies led to phenotypes that are highly similar to Parkin-null flies (Clark et al., 2006). The subtle neuronal death observed in PINK1 or Parkin mutants can be prevented by overexpression of antioxidants (Wang et al., 2006; Whitworth et al., 2005) supporting the contention that oxidative stress is important to PD pathology. Indeed, oxidative damage to cell macromolecules is consistently observed in the substantia nigra of PD patients (Jenner, 2003) and elevated reactive oxygen species generation may occur as a result of impaired respiratory chain function.

Several lines of evidence suggest a genetic interaction between PINK1 and Parkin. For example, overexpression of Parkin rescued all phenotypes resulting from PINK1 deficiency although a reciprocal rescue effect of PINK1 overexpression in Parkin mutants was not found (Park et al., 2006). Similarly, loss of mitochondrial potential, abnormal mitochondrial morphology and reduced cristae seen in HeLa cells with PINK1 deficits can be rescued by increased expression of wild-type but not PD-associated mutant Parkin (Exner et al., 2007). These lines of evidence have led to the hypothesis that Parkin acts downstream of PINK1 to preserve mitochondrial function (Dodson and Guo, 2007). Recent studies in *Drosophila* have suggested a possible link between PINK1, Parkin and mitochondrial function by demonstrating that both appear to regulate mitochondrial dynamics by either promoting fission or inhibiting fusion of the organelle (Poole et al., 2008; Deng et al., 2008). Genetic manipulations of the fly mitofusin homolog (Mfa), Opa1 (optic atrophy 1) or drp1 in favor of mitochondrial fission are sufficient to rescue mitochondrial pathology, cell death and muscle degeneration in Parkin or PINK1 mutants (Deng et al., 2008). However, these data and their relevance to human disease should be interpreted cautiously due to discrepancies in mitochondrial morphology abnormalities that exist between fly and mammalian model systems. Nonetheless, impaired mitochondrial respiration has been detected in peripheral tissues taken from human PD patients with PINK1 (Hoepken et al., 2007) or Parkin mutations (Muftuoglu et al., 2004) suggesting that the mitochondrial dysfunction observed in animal models may be relevant to human disease. Hence, considerable evidence supports a role for PINK1 and Parkin in protecting against cell death due to mitochondrial dysfunction and oxidative stress.

Mutations and multiplications in SNCA may also promote mitochondrial dysfunction leading to neuronal death. Mitochondrial pathology following MPTP exposure is exacerbated in α-synuclein transgenic mice (Song et al., 2004) and neuronal cells expressing mutant α-synuclein showed a selective increase in mitochondrial dysfunction and apoptotic cell death when treated with a proteasome inhibitor (Tanaka et al., 2001). Inhibition of the mitochondrial respiratory chain complex I, which is caused by pesticides and certain other environmental toxins, commonly leads to the accumulation of α-synuclein-positive inclusions suggesting that α-synuclein aggregation may be a consequence of mitochondrial

dysfunction (Betarbet et al., 2000; Manning-Bog et al., 2002). Interestingly, α-synuclein knock-out mice are resistant to the toxic effects of MPTP on neurons while α-synuclein transgenic mice are more sensitive indicating that α-synuclein might be necessary for neuronal toxicity associated with impaired complex I activity (Dauer et al., 2002; Song et al., 2004). Taken together, this evidence suggests that α-synuclein, likely in aggregate form, may have a toxic role both in causing mitochondrial dysfunction and in the deleterious effects resulting from it. Future studies will hopefully elucidate the nature of the relationship between α-synuclein and mitochondrial dysfunction.

Ubiquitin-proteasome system impairment

Compelling evidence from genetic studies links ubiquitin-proteasome system (UPS) dysfunction to development of PD. Mutations in Parkin associated with the disease are widely believed to cause impairment of UPS function with consequent accumulation of potentially cytotoxic proteins that may result in death of dopamine neurons (Chung et al., 2001; Moore et al., 2005). In support of this, proteasome inhibitors are found to cause a number of phenotypes that closely recapitulate those in PD when injected into rats (McNaught et al., 2004) and genetic knock-out of a 26 proteasomal subunit in mice impairs ubiquitin-mediated protein degradation and leads to intraneuronal Lewy-like inclusion formation and substantial degeneration in the nigrostriatal pathway (Bedford et al., 2008). The accumulation of aggregated proteins such as α-synuclein in nigral neuron Lewy bodies in sporadic PD also indicates mishandling of protein turnover perhaps due to impaired UPS function. As previously mentioned, Lewy bodies are often absent in certain familial forms of PD suggesting that they may not be neuropathological in PD but are, instead, a hallmark of protein aggregation and therefore still supportive of a role for protein mishandling in PD pathology. Aggregated α-synuclein has been shown to strongly bind to and inhibit the 26S proteasome *in vitro* (Snyder et al., 2003) and overexpression of mutant α-synuclein in cells was observed to decrease proteasome function and cause selective toxicity to catecholaminergic neurons (Petrucelli et al., 2002). Interestingly, co-expression of Parkin was reported to reduce sensitivity of α-synuclein-expressing cells to proteasome inhibitors suggesting that Parkin protects against mutant α-synuclein-mediated toxicity. Similarly, overexpression of the molecular chaperone Hsp70 in flies (Auluck et al., 2002) or transgenic expression of the yeast chaperone Hsp104 in rats (Lo Bianco et al., 2008) prevents degeneration of dopamine neurons caused by expression of mutant α-synuclein indicating that chaperones function may protect against PD pathology related to α-synuclein. Consistent with this, Lewy bodies examined from postmortem human brain were found to contain molecular chaperones (Auluck et al., 2002), which may indicate that in the PD brain, these fail to effectively prevent protein aggregation at physiological levels. Further investigations assessing the ability of molecular chaperones to prevent neuronal toxicity associated with α-synuclein aggregation will hopefully lead to new therapeutic strategies for PD.

Conclusion

Although the majority of PD is sporadic, the discovery of rare familial forms of PD and subsequent identification of disease-causing mutations have provided extremely valuable

tools to begin to understand the cellular network of dysfunction that ultimately results in neuronal demise and manifestation of disease phenotypes. Through the generation of cellular and small animal models expressing PD-linked genetic mutations, new insights into mechanisms of disease pathogenesis have been achieved. Further study will hopefully lead to new disease-modifying treatments for PD that will provide more then temporary symptomatic relief.

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List of Abbreviations

PD	Parkinson’s Disease
SNARE	soluble NSF attachment protein receptors
MEF2D	myocyte enhancer factor 2D
LRRK2	leucine-rich repeat kinase 2
eIF4E	eukaryotic initiation factor 4E
4E-BP	eukaryotic initiation factor 4E binding protein
ERM	ezrin/radixin/meosin
MAPK	mitogen-activated protein kinase
MAPKK	mitogen-activated protein kinase kinase
JNK	c-Jun N-terminal kinase
PINK1	PTEN-induced putative kinase 1
TRAP1	TNF receptor-associated protein 1
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

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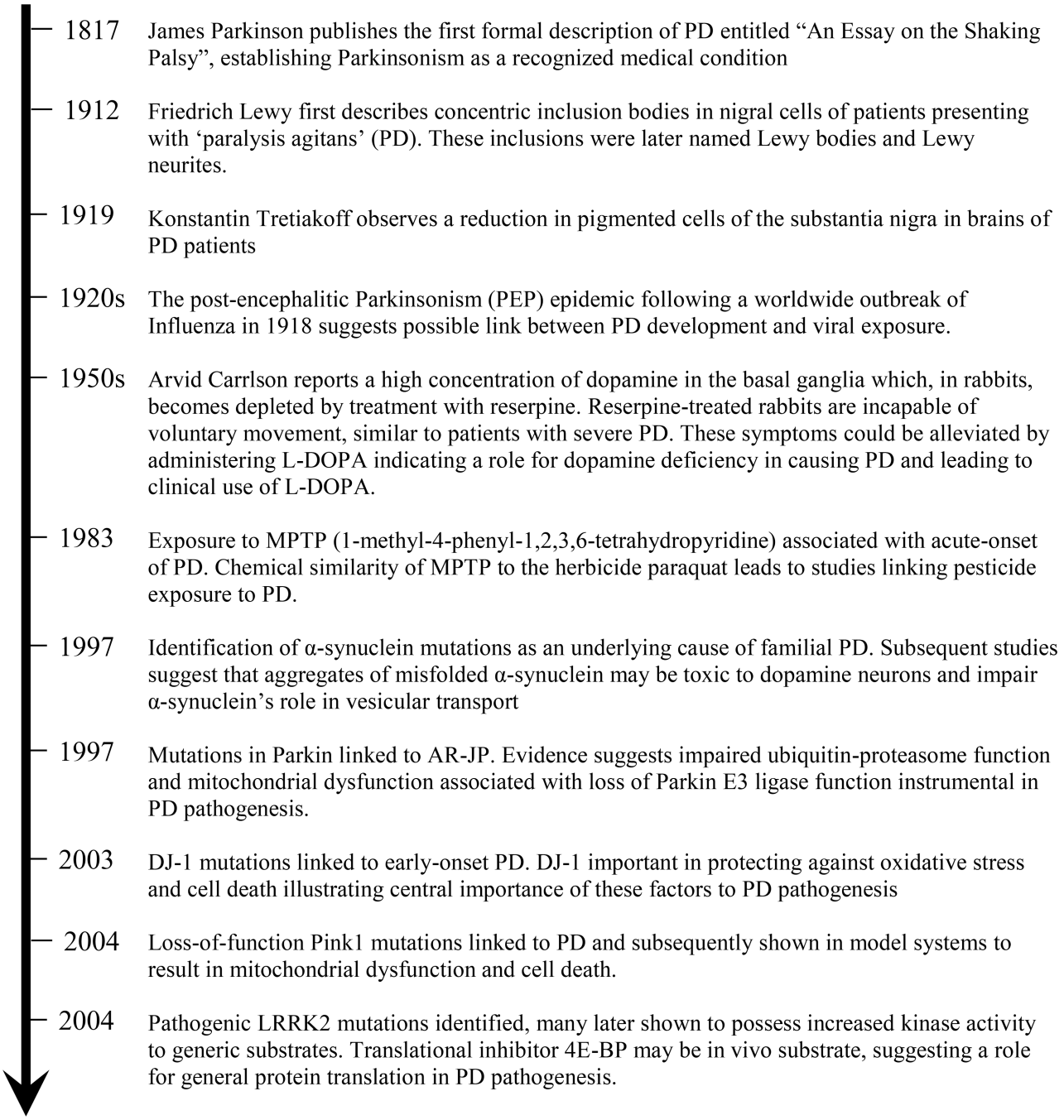

Figure 1. Timeline of key discoveries in PD pathogenesis

Parkinson’s disease was first formally described in 1817 by James Parkinson. From then until the late twentieth century, advances were made in describing the pathological features of PD and in understanding possible causes of the disease, such as exposure to pesticides and MPTP. The recent discovery of multiple genetic causes of PD has generated insight into novel mechanisms of PD etiology. Studies using genetic models of PD will, no doubt, continue to advance our understanding of disease pathogenesis.

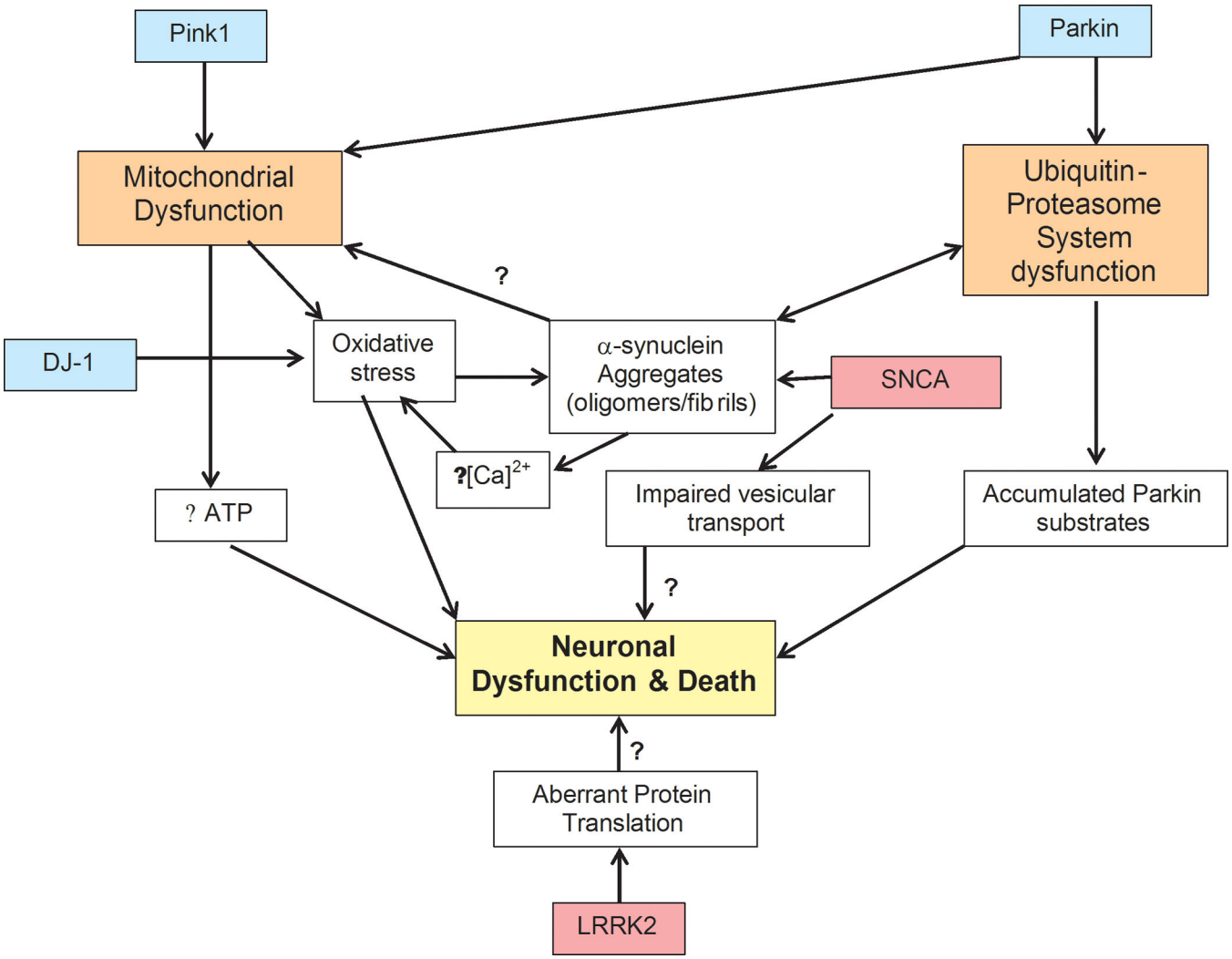

Figure 2. Pathogenic mechanisms implicated by genetic studies of PD

This model links genetic mutations (autosomal recessive mutations in blue boxes and autosomal dominant mutations in purple boxes) to neurodegeneration via pathways involving mitochondrial dysfunction, oxidative stress and impaired ubiquitin-proteasome function. Loss-of-function mutations in PINK1 or Parkin cause PD possibly through a mechanism involving mitochondrial pathology and dysfunction. Deleterious effects of mitochondrial dysfunction include reduced ATP generation and oxidative stress due to elevated ROS generation. Loss of Parkin's E3 ubiquitin ligase activity, may also lead to dopamine neuron toxicity via impaired ubiquitin-proteasome function and accumulation of Parkin's substrates. Loss of DJ-1 antioxidant function may promote neuronal oxidative stress, as might reduced respiratory chain function and elevated intracellular calcium influx via pores created by α-synuclein oligomers. LRRK2 mutations might be linked to PD through altered protein translation further supporting a role for protein turnover in PD pathogenesis.

Table

Genes underlying familial PD

Genes with variants that segregate with PD are listed. The inheritance pattern, typical age of disease-onset and characteristic phenotypes observed are described.

Locus	Gene	Inheritance pattern	Typical age of onset	Phenotype characteristics
PARK1 and PARK4	SNCA	Dominant	24–65	Parkinsonism (progression related to gene dose) with common dementia and autonomic dysfunction
PARK2	Parkin	Recessive	16–72	Slow-progressing Parkinsonism
PARK6	PINK1	Recessive	20–40	Slow-progressing Parkinsonism
PARK7	DJ1	Recessive	20–40	Slow-progressing Parkinsonism sometimes with behavioral disturbances
PARK8	LRRK2	Dominant	32–79	Classic PD